SCHOOL OF PHARMACY

# Hypoglycaemia in Diabetes and Dementia Population

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# Declaration by author

I, Alaa Ahmed Alsharif, 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.

# Abstract

**BACKGROUND:** Diabetes mellitus (DM) and dementia are common long-term conditions that co-exist in a large proportion of the elderly. Diabetic patients with dementia may be less able to self-manage and control their diabetes, placing them at a higher risk of complications such as hypoglycaemia.

**AIM:** This thesis aimed to investigate the risk of hypoglycaemia associated with dementia diagnosis among patients with DM.

**METHODS:** This thesis describes work conducted using The IQVIA Medical Research Data (IMRD)-UK database. Firstly, a descriptive, population-based study was conducted to estimate the prevalence and incidence of dementia in the diabetes population. Secondly, a descriptive, drug utilisation study was conducted to describe the prescribing pattern of antidiabetic medications and the rate of hypoglycaemia. Thirdly, a cohort study was conducted to investigate the association between dementia diagnosis and hypoglycaemia among patients with DM. Finally, a retrospective, pre-post exposure study was conducted to explore the glycaemic control and the rate of hypoglycaemia in diabetes patients pre- and post-dementia diagnosis.

**RESULTS:** There was a trend of increasing prevalence and incidence of dementia, annual antidiabetic medication prescribing and hypoglycaemia rate in patients diagnosed with both DM and dementia over the period of 2000–2016. Patients diagnosed with dementia were at a twofold increased risk for hypoglycaemic events compared with those not diagnosed with dementia for whom the adjusted hazards ratio (HR) was 2.00 (95% CI,1.63–2.66). Glycaemic control was tighter in patients after

dementia diagnosis compared to glycaemic control before dementia diagnosis. The rate of hypoglycaemia six months after dementia diagnosis was significantly higher at 3.05% (95% CI 3.0%–3.1%) compared to the rate of hypoglycaemia before dementia diagnosis at 2.18% (95% CI 2.1%–2.2%).

**Conclusion:** This project highlighted the clinical impact of dementia on patients with DM and confirmed that dementia was associated with an increased risk of hypoglycaemia. Therefore, physicians need to take extra care regarding diabetes management, especially for patients who have been diagnosed with dementia.

# Impact statement

The incidence and prevalence of dementia are rapidly rising among the diabetes population. Dementia is associated with a negative impact on diabetes patients, including reduced quality of life and clinical complications of cardiovascular disease. Hypoglycaemia is one of the most commonly experienced adverse drug events associated with antidiabetic therapy and is one of the major side effects when trying to achieve optimal glycaemic control. This PhD project highlighted that dementia is prevalent among the diabetes population. The coexistence of dementia is associated with a higher risk of hypoglycaemia compared to diabetes patients without dementia. The risk of hypoglycaemia was higher in older patients, those under tighter glycaemic control or those using insulin or sulfonylurea-based regimens. Patients with diabetes and dementia require some unique considerations that are not traditionally associated with diabetes care. Healthcare professionals should be aware of these coexisting conditions when dealing with those patients and consider the risk of them experiencing hypoglycaemia by providing them with individualised care and treatment strategies; this may lead to safer use of antidiabetic therapy and better outcomes. Several strategies could be implemented with regard to this concern according to the findings of this PhD work which will improve the individualised care approach for the benefit of patients in the short term by avoiding or preventing the risk of experiencing hypoglycaemic events and better quality of life for the long-term, such as: early recognition and management of hypoglycaemia; avoiding prescribing antidiabetic medications with a high risk of hypoglycaemia if possible, specifically sulfonylurea or insulin; focusing less on achieving glycaemic targets and more on symptom control with avoidance of hypoglycaemic episodes; ongoing assessment of the patient's self-management skills should be provided, not just regarding food intake but also the

ability to administer medication appropriately—this should be extended to the patient's relatives/caregivers and according to their needs or abilities; regular update and revision of the medication profile should be implemented due to the progressive nature of diabetes and dementia, to ensure that the current regimen is appropriate and to aid decision making in stepping up or down of therapy. In addition, healthcare policies and guidelines should improve the management of diabetes in patients with dementia by providing educational programmes for healthcare professionals. The aim of these programmes is to ensure that all clinicians possess a set of core competencies to keep their patients safe and to promote individualised, patient-centred care.

Future studies in could use the research that has been conducted in this PhD project as a base for further epidemiological and clinical research. Future research could be expanded from the findings and the limitations highlighted in this PhD. This could include: a) applying the same methodologies (analytical and cross-sectional studies from a clinical perspective) to other comorbidities, life-threatening and costly adverse drug events; b) conducting further studies to understand the patients' attitudes and perceptions regarding their hypoglycaemia; c) conducting further studies that identify preventive strategies to help decrease the occurrence of adverse drug events in diabetes patients with dementia, specifically hypoglycaemia; and d) conducting clinical trials that examine the safety and efficacy of newer classes of antidiabetic medications to have a good comparative effectiveness data and to guide choice of prescribing specific agent.

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## List of Abbreviations

**ADA** American Diabetes Association

**ACCORD** Action to Control Cardiovascular Risk in Diabetes

**ADI** Alzheimer's Disease International

**ADVANCE** The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial

**ASC** Alzheimer Society Canada

**BMI** Body Mass Index

**BNF** British National Formulary

**CDSR** Cochrane Database of Systematic Reviews

**CENTRAL** Cochrane Central Register of Controlled Trials

**CeVD** Cerebrovascular disease

**CI** Confidence Interval

**CMR** Cochrane Methodology Register

**CPRD** Clinical Practice Research Datalink

**CVA** Cerebrovascular accidents

**CVD** Cardiovascular Disease

**DARE** Database of Abstracts of Reviews of Effects

**DCCT** the Diabetes Control and Complications Trial

**DM** Diabetes Mellitus

**DPP-4** Dipeptidyl Peptidase- IV Inhibitors

**EMA** European Medicines Agency

**EMBASE** Excerpta Medica database

**EMRs** Electronic Medical Records

**FBG** Fasting Blood Glucose

**GI** Gastrointestinal

**GLP-1** Glucagon-like peptide-1

**GP** General Practitioner

**HbA1c** Glycated haemoglobin A1c

**HCP** Health Care Professional

**HES** Hospital Episode Statistics

**HF** Heart Failure

**HR** Hazard Ratio

**ICD** International Statistical Classification of Diseases and related health problems.

**IDF** International Diabetes Federation

**IHD** Ischemic Heart Disease

**IMRD-UK** IQVIA Medical Research Data-UK

**IRR** Inter-rater Reliability

**MEDLINE** Medical Literature Analysis and Retrieval System Online

**MeSh** Medical Subject Heading

**MI** Myocardial Infarction

**NCD** Non-Communicable Disease

**NCDEG** National Centre for Diabetes, Endocrinology, and Genetics

**NGSP** the National Glycohemoglobin Standardization Program

**NHS** National Health Service

**NICE** National Institute for Health and Care Excellence

**NOS** Newcastle Ottawa Scale

**NWIS** NHS Wales Informatics Service OAD Oral Antidiabetic

**OGTT** Oral Glucose Tolerance Test

**ONS** Office for National Statistics

**OR** Odd's Ratio

**PG** Plasma Glucose

**PICO** Population, Intervention, Comparator, and Outcome

**PRISMA** Preferred Reporting items for Systematic Review and Meta - Analysis

**RCT** Randomised Controlled Trial

**SAS** Statistical Analysis Software

**SD** Standard Deviation

**SGLT-2** Sodium-Glucose Cotransporter-2

**T1DM** Type 1 Diabetes Mellitus

**T2DM** Type 2 Diabetes mellitus

**THIN** The Health Improvement Network

**UCL** University College London

**UK** United Kingdom

**VADT** the Veterans Affairs Diabetes Trial

**WHO** World Health Organization

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# Publications and presentations from the PhD work

## Publications:

1. **Hassan Alwafi*, Alaa A. Alsharif*,** , Li Wei, Dean Langan, Abdallah Y Naser, Pajaree Mongkhon, J Simon Bell, Jenni Ilomaki, Mansour S Al Metwazi, Kenneth K C Man, Gang Fang, Ian C K Wong. Incidence and prevalence of hypoglycaemia in type 1 and type 2 diabetes individuals: A systematic review and meta-analysis. Diabetes research and clinical practice. 2020;170:108522. * joint first author Refer to **Appendix 12.**

2. **Alaa A. Alsharif**, L. Wei, T. Ma, K. Man, W. Lau, R. Brauer, M. Almetwazi, R. Howard and I. Wong. Prevalence and Incidence of Dementia in People with Diabetes Mellitus. Journal of Alzheimer's disease : JAD. 2020;75(2):607-15. Refer to **Appendix 12.**

3. **Alaa A. Alsharif**, I. Wong, K. Man, W. Lau, R. Brauer, M. Alhamed, H. Alwafi, C. Whittlesea, L. Wei. Anti-hyperglycaemic agents prescribing and the hypoglycaemia rate in patients with diabetes mellitus and dementia: a population-based study in the United Kingdom. A revision has been submitted to Diabetes Research and Clinical Practice Journal.

4. Dementia and the Risk of Hypoglycaemia Events Among Patients With Diabetes Mellitus: A Propensity Score Matched Cohort Analysis. The manuscript has been submitted to the journal of Internal Medicine.

## Conference Presentations:

**Oral presentation:**

1. A. Alsharif, L. Wei, T. Ma, K. Man, W. Lau, R. Brauer, M. Almetwazi, R. Howard and I. Wong. Prevalence and Incidence of Dementia in People with Diabetes Mellitus.

Journal of Alzheimer's disease: JAD. 2020. **The PharmAlliance Graduate E-symposium, 29 September and 1 October 2020.**

**Poster presentation:**

1. A. Alsharif, H. Alwafi, M. Almetwazi, L. Wei, A. Naser, J. Bell, J. Ilomaki, G. Fang, I. Wong. The rate of hypoglycaemic events in individuals with type 1 diabetes; systematic review and meta-analysis of observational studies. **The 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2018). Prague, Czech Republic 22–26 August 2018.** And presented in **the 4th Scientific Meeting for Medication safety- November 2018.**

2. Alaa Alsharif, Li Wei, Mansour Almetwazi, Tian Ma, Rob Howard, Ian Wong. Prevalence and Incidence of Dementia in People with Diabetes Mellitus. **Pharmacology 2019, 15–17 December, Edinburgh International Conference Centre.**

# 1 CHAPTER ONE: Introduction

This chapter consists of four sections that together represent an overview of the research topic. The first and second sections provide a brief overview of diabetes mellitus (DM) and dementia and their epidemiology worldwide and particularly in the United Kingdom (UK), the third section gives general information about hypoglycaemia, and the fourth section focuses on the association between diabetes and dementia and the challenges associated with diabetes management, along with the risk of hypoglycaemia.

## 1.1 Overview of diabetes mellitus

Diabetes is one of the main chronic disorders and well known as leading to a potential risk of disability and multiple organ failure, especially in relation to the heart, kidneys, eyes, nerves and blood vessels. It requires continuous medical care and complicated disease management strategies to improve diabetic individuals' quality of life (American Diabetes Association, 2017, International Diabetes Federation, 2019, National Institute for Health and Care Excellence, 2015b).

### 1.1.1 Epidemiology of diabetes mellitus

DM is a serious global metabolic disorder that affects over 463 million people aged 20 to 79 years worldwide, about 9.3% of people in 2019 (International Diabetes Federation, 2019). The number of people with diabetes is expected to reach 700.2 million or 10.9% of the world's population by 2045 (International Diabetes Federation, 2019). In 2019, the prevalence of DM among people aged 65 to 99 years was 19.3%, accounting for 135.6 million and is expected to reach 19.6% or 276.2 million people by 2045 (International Diabetes Federation, 2019).

In the UK, there are more than 4.8 million people with diabetes, including those unaware of their condition, 3.9 million people with a confirmed diagnosis of diabetes,

which is estimated to be about 7% of the UK population (Diabetes UK, 2019a, Whicher et al., 2020). **Table 1** presents the number of patients with diagnosis of DM across countries in the UK.

**Table 1 Number of Patients Diagnosed With Diabetes in the UK**

| Country | Number of patients 2018-2019 |
|---|---|
| **England** | 3,319,266 |
| **Northern Ireland** | 99,833 |
| **Scotland** | 301,523 |
| **Wales** | 198,883 |
| **UK** | 3,919,505 |

**UK** United Kingdom (Diabetes UK, 2019a)

### Prevalence of DM by type

There are four main types of DM: type I DM (T1DM), type II DM (T2DM), gestational DM and secondary DM, which is caused by genetic mutation, other diseases or hormonal disturbance (American Diabetes Association, 2010). T2DM is considered to be the most common and prevalent type of diabetes (International Diabetes Federation, 2019). In the UK, approximately 90% of adult DM patients have T2DM. Only 8% of DM patients have been diagnosed with T1DM and it is more frequently seen in children and adolescents than adults (Diabetes UK, 2019b). The global prevalence of gestational DM was estimated to be about 15% of the women who gave birth in 2019 (International Diabetes Federation, 2019).

### Prevalence of DM by gender

DM was slightly more prevalent in males than females globally (9.6% vs 9.0%) in 2019 and it is expected to increase to 11.1% vs 10.8% by 2045 (International Diabetes Federation, 2019).

### 1.1.2 Definition and classification of Diabetes mellitus

DM is a chronic health condition characterised by an increased level of blood glucose that occurs when the pancreas fails to produce sufficient insulin or when the body cannot properly use the insulin it produces. Insulin is a hormone that plays an important role in regulating blood glucose level (International Diabetes Federation, 2019). The World Health Organization (WHO), American Diabetes Association (ADA) and International Diabetes Federation (IDF) have defined DM as shown in **Table 2**.

**Table 2 Definitions of Diabetes Mellitus**

| Source | Definition |
|---|---|
| **WHO** | "A metabolic disorder of multiple aetiologies characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both." |
| **ADA** | "A group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both." |
| **IDF** | "A serious, chronic condition that occurs when there are raised levels of glucose in a person's blood because their body cannot produce any or enough of the hormone insulin, or cannot effectively use the insulin it produces." |

**WHO** World Health Organization, **ADA** American Diabetes Association and **IDF** International Diabetes Federation. (World Health Organisation, 1999, American Diabetes Association, 2010, International Diabetes Federation, 2019)

**T1DM** is known as insulin-dependent DM (IDDM) and is caused by autoimmune destruction of beta cells in the pancreas, leading to absolute insulin deficiency

(Atkinson, 2012). T1DM is most commonly seen in children, adolescents and younger adults (Wells, 2009, Atkinson, 2012). T1DM common symptoms are: weight loss; polyuria (frequent urination); polyphagia (constant hunger); polydipsia (excessive thirst); and lethargy (lack of energy) (Wells, 2009). In addition, 20–40% of T1DM patients may develop diabetic ketoacidosis (DKA), a life-threatening condition that requires emergency treatment. It occurs by the breaking down of fat and build-up of ketones to produce energy (International Diabetes Federation, 2019, Wells, 2009).

**T2DM** is known as non-insulin-dependent diabetes mellitus (NIDDM) or adult onset diabetes. It is considered to be the most common diabetes type (World Health Organization, 1999) and is caused by insufficient insulin secretion or insulin resistance (Wells, 2009, Atkinson, 2012). T2DM occurs most frequently in the elderly, but it can be seen in the younger population due to poor diet, no exercise and obesity (International Diabetes Federation, 2019). T2DM patients are usually asymptomatic, but with time they develop symptoms similar to those of T1DM but less serious (International Diabetes Federation, 2019). T2DM has multiple risk factors, including age, obesity, lack of physical activity and family history; however, the specific causes of T2DM are not well known.

**Gestational diabetes** is defined as an increase in blood glucose level during pregnancy and usually occurs in the second trimester of pregnancy (Kaaja and Rönnemaa, 2008). Gestational diabetes symptoms are uncommon and normally disappear after delivery; therefore, an oral glucose tolerance test is recommended between the $24^{th}$ and $28^{th}$ weeks of pregnancy to screen for gestational DM (Kaaja and Rönnemaa, 2008). The screening can be conducted earlier in pregnancy in cases of high-risk females (American Diabetes Association, 2010).

**Secondary diabetes** is caused by other diseases, such as pancreatic damage,

hepatic cirrhosis, drug-induced diabetes, especially with glucocorticoid use, HIV or AIDS therapy (American Diabetes Association, 2010, National Institute for Health and Care Excellence, 2015b).

### 1.1.3 Diagnosis of diabetes mellitus

According to the ADA and IDF, diabetes can be diagnosed based on specific diagnostic tests, including plasma glucose criteria **(Table 3)**, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75g oral glucose tolerance test (OGTT), or A1C criteria, and upon presenting hyperglycaemia-associated symptoms, such as polydipsia, polyuria, polyphagia, weight loss and blurred vision. Often symptoms are mild or might be absent (American Diabetes Association, 2010, International Diabetes Federation, 2019).

**Table 3 Criteria for the Diagnosis of Diabetes Mellitus**

| Diagnostic test | Definition |
|---|---|
| **Fasting plasma glucose (FPG)** | FPG ≥ 126 mg/dL (7.0 mmol/L) at two different times.<br><br>Fasting is defined as no food or drink intake except water for at least 8h.* |
| **2-h plasma glucose level (2-h PG)** | (2-h PG) value ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. * |
| **Glycosylated haemoglobin (HbA1c)** | A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardised to the DCCT assay. * |
| **Random plasma glucose level** | In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose > 200 mg/dL (11.1 mmol/L). |

*In the absence of unequivocal hyperglycaemia, results should be confirmed by repeat testing. **NGSP =** National Glycohemoglobin Standardization Program; **DCCT** = Diabetes Control and Complications Trial (American Diabetes Association, 2010, International Diabetes Federation, 2019)

### 1.1.4 Clinical management of Diabetes mellitus

Over time, an increased blood glucose level, or hyperglycaemia, leads to disability and multiple organ failure, especially in relation to the heart, kidneys, eyes, nerves and blood vessels, requiring continuous medical care and complicated strategies to improve diabetic patients' quality of life. However, if optimal glycaemic control is achieved it might prevent or delay these life-threatening complications (Hanssen, 1997). Therefore, DM patients should be managed properly to avoid or delay these complications. Diabetes management can be divided into two approaches: the non-pharmacological approach and the pharmacological approach.

#### 1.1.4.1 Non-pharmacological management

As a first step in DM prevention and management, healthcare providers should support and encourage high-risk DM patients to participate in diabetes self-management education and support through lifestyle modification (Powers et al., 2016). This will help in preventing the development of DM in cases of impaired blood glucose and will improve health outcomes in those with pre-diabetes or early stages of diabetes, especially T2DM. Lifestyle modification includes the following: a) dietary control by reducing sugar and fatty foods, increasing wholemeal products and eating at regular intervals; b) encouragement of physical activity by exercising regularly to improve insulin sensitivity and reduce insulin resistance, which result from obesity; c) smoking cessation; d) weight loss for obese people will help in reducing insulin resistance and the associated consequences of metabolic disorders, including hypertension and dyslipidaemia (Scottish Intercollegiate Guidelines Network, 2010).

### 1.1.4.2 Pharmacological management

Pharmacological treatment is aimed at controlling blood glucose levels and at achieving optimal glycaemic control to prevent the development of diabetes' life-threatening complications.

### Antidiabetic medication classes

There are nine therapeutic classes for antidiabetic medication to treat DM based on their mechanism. The following section explains the mechanism of action and lists the agents of each antidiabetic therapeutic class **(Figure 1)** (Wells, 2009, British National Formulary (BNF), 2017).

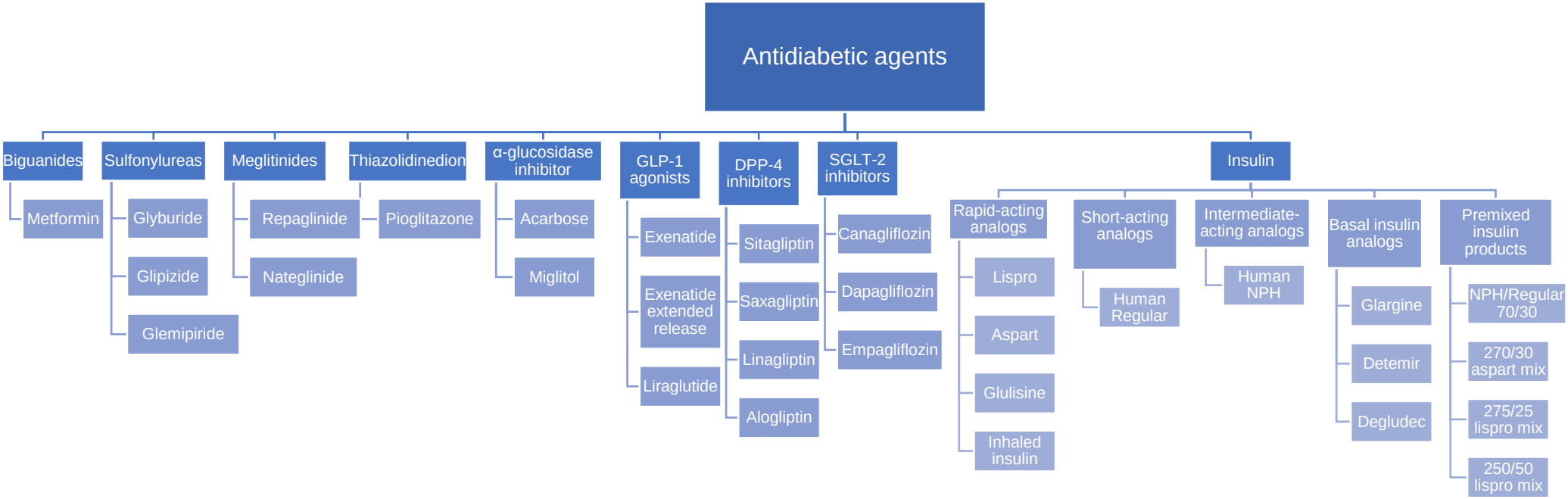



**Figure 1 Antidiabetic Therapeutic Classes (British National Formulary (BNF), 2017, American Diabetes Association, 2017)**

## Insulin therapy

Insulin is a hormone that plays an important role in treating patients with diabetes by regulating blood glucose levels in the body (Wilcox, 2005). Patients diagnosed with T1DM are known as insulin dependent due to insulin deficiency (Atkinson, 2012). However, patients with T2DM might require insulin therapy if oral antidiabetic agents fail to control their blood glucose levels. Multiple formulations of insulin are available to be used in diabetes management and are classified based on their rate of absorption and how fast they reach peak level (the highest concentration reached by insulin in the body) and start to act (Hirsch, 2005). Insulin formulations are listed in **Table 4**.

**Table 4 Insulin Formulations, Peak of Action and Dosage**

| Insulin type | Formulation | Peak of action | Effective duration | Rout of administration | Dosing and coverage |
|---|---|---|---|---|---|
| **Long-acting insulin** | | | | | |
| **Insulin glargine** | injectable solution/ prefilled pen | 6-10 hours | 24 hours | SC | Once daily, basal |
| **Insulin detemir** | injectable solution/ prefilled syringe | 4-7 hours | 14 hours | SC | Twice or once daily, basal |
| **Intermediate-acting insulin** | | | | | |
| **Neutral Protamine Hagedorn (NPH)** | injectable suspension | 4-12 hours | 12-18 hours | SC | Twice daily, basal |
| **Short-acting insulin** | | | | | |
| **Regular insulin** | injectable solution | 2-3 hours | 6-8 hours | SC/ continuous SC insulin infusion/ IV | 30 minutes before meal, prandial |
| **Rapid-acting insulin** | | | | | |
| **Insulin lispro** | injectable solution/ prefilled pen | Dual | 10-16 hours | SC/ continuous SC insulin infusion/ IV | Up to 15 minutes before meal or immediately after meal, prandial |
| **Insulin aspart** | injectable solution/ prefilled syringe | Dual | 10-16 hours | SC/ continuous SC insulin infusion/ IV | Up to 15 minutes before meal or immediately after meal, prandial |
| **Insulin glulisine** | injectable solution/ prefilled pen | 3-4 hours | | SC/ continuous SC insulin infusion/ IV | Up to 15 minutes before meal or immediately after meal, prandial |
| **Premixed insulin (human)** | | | | | |
| **70% NPH, 30% regular insulin** | injectable suspension/ prefilled pen | 16-24 hours | | SC | Before breakfast and before supper, prandial-basal |

| Insulin type | Formulation | Peak of action | Effective duration | Rout of administration | Dosing and coverage |
|---|---|---|---|---|---|
| **50% NPH, 50% regular insulin** | | | | | |
| **Premixed insulin (insulin analogues)** | | | | | |
| **70% insulin protamine aspart, 30% insulin aspart**<br><br>**50% insulin protamine lispro, 50% insulin lispro**<br><br>**75% insulin lispro protamine suspension and 25% insulin lispro** | injectable suspension/ prefilled pen | 16-24 hours | | SC | Before breakfast and before supper, prandial-basal |

***SC****= subcutaneous,* ***IV=*** *intravenous (Hirsch, 2005)*

Insulin therapy is delivered for DM patients either as a subcutaneous or an intravenous injection or via an insulin pump. For routine use, a subcutaneous insulin injection is preferred and can be injected using a needle and syringe, a pre-filled pen system or a cartridge system. The starting dose of insulin is calculated based on the patient's weight and sensitivity to insulin, which varies from person to person. Subcutaneous insulin injections should be divided into two doses, with the morning dose being equal to two-thirds of the total daily dose and the evening dose providing the other third (National Institute for Health and Care Excellence, 2015b).

### Oral antidiabetic agents

Oral antidiabetic agents are used to treat T2DM patients to manage their blood glucose levels. There are eight main categories, which are described in brief below:

1. **Biguanides**: metformin is the only drug in this category and it is a first-line monotherapy or combination therapy in T2DM patients (National Institute for Health and Care Excellence, 2015b). It reduces the glucose output by the liver and increases the sensitivity of body tissues (the peripheral tissues and skeletal muscle) to insulin

(Shaw et al., 2005). The common side effects of metformin are gastrointestinal (GI) upset, weight loss, lactate acidosis and renal toxicity, and therefore metformin is contraindicated in individuals with diabetic ketoacidosis and renal dysfunction (Scarpello and Howlett, 2008, Chaudhury et al., 2017). Hypoglycaemia is considered the main side effect of antidiabetic medication; however, the rate of hypoglycaemia in patients using metformin as a monotherapy is low (0.3%) (Wright et al., 2006) but the risk increases significantly if metformin is combined with sulfonylureas (Bolen et al., 2007).

2. **Sulfonylureas and secretagogues**: these are indicated as a second-line therapy and are the drugs of choice for patients diagnosed with T2DM for whom metformin did not control their blood glucose levels (National Institute for Health and Care Excellence, 2015b, American Diabetes Association, 2017). These agents increase the plasma insulin levels through two mechanisms (Proks et al., 2002a). Firstly, they stimulate insulin secretion by binding to the sulfonylurea receptor on the pancreatic β-cells and blocking the ATP-sensitive K+ channel. Secondly, they reduce the hepatic metabolism of insulin. There are three types of sulfonylureas (British National Formulary (BNF), 2017): the first type are long-acting sulfonylureas (glibenclamide, glimepiride and chlorpropamide); the second type are intermediate-acting sulfonylureas including acetohexamide and tolazamide; the third type are short-acting sulfonylureas, such as glipizide, tolbutamide and gliclazide. The most common side effect of sulfonylureas is hypoglycaemia; weight gain and disulfiram reaction (skin reactions) are considered to be infrequent side effects (Chaudhury et al., 2017, Wells, 2009, Holstein et al., 2010). The risk of hypoglycaemia increases in patients with long-acting sulfonylureas (Boyle and Zrebiec, 2008).

3. **Thiazolidinediones**: these are indicated for treating T2DM patients as an add-on therapy. Pioglitazone and rosiglitazone are selective agonists of peroxisome proliferative-activated receptor γ (PPARγ) receptors, thus improving insulin sensitivity, increasing the clearance of fasting and postprandial glucose and decreasing gluconeogenesis (Wells, 2009, Wagstaff and Goa, 2002). Thiazolidindiones-associated side effects include GI upset, fractures, increased risk of congestive heart failure, oedema and weight gain (Chaudhury et al., 2017, Wells, 2009). A greater risk of hypoglycaemia is associated with patients on a combination therapy of thiazolidindiones and sulfonylureas compared to sulfonylurea monotherapy (Bolen et al., 2007).

4. **Alpha-glucosidase inhibitors**: these are indicated as an add-on therapy. Acarbose, miglitol and voglibose are alpha glucosidase inhibitor derivatives, isolated from bacterial cultures, that behave as pseudo-carbohydrates (Wells, 2009). They are competitive inhibitors of the alpha glucosidase enzyme in the brush border of the intestine, which is responsible for breaking down oligosaccharides into monosaccharides, which are easily absorbed in the intestine, resulting in a reduction in the absorption of starch (Derosa and Maffioli, 2012). GI upset appears due to the delay in carbohydrate digestion and includes malabsorption, flatulence and diarrhoea (van de Laar, 2008, Wells, 2009).

5. **Meglitinides**: these are indicated as an add-on therapy for patients with T2DM. Meglitinide and repaglinide have a similar mechanism of action to sulfonylureas: they increase the secretion of pancreatic insulin and decrease postprandial glucose excretion (Guardado-Mendoza et al., 2013). Hypoglycaemia and headache are side effects of meglitinides. A lower risk of hypoglycaemia is associated with meglitinides

compared to sulfonylureas due to their weaker binding with the β-cell receptors of the pancreas (Wells, 2009, Chaudhury et al., 2017).

6. **Dipeptidyl peptidase IV (DPP-IV) inhibitors (gliptins**): these are indicated as an add-on therapy with metformin. There are five oral DPP-IV inhibitors globally available: sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin. These agents act by inhibiting the DPP-IV enzyme, which metabolises incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)), leading to enhancement of their concentration (Pathak and Bridgeman, 2010, Wells, 2009). They are associated with fewer adverse events as a monotherapy compared to other oral antidiabetic agents but, in combination therapy with sulfonylureas, the risk of hypoglycaemia increases (Chaudhury et al., 2017, Pathak and Bridgeman, 2010).

7. **Glucagon-Like Peptide-1 (GLP-1):** incretin analogues/agonists are indicated as an add-on therapy. They stimulate insulin secretion in response to glucose, downregulating glucagon levels and resulting in lowering blood glucose levels and slow gastric emptying (Drucker and Nauck, 2006, Kalra et al., 2016). Exenatide, dulaglutide and liraglutide are the most commonly used agents for treating T2DM under this therapeutic class. Slowing gastric emptying results in nausea, abdominal pain, weight loss and acute pancreatitis associated with exenatide and hypoglycaemia, only in combination therapy with sulfonylurea or in insulin (Juhl et al., 2002, Nauck et al., 2009, Ohneda et al., 1991).

8. **Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors:** these antidiabetic agents are the newest insulin-independent glucose-lowering agents and are indicated as an add-on therapy to treat T2DM. Canagliflozin, dapagliflozin and empagliflozin act by inhibiting SGLT2, resulting in blocking the reabsorption of glucose in the proximal renal tubule and increasing glucose excretion in urine (Riser Taylor and Harris, 2013, Kalra,

2014). Diabetic ketoacidosis is a serious side effect of SGLT2 in the absence of significant hyperglycaemia but it rarely occurs. Urogenital tract infections and fractures are associated with the use of SGLT2 (Chaudhury et al., 2017, Kalra, 2014).

DM management differs according to the type of diabetes, whether T1DM or T2DM. In T1DM, in addition to lifestyle modifications, insulin is considered the foundation for the management of diabetes. NICE guidelines recommend that the treatment approach be individualised for children and young adults with T1DM (National Institute for Health and Care Excellence, 2015a). There are three strategies of insulin regimens: 1) multiple daily doses of basal-bolus insulin; 2) insulin pump therapy, a programmable device to pump and store regular or continuous amounts of short-acting or rapid-acting insulin through a subcutaneous cannula or needle; 3) up to three insulin doses per day (usually mixed insulin analogues short/rapid-acting insulin and intermediate/long-acting insulin) (National Institute for Health and Care Excellence, 2015a). For all adults with T1DM, NICE guidelines recommend multiple daily doses of basal-bolus insulin, instead of twice daily mixed insulin, except if multiple doses are not appropriate for the patient (National Institute for Health and Care Excellence, 2015b): refer to **Appendix 1**.

Based on the National Institute for Health and Care Excellence (NICE) guidelines, patients with diabetes should keep their fasting blood glucose between 5 and 7 mmol/L and their random plasma glucose levels, before meals or at any time of the day, at 4–7 mmol/L. HbA1c levels should be measured every three to six months and are recommended to be between 6.5% (48 mmol/mol) and 7%(53 mmol/mol) for patients at higher risk of hypoglycaemia (American Diabetes Association, 2017, National Institute for Health and Care Excellence, 2015b, National Institute for Health and Care Excellence, 2015b). While, the ADA recommended less stringent HbA1c level of

patients with comorbid conditions, long DM duration and increased risk of hypoglycaemia < 8% (American Diabetes Association, 2019).

However, T2DM management is different from T1DM management. NICE guidelines recommend starting first with oral antidiabetic medication before insulin therapy if diet and lifestyle modifications have not shown proper control. NICE recommendations for T2DM management by pharmacological regimen are displayed in **Figure 2**: refer to **Appendix 2**.

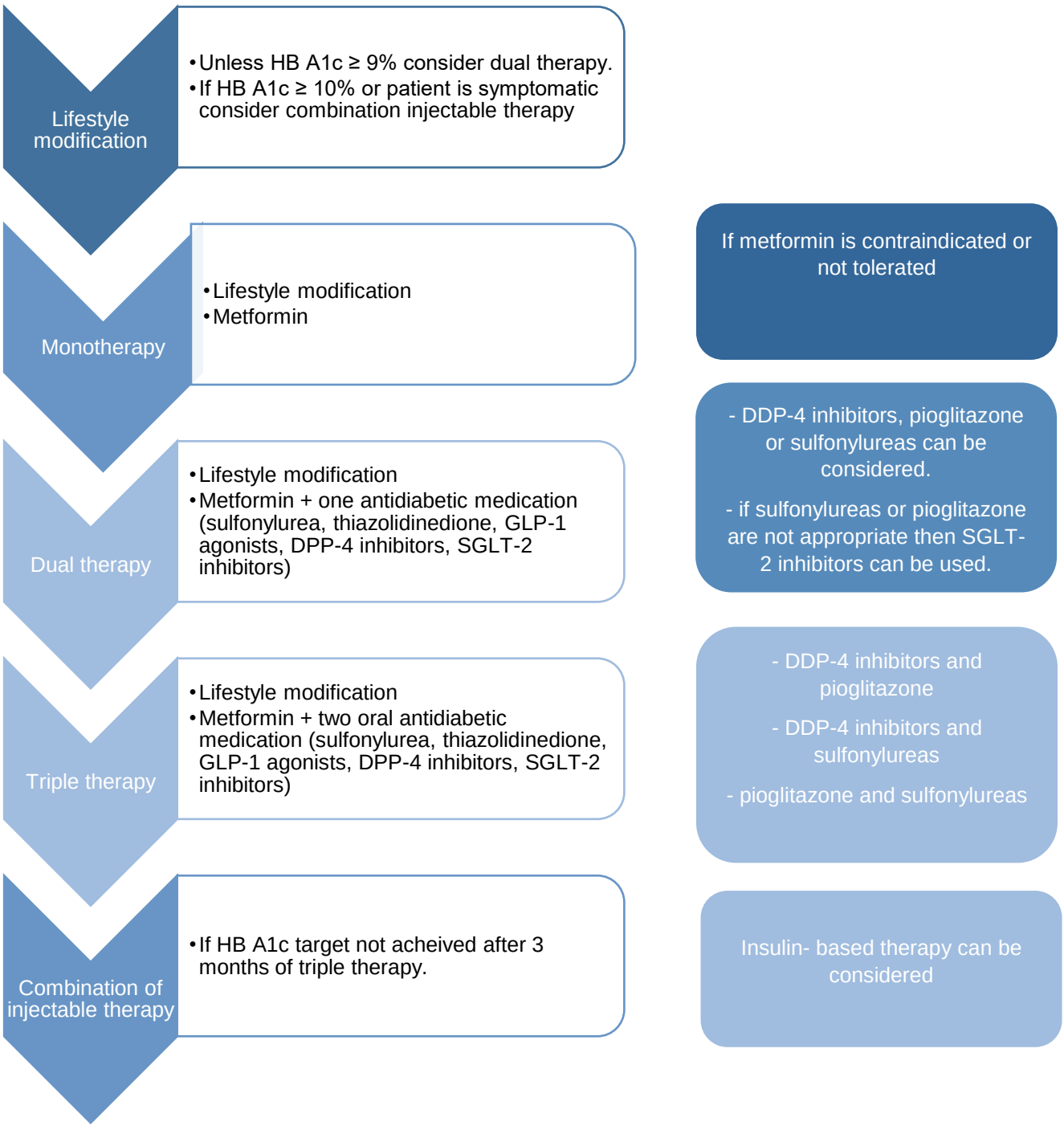



**Figure 2 Diabetes Mellitus Pharmacological Regimens (National Institute for Health and Care Excellence, 2015b)**

### 1.1.5 Complications of diabetes mellitus

Uncontrolled DM is associated with long-term damage in several body systems and increased rates of disability and death (Papatheodorou et al., 2018). Diabetes complications vary from acute and life-threatening conditions, such as severe hypoglycaemia, to chronic serious complications. Complications can be classified into two major classes (Chawla et al., 2016):

a) Acute complications, including hypoglycaemia, hyperglycaemic diabetic coma, seizures, diabetic ketoacidosis and infections.

b) Chronic complications, including macrovascular and microvascular complications. Complications are presented below in detail:

#### 1.1.5.1 Acute complications

Uncontrolled DM could cause acute complications. Hyperosmolar hyperglycaemic state (HHS) and diabetic ketoacidosis (DKA) are the two most common, life-threatening acute metabolic complications resulting in diabetic coma and death (Kitabchi et al., 2009).

HHS is a serious and potentially fatal complication of T2DM patients who experience a very high level of blood glucose (high osmolarity) without significant ketoacidosis (Adeyinka A, 2021). It is most commonly seen in DM patients with obesity and high body mass index (BMI). HHS is characterised by dehydration, weakness, leg cramps, vision problems and an altered level of consciousness. The mortality rate for HHS ranges from 5–20%, which is around ten times higher than the mortality rate for diabetic ketoacidosis (Kitabchi et al., 2009).

DKA is a serious complication of T1DM that occurs when high levels of blood ketones are produced by the body because of persistent hyperglycaemia and lack of insulin (Kitabchi et al., 2009). Ketones are chemicals created by fat breaking down to be used for energy (American Diabetes Association, 2021). DKA is characterised by dehydration, confusion and a fruity odour on the breath (Kitabchi et al., 2009). A mortality rate for DKA of >5% has been reported in older patients with comorbid conditions (Kitabchi et al., 2009).

#### 1.1.5.2 Macrovascular complications

Persistent, uncontrolled DM can increase the risk of developing atherosclerosis, which results in narrow blood vessels, leading to injury and chronic inflammation of the blood vessel walls within the coronary vascular system (Boyle, 2007). Diabetes is an independent, predisposing factor of cardiovascular disease (CVD), which is considered to be the primary cause of diabetic individuals' mortality (Beckman et al., 2002, Soedamah-Muthu et al., 2006). Patients with T2DM have an increased risk of developing stroke, stroke-related dementia and stroke-related mortality (Beckman et al., 2002). Patients with T1DM also have a higher mortality rate due to ischaemic heart disease (Paterson et al., 2007), (Soedamah-Muthu et al., 2006). In 2019, the WHO reported that DM was the ninth leading cause of death (World Health Organisation, 2020). It is responsible for about 4.2 million deaths or 11.3% of all deaths of adults aged 20–79 years globally (International Diabetes Federation, 2019).

#### 1.1.5.3 Microvascular complications

Diabetic retinopathy is probably the most common microvascular complication, affecting 34.6% of diabetes patients globally (Yau et al., 2012). Diabetic retinopathy affects the

eyes and leads to vision loss due to blocking of the blood vessels that supply the retina (Stratton et al., 2000, Zinman et al., 2014, Fowler, 2008). The period and severity of diabetes possibly contributes to the risk of developing retinopathy (UKPDS group, 1998). Background retinopathy is characterised by small haemorrhages in the middle layers of the retina, appearing as “red dots” (Fowler, 2008). Proliferative retinopathy includes such features as the formation of new blood vessels on the surface of the retina, resulting in white areas on the retina (“cotton wool spots”) due to vitreous haemorrhages (Watkins, 2003).

A further complication is diabetic nephropathy, with around 7% of diabetic individuals potentially already having microalbuminuria at the time of their diabetes diagnosis (Coca et al., 2012). Microalbuminuria (albumin excretion of 30–299 mg/day) typically might progress to proteinuria (the proteinuria level is 500 mg or more in 24 hours), which manifests as diabetic nephropathy. Diabetic nephropathy results in renal failure due to CKD, which describes abnormal renal function and/or structure (Coca et al., 2012). The risk of developing CKD increases with age and, as kidney dysfunction progresses, some coexisting conditions become more common and increase in severity (Fowler, 2008). CKD can progress to end-stage renal disorder in a small but significant proportion of individuals (Gross et al., 2005).

Diabetic neuropathy, also known as diabetic foot, is a complication that can result in amputation (Fowler, 2008). The risk of foot problems in patients with diabetes is increased, largely owing to either diabetic neuropathy or peripheral blood vessel disease, or both (Fowler, 2008). The ADA recognises diabetic neuropathy as “the presence of

symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of alternative causes" (American Diabetes Association, 2007, Tesfaye et al., 2010). The most common form of neuropathy is chronic sensorimotor distal symmetric polyneuropathy. Typical clinical symptoms of diabetic foot are burning, tingling and "electrical" pain but sometimes it is asymptomatic (Tesfaye et al., 2010). Diabetes is the most common reason behind non-traumatic limb amputation with diabetic foot ulcers causing over 80% of amputations in DM patients (Tesfaye et al., 2010).

## 1.2 Overview of dementia

Dementia has become a global public health concern (Prince, 2014b). Living with dementia impacts not only the patient also the patient's family, carers and society everywhere with physical, mental, social and financial consequences (World Health Organisation, 2019).

### 1.2.1 Epidemiology of dementia

In 2015, Alzheimer's Disease International (ADI) reported on the expected global impact of dementia over the next four decades. Approximately 50 million patients have been diagnosed with dementia worldwide and this estimation is expected to rise threefold by 2050 (Alzheimer's Disease International, 2015). In the UK, dementia prevalence had an estimated rate of about 4.3% among people aged over 65 years in 2019 (Public Health England, 2020).

In 2020, there were 525,315 patients diagnosed with dementia in the UK, as reported by Alzheimer's Research UK, and it is estimated to exceed 1,000,000 individuals by 2025 (alzheimer's Reasearch UK, 2020).

### 1.2.2 Definition and classification of dementia

Dementia can be described as a clinical syndrome associated with progressive neurodegenerative brain disorders, characterised by difficulties in memory, thinking, communication and behaviour, contributing to impairment in daily functional abilities. Dementia affects mainly older individuals and is considered to be one of the most common causes of disability and death (Prince, 2014b, National Institute for Health and Care Excellence, 2018c). Dementia definitions are shown in **Table 5**.

**Table 5 Definitions of Dementia**

| Source | Definition |
|---|---|
| **WHO** | "Is a syndrome – usually of a chronic or progressive nature – in which there is deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement." |
| **NICE** | "Is a term used to describe a range of cognitive and behavioural symptoms that can include memory loss, problems with reasoning and communication and change in personality, and a reduction in a person's ability to carry out daily activities." |
| **ASC** | "Is an overall term for a set of symptoms that are caused by disorders affecting the brain. Symptoms may include memory loss and difficulties with thinking, problem solving or language, severe enough to reduce a person's ability to perform everyday activities." |

**WHO** World Health Organization, **NICE** National Institute for Health and Care Excellence, **ASC** Alzheimer Society Canada (World Health Organisation, 2019, National Institute for Health and Care Excellence, 2018c, alzheimer Society Canada, 2017)

Dementia can be classified into five types. All types have a similar clinical presentation with different aetiologies **(Figure 3)**. Alzheimer's disease is the most common form of dementia, accounting for 50–75% of overall dementia individuals in the UK (Duong et al., 2017, Alzheimers Society, 2019). It is caused by the presence of cortical amyloid plaques

and neurofibrillary tangles in the brain and it presents with short-term memory loss and symptoms of depression, then gradual progressive loss of executive functions (Duong et al., 2017). Cerebrovascular disease (CeVD) (such as stroke) and atherosclerotic conditions (such as DM, coronary heart disease and hypertension) are responsible for the second most common type of dementia, which is vascular dementia, making up about 20% of dementia cases in the UK (Alzheimers Society, 2019). Vascular dementia follows a vascular event and is associated with similar symptoms to Alzheimer's disease. Dementia with Lewy bodies, characterised by cognitive fluctuations and Parkinsonism, accounts for 10–15% of dementia cases in the UK (Alzheimers Society, 2019). The last type of dementia is frontotemporal dementia (2%), which is more frequently seen in younger adults and associated with more personality and behavioural changes, including apathy, aggression and less memory loss in the early stages (Duong et al., 2017, Alzheimers Society, 2019). The coexistence of both Alzheimer's disease and vascular dementia, or Alzheimer's disease and dementia with Lewy bodies is called mixed dementia (Duong et al., 2017).

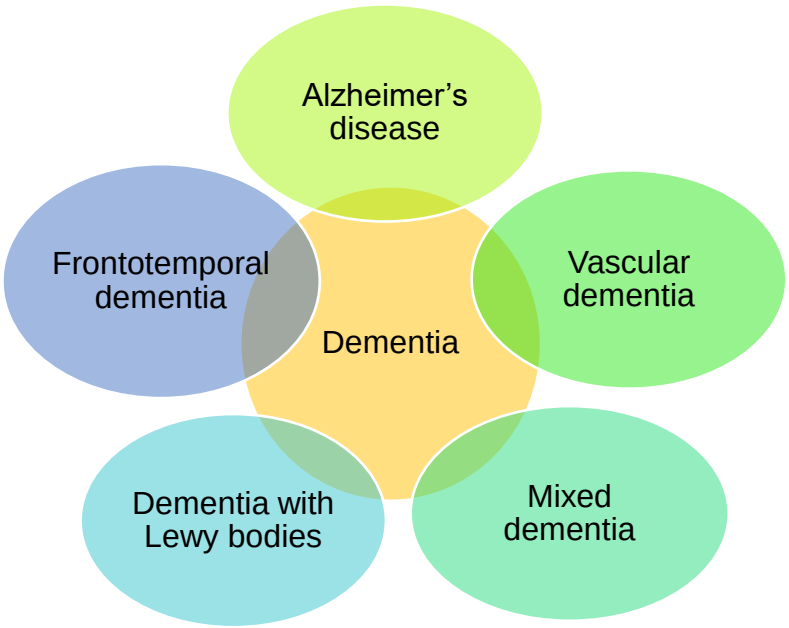



**Figure 3 Dementia Types**

### 1.2.3 Diagnosis of dementia

Suspected patients with dementia should undergo an initial, comprehensive assessment in a primary care setting and then they should be referred to a memory clinic or dementia specialist (National Institute for Health and Care Excellence, 2018c). The initial assessment should include:

- Taking a history of the behaviour, cognitive and psychological symptoms from the suspected person or relative.
- Conducting a physical examination and lab tests.
- Testing cognitive and mental status. Formal cognitive testing should be undertaken using a validated instrument in those with suspected dementia.

The most commonly used test for complaints of memory loss or mental disability is the Mini-Mental State Examination (MMSE). It can be used to help in dementia diagnosis and

to assess its progression and severity. It consists of a series of questions and tests, each of which scores points if answered correctly. A number of different examinations are now available, including the 6-item Cognitive Impairment Test (6-CIT), the 6-item screener, the memory impairment screen (MIS) and test your memory (TYM) (National Institute for Health and Care Excellence, 2018c). If dementia is still suspected, the patient should be referred to a specialist or memory clinic for further examinations to confirm the diagnosis of dementia and its subtype (National Institute for Health and Care Excellence, 2018c). Structural imaging, including brain scans, should be used in the assessment of people with suspected dementia to show any structural changes to brain tissue, identify other cerebral pathologies and help establish the subtype diagnosis. Magnetic resonance imaging (MRI) is the preferred modality to assist with early diagnosis and detect changes caused by diseased blood vessels in the brain, indicating stroke or possible vascular dementia. FDG-PET (fluorodeoxyglucose-positron emission tomography-CT) scanning could be used (National Institute for Health and Care Excellence, 2018c).

Following the confirmation of dementia diagnosis, dementia services (such as memory clinics) should be offered to dementia patients and their carers to provide them the support and care plan to cope with the challenges faced with dementia (National Institute for Health and Care Excellence, 2018c): refer to **Appendix 3**.

### 1.2.4 Clinical management of dementia

According to NICE guidelines, there is no cure for dementia but there are two general approaches: non-pharmacological and pharmacological interventions to manage dementia symptoms and to delay disease progression (National Institute for Health and Care Excellence, 2018c). Patients living with dementia who have mild to moderate

dementia of all types are currently offered individualised, non-pharmacological interventions to promote well-being and independence (National Institute for Health and Care Excellence, 2018c). These interventions give patients the opportunity to participate in a range of general activities, such as cognitive behavioural therapy (CBT) and/or other strategies including cognitive rehabilitation and cognitive stimulation, aiming to improve memory and related cognitive functions (National Institute for Health and Care Excellence, 2018c, Bahar-Fuchs et al., 2013). Cognitive stimulation therapy is a programme involving various group activities that help to maintain and enhance the mental abilities and social functioning (National Institute for Health and Care Excellence, 2018c). Cognitive rehabilitation is an individualised therapy strategy using specific exercises to help patients with mild dementia function better in everyday activities and maintain their independence (National Institute for Health and Care Excellence, 2018c). Reminiscence therapy can also be considered, using music and/or dancing and arts and crafts (National Institute for Health and Care Excellence, 2018c). Patients with vascular dementia, Alzheimer's disease, dementia with Lewy bodies or mixed dementia with mild to moderate symptoms should not be offered herbal formulations or supplements, cognitive training or non-invasive brain stimulation (National Institute for Health and Care Excellence, 2018c). Furthermore, antipsychotic medication should not be prescribed for patients with dementia due to their side effect profile based on the warning issued by the FDA, the European Medicines Agency and the UK Medicines and Healthcare Products Regulatory Agency (Mittal et al., 2011). However, those with persistent and severe non-cognitive symptoms (psychosis, agitated behaviour and associated depression) who have failed to respond to non-pharmacological interventions might be offered treatment, such as

antipsychotic drugs for psychosis, antidepressants for depression, anxiolytics and hypnotics (Maher et al., 2011). However, these medications are likely to be more harmful than beneficial due to the side effect profile and the risk of death (Wolf et al., 2017).

Currently, there are two pharmacological therapy classes licensed and available for dementia management: acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine (National Institute for Health and Care Excellence, 2018c). Acetylcholinesterase inhibitors work by inhibiting the acetylcholinesterase enzyme that is responsible for acetylcholine hydrolysis (Anand and Singh, 2013). Acetylcholine is a neurotransmitter responsible for conducting electrical impulses from one nerve cell to another nerve cell (Anand and Singh, 2013). Nausea, vomiting and diarrhoea are the most frequently reported side effects, along with mild cholinergic side effects (Kavirajan and Schneider, 2007, McGleenon et al., 1999). Memantine is the drug of choice for patients with severe Alzheimer's disease and an alternative drug to acetylcholinesterase inhibitors in cases of moderate Alzheimer's disease. It acts by antagonising the N-methyl-d-aspartate (NMDA) receptors, blocking excess glutamate. Glutamate is released in excessive amounts when brain cells are damaged by Alzheimer's disease (Johnson and Kotermanski, 2006). Mementine is considered safe and is well tolerated as a monotherapy or in combination with acetylcholinesterase inhibitors. The most common side effects as shown in previous clinical trials are headache and dizziness (Hartmann and Möbius, 2003, Tariot et al., 2004b, Wilcock et al., 2002). Acetylcholinesterase inhibitors are recommended to be prescribed by a healthcare professional (specialised in diagnosing and treating dementia) as a monotherapy or in combination with memantine for the management of mild to moderate Alzheimer's disease (National Institute for Health

and Care Excellence, 2018c). Donepezil and rivastigmine can be prescribed for patients diagnosed with dementia with Lewy bodies, but if these are not tolerated or are contraindicated, memantine can be considered (National Institute for Health and Care Excellence, 2018c). For the management of vascular dementia, acetylcholinesterase inhibitors or memantine can prescribed only if patients also have Alzheimer's disease, dementia with Lewy bodies or Parkinson's disease dementia (National Institute for Health and Care Excellence, 2018c). Neither acetylcholinesterase inhibitors nor memantine can be prescribed for patients with frontotemporal dementia (National Institute for Health and Care Excellence, 2018c): refer to **Appendix 4**.

The rate of prescribing of anti-dementia medication was described in a retrospective observational study using a UK primary care database over a 10-year follow-up period (Donegan et al., 2017). Anti-dementia medications were prescribed for 15% of patients diagnosed with dementia and identified in the Clinical Practice Research Datalink (CPRD) from 2005 to 2015 (Donegan et al., 2017).

The evidence for the efficacy of acetylcholinesterase inhibitors and memantine in the management of dementia symptoms remains inconsistent and unknown (Tan et al., 2020, Thomas and Grossberg, 2009). In a recent meta-analysis of randomised clinical trials (RCTs) for patients diagnosed with dementia with Lewy bodies or Parkinson's disease dementia, it was reported that the use of acetylcholinesterase inhibitors was associated with significant improvements in cognitive functions, behavioural disturbances and daily living activities (Matsunaga et al., 2015). Another meta-analysis was performed to measure the efficacy of acetylcholinesterase inhibitors in the management of Alzheimer's disease symptoms, and it found modest improvements in both neuropsychiatric and

functional outcomes (Trinh et al., 2003). On the other hand, two other meta-analyses found that the use of acetylcholinesterase inhibitors was not significantly effective for neuropsychiatric symptoms in patients diagnosed with Alzheimer's disease (Blanco-Silvente et al., 2017, Kobayashi et al., 2016).

Three RCTs were submitted to the FDA in the application for a new drug to study the safety and efficacy of memantine in patients diagnosed with moderate to severe Alzheimer's disease (Winblad and Poritis, 1999, Reisberg et al., 2003, Tariot et al., 2004a). The results of two of these trials found that a significant improvement in global and functional parameters (Behavioural Rating Scale for Geriatric Patients and the Clinical Global Impression of Change) and better cognitive functions were associated with memantine but there was no significant improvement in behavioural measurements compared to the use of placebo (Winblad and Poritis, 1999, Reisberg et al., 2003). The third trial compared the safety and efficacy of combination therapy mementine/donepezil vs. donepezil/placebo and reported similar findings to the previous studies with the addition of an improvement in behavioural outcomes (Tariot et al., 2004a). Conversely, another trial followed similar selection criteria and protocols to the Reisberg et al. study (Reisberg et al., 2003) and found there were no significant improvements at week 24, which contradicts the findings of the previous trials (van Dyck et al., 2007).

Several studies have shown beneficial outcomes with the use of mementine/acetylcholinesterase inhibitors as a combination therapy in the management of Alzheimer's disease (Cummings et al., 2006, Feldman et al., 2006, Riepe et al., 2007). In summary, the current evidence of most of these medications does not show any clinical benefits for dementia patients (Stella et al., 2015).

### 1.2.5 Complications of dementia

In 2019, the WHO reported that dementia was the seventh leading cause of death worldwide (World Health Organisation, 2020) and in the UK it was the leading cause of death, accounting for 12.7% of all deaths in 2018 (Office of National Statistics, 2020). By definition, dementia is a progressive disorder associated with memory deficits, psychiatric illnesses (e.g. depression and psychosis) and significant changes in autonomic functions, personal care, physical activity, eating habits and sleeping patterns (Mitchell, 2015). Therefore, patients with dementia are at higher risk of increased hospitalisation due to major health complications, including eating disorders, infections and therapeutic non-compliance, which increases the challenge of managing the dementia patient's medical conditions and leads to death (Mitchell et al., 2009). Furthermore, patients with dementia become disabled and dependent, requiring additional assistance from family members or other carers to improve the patient's quality of life (Brodaty and Donkin, 2009).

## 1.3 Hypoglycaemia

Hypoglycaemia means an abnormal low level of blood glucose. It is a serious, acute, frequent but preventable side effect of diabetes management, resulting in an inadequate cerebral glucose supply and causing neurogenic (autonomic) and neuroglycopenic symptoms, which in turn can impact the diabetic individual's quality of life and lead to death, if not treated on time (Cryer, 2007). Elderly people with diabetes are at high risk of experiencing hypoglycaemia, which is the most common metabolic complication; therefore, addressing hypoglycaemia is a highly important aspect of improving diabetic care (Seaquist et al., 2013b).

### 1.3.1 Epidemiology of hypoglycaemia

Hypoglycaemia is more prevalent among patients diagnosed with T1DM compared with those with T2DM (Morales and Schneider, 2014, Cryer, 2008). A Danish-British multicentre cross-sectional study (Pedersen-Bjergaard et al., 2004b) reported that the rate of severe hypoglycaemia in patients with T1DM was 130 episodes per 100 patient-years (almost double the rate reported in the Diabetes Control and Complications Trial - DCCT) (Nathan et al., 1993). Based on systematic review findings, which included 532,542 patients diagnosed with T2DM treated with insulin or oral antidiabetic medication, the prevalence of mild or moderate hypoglycaemia was 45% (95% CI, 0.34–0.57) (Edridge et al., 2015). Additionally, the rate of hypoglycaemic episodes was 19 episodes per patient-year for mild to moderate episodes and 0.8 episodes per patient-year for severe hypoglycaemia (Edridge et al., 2015). The frequency of hypoglycaemia was higher among patients treated with insulin compared to those who were treated with sulfonylureas (Edridge et al., 2015).

Hypoglycaemic events are also associated with patients' age; elderly people are more prone to experience hypoglycaemia (Morales and Schneider, 2014). A previous observational study in Germany using primary care data reported a higher rate of hypoglycaemia in people diagnosed with DM aged ≥70 years than in younger people aged <60 years (12.8% vs. 9.0%, p<0.01) (Bramlage et al., 2012). However, the incidence of hypoglycaemia in older people is difficult to estimate accurately because of the limited number of clinical trials included this age group, and because there is no standardisation in the diagnosis of hypoglycaemia (Abdelhafiz et al., 2015).

### 1.3.2 Definition and classification of hypoglycaemia

According to the ADA and European Medicines Agency (EMA), the definition of hypoglycaemia is an abnormal decrease in the blood glucose level. It can be classified based on blood glucose levels and severity of symptoms as in the following **(Table 6)**:

**Table 6 Definitions and Classifications of Hypoglycaemia**

| Source | Class |
|---|---|
| **ADA** | **Level 1 hypoglycaemia** when 54 mg/dl (3.0 mmol/L) ≤ blood glucose level is < 70 mg/dL (3.9 mmol/L), either accompanied or not by typical hypoglycaemia symptoms.<br><br>**Level 2 hypoglycaemia** when the blood glucose level is < 54 mg/dL (3.0 mmol/L), which is considered as clinically significant hypoglycaemia.<br><br>**Level 3 hypoglycaemia** is associated with severe cognitive impairment and requires third-party assistance for recovery. |
| **EMA** | **Asymptomatic hypoglycemia** when blood glucose level is ≤ 3.9 mmol/L (70 mg/dL) with no typical symptoms of hypoglcaemia.<br><br>**Documented symptomatic hypoglycemia** the presence of typical symptoms of hypoglycemia and blood glucose level ≤ 3.9 mmol/L (70 mg/dL).<br><br>**Severe hypoglycemia** is associated with neurogenic (autonomic) and neuroglycopenic symptoms, and third-party assistance is required for recovery. |

**ADA** American Diabetes Association, **EMA** European Medicines Agency (American Diabetes Association, 2019, European Agency for Evaluation of Medicinal Products (EMEA), 2012, Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018)

The symptoms of hypoglycaemia can be categorised into two categories: (1) neurogenic (autonomic) mild symptoms that can be noted by the patient, including hunger, anxiety, sweating and palpitations, and (2) neuroglycopenic severe symptoms, such as loss of consciousness, convulsions and coma or death (American Diabetes Association, 2019, Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018).

### 1.3.3 Risk factors of hypoglycaemia

The risk of hypoglycaemia is associated with multiple predisposing factors in DM patients. The majority of hypoglycaemic episodes occur in patients treated with antidiabetic medication, especially insulin and sulfonylureas. Insulin therapy duration may also contribute to the risk of hypoglycaemia (Fisher, 2010, Boyle and Zrebiec, 2008, Phung et al., 2010, Donnelly et al., 2005b). In addition to antidiabetic medication, polypharmacy is an important risk factor for hypoglycaemia (Bramlage et al., 2012). Other non-diabetic medications may also interact when concurrently administered, stimulating hypoglycaemia, including warfarin, beta blockers, fibrates, aspirin, NSAIDs and allopurinol (Fisher, 2010, Jennings et al., 1989, Romley et al., 2015, Seltzer, 1972, Vue and Setter, 2011).

There are several risk factors for hypoglycaemia, including diabetes duration, increased age, presence of comorbidities including CKD, CVD, depression, recurrent hypoglycaemia, and cognitive impairment or dementia. These may be considered predictors and increase the risk of developing hypoglycaemia (Donnelly et al., 2005b, Fisher, 2010, Morales and Schneider, 2014, Henderson et al., 2003, Kim et al., 2016). Furthermore, hypoglycaemia is associated with a patient's lifestyle factors, such as diet habits and lower intake of water/food, alcohol consumption, history of or active smoking and vigorous exercise (Miller et al., 2001, Murata et al., 2005, Cryer et al., 2003, Bonds et al., 2012).

### 1.3.4 Complications of hypoglycaemia

Hypoglycaemia can cause clinically significant harm, have a major impact on a DM patient's quality of life and that of their families and can be fatal (Seaquist et al., 2013b). Mortality associated with hypoglycaemic episodes has been clearly demonstrated in many trials, with a similar pattern being found in VADT, ADVANCE and ACCORD (The VADT Investigators et al., 2009, The ADVANCE Collaborative Group et al., 2008, The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008). T2DM patients who have experienced severe hypoglycaemia are at increased risk of death compared to patients without hypoglycaemia history. The mortality rate associated with severe hypoglycaemia is 19.5% (Zoungas et al., 2010). Previous literature has reported a mortality rate due to hypoglycaemia of 4–10% among T1DM patients (Patterson et al., 2007, Skrivarhaug et al., 2006). In addition to all-cause mortality, cardiovascular deaths are also associated with severe hypoglycaemia (Zoungas et al., 2010). Severe hypoglycaemia is associated with a significant increase in the risk of microvascular and macrovascular complications leading to hospitalisation (Zoungas et al., 2010).

In a retrospective cohort study conducted in England using the Clinical Practice Research Datalink (CPRD), there was an annual increase in hypoglycaemic hospitalisations in both T1DM and T2DM patients. The annual incidence of hypoglycaemia hospitalisation increase was 3.5% in adults with T1DM, 4.12% in young and middle-aged adults with T2DM and 8.59% in elderly adults with T2DM from 1998 to 2013 (Zhong et al., 2017a). Another observational study estimated the rate of hypoglycaemic hospitalisations over ten years, with a 49% increase in the number of admissions between 2005 and 2010. The

number of admissions was higher among older patients, who accounted for 72% of the total admissions caused by hypoglycaemia (Zaccardi et al., 2016).

Additionally, the literature has shown links between severe hypoglycaemia and cognitive impairment (Whitmer et al., 2009). However, the pathophysiological link between hypoglycaemia and cognitive impairment in diabetic patients is not well known (Aung et al., 2012). Limited evidence has been found on the association between hypoglycaemic episodes and cognitive decline (Jacobson et al., 2007). Several studies have investigated the association between a history of hypoglycaemic episodes and cognitive decline (dementia) and have concluded that previous exposure to one or more hypoglycaemic episodes increases the risk of dementia and cognitive impairment significantly (Yaffe et al., 2013, Whitmer et al., 2009, Feil et al., 2011).

Signs and symptoms of hypoglycaemia range from dizziness, weakness and sweating to more serious symptoms, including confusion, visual disturbances and loss of consciousness, leading to an increased risk of falls and accidents. Falls and motor vehicle accidents are major complications of severe hypoglycaemia, resulting in fractures that increase the hospitalisation and death rate among the elderly (Johnston et al., 2012). There is a 40% increase in the risk of accidents, including accidental falls and motor vehicle accidents, in patients diagnosed with diabetes compared to those who have not experienced hypoglycaemic events (Signorovitch et al., 2013). Therefore, the Driver and Vehicle Licensing Agency recommended that if a patient has experienced more than one episode of severe hypoglycaemia in the last year, then their driving licence could be cancelled (Driver and Vehicle Licensing Agency, 2016).

### 1.3.5 Management of hypoglycaemia

At the time of hypoglycaemic event occurrence, rapid action to restore the blood glucose level is required (Vindedzis et al., 2012). NICE guidelines recommended treating mild to moderate hypoglycaemia (conscious patients and those able to eat by mouth) by administering food containing 15–20 grams of carbohydrates or four teaspoons of sugar (glucose) to induce a rise in blood glucose level, repeated every 10–15 minutes if necessary (National Institute for Health and Care Excellence, 2018d). If the blood glucose level remains < 4mmol/L after three treatment cycle of carbohydrates, intramuscular glucagon or intravenous glucose should be administered (National Institute for Health and Care Excellence, 2018d). In severe hypoglycaemia (unconscious patients), an immediate intramuscular administration of glucagon by a family member at home is required (National Institute for Health and Care Excellence, 2018d). Glucagon is a counter-regulatory hormone to insulin, promoting liver gluconeogenesis. It is considered the first-line agent in managing severe hypoglycaemia (Fonjallaz and Loumaye, 2000, Pearson, 2008).

There are different strategies to prevent and minimise the occurrence of hypoglycaemia, such as: a) improving the patient's ability to self-manage their condition and identifying hypoglycaemic predisposing factors for hypoglycaemia (Morales and Schneider, 2014), b) evaluating the patient's knowledge and educating them about hypoglycaemia and their medical condition so that they are able to administer antidiabetic medication and follow healthcare professionals' instructions (American Diabetes Association, 2019), c) lifestyle and therapy modification are essential to minimise the risk of hypoglycaemia; patients have to balance between carbohydrate intake and exercise and antidiabetic medication

dose (Morales and Schneider, 2014). It is also important that patients contact their healthcare professionals and consider the use of particular diabetes treatment regimens associated with low or no risk of hypoglycaemia and de-intensify their treatment regimen as appropriate.

## 1.4 Diabetes and dementia

### 1.4.1 Association between diabetes and dementia

DM is considered a risk factor of dementia and accelerates cognitive decline (Biessels et al., 2006). Diabetes and dementia are prevalent among elderly people and are considered a serious public health concern. In 2019, the IDF reported that almost 20% of the older population (> 65 years) are living with diabetes (International Diabetes Federation, 2019). The WHO reported that the rate of dementia is between 5% and 8% among the older population aged ≥ 60 years (World Health Organisation, 2019). According to the literature, the rate of diabetes in patients with dementia ranges from 13–20% (Bunn et al., 2014).

Several studies have found that DM is associated with a high risk of dementia. In 2009, a meta-analysis was carried out on nine studies and it was reported that patients with diabetes are one and a half to two times more likely to develop dementia compared to patients without diabetes. The risk is increased fourfold in insulin-treated diabetic patients (Profenno et al., 2010, Ott et al., 1999).

The exact pathophysiological link between diabetes and dementia remains unclear (Santos et al., 2017). The literature has reported different mechanisms linking diabetes and dementia **(Figure 4)**, including: a) the presence of microvascular or macrovascular

complications, atherosclerosis and severe hypoglycaemic events (Exalto et al., 2012); b) chronic hyperglycaemia - a higher level of HbA1c is associated with a poor level of cognition (Strachan, 2010, Ninomiya, 2014); c) insulin resistance leading to chronic peripheral hyperinsulinemia - the reduction in insulin's neurotropic effect on the brain and hyperinsulinemia lead to toxic effects due to accumulation of amyloids, which may indirectly cause memory loss and cognitive impairment (Kravitz et al., 2013, Ninomiya, 2014); d) chronic inflammation - the increased level of inflammatory cytokines is associated with low cognitive functions in patients with diabetes (Strachan, 2010); e) dysregulation of the hypothalamic and pituitary axis and increased levels of cortisol (Strachan, 2010).

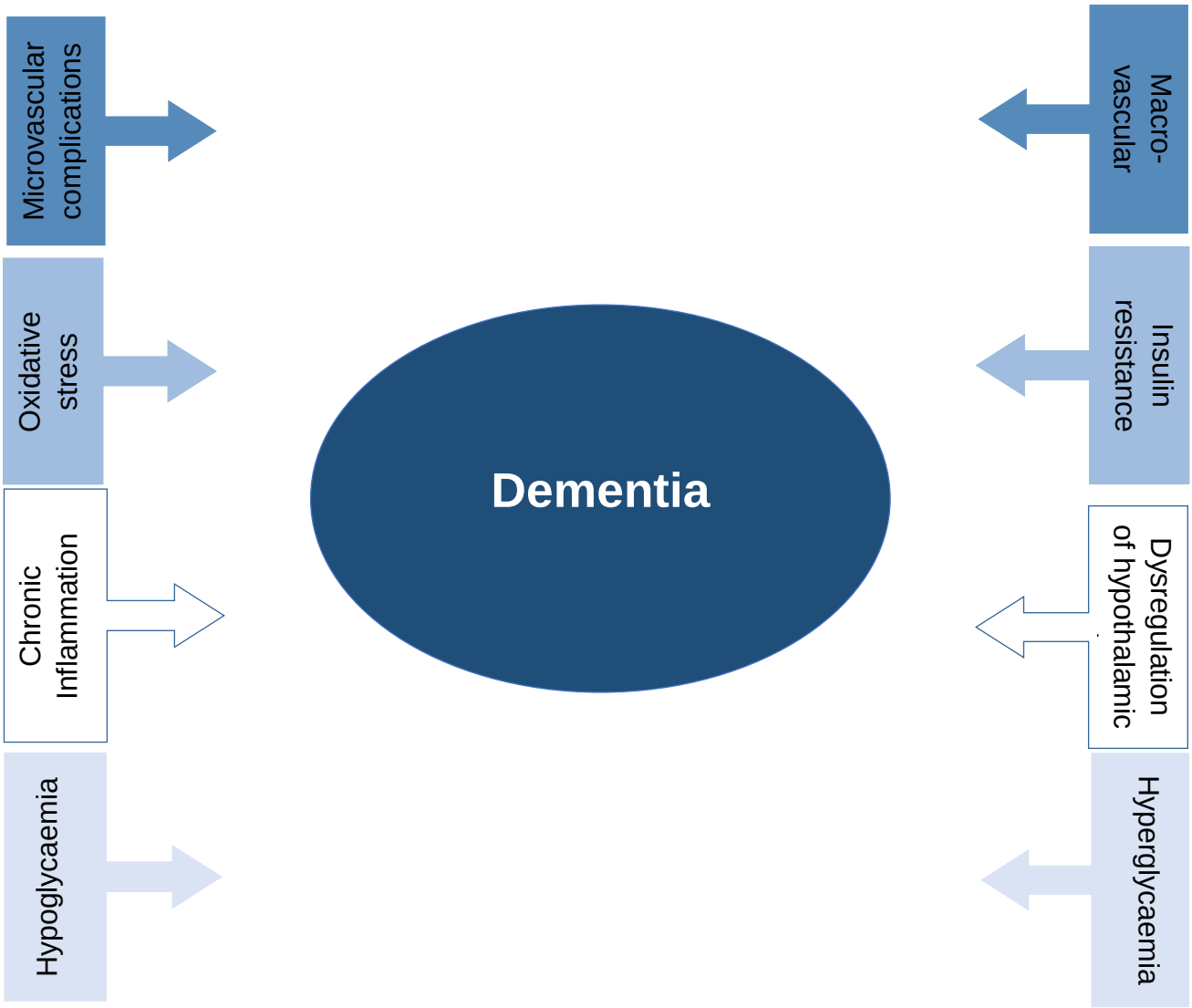



**Figure 4 Pathophysiological Links between Diabetes Mellitus and Dementia**

### 1.4.2 Challenges of diabetes mellitus management in patients living with dementia

Dementia by definition is a progressive disease that affects brain functions. The early stages of dementia are characterised by mild symptoms, including short-term memory loss, repetitiveness, forgetfulness. These gradually worsen over time until the patients become dependent, are unable to perform their daily activities, face difficulties with

communication, problem solving and judgments: refer to **section 1.4.2** (Alzheimer's Association, 2013). In the later stages, patients with dementia may need assistance by family members with basic personal activities, such as feeding, continence and dressing, and close supervision by specialists to manage other medical conditions associated with aging including comorbidities. They may also need a psychiatrist, polypharmacy and nutritional support (Karon, 2015, Jennings et al., 2015).

Diabetes management is a complicated and lifelong commitment. The patient's role is crucial in diabetes management and they should be aware and fully understand the medical condition and the importance of participating in their self-care (Hopkins et al., 2016). Self-care tasks include seven necessary behaviours: regular monitoring of blood glucose level; appropriate eating habits; engaging in physical activity; adherence to medications as directed; ability to cope healthily, solve problems and make decisions such as recognising and managing hypoglycaemia; having the skills to prevent or reduce risks (Shrivastava et al., 2013, Donna Tomky, 2008). These behaviours result in effective self-care management and positive outcomes, adequate glycaemic control, preventing or reducing complications and improving their quality of life (Shrivastava et al., 2013).

There are multiple challenges faced by patients with dementia and healthcare providers for successful management. Cognitive impairment may cause difficulties in self-care management, leading to increased risk of poor glycaemic control, developing complications especially hypoglycaemia and non-adherence to medications as indicated. **Table 7** illustrates some of the challenges faced by patients with dementia in performing self-management.

**Table 7 Cognitive Impairments and their Impacts on Self-management of Diabetes Mellitus**

| Impairment | Impact on self-management of diabetes |
|---|---|
| **Agnosia** | Inability to recognise familiar objects such as food, devices of insulin administration (including insulin pens, insulin syringes, or an insulin pump). |
| **Dysphagia** | Difficulties in swallowing, lead to weight loss and poor nutrition, putting the patients in increased risk of hypoglycaemia. |
| **Dysphasia** | Difficulties in speech (language disorder), inability to use the words in case of feeling hungry or hypoglycaemic. |
| **Dyspraxia** | Physical co-ordination disorder affects the patient's performance in daily and physical activity causing slower gait or speed, imbalances and increase the risk of falls. |
| **Executive functions** | Inability to perform meal planning or meal preparation tasks.<br>Inability to make decisions and take the appropriate actions based on blood glucose level (managing hypoglycaemia).<br>Inability to adjust the dose of insulin.<br>Inability to interpret blood glucose level. |
| **Memory impairment** | All element of diabetes management affected by memory impairment include scheduling and tracking medical appointments, taking medication correctly, monitoring blood glucose level and recognising or dealing with hypoglycaemia. |

(Hill, 2019, Hopkins et al., 2016)

### 1.4.3 Risk of hypoglycaemia in diabetic patients with dementia

Recently, increasing attention has focused on the role of dementia in the occurrence of hypoglycaemia among people with diabetes (Yaffe et al., 2013). The elderly population diagnosed with both diabetes and dementia is at a higher risk of experiencing hypoglycaemic events (Abdelhafiz et al., 2015). DM patients living with dementia are less able to recognise hypoglycaemic symptoms and to control hypoglycaemia by initiating appropriate responses and communicating their needs for help (Alzheimer's Association, 2013). In addition, this population is likely to take medication overdoses due to confusion and repetitive behaviour and, therefore, hypoglycaemic events might occur frequently

(Kim et al., 2016). Previous studies have suggested that patients with dementia or lower cognitive levels are at a higher risk of developing severe hypoglycaemia (Yaffe et al., 2013, Punthakee et al., 2012, Feil et al., 2011, Feinkohl et al., 2014). However, few clinical studies have been conducted to evaluate the risk of hypoglycaemia among patients with dementia outside the restrictive trial setting. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCED) trial, cognitive dysfunction increased the risk of severe hypoglycaemia by 2-fold (hazard ratio [HR]=2.10, 95% confidence interval [CI]=1.14–3.87) (de Galan et al., 2009). One observational cohort study examined 783 diabetic patients in the United States and reported that dementia was associated with a 3-fold risk of severe hypoglycaemia (HR=3.10, 95%CI=1.46–6.58) (Yaffe et al., 2013). However, the study was based on a selective cohort of community dwelling patients, with the use of self-reported data for the assessment of confounders at baseline (Yaffe et al., 2013). Other studies were smaller size (~1000 or fewer subjects) cross-sectional studies (Feil et al., 2011, Bruce et al., 2009, Aung et al., 2012) of which the results are often unable to give reliable inference about causality (Sedgwick, 2014). Moreover, the effect of dementia on glycaemic level control remains unclear (Meneilly and Tessier, 2016) and has not been studied in a population-wide perspective in the UK setting. It is an important knowledge gap because it has been demonstrated in many studies that there is a bidirectional association between cognitive impairment and hypoglycaemia (Mattishent and Loke, 2016). Recurrent hypoglycaemia is associated with increased risk of physical and cognitive dysfunction, leading to a negative impact on the patient's health, including frailty and disability (Yaffe et al., 2013). Hypoglycaemia may increase the risk of developing dementia through several

pathophysiological mechanisms; a) hypoglycaemia result in neuronal cell damage and death, some evidence suggests that neuronal damage resulting from hypoglycaemia due to loss of ionic homeostasis or increase in reactive oxygen species; b) hypoglycaemia can damage brain receptors in region critical for learning and memory; c) hypoglycaemia increases platelet aggregation which could lead to microvascular events (Meneilly and Tessier, 2016). Therefore, the risk of hypoglycaemia among patients with dementia needs to be better clarified.

## 1.5 Pharmacoepidemiological studies of hypoglycaemia

Research into hypoglycaemia within DM real world population based studies is limited, particularly for prevalence, incidence and risk factors (Heller et al., 2020). Data is needed to better understand the scale of the problem, its impact on the individual and how it is currently managed (Heller et al., 2020). Doing pharmacoepidemiological studies using observational study design enables us to explore the risk factors associated with hypoglycaemia in real-world settings, unlike randomised controlled trials that are characterised by more standardised settings, which are not always comparable to real-life situations.

Therefore, a thorough systematic review and meta-analysis took place at the first stage of my PhD that summarises the available literature on the prevalence, incidence and the risk factors of hypoglycaemia in DM population in order to collate, evaluate, better understand the current literature in this area from which we found the gap and the key of the whole project. **(refer to Chapter two)**

This PhD project used different types of pharmacoepidemiological study designs: first, a descriptive observational study to estimate the annual prevalence and incidence of dementia among DM population; second, a drug utilisation study design was conducted to describe the prescribing of antidiabetic medications and the annual rate of hypoglycaemia in DM and dementia patients; third, the analytical cohort study design is a useful design to provide an evidence to support or to be against a specific hypothesis. This was followed by a pre-post observational study, it enabled us to explore further our primary research question on the individual level. Each type of these study designs has its own advantages and disadvantages, and the selection of the appropriate study design depends on the type of outcome and exposure of interest of the study.

## 1.6 Concluding remarks

This chapter has provided a background to DM, dementia and hypoglycaemia for the work presented in the following chapters. DM and dementia are chronic disorders and a major public health concern. Hypoglycaemia is the most common side effect associated with the management of diabetes and can be defined as an abnormally low blood glucose level associated with symptoms ranging from mild, such as nausea and shakiness, to severe, such as confusion and loss of consciousness. Hypoglycaemic episodes can have a great impact on the patient's quality of life. The coexistence of dementia or cognitive impairment makes them particularly at risk of an episode and potentially serious consequences. To a degree, diabetes management focuses on the avoidance of complications and hyperglycaemia. The introduction of newer therapies and patient empowerment and involvement makes it difficult for patients living with dementia.

The next chapter is a systemic review that summarises the available literature on the prevalence, incidence and the risk factors of hypoglycaemia in DM population. **(Chapter Two)**.

# 2 CHAPTER TWO: Prevalence, Incidence, and Risk factors of Hypoglycaemia in Individuals with Diabetes: A Systematic Review and Meta-Analysis of Observational Studies

The incidence and prevalence findings from this study in this chapter have been published in the Diabetes Research and Clinical Practice Journal, in Oct 2020, under the title: ““Incidence and Prevalence of Hypoglycaemia in Type 1 and Type 2 Diabetes Individuals: A Systematic Review and Meta-analysis”.

This chapter presents a systematic review was conducted to explore and review the current literature of the incidence, prevalence and risk factors of hypoglycaemia in patients diagnosed with DM.

The chapter outlines with an introduction of the systematic review followed by the review question, aims and objectives. A detailed search strategy, inclusion and exclusion criteria and systematic review process were also described. The limitations of these studies were also discussed to highlight further research opportunities. Finally, the thesis’s aims and questions are presented to target this research towards closing those identified gaps in knowledge.

## 2.1 Introduction

Diabetes is a burdensome disease affecting approximately 463 million adults worldwide, with estimations that almost to 700 million adults will be affected by 2045 (International Diabetes Federation, 2019). It is requiring continuous medical care, with complicated risk-reduction strategies, to achieve optimal glycaemic control and to prevent long-term complications (Hanssen, 1997). Optimal glycaemic control, i.e. keeping blood glucose as near to normal as possible, can be achieved by using the maximum recommended dose of antidiabetic medication monotherapy or by using combination therapy of two or three antidiabetic medication, this is called intensive diabetes therapy strategies (LeRoith and

Rayfield, 2007, Wong et al., 2016, Turner et al., 1999, Riedel et al., 2007, Lavernia et al., 2015). Intensive diabetes therapy strategies have advantages by providing adequate glycaemic control which prevents complications, and disadvantages including side effects and polypharmacy which may affect patient's compliance (Lavernia et al., 2015).

The most common and serious side effect of intensive diabetes therapy is hypoglycaemia (Umpierrez and Korytkowski, 2016a). Hypoglycaemia is associated with significant impacts on diabetic patients' quality of life, the healthcare budget and quality of care (Stargardt et al., 2009, Williams et al., 2011). In addition, it is associated with an indirect impact on serious long-term health complications from patient compliance and purposeful hyperglycaemia, due to fear of hypoglycaemia (Wild et al., 2007).

Several systematic reviews have been conducted to estimate the frequency, and to explore the risk factors of hypoglycaemia. The Department of Veterans Affairs conducted a similar to this systematic review in 2012 that identified and highlighted findings from the literature available about the incidence of, predictors and risk factors and the effect of severe hypoglycaemia in T2DM patients from veteran populations (Bloomfield et al., 2012a). However, the review was limited as it included industry-funded randomised trials of highly selective populations, which did not represent the general population as clinical trials tend to exclude high-risk patients. In addition, all the reported findings were only for T2DM, which might under estimate the hypoglycaemia's impact as T1DM patients are at higher risk of developing hypoglycaemic events (Bloomfield et al., 2012a).

In 2015, another systematic review and meta-analysis has investigated the incidence and prevalence of hypoglycaemia in a population-based setting only for T2DM patients,

stratified by the severity of the hypoglycaemia (Edridge et al., 2015). However, they did not report an overall estimate of hypoglycaemic events and the risk factors of hypoglycaemia were not systemically reviewed (Edridge et al., 2015).

Further investigation is needed to investigate the incidence, prevalence and risk factors of hypoglycaemia among patients diagnosed with diabetes in population-based settings, without restricting the comparison to specific DM type or antidiabetic medication. This systematic review will enable the summarisation of any scientific evidence assessing the frequency and risk factors of hypoglycaemia in order to support future studies in narrowing the gaps present in the literature.

## 2.2 Research question

What are the incidence, prevalence and risk factors of hypoglycaemia among DM patients treated with antidiabetic medications?

## 2.3 Aim and objectives

This systematic review aimed to summarise the current literature reporting the incidence, prevalence and risk factors, and risk factors associated with hypoglycaemia among diabetic patients.

The primary objective of this review was to investigate the rate of hypoglycaemic episodes (incidence), the proportion of patients experienced hypoglycaemia (prevalence) in treated DM patients including T1DM and T2DM. In addition, this review investigated the risk factors associated with hypoglycaemia among type T1DM and T2DM patients treated with insulin and oral antidiabetic medication.

## 2.4 Methods

### 2.4.1 Data source

A systemised literature search was performed and three electronic bibliographic databases were searched for related literature up to October 2018. These databases were recommended by University College London school of pharmacy library services.

The searched databases included:

1) PubMed

2) The Excerpta Medical database (EMBASE).

3) The Cochrane Library database for systematic review

The most commonly used and recommended databases for searching articles and papers related to health care interventions are PubMed, EMBASE and the Medical Literature Analysis and Retrieval System Online (MEDLINE). PubMed produces the same articles as MEDLINE, with a few exceptions as new references are added to PubMed earlier than they are to MEDLINE and, therefore, PubMed is slightly broader and more comprehensive than MEDLINE (Kelly and St Pierre-Hansen, 2008). The PubMed database has more than 30 million references since 1996 covering MEDLINE, PubMed Central (PMC) and the National Centre for Biotechnology Information (NCBI) (National Library of Medicine, 2020).

EMBASE (OVID) database comprises over 29 million citations of biomedical literature from 8,500 journals including MEDLINE (Wolters Kluwer Health, 2020). Around 70% of sourced journals originate in Europe (Wolters Kluwer Health, 2020). The MeSH terms and

Emtree can be used as descriptors in retrieving and expanding the search to all relevant terms (KEMH Medical Library, 2017).

The Cochrane Library is a group of databases which considered as one of the largest medical databases, and it contains more than 7,500 published high quality systematic reviews providing the evidence to healthcare professionals, therefore, it is also considered to be the primary source for systematic reviews (The Cochrane Library, 2020).

Additionally, snowball technique was performed in this review, in order to ensure comprehensiveness of search, where further studies were manually or electronically collected from the reference lists of relevant journals (Wohlin, 2014). The systematic review was searched the previous sources from the beginning of each database to the specified date and updated constantly at different stages of the research (Aveyard, 2011).

### 2.4.2 Search Strategy and Study Selection

This review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses and the Meta-analysis of Observational Studies in Epidemiology (PRISMA and MOOSE) to ensure clear and comprehensive reporting (Moher et al., 2009, Stroup et al., 2000). The review protocol was registered with PROSPERO (Ref: CRD42017077013). For details refer to (**Appendix 5**).

Further, an extensive search strategy was constructed using the Population, Intervention, Comparison, Outcome (PICO) model for clinical questions. This model enables the identification of clinically relevant evidence in literature and the formulation of the research

question (Aslam and Emmanuel, 2010). The keywords used for this systematic search are shown in the table below **Table 8**.

**Table 8 PICO Approach for the Systemic Review**

| PICO | |
|---|---|
| **Population /participants of interest** | Patients diagnosed with DM (all types of DM are included) |
| **Intervention(s)/exposure(s)** | Non-pharmacological therapy and/or treated with Antidiabetic medication |
| **Comparator(s)/control** | No control group |
| **Outcomes** | Hypoglycaemia incidence, prevalence and risk factors |

**DM** diabetes mellitus

All searched keywords and search strategies were developed and verified by a specialised librarian UCL School of Pharmacy. The keywords and their synonyms for this search were inserted into the databases and the relevant Medical Subject Heading (MeSH) terms and free texts were identified from the search. Therefore, various search strategy enhancing techniques were used, including:

- The Boolean operators (AND, OR, NOT) were used to combine the keywords.
- MeSH terms and free texts were included within the search strategy with both British English and American English spellings to facilitate all required suffix variations of the root word for the review.
- Truncation marks (*) were used to ensure that the search was comprehensive and included all possible roots of the free text search.

All relevant literature was retrieved manually or electronically from the previously mentioned databases, or requested from the library and they were imported to EndNote®,

citations and references management software, version 8. A detailed search strategy for each database can be found in **Appendix 6**.

### 2.4.3 Inclusion and exclusion criteria

All observational studies that met the following inclusion criteria and published in the English language were included, regardless of the origin of the country on which they focussed.

#### 2.5.3.1 Types of study included

**Inclusion criteria:**

Only full text original observational studies were included in this review, including cohort, cross-sectional and case-control studies that identified the incidence and/or prevalence and/or risk factors of hypoglycaemia in T1DM and T2DM as a primary or secondary objective, or on the data to allow the calculation of one of these measures. I included only observational studies in order to have valid findings from real-life settings.

**Exclusion criteria:**

Randomised controlled trials (RCT), book, an editorial, meeting/conference abstracts, expert opinion or narrative/systematic review nature, case series/ reports and other summaries were excluded.

#### 2.5.3.2 Types of participants

**Inclusion criteria:**

The participants were patients diagnosed with DM, without any limitations regarding the patients' demographic characteristic or ethnic group or the type of DM, who were treated

by antidiabetic medication as their diabetes treatment. In addition, no restrictions were applied on the classification and severity of hypoglycaemia (mild or severe).

**Exclusion criteria:**

Studies were excluded if the participants were animals or pregnant (gestational diabetes).

#### 2.5.3.3 Types of interventions/exposure

This review focused on hypoglycaemia experienced by patients diagnosed with DM and treated with antidiabetic medications. Therefore, the intervention/exposure was patients who used one or more antidiabetic medication, with no control group. No restrictions were applied on the use of antidiabetic medication, insulin or oral antidiabetic medication using any route of administration were included. However, studies that investigated the safety and efficacy of antidiabetic medication with no evaluation of hypoglycaemia were not considered.

#### 2.5.3.4 Types of outcome measures

**The primary outcome:**

The primary outcomes of interest were the prevalence rate and the incidence rate of hypoglycaemia, without any specification relating to the classification, definition or how the studies measured the hypoglycaemia. The rate of hypoglycaemia was considered if they were reported using any of the following eligible measures such as a percentage for prevalence and as incidence rate (IR) for new cases or events rate for events per 1000 person-years.

**The secondary outcome:**

The risk factors associated with hypoglycaemia were investigated in this systematic review. These risk factors were reported as odds ratio (OR), relative risk (RR) and hazard ratio (HR) with 95% confidence interval.

**Exclusion criteria:**

Studies that did not clearly report the numerical results or the method used to calculate the prevalence, incidence of hypoglycaemia were excluded.

These criteria were used to find this thesis' research questions and to narrow the search findings.

## 2.4.4 Data collection and analysis

### 2.4.4.1 Selection of studies

Once the search had been conducted and the articles had been identified, they were screened for duplications across the two databases. Following the removal of duplicate articles using EndNote, a manual de-duplication was carried out to ensure that all duplicates were removed. The identified publications' titles and abstracts were screened independently by two reviewers (AA, HA) in order to determine studies that met the inclusion criteria with minimal error that might result from the review.

Furthermore, another screening was made for interesting studies for full text article reading and the relevant studies were selected, retrieved and reviewed. Any scientific discrepancies between the reviewers were resolved by third reviewer's decision (AN). The remaining studies were excluded with reasoning. Searches were repeated at least once every six months, with regular checks for newer studies that might have been

published or cited after the previous search update. The final update was done on up to October 2018. **Figure 5** displays the PRISMA flow diagram which was used to summarise the process of selection the studies included in the meta-analysis. A detailed flow chart of selection the studies included in the systematic review is listed in **Appendix 7.**

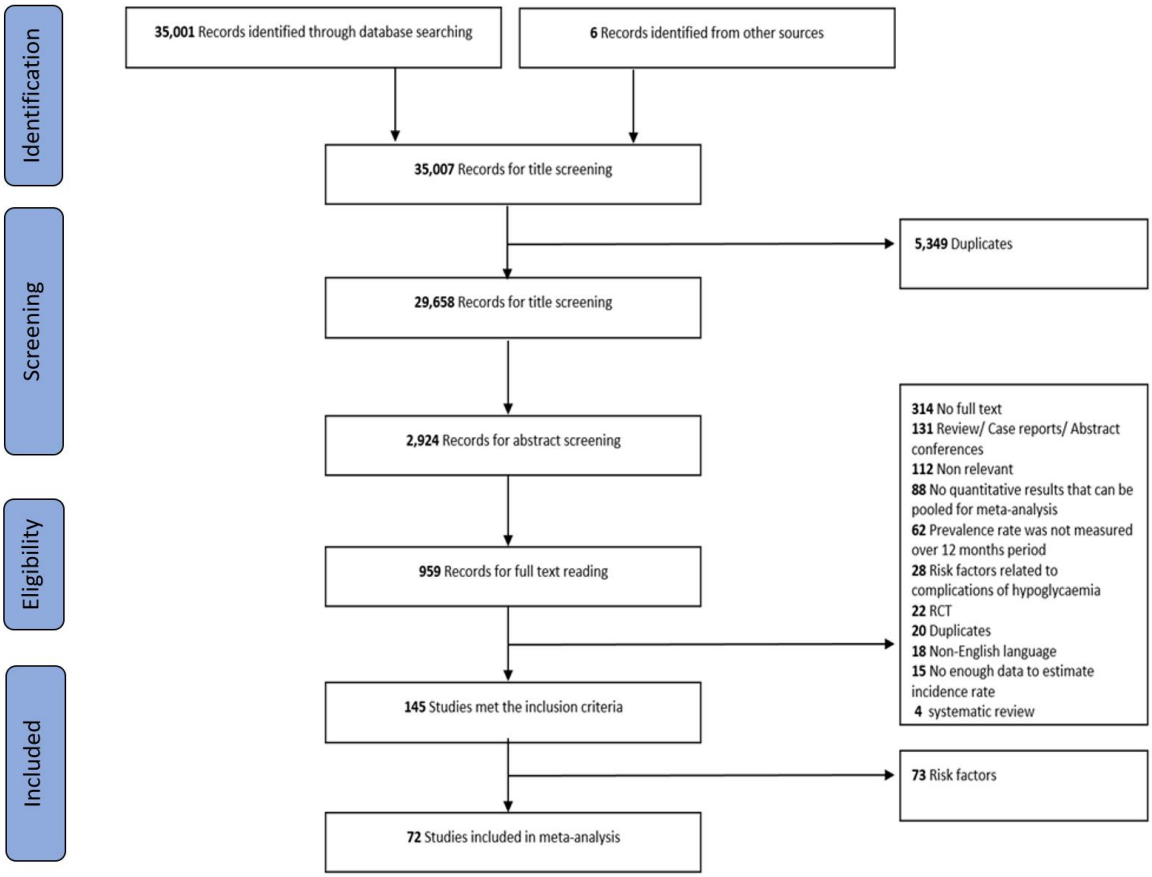



**Figure 5 PRISMA Flow Diagram for Studies Selection' Process included in the Meta-Analysis**

### 2.5.4.2 Data extraction

The data was extracted independently from the included studies by two reviewers (AA, HA) using a data collection sheet developed by the reviewers. The following information

were extracted for each included study:

1) Study characteristics: the author's name, year published, country, study design and the source of data (including self-report questionnaires, clinical records from emergency department admission records, hospital charts and electronic health databases).

2) Population characteristics: the sample size, mean HbA1c, mean age, gender, diabetes type and diabetes duration.

3) Intervention/ exposure characteristics: treatment regimens.

4) Outcome data: The International Classification of Diseases (ICD) codes, third-party assistance, blood glucose level or symptoms of hypoglycaemia were used for hypoglycaemia definition in this review. The percentage of DM patients who had experienced hypoglycaemic events (prevalence rate), and the incidence rate of hypoglycaemia (expressed as the number of episodes per 1000 person-years) were extracted. In addition, the outcome data for the risk factors of hypoglycaemia (IR, OR, HR, RR) were extracted. For full details about the data extraction: refer to **Appendix 8.**

#### 2.5.4.3 Quality assessment and publication bias

(AA, HA) independently assessed the methodological quality and risk of bias for the included studies independently using the Newcastle Ottawa scale (NOS) for non-interventional studies (Wells et al., 2014), which was adapted and modified for the purpose of this review (Park et al., 2020, Herzog et al., 2013, Magliano et al., 2019). The quality of the included studies was evaluated based on a total of four main domains, which included the following:

1) Selection bias: the representativeness of the population.

2) Performance bias: the sample size and identifying and adjustments for the confounding factors.

3) Detection bias: the statistical analysis used in the study and dealing with the missing data.

4) Information bias: the methods to report the outcome of interest and the methods to detect the outcome of interest or to report it.

Each criterion of the tool uses a scale ranging from 0 to 3, where zero is scored for high risk of bias and three is scored for low/no risk of bias. The modified NOS is out of maximum 18 points and the study is considered to have good quality if the overall score > 14 points, and studies with moderate quality were scored ≤ 14 and ≥ 7 points. All studies scored 7 points or below were considered low quality. The modified NOS tool of quality assessment for observational studies is available in **Appendix 9.** The quality of studies included in the meta-analysis was assessed separately due to the descriptive design of some studies where the confounder adjustments were not possible.

Publication bias defined as the bias which occurs when studies with statistically significant or clinically favourable results are more likely to be published than studies with non-significant or unfavourable results (Dickersin, 1990). Publication bias is considered to be one of the possible factors leading to asymmetrical funnel plots. Therefore, it is important to address publication bias by using funnel plots (Jonathan A. C. Sterne and Roger M. Harbord, 2004).

### 2.5.4.4 Data synthesis and analysis

For the meta-analysis purpose, only studies that reported their study duration to be a period of 12 months (1 year) were included in the meta-analysis of prevalence. This is because of the wide variations in study durations, thus the majority of the studies were classified under 12 months' study period. In the meta-analysis of the incidence rate, only studies reported the incidence rate or both the number of episodes and the follow-up time (which enable us to calculate the incidence rate) were included in the analysis. In order to normalise the unit of patient's years of incidence and episodes all the results of the studies were changed to rates 1000 patient-years whenever it was not provided in this format by the original study. The standard error (SE) was calculated whenever it was not reported in the original research article.

An overall analysis for both T1DM and T2DM was conducted and also a subgroup analysis to address the possible sources of heterogeneity. The analyses were stratified by type of diabetes (T1DM and T2DM), origin of the study, treatment regimen and by the source of the data. Data source were classified into two groups: self- reported (where hypoglycaemia was reported by the patients, either by questionaries or in clinic) and electronic databases (where hypoglycaemia was recorded through healthcare databases or clinical data registries). Sensitivity analysis was conducted to investigate the pooled estimate of prevalence after removing outlier studies (Conceicao et al., 2017, Henderson et al., 2003).

The overall estimates of the prevalence and incidence rates were calculated with random effects models. This model was chosen to consider the baseline variability and between

study heterogeneity of the included studies (Borenstein et al., 2010). In order to perform meta-analysis of prevalence rate, the function Metaprop was used which uses a logit transformation of the outcome. Also, to pool the incidence rates, the Metarate function was applied, which uses a natural log transformation. All meta-analyses of prevalence and incidence rate were performed using R, the package for meta-analysis (Schwarzer G, 2007). The heterogeneity was assessed among the included studies in the meta-analysis using the Chi-square ($\chi^2$) tests and the $I^2$ statistic, which rate the heterogeneity between the studies in percentages from 0 to 100%, where $I^2$ value <25% indicated low, 25–75% moderate, and >75% high heterogeneity (Higgins et al., 2003). Confidence intervals were also calculated whenever the authors did not report them. Publication bias of prevalence and incidence was assessed via funnel plots with pseudo 95% confidence interval around the fixed effect.

## 2.5 Results

35,007 citations were identified from my search strategy between 1989 and 28th October 2018: refer to **Appendix 7** for detailed flow chart of the studies included in the review, 23,591citations from PubMed and 11,410 citations from EMBASE, from which 959 citations were screened for full text. 219 studies met the inclusion criteria were included in the systematic review and only 72 studies in the meta-analysis.

### 2.5.1 Description of the included studies

**Appendix 8** summarises the descriptive characteristics including authors, year of publication, country, sample source, study design, sample size, type of diabetes, mean age, gender, diabetes duration and definition of hypoglycaemia. The majority of the

included studies were Europe (66), North American (46), Asia (23), Australia (5) and multinational studies (4), while one study was with missing location data. All of the included studies were observational, the majority of studies being retrospective (n=128; 88%), and (n=17; 12%) were prospective, while the remaining studies were both retrospective and prospective in their design. Half of the studies hypoglycaemia were based on health care databases (n=81; 52%), and (n=61; 42%) were self-reported by the patients, while the other studies with no data on data source. Most of the studies (N=71; 49%) included in the review were on T2DM while only (n=27; 19%) were on T1DM, other studies were either for both types of diabetes or not specified by the authors. The ethnicity of the population included in the review were poorly reported by the most of the authors. Insulin was the most used DM treatment in the studies included in this review (n=31; 21%), followed by a combination of oral antidiabetic medications and insulin (n=25; 17%), only oral antidiabetic medications (n=18;12%) and sulfonylureas (n=12;8%), while the remaining studies were with no available data. The definition of hypoglycaemia was very heterogeneous between included studies, with some studies reporting it as the need for third-party assistance or hospitalisation, others reporting it as loss of consciousness, and some studies depended only on ICD codes, with no clear definition based on guidelines or classification.

### 2.5.2 Quality of the included studies

The Modified Newcastle Ottawa scale was used to assess the quality of the studies in this review. I found that the overall quality of studies included in this review was of good quality (70%), while the quality of other studies scored moderate. The quality of studies included in this review varied considerably, which can be explained by several reasons,

including the data source, the definition of the hypoglycaemia, variation in publication year or the study design chosen to conduct the study. Full details of the quality of the studies included in this review are provided in **Table 9**.

**Table 9 Quality of the Studies included in the Review**

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Jabbar et al., 2017) | 2017 | 3 | 1 | 2 | 3 | 0 | 3 | 1 | 13 |
| (Lee et al., 2017) | 2017 | 3 | 2 | 2 | 2 | 2 | 3 | 3 | 17 |
| (Allen et al., 2001) | 2001 | 3 | 1 | 1 | 2 | 3 | 3 | 3 | 16 |
| (Akirov et al., 2018) | 2018 | 3 | 2 | 0 | 3 | 0 | 3 | 2 | 13 |
| (Aung et al., 2012) | 2012 | 3 | 2 | 0 | 3 | 0 | 3 | 3 | 14 |
| (Barkai et al., 1998) | 1989 | 2 | 1 | 1 | 2 | 0 | 2 | 2 | 10 |
| (Basu et al., 2017) | 2017 | 3 | 3 | 3 | 2 | 0 | 2 | 3 | 16 |
| (Berkowitz et al., 2012) | 2012 | 2 | 3 | 1 | 2 | 1 | 2 | 2 | 13 |
| (Birkebaek et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Blasetti et al., 2011) | 2011 | 3 | 1 | 1 | 2 | 0 | 3 | 3 | 13 |
| (Bognetti et al., 1997) | 1997 | 2 | 1 | 2 | 3 | 0 | 3 | 3 | 14 |
| (Borzi et al., 2016) | 2016 | 3 | 3 | 2 | 3 | 0 | 3 | 3 | 17 |
| (ter Braak et al., 2000) | 2000 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Bramlage et al., 2012) | 2012 | 2 | 2 | 1 | 2 | 0 | 3 | 1 | 11 |
| (Bron et al., 2012) | 2012 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Bruce et al., 2009) | 2009 | 2 | 2 | 3 | 3 | 1 | 3 | 3 | 17 |
| (Bruderer et al., 2014a) | 2014 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 13 |
| (Buyken et al., 1998) | 1998 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Cherubini et al., 2013) | 2013 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Chou et al., 2013) | 2012 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Alexiu et al., 2017) | 2017 | 3 | 3 | 0 | 3 | 3 | 3 | 3 | 18 |
| (Conceicao et al., 2017) | 2017 | 2 | 1 | 0 | 2 | 2 | 3 | 3 | 13 |
| (Corsonello et al., 1999) | 2017 | 2 | 3 | 2 | 2 | 3 | 2 | 1 | 15 |
| (Davis et al., 1998) | 1998 | 3 | 2 | 2 | 3 | 0 | 3 | 3 | 16 |
| **(Davis et al., 2010)** | 2010 | 3 | 1 | 1 | 3 | 0 | 3 | 2 | 13 |
| (Davis et al., 2011) | 2011 | 2 | 1 | 1 | 2 | 0 | 3 | 3 | 12 |
| (Dendy et al., 2014) | 2014 | 3 | 3 | 0 | 2 | 0 | 2 | 2 | 12 |
| (Derijks et al., 2008) | 2008 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Desjardins et al., 2014) | 2014 | 2 | 1 | 2 | 3 | 0 | 2 | 3 | 13 |
| (Deusenberry et al., 2012) | 2012 | 2 | 2 | 3 | 2 | 2 | 1 | 2 | 14 |
| (Donnelly et al., 2005a) | 2004 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Durán-Nah et al., 2008) | 2008 | 3 | 1 | 3 | 2 | 3 | 3 | 3 | 18 |
| (Egger et al., 1991) | 1991 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Elwen et al., 2015) | 2015 | 2 | 1 | 2 | 3 | 0 | 1 | 3 | 12 |
| (Endo et al., 2000) | 2000 | 3 | 1 | 1 | 1 | 0 | 3 | 3 | 12 |
| (Eriksson et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Faerch et al., 2011) | 2011 | 3 | 2 | 1 | 2 | 0 | 3 | 3 | 14 |
| (Feher et al., 2016) | 2016 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Fang et al., 2015) | 2013 | 2 | 2 | 3 | 3 | 0 | 3 | 3 | 16 |
| (Farmer et al., 2012) | 2012 | 2 | 2 | 1 | 2 | 2 | 1 | 2 | 12 |
| (Feil et al., 2011) | 2011 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Freathy et al., 2006) | 2006 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Fu et al., 2014) | 2014 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Ganz et al., 2014) | 2014 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Geller et al., 2014) | 2014 | 3 | 3 | 1 | 3 | 0 | 3 | 3 | 16 |
| (Green et al., 2012) | 2012 | 3 | 2 | 3 | 0 | 3 | 3 | 14 | 3 |
| (Gu et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 20 |
| (Guisasola et al., 2008) | 2008 | 2 | 2 | 2 | 3 | 1 | 3 | 2 | 15 |
| (Henderson et al., 2003) | 2013 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 20 |
| (Herings et al., 1995) | 1995 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Hirai et al., 2007) | 2007 | 1 | 1 | 1 | 2 | 1 | 2 | 3 | 11 |
| (Holstein et al., 2009) | 2009 | 2 | 1 | 3 | 3 | 0 | 3 | 3 | 15 |
| **Holstein et al 2011** (Holstein et al., 2011) | 2011 | 2 | 1 | 0 | 1 | 0 | 2 | 2 | 8 |
| (Honkasalo et al., 2011) | 2011 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Ishikawa et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Ishtiak-Ahmed et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Yun et al., 2018) | 2018 | 3 | 3 | 0 | 3 | 0 | 3 | 3 | 15 |

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Yun et al., 2015) | 2015 | | | | | | | | |
| (Jeon et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Jick et al., 1990) | 1990 | 3 | 3 | 2 | 1 | 3 | 3 | 3 | 18 |
| (Johnston et al., 2012) | 2012 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 16 |
| (Johansen et al., 2015a) | 2015 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Kajiwara et al., 2015) | 2015 | 3 | 3 | 0 | 2 | 0 | 0 | 0 | 8 |
| (Karges et al., 2015) | 2015 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Karter et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Katon et al., 2013) | 2013 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Katz et al., 2012) | 2012 | 2 | 2 | 2 | 3 | 0 | 2 | 2 | 13 |
| (Kim et al., 2016) | 2012 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Kostev et al., 2014) | 2014 | 0 | 0 | 3 | 3 | 0 | 1 | 2 | 9 |
| (Kostev et al., 2015) | 2015 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Leckie et al., 2005) | 2005 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Leese et al., 2003) | 2003 | 3 | 3 | 1 | 3 | 1 | 3 | 3 | 17 |
| (Leonard et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Li et al., 2014) | 2014 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Lin et al., 2010) | 2010 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Lipska et al., 2013a) | 2013 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Lipska et al., 2014) | 2014 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Loke et al., 2010) | 2010 | 2 | 1 | 0 | 1 | 2 | 2 | 2 | 10 |

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Lundkvist et al., 2005) | 2005 | 3 | 3 | 1 | 3 | 1 | 3 | 3 | 17 |
| (Ly et al., 2009) | 2009 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Maltoni et al., 2013) | 2013 | 2 | 1 | 0 | 2 | 3 | 3 | 3 | 14 |
| (Mantovani et al., 2016) | 2016 | 3 | 1 | 1 | 2 | 0 | 3 | 3 | 13 |
| (Mauricio et al., 2015) | 2016 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (McCoy et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Miller et al., 2001) | 2001 | 3 | 2 | 1 | 1 | 2 | 3 | 3 | 15 |
| (Alonso-Moran et al., 2015) | 2015 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Morris et al., 1997) | 1997 | 3 | 1 | 1 | 2 | 2 | 2 | 2 | 13 |
| (Muhlhauser et al., 1985) | 1985 | 3 | 2 | 1 | 3 | 1 | 3 | 3 | 16 |
| (Muhlhauser et al., 1998) | 1998 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Muller et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Murata et al., 2005) | 2004 | 3 | 2 | 3 | 3 | 3 | 3 | 3 | 20 |
| (Nam et al.) | 2018 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Nunes et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 2 | 3 | 3 | 20 |
| (Nunes et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Odawara et al., 2014) | 2014 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Olsen et al., 2014) | 2014 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Yu et al., 2018) | 2017 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Ooi et al., 2011) | 2011 | 2 | 1 | 2 | 0 | 0 | 3 | 3 | 15 |

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Pathak et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Lyngsie et al., 2016) | 2016 | 3 | 3 | 0 | 3 | 3 | 3 | 3 | 18 |
| (Pedersen-Bjergaard et al., 2003) | 2003 | 1 | 2 | 3 | 3 | 0 | 3 | 2 | 14 |
| **(Pedersen-Bjergaard et al., 2004a)** | 2004 | 2 | 3 | 3 | 3 | 1 | 3 | 3 | 18 |
| (Pilemann-Lyberg et al., 2015) | 2016 | 2 | 2 | 1 | 2 | 2 | 1 | 2 | 12 |
| (Pirags et al., 2012) | 2012 | 3 | 2 | 2 | 3 | 3 | 3 | 3 | 19 |
| (Quilliam et al., 2011) | 2011 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Radosevich et al., 2015) | 2015 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Ragia et al., 2012) | 2013 | 2 | 1 | 3 | 3 | 0 | 3 | 1 | 13 |
| (Rajendran et al., 2015) | 2015 | 3 | 1 | 2 | 2 | 0 | 2 | 3 | 13 |
| (Raju et al., 2016) | 2016 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Rathmann et al., 2013) | 2013 | 2 | 3 | 2 | 3 | 0 | 1 | 1 | 12 |
| **Ren et al 2016 (Ren et al., 2016)** | 2016 | 3 | 2 | 2 | 2 | 0 | 3 | 3 | 15 |
| (Romley et al., 2015) | 2015 | 3 | 3 | 2 | 3 | 0 | 3 | 3 | 17 |
| (Roumie et al., 2016) | 2015 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Rubin et al., 2011) | 2011 | 3 | 2 | 3 | 3 | 3 | 3 | 3 | 20 |

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Sako et al., 2015) | 2015 | 3 | 3 | 3 | 3 | 0 | 3 | 2 | 17 |
| (Sämann et al., 2013) | 2013 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Sarkar et al., 2010) | 2010 | 2 | 3 | 1 | 3 | 1 | 2 | 2 | 14 |
| (Sato et al., 2010) | 2010 | 2 | 1 | 2 | 2 | 1 | 2 | 1 | 11 |
| (Schloot et al., 2016) | 2016 | 1 | 2 | 3 | 3 | 1 | 3 | 3 | 16 |
| (Seewi et al., 2008) | 2008 | 2 | 1 | 2 | 2 | 0 | 2 | 2 | 11 |
| (Seligman et al., 2010) | 2010 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Shriraam et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Solomon et al., 2013) | 2013 | 3 | 3 | 3 | 2 | 0 | 3 | 3 | 17 |
| (Sreenan et al., 2014) | 2014 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 12 |
| (Strandberg et al., 2015) | 2017 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Stuart et al., 2017) | 2017 | 1 | 2 | 2 | 2 | 2 | 2 | 1 | 12 |
| (Takeishi et al., 2016) | 2016 | 3 | 1 | 2 | 3 | 0 | 1 | 3 | 13 |
| (Tan et al., 2015) | 2015 | 3 | 3 | 3 | 1 | 0 | 3 | 3 | 16 |
| (Thamer et al., 1999) | 1999 | 3 | 3 | 2 | 3 | 0 | 2 | 3 | 16 |
| (Tschope et al., 2012) | 2012 | 3 | 2 | 2 | 3 | 0 | 2 | 2 | 14 |
| (Tschope et al., 2011) | 2012 | 3 | 3 | 3 | 3 | 3 | 3 |  | 18 |

| Author | Year of publication | Representative population | Sample size | Confounders adjustments | Appropriate statistical analysis | Missing data | Methodology of the outcome measurement | Methods to detect hypoglycaemia | Total |
|---|---|---|---|---|---|---|---|---|---|
| (Van Keulen et al., 2015) | 2015 | 3 | 3 | 2 | 3 | 0 | 2 | 3 | 16 |
| (Vlckova et al., 2010) | 2009 | 3 | 2 | 2 | 3 | 1 | 3 | 2 | 16 |
| (Wang et al., 2015) | 2015 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Weinstock et al., 2013) | 2013 | 2 | 3 | 3 | 3 | 1 | 3 | 3 | 18 |
| (Weir et al., 2011) | 2010 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Williams et al., 2014) | 2014 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |
| (Wohland et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 1 | 3 | 3 | 19 |
| (Chu et al., 2017) | 2017 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Cho and Cho, 2018) | 2018 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Yu et al., 2016) | 2016 | 2 | 3 | 2 | 3 | 0 | 3 | 3 | 16 |
| (Ikeda et al., 2018) | 2018 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| (Yun et al., 2013) | 2013 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 17 |
| (Zaccardi et al., 2017) | 2016 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 18 |
| **(Zhong et al., 2017b)** | 2017 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 21 |

Methodology of the outcome measurements (Percentage, OR, RR, IR, HR); Methods to detect hypoglycaemia (ICD codes, self-reported or lab test)

### 2.5.3 Prevalence of hypoglycaemia

Overall 39 studies were included in the meta-analysis of the prevalence (**Table 10**), comprising a total of 2,462,810 patients with DM. only studies that measured hypoglycaemia prevalence over a period of 12 months were included in the meta-analysis. The prevalence rate of hypoglycaemia varied between studies, the highest prevalence rate was 73% reported by (Henderson et al., 2003), while the lowest prevalence rate was less than 1% reported by (Conceicao et al., 2017). The pooled estimate of annually prevalence of hypoglycaemia in diabetes was 11.0% (95%CI, 7.0 – 17.0) (**Figure 6**). Sensitivity analysis was conducted to remove two outliers' studies that may affect the pooled estimate of hypoglycaemia prevalence (Henderson et al., 2003, Conceicao et al., 2017). The pooled estimate of prevalence of hypoglycaemia after the sensitivity analysis increased to 12.0 % (95% CI, 8.0 – 17.0) (**Figure 7**). However, the 39 included studies in the meta-analysis of prevalence had a high level of heterogeneity (I-squared = 100.0 %,). A possible explanatory variable for this was the large variations in the definition of hypoglycaemia was used over between studies, This along with other explanatory variables: different year of publication, geographical locations, study designs, and the data source.

**Table 10 Study Characteristics included in Prevalence Meta-Analysis**

| Author (s) | Year of publication | Country (s) | Study design | Sample size | Follow up | Sample Source | DM type | Treatment | Prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|
| (Jabbar et al., 2017) | 2017 | Multinational | retrospectively | 3250 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 7.1 |
| (Akirov et al., 2018) | 2018 | N/A | prospective | 5301 | 1 year | Self-reported | Both types of diabetes | A combination of oral and insulin | 15 |
| (Aung et al., 2012) | 2012 | Europe | retrospectively | 1066 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 8 |
| (Bognetti et al., 1997) | 1997 | Europe | retrospectively | 187 | 1 year | Self-reported | Both types of diabetes | Insulin only | 19.2 |
| (Bramlage et al., 2012) | 2012 | Europe | retrospectively | 3810 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 10.7 |
| (Buyken et al., 1998) | 1998 | Europe | retrospectively | 2065 | 1 year | Self-reported | T1DM | Insulin only | 31.8 |
| (Cherubini et al., 2013) | 2013 | Europe | retrospectively | 2025 | 1 year | Self-reported | T2DM | Insulin only | 5 |
| (Conceicao et al., 2017) | 2017 | Europe | retrospectively | 425706 | 1 year | Self-reported | Both types of diabetes | A combination of oral and insulin | 0.074 |
| (Deusenberry et al., 2012) | 2012 | North America | retrospectively | 692 | 1 year | Database | T2DM | sulfonylureas | 19 |
| (Faerch et al., 2011) | 2011 | Europe | prospective | 128 | 1 year | Self-reported | T1DM | Insulin only | 38 |
| (Feher et al., 2016) | 2016 | Europe | retrospectively | 1569 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 62 |
| (Farmer et al., 2012) | 2012 | Europe | retrospectively | 3562 | 1 year | Database | Both types of diabetes | NA | 2.1 |
| (Green et al., 2012) | 2012 | North America | retrospectively | 3000 | 1 year | Self-reported | T2DM | NA | 23 |
| (Guisasola et al., 2008) | 2008 | Europe | retrospectively | 1709 | 1 year | Self-reported | T2DM | A combination of oral only | 38.4 |
| (Henderson et al., 2003) | 2003 | Europe | retrospectively | 215 | 1 year | Self-reported | T2DM | Insulin only | 73 |
| (Hirai et al., 2007) | 2007 | North America | retrospectively | 537 | 1 year | Self-reported | T1DM | Insulin only | 14.3 |
| (Honkasalo et al., 2011) | 2011 | Europe | retrospectively | 1005 | 1 year | Self-reported | T2DM | NA | 12.3 |

| Author (s) | Year of publication | Country (s) | Study design | Sample size | Follow up | Sample Source | DM type | Treatment | Prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|
| (Honkasalo et al., 2011) | 2011 | Europe | retrospectively | 771 | 1 year | Self-reported | T1DM | Insulin only | 31 |
| (Yun et al., 2018) | 2018 | Asia | retrospectively | 1366692 | 1 year | Database | T2DM | NA | 2.7 |
| (Johnston et al., 2012) | 2012 | North America | retrospectively | 361210 | 1 year | Database | T2DM | A combination of oral only | 4.7 |
| (Kostev et al., 2014) | 2013 | Europe | retrospectively | 32545 | 1 year | Database | T2DM | Insulin only | 2.2 |
| (Leese et al., 2003) | 2003 | Europe | retrospectively | 977 | 1 year | Database | T1DM | Insulin only | 7.1 |
| (Leese et al., 2003) | 2003 | Europe | retrospectively | 7678 | 1 year | Database | T2DM | A combination of oral and insulin | 1.1 |
| (Lipska et al., 2013a) | 2013 | North America | retrospectively | 9094 | 1 year | Database | T2DM | A combination of oral and insulin | 10.8 |
| (Muhlhauser et al., 1985) | 1985 | Europe | prospective | 384 | 1 year | Self-reported | T1DM | Insulin only | 14.6 |
| (Murata et al., 2005) | 2003 | North America | prospective | 344 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 51.2 |
| (Nunes et al., 2017) | 2017 | North America | retrospectively | 143635 | 1 year | Database | T2DM | sulfonylureas | 8.5 |
| (Olsen et al., 2014) | 2014 | Europe | retrospectively | 440 | 1 year | Self-reported | T1DM | Insulin only | 37 |
| (Ooi et al., 2011) | 2011 | Asia | retrospectively | 170 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 61.8 |
| **(Pedersen-Bjergaard et al., 2004a)** | 2004 | Europe | retrospectively | 1076 | 1 year | Self-reported | T1DM | Insulin only | 36.7 |
| (Pirags et al., 2012) | 2012 | Multinational | prospective | 991 | 1 year | Self-reported | T1DM | Insulin only | 2.5 |
| (Rajendran et al., 2015) | 2015 | Europe | retrospectively | 132 | 1 year | Database | Both types of diabetes | A combination of oral and insulin | 1 |
| (Sämann et al., 2013) | 2013 | Europe | retrospectively | 373 | 1 year | Self-reported | T1DM | A combination of oral and insulin | 1.3 |
| (Sämann et al., 2013) | 2013 | Europe | retrospectively | 4481 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 0.5 |
| (Sarkar et al., 2010) | 2010 | North America | retrospectively | 14357 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 11 |
| (Schloot et al., 2016) | 2015 | Europe | retrospectively | 29485 | 1 year | Database | T2DM | sulfonylureas | 2.8 |
| (Seligman et al., 2010) | 2011 | North America | retrospectively | 711 | 1 year | Self-reported | T2DM | NA | 28 |

| Author (s) | Year of publication | Country (s) | Study design | Sample size | Follow up | Sample Source | DM type | Treatment | Prevalence (%) |
|---|---|---|---|---|---|---|---|---|---|
| (Shriraam et al., 2017) | 2017 | Asia | retrospectively | 366 | 1 year | Self-reported | T2DM | A combination of oral and insulin | 23 |
| (Stuart et al., 2017) | 2017 | Europe | retrospectively | 9584 | 1 year | Self-reported | Both types of diabetes | A combination of oral and insulin | 13.8 |
| (Tschope et al., 2012) | 2012 | Europe | prospective | 3347 | 1 year | Self-reported | T2DM | A combination of oral only | 14.1 |
| (Weinstock et al., 2013) | 2013 | North America | retrospectively | 4973 | 1 year | Self-reported | T1DM | A combination of oral and insulin | 11.8 |
| (Chu et al., 2017) | 2017 | Asia | retrospectively | 20845 | 1 year | Database | Both types of diabetes | NA | 14.48 |

**NA** Not available, **DM** diabetes mellitus

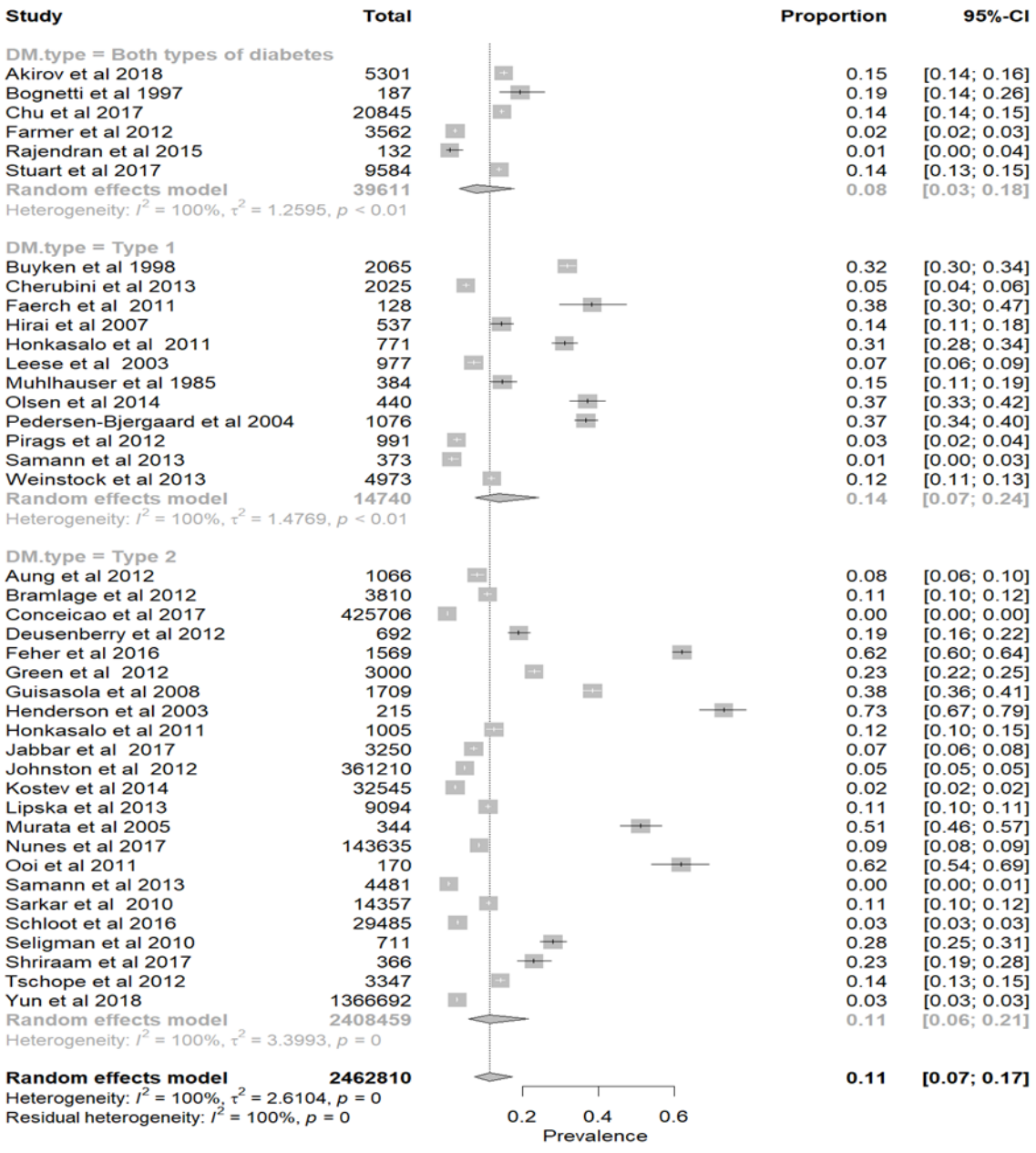



**Figure 6 Forest Plot of Overall Prevalence Meta-Analysis of Hypoglycaemia in DM Patients**

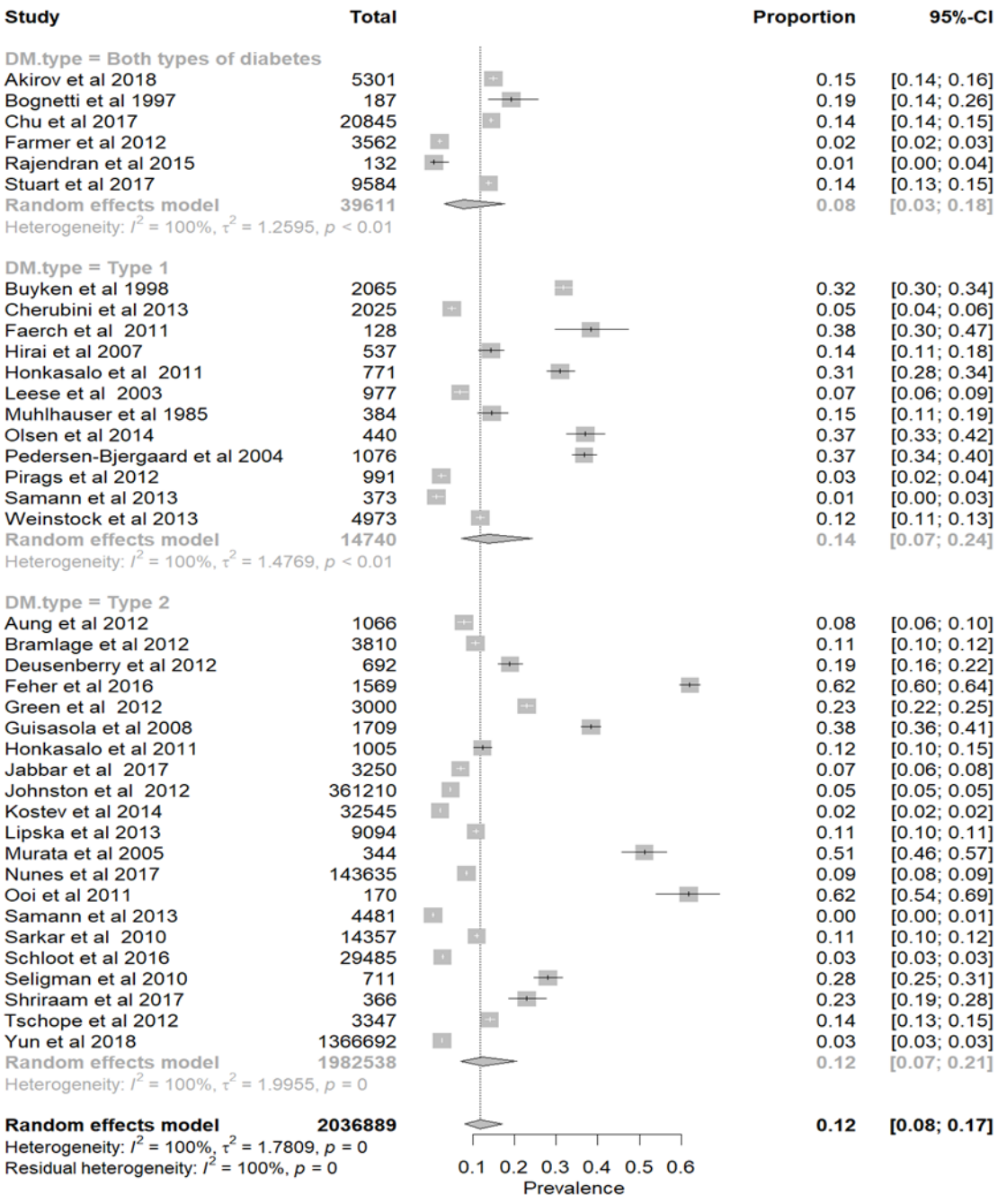



**Figure 7 Forest Plot of Overall Prevalence Meta-Analysis of Hypoglycaemia in DM Patients after Sensitivity Analysis**

### 2.5.3.1 Subgroup analysis

Subgroup analysis was performed by type of diabetes stratification, the pooled estimates of hypoglycaemia for T1DM and T2DM were 14.0 % (95% CI, 7.0 – 24.0)

and 11.0 % (95% CI, 6.0 – 21.0), respectively. Further stratification by origin of the study showed that the pooled estimate of hypoglycaemia for studies based in Europe and North America was 10.0 % (95% CI, 5.0 – 19.0) and 15.0 % (95% CI, 10.0 – 23.0), respectively, while, it was higher in Asia 18.0 % (95% CI, 5.0 – 47.0) (**Figure 8).** When stratified by treatment regimen, studies that included only patients treated with insulin as a treatment regimen were relatively higher prevalence of hypoglycaemia 17.0 % (95% CI, 10.0 – 27.0), compared to studies that included patients treated with regimens involving sulfonylureas 8.0 % (95% CI, 3.0 – 18.0) (**Figure 9**). The pooled estimate of hypoglycaemia when stratified by data source was interestingly varied between studies; self-reported studies had a higher pooled estimate compared to electronic health records studies being 15.0 % (95% CI, 9.0 – 24.0) and 5.0 % (95% CI, 3.0 – 8.0), respectively (**Figure 10**).

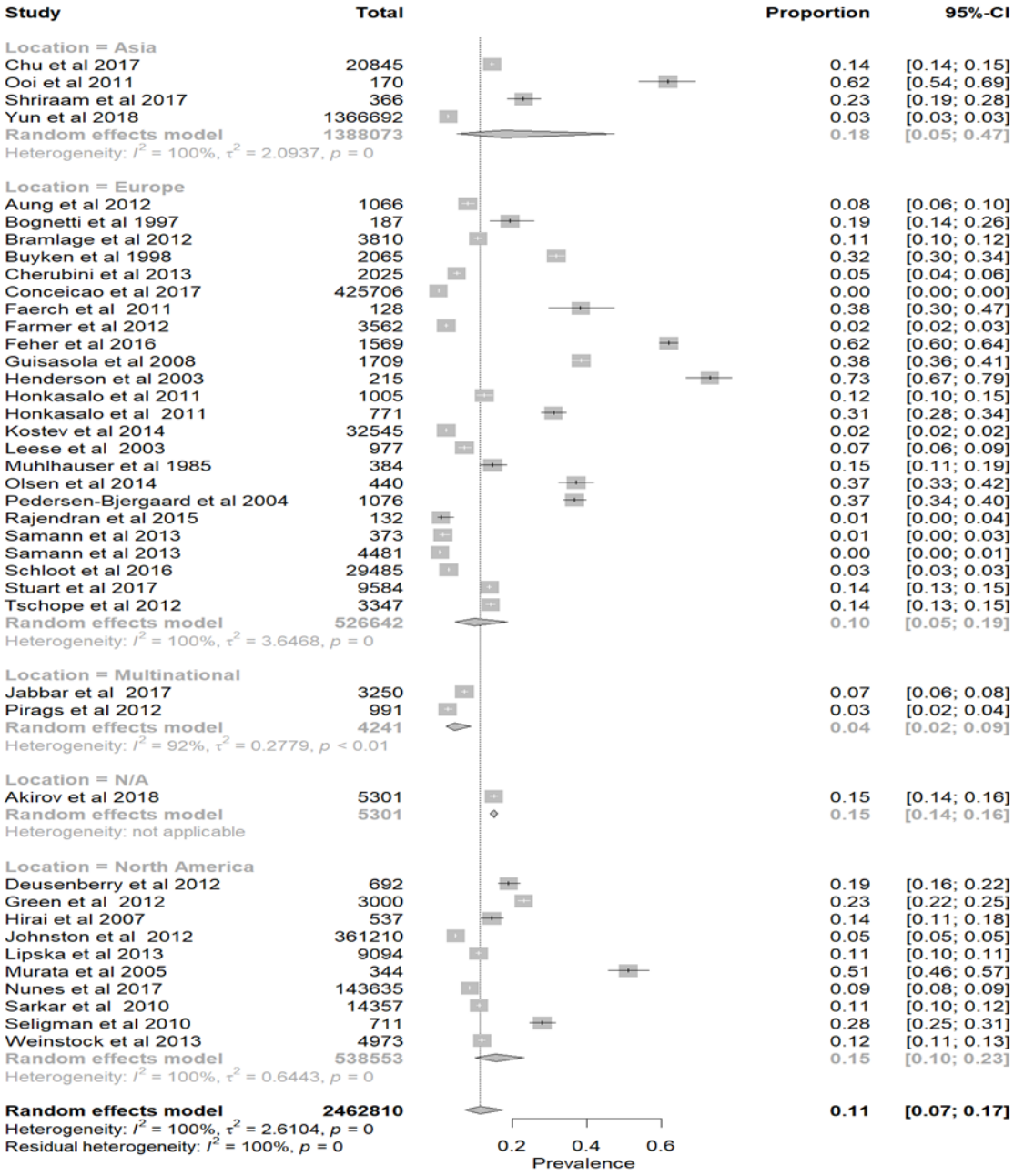



**Figure 8 Forest Plot of Prevalence Meta-Analysis of Hypoglycaemia Stratified by Study Origin.**

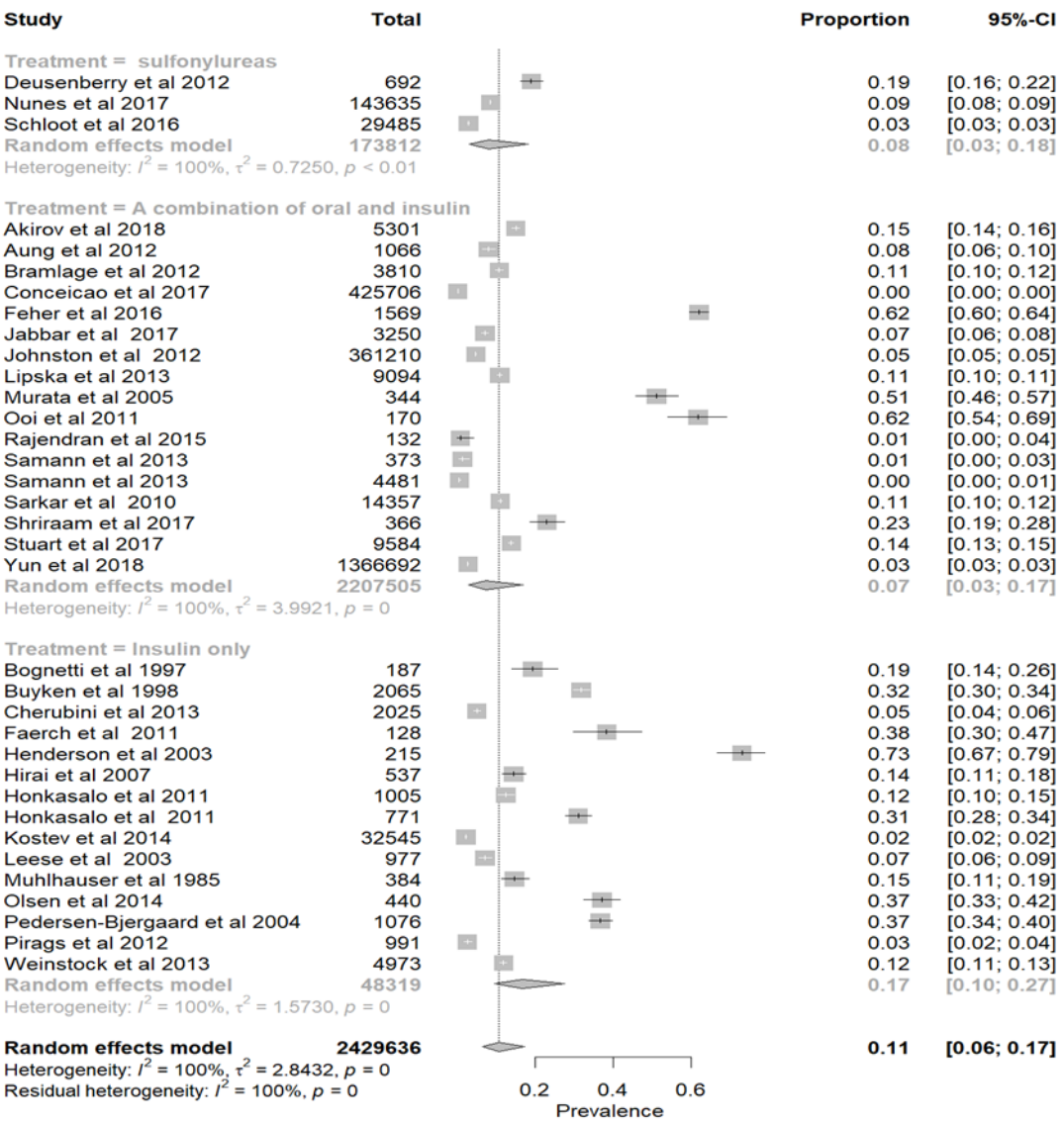



**Figure 9 Forest Plot of Prevalence Meta-Analysis of Hypoglycaemia Stratified by Treatment Regimens.**

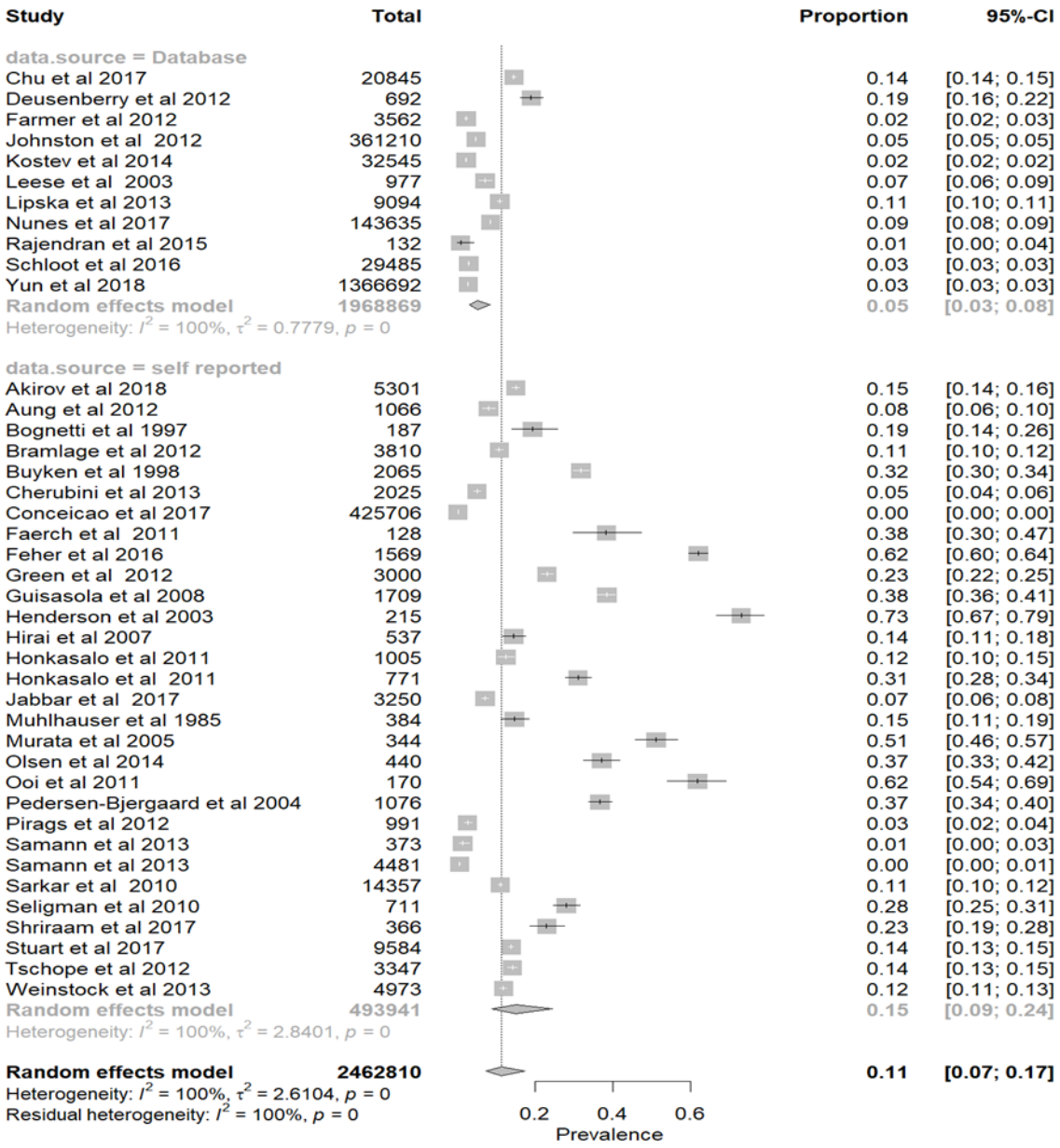



**Figure 10 Forest Plot of Prevalence Meta-Analysis of Hypoglycaemia Stratified by Data Source.**

In order to address the heterogeneity additional stratification was done by combining studies from similar origin, study design and data source showed that the pooled estimate of prevalence of hypoglycaemia was 35.0 % (95% CI, 32.0 – 38.0) ($I^2$=59%) among European studies with cross-sectional study design and self-reported in source of data (**Figure 11**). While the pooled estimate of prevalence of

hypoglycaemia among North American studies with cross-sectional study design and self-reported in source of data was 11.0 % (95% CI, 11.0 – 13.0) ($I^2$=38%) (**Figure 12**).

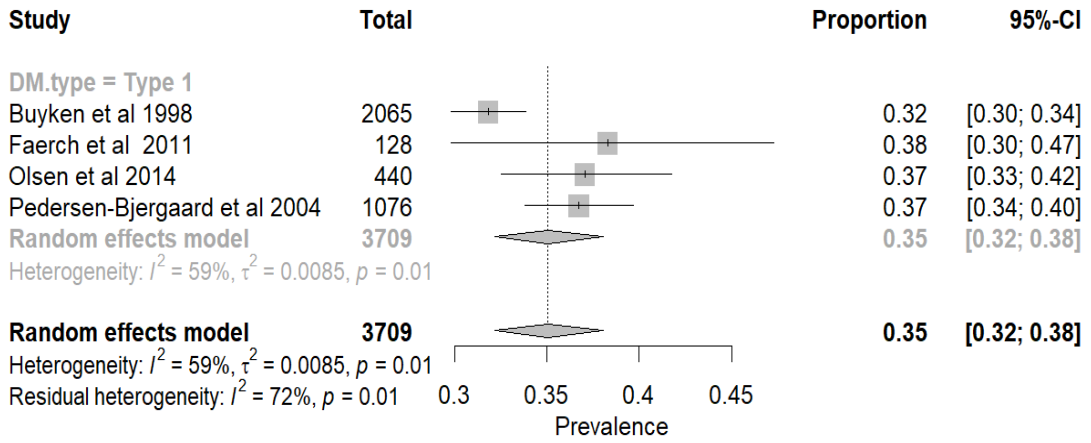



**Figure 11 Forest Plot of Prevalence Meta-Analysis of Hypoglycaemia Stratified by European studies, Self-reported and Cross-sectional studies.**

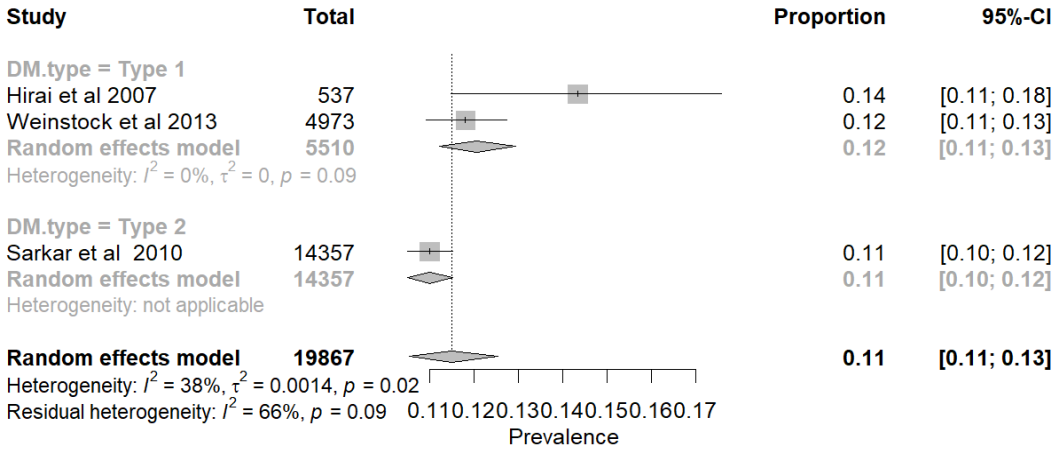



**Figure 12 Forest Plot of Prevalence Meta-Analysis of Hypoglycaemia Stratified by North American studies, Self-reported and Cross-sectional studies.**

## 2.5.4 Incidence of hypoglycaemia

A total of 39 studies, involving 45,768,950 participants met my inclusion criteria (i.e. full text, original, observational studies containing hypoglycaemia IR or events per 1000 person years) and were included in the meta-analysis (**Table 11**). The overall pooled incidence rate of hypoglycaemic episodes was 64.1 episodes per 1,000

person-years (95% CI, 29.4 – 139.7) (**Figure 13**). The pooled incidence rate of hypoglycaemia was stratified by diabetes type was 156.5 episodes per 1,000 person-years (95% CI, 61.6 – 397.6) experienced by T1DM patients and 40.9 episodes per 1,000 person-years (95% CI, 9.5 - 174.9) experienced by patients with T2DM (**Figure 13**). Stratification based on the treatment regimens, the pooled incidence rate of hypoglycaemia was 222.6 episodes per 1,000 person-years (95% CI, 91.9 – 539.3) for insulin-treated patients, while it was 18.0 episodes per 1,000 person-years (95% CI, 1.8 – 178.2) for patients treated by combination therapy of both insulin and oral antidiabetic medications (**Figure 14**). Furthermore, the self-reported hypoglycaemia showed a pooled incidence rate of 160.0 episodes per 1,000 person-years (95% CI, 28.3 – 903.6) and 43.3 episodes per 1,000 person-years (95% CI, 19.2 - 97.3) retrieved from databases (**Figure 15).**

**Table 11 Details of the Included Studies in the Incidence Rate Meta-Analysis.**

| Author | Year of publication | Geographical region | Sample size | Sample Source | DM type | TTT regimen | Incidence rate Per 100 Pys |
|---|---|---|---|---|---|---|---|
| (Barkai et al., 1998) | 1998 | NA | 130 | Self-reported | T1DM | Insulin | 38.5 |
| (Birkebaek et al., 2017) | 2017 | Europe | 8806 | Database | T1DM | Insulin | 6 |
| (Pedersen-Bjergaard et al., 2003) | 2003 | Europe | 171 | Database | T1DM | Insulin | 110 |
| (Blasetti et al., 2011) | 2011 | Europe | 195 | Database | T1DM | Insulin | 9.4 |
| (Bognetti et al., 1997) | 1997 | Europe | 187 | Self-reported | Both types of diabetes | NA | 14.9 |
| (Bron et al., 2012) | 2012 | North America | 212061 | Database | T2DM | Oral medication only | 5.4 |
| (Cherubini et al., 2013) | 2013 | Europe | 2025 | Database | T1DM | Insulin | 7.7 |
| (Alexiu et al., 2017) | 2017 | North America | 232898 | Database | Both types of diabetes | A combination of oral and insulin | 26.63 |
| **(Davis et al., 2010)** | 2010 | Australia | 616 | Self-reported | T2DM | NA | 1.7 |
| (Davis et al., 1998) | 1998 | Australia | 709 | Self-reported | T1DM | Insulin | 23.2 |
| (Donnelly et al., 2005a) | 2004 | Europe | 173 | Self-reported | T2DM | Insulin | 1636 |
| (Donnelly et al., 2005a) | 2004 | Europe | 94 | Database | T1DM | Insulin | 4289 |
| (Henderson et al., 2003) | 2003 | Europe | 215 | Self-reported | T2DM | Insulin | 28 |
| (Ishtiak-Ahmed et al., 2017) | 2017 | Europe | 17230 | Database | T1DM | Insulin | 3.38 |
| (Johansen et al., 2015b) | 2015 | Europe | 3320 | Database | T1DM | Insulin | 15.1 |
| (Karges et al., 2015) | 2015 | North America | 31330 | Database | T1DM | Insulin | 4.81 |
| (Katz et al., 2012) | 2012 | Australia | 255 | Self-reported | T1DM | Insulin | 37.6 |
| (Kim et al., 2016) | 2016 | Asia | 307107 | Database | T2DM | A combination of oral and insulin | 0.933 |

| Author | Year of publication | Geographical region | Sample size | Sample Source | DM type | TTT regimen | Incidence rate Per 100 Pys |
|---|---|---|---|---|---|---|---|
| (Leckie et al., 2005) | 2005 | Europe | 243 | Database | Both types of diabetes | Insulin | 98 |
| (Leese et al., 2003) | 2003 | Europe | 977 | Database | T1DM | Insulin | 11.5 |
| (Leonard et al., 2016) | 2016 | North America | 592872 | Database | T2DM | Oral medication only | 5.8 |
| (Lipska et al., 2014) | 2014 | North America | 33952331 | Database | Both types of diabetes | NA | 0.105 |
| (Lundkvist et al., 2005) | 2005 | Europe | 309 | Self-reported | T2DM | A combination of oral and insulin | 0.0072 |
| (Ly et al., 2009) | 2009 | Europe | 656 | Self-reported | T1DM | Insulin | 24.5 |
| (Maltoni et al., 2013) | 2013 | Europe | 269 | Self-reported | T1DM | Insulin | 15.6 |
| (Alonso-Moran et al., 2015) | 2015 | Europe | 134413 | Database | T2DM | NA | 63 |
| (Muller et al., 2017) | 2017 | Europe | 7900000 | Database | T2DM | A combination of oral and insulin | 0.49 |
| (Murata et al., 2005) | 2003 | North America | 344 | Self-reported | T2DM | A combination of oral and insulin | 610 |
| (Nunes et al., 2016) | 2016 | North America | 844683 | Database | T2DM | Oral medication only | 6.28 |
| (Odawara et al., 2014) | 2014 | Asia | 4219 | Database | T2DM | A combination of oral and insulin | 3.5 |
| (Pathak et al., 2016) | 2016 | North America | 917440 | Database | Both types of diabetes | NA | 1.47 |
| (Lyngsie et al., 2016) | 2016 | Europe | 307016 | Database | Both types of diabetes | NA | 0.7 |
| (Pilemann-Lyberg et al., 2015) | 2015 | Europe | 3156 | Database | T2DM | Oral medication only | 0.43 |
| (Pirags et al., 2012) | 2012 | Australia | 991 | Self-reported | T1DM | Insulin | 4 |
| (Raju et al., 2016) | 2016 | North America | 11536 | Database | T2DM | Oral medication only | 3.37 |

| Author | Year of publication | Geographical region | Sample size | Sample Source | DM type | TTT regimen | Incidence rate Per 100 Pys |
|---|---|---|---|---|---|---|---|
| (Sako et al., 2015) | 2015 | Asia | 25071 | Database | Both types of diabetes | NA | 0.412 |
| (Wang et al., 2015) | 2015 | North America | 63972 | Database | Both types of diabetes | NA | 1.4 |
| (Ikeda et al., 2018) | 2018 | Asia | 166806 | Database | T2DM | A combination of oral and insulin | 0.37 |
| (Yun et al., 2013) | 2013 | Asia | 878 | Database | T2DM | A combination of oral and insulin | 1.55 |
| **(Zhong et al., 2017b)** | 2017 | Europe | 23246 | Database | T1DM | Insulin | 1.48 |

**TTT** treatment regimen, **DM** diabetes mellitus, **NA** not available, **IR** incidence rate. **PY** patient-years, **T1DM** type 1 diabetes mellitus, **T2DM** type 2 diabetes mellitus

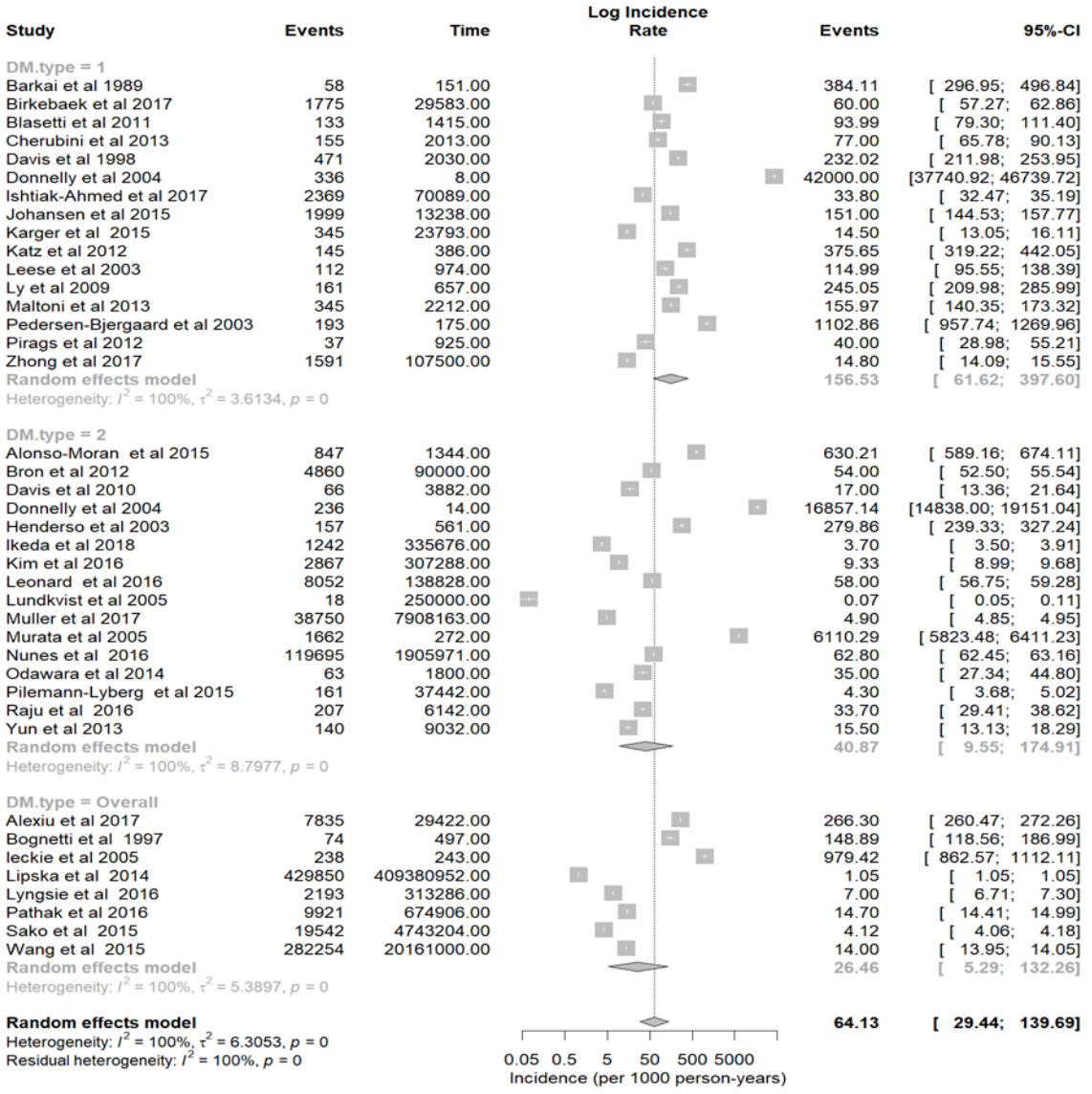



**Figure 13 Forest Plot of Incidence Rate Meta-Analysis of Hypoglycaemia (episode per 1000 person-years) Stratified by DM Type.**

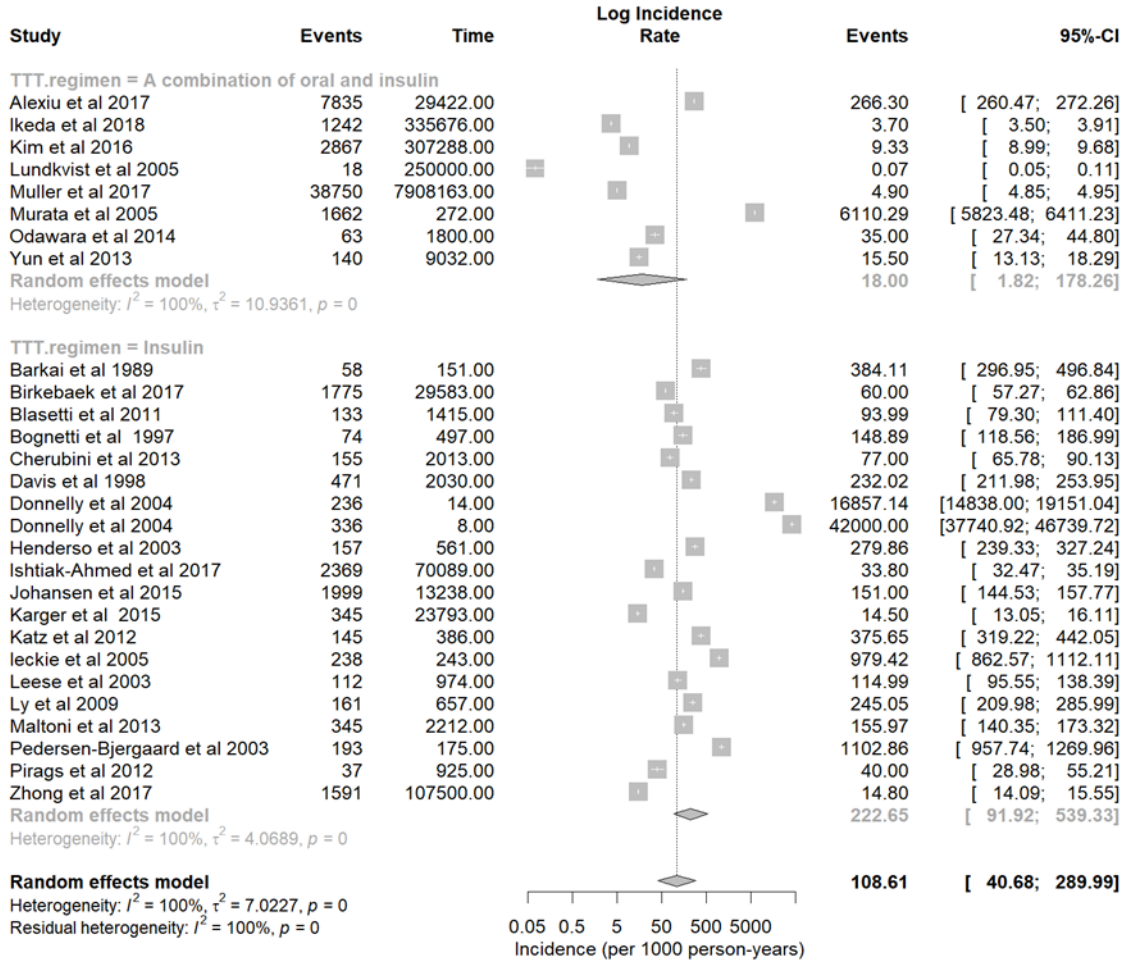



**Figure 14 Forest Plot of Incidence Rate Meta-Analysis of Hypoglycaemia (episode per 1000 person-years) Stratified by Treatment Regimens**

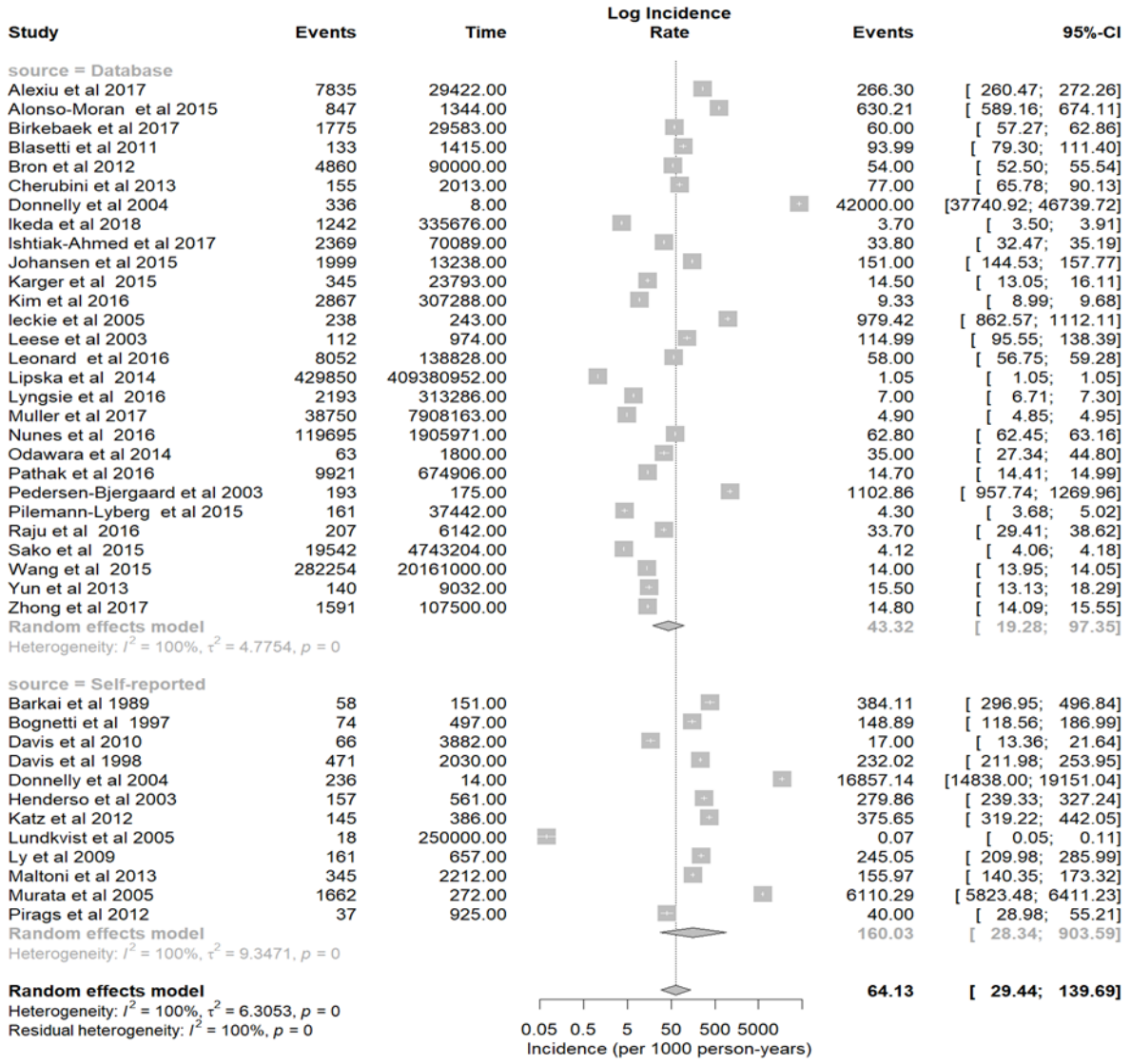



**Figure 15 Forest Plot of Incidence Rate Meta-Analysis of Hypoglycaemia (episode per 1000 person-years) Stratified by Data Source**

## 2.5.5 Publication bias

Funnel plots were generated for the prevalence and incidence to compare between the transformed effect sizes and the estimated SE and to examine the relationship between the outcome and studies' size. Asymmetrical funnel plots were presented in **Figure 16** and an obvious contrast of the results between the fixed effect and random effects models were shown.

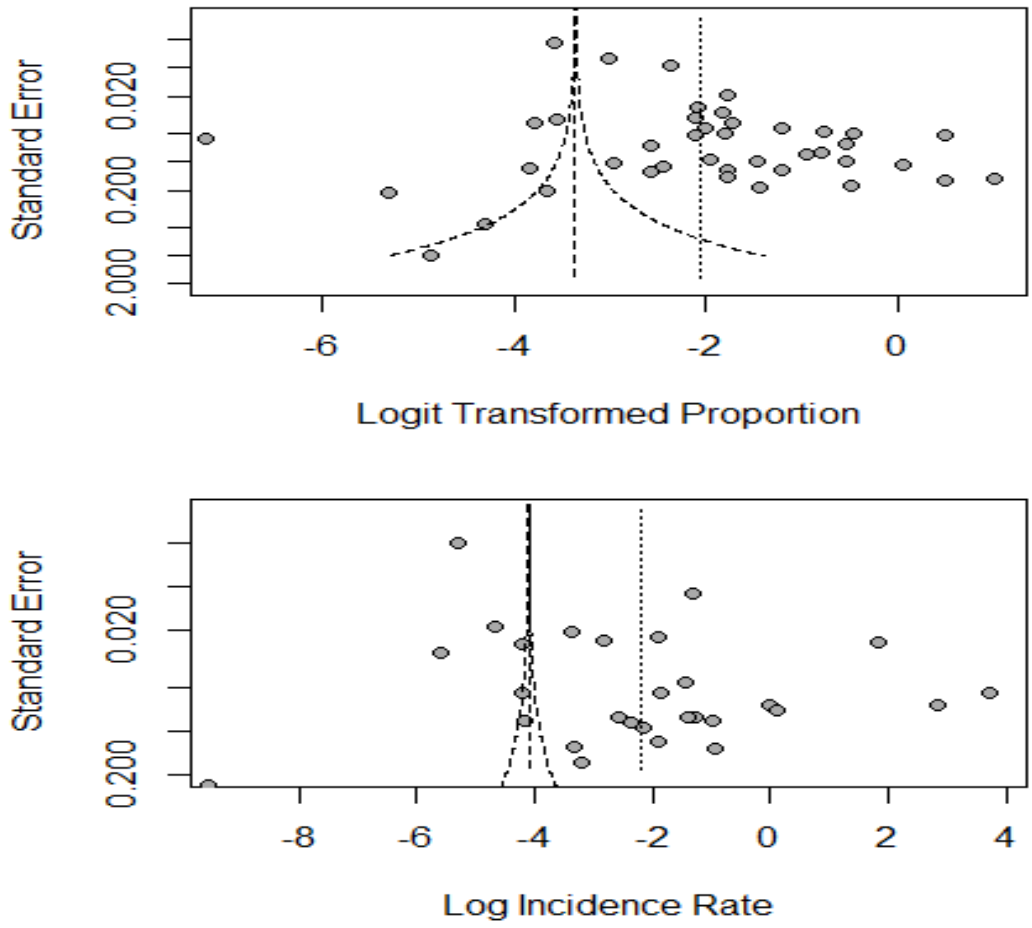



**Figure 16 Funnel Plots of the Standard Error by the Logit of the Prevalence/Incidence with the Observed Estimates.**

Funnel plot for prevalence and incidence on the transformed scale, presented with pseudo 95% confidence interval around the fixed effect. The separate vertical line corresponds to the pooled effect from the random effects model.

### 2.5.6 Risk factors of hypoglycaemia

A total of 102 citations reported risk factors that are associated with hypoglycaemia in patients with DM. Some of the studies reported multiple risk factors in their study and this was noted in citations that studied clinical or demographic characteristics. Different risk factors have been reported in the studies included in this review; majority of the risk factors were associated with an increased risk of hypoglycaemia, while others were associated with a protective effect. Also, different designs of the studies

included in this review as some of the citations were prospective, while others were retrospective. Studies reported risk factors were classified into the 4 categories: (1) demographics, (2) medication-induced hypoglycaemia, (3) comorbidities and (4) others.

#### 2.5.6.1 Demographics characteristics

The majority of the studies included in this review reported some results about demographic characteristics and their association with hypoglycaemia. The demographics risk factors reported in this review are age, gender, HbA1c, diabetes duration, race and body mass index (BMI). A total of 26 studies identified demographics risk factors and their association with hypoglycaemia. Seven studies measured age and the risk of hypoglycaemia. However, the results were controversial as all of the studies reported that old age is an independent risk factor for hypoglycaemia, Deusenberry and colleagues reported that elderly DM patients were at threefold increased risk of hypoglycaemia (Deusenberry et al., 2012). While Guisasola et al. reported that old age was a protective factor for hypoglycaemia OR 0.98 (95%CI 0.97–0.99). Regarding to the difference in gender and the risk of hypoglycaemia, there were 6 studies measured the association between gender and the risk of hypoglycaemia. Four studies reported that female patients at an increased risk of hypoglycaemia compared to males (Kajiwara et al., 2015, Sämann et al., 2013, Vlckova et al., 2010, Zaccardi et al., 2017), while Li et al. reported that male patients are at higher risk compared to females (Li et al., 2014), and no risk difference was reported by one study (Dendy et al., 2014). In terms of HbA1c, 10 studies examined the risk of hypoglycaemia and levels of HbA1c; however, there was variations in the results between the studies. 6 studies reported that higher levels of HbA1c are associated with an increased risk of hypoglycaemia (Weinstock et al., 2013, Gu et al.,

2016, Williams et al., 2014, Alonso-Moran et al., 2015, Fang et al., 2015, Mauricio et al., 2015). However, the other 4 studies reported that lower levels of HbA1c are associated with an increased risk of hypoglycaemia (Li et al., 2014, Yu et al., 2016, Tschope et al., 2012, Egger et al., 1991). Four studies have measured the association between diabetes duration and the risk of hypoglycaemia in this review; all studies demonstrated that those patients with a longer diabetes duration had a higher risk of developing hypoglycaemia, (Gu et al., 2016) reported the highest odds ratio was OR 4.14 (3.03–5.67). In regards to the race as a risk factor for hypoglycaemia, only one study examined this association and the Karter et al. reported that the risk is increased among African and Asian populations, the incidence rates were IR 4.3 (95% CI, 2.1 – 6.5) and 3.9 (95% CI, 3.6 – 12), respectively (Karter et al., 2017). BMI was examined as a risk factor of hypoglycaemia and reported in three studies in this review: further details on demographics risk factors are available in **Table 12**.

**Table 12 Studies Reported Demographics Risk Factors of Hypoglycaemia in DM Patients**

| Author | Age | Race | BMI | Gender | HbA1C | Diabetes duration |
|---|---|---|---|---|---|---|
| (Tschope et al., 2011) | | | | | ↑ Low HbA1c OR 1.68 (1.31-2.14) | |
| (Borzi et al., 2016) | ↑ OR 1.39 (1.00 -193) | | | | | |
| (Gu et al., 2016) | ↑ OR 1.33 (0.78–2.28) | | ↓ Risk of Low BMI OR: 0.86 (0.82–0.90) | | ↑ High HbA1c OR 2.14 (0.87- 5.24). | ↑ OR 4.14 (3.03–5.67) |
| (Elwen et al., 2015) | ↑RR 1.041 (1.014-1.069) | | | | | |
| (Dendy et al., 2014) | | | | No risk male OR 0.91 (0.55, 1.49) | | |
| (Durán-Nah et al., 2008) | | | | | | ↑ OR 1.119 (1.05-1.2) |
| (Kajiwara et al., 2015) | | | | ↑ Risk female OR 2.04 (1.22–3.41) | | |
| (Bramlage et al., 2012) | | | | | | ↑ OR 1.29 (0.97-1.71) |
| (Yu et al., 2016) | | | | | ↑ Risk low HbA1c OR 1.66 (1.21- 2.28). | |
| (Karter et al., 2017) | | No risk White IR - 0.9 (−4.4 –2.8). No risk Latina IR 0.5 (−0.6 –1.7). ↑ African IR 4.3 (2.1–6.5) ↑ Asian IR 3.9 (−3.6–12) | | | | |
| (Karges et al., 2015) | ↑ Risk of 15-20 years RR 1.63 (1.32–2.02) | | | | | |
| (Sämann et al., 2013) | | | | ↑ female patients OR (2.84, 1.19, 6.70) | | |
| (Bruderer et al., 2014a) | ↑ OR 2.27(1.65–3.12) | | | | | |

| Author | Age | Race | BMI | Gender | HbA1C | Diabetes duration |
|---|---|---|---|---|---|---|
| (Vlckova et al., 2010) | | | | ↑ risk of female HR 2.05 (1.24- 3.41) | | |
| (Deusenberry et al., 2012) | ↑ OR 3.07 | | | | | |
| (Li et al., 2014) | | | ↓ High BMI RR 0.62<br>↑ Low BMI RR 1.44 | ↑ male gender RR 1.71 | ↑ low Hba1C RR=1.46 | ↑ RR=1.22 |
| (Weinstock et al., 2013) | | | | | ↑ HbA1C=9-10 OR=6.26 (3.99, 9.83) | |
| (Williams et al., 2014) | | | | | ↑ high HbA1C OR 1.17 (1.13, 1.21) | |
| (Egger et al., 1991) | | | | | ↑ low HbA1C OR 4.5 (1.9-10.5) | |
| (Alonso-Moran et al., 2015) | | | | | ↑ HbA1C > 9 OR 2.216 | |
| (Guisasola et al., 2008) | ↓ OR 0.98 (0.97–0.99) | | ↓ OR 0.990 (0.984–0.997) | | | |
| (Zaccardi et al., 2017) | | African (0.93 (0.79-1.8).<br>↓ Bangladeshi 0.61 (0.51-0.73).<br>↑ Caribbean (1.59 (1.46-1.75).<br>↓Indian (0.86 (0.77-0.93). ↓Pakistani 0.58 (0.53-0.63) | | ↑ female 1.01 (0.97-1.05) | | |
| (Chu et al., 2017) | | | | | | |
| (Fang et al., 2015) | | | | | ↑ OR = 6.4 | |
| (Mauricio et al., 2015) | | | | | ↑ OR, 3.70 [95% CI, 3.41-4.00] | |

**HbA1c** glycated haemoglobin, **BMI** body mass index, **OR** odds ratio, **IR** incidence rate, **HR** hazard ratio, **RR** relative risk

### 2.5.6.2 Drug-induced hypoglycaemia

Out of 101 studies, 50 studies investigated different medications as a risk factor of hypoglycaemia including antidiabetic medications and other medications. Insulin was the most antidiabetic medication associated with the risk of hypoglycaemia and almost all of the studies demonstrated that insulin is an independent risk factor for hypoglycaemia. The highest odds of developing hypoglycaemia associated with the use of insulin was reported by Muller et al. OR 14.6 (13.3–15.9) (Muller et al., 2017). However, only one study found there was no risk of hypoglycaemia associated with glargine insulin HR 0.92 (0.74-1.15) and detemir insulin HR 0.70 (0.51-0.94) (Strandberg et al., 2015). Following insulin, sulfonylureas were the second most common medication to be associated with hypoglycaemia and almost all of the studies reported that sulfonylureas are risk factors for hypoglycaemia except one study reported that sulfonylureas are protective factors against hypoglycaemia with an odds ratio of OR 0.21 (0.08–0.57) by (Rathmann et al., 2013). 3 studies examined the association between the use of the remaining oral antidiabetic medications classes and the risk of hypoglycaemia. However, a protective effect against hypoglycaemia was demonstrated by all of these studies. Intensive therapy was also associated with a higher risk of hypoglycaemia, with the highest odds ratio at OR 4.74 (3.67-6.06) reported by Fu et al. (Fu et al., 2014).

Other medications have been demonstrated to increase the risk of hypoglycaemia.

1) Cardiac medications including:

a) Four studies reported that the use of beta blockers (BB) was associated with higher risk of developing hypoglycaemia among hypertensive patients, with the highest odds ratio with OR 4.48 (2.33 - 8.61) reported by Lin et al. (Lin et al., 2010); however, one

study reported that there was no risk of developing hypoglycaemia associated with BB use (Corsonello et al., 1999).

b) Three studies reported that the use of angiotensin-converting enzyme inhibitors (ACEI) was associated with an increased risk of hypoglycaemia(Lin et al., 2010, Herings et al., 1995, Pedersen-Bjergaard et al., 2003), while one study demonstrated no risk (Corsonello et al., 1999).

c) One study reported that the use of calcium channel blockers (CCB), Thamer et al. reported that CCB use can increase the risk of hypoglycaemia in DM patients OR 1.1 (0.5 to 2.6) (Thamer et al., 1999). However, Lin et al. reported different results and found that the use of CCB was considered as a protective factor against hypoglycaemia with OR 0.19 (0.08-0.46) (Lin et al., 2010).

2) Three studies reported that anticoagulant medications were associated with an increased risk of hypoglycaemia by 1-3 folds, which was highlighted by Romley et al. OR 1.22 (1.05 - 1.42) (Romley et al., 2015), Davis et al. OR 2.93 (1.06–8.1) (Davis et al., 2010) and Nam et. al. OR 1.73 (1.38-2.16) in their studies(Nam et al., 2018).

3) One study found that anti-hyperlipidaemic medications increase the risk of hypoglycaemia when used with sulfonylureas medications in DM patients. Leonard et al. to reported that fibrates were associated with a higher risk of hypoglycaemia, while statins were reported to be either no risk or protective for hypoglycaemia (Leonard et al., 2016).

4) One study reported that antidepressant medications increase the risk of hypoglycaemia among DM patients, this was highlighted in a study by Derijks et al. and found an increased risk of hypoglycaemia with the use of antidepressants at OR 2.75 (1.31–5.77) (Derijks et al., 2008).

5) Three studies examined the use of antibiotic medications and reported an increased risk of hypoglycaemia, as was demonstrated in different studies and in relation to different antibiotics, including fluoroquinolones, co-trimoxazole and trimethoprim. Co-trimoxazole was the highest antibiotic reported to be associated with an increased risk of hypoglycaemia with an OR 3.89 (2.29–6.60) (Tan et al., 2015).

In addition, polypharmacy was also reported to increase the risk of hypoglycaemia by two studies in this review. Polypharmacy can increase the risk of hypoglycaemia by four-folds (Durán-Nah et al., 2008). For further details on drug-induced hypoglycaemia, refer to the table below (**Table 13**).

**Table 13 Studies Reported Medications induced Risk Factors of Hypoglycaemia in DM Patients**

| Author | Polypharmacy | Intensive therapy | Insulin | SU | Oral antidiabetic other than SU | Cardiac | CNS | Antibiotics |
|---|---|---|---|---|---|---|---|---|
| (Lee et al., 2017) | | ↑ HR 2.20; 95% CI 1.28–3.76) | | | | | | |
| (Bron et al., 2012) | | | ↑ HR 2.10 (1.98-2.24) | | | | | |
| (Fu et al., 2014) | | ↑ OR 4.74 (3.67-6.06) | ↑ OR 4.20 (3.39-5.19) | ↑ OR 3.94 (3.42-4.55) | | | | |
| (Solomon et al., 2013) | | | ↑ Risk of premix insulin HR 2.12 (1.26–3.55) ↑ Risk of Rapid-acting insulin HR 2.75 (1.88-4.04) ↑ Risk of Ishophane insulin HR 2.19 (1.36–3.52) ↑ Risk of detemir insulin HR 1.20 (0.43–3.34) | | | | | |
| (Cho and Cho, 2018) | | ↑ HR 2.20; 95% CI 1.28–3.76) | | | HRs (95% CI), ↓ 0.39 (0.18-0.83) metformin and THZ versus metformin + SU | | | |
| (Yu et al., 2018) | | | | ↑ HR, 4.53; 95% CI, 2.76-7.45). SU Vs metformin | | | | |
| (Strandberg et al., 2015) | | | No Risk of glargine insulin HR 0.92 (0.74-1.15) ↓ Risk of detemir insulin HR 0.70 (0.51-0.94) | | | | | |
| (Radosevich et al., 2015) | | | ↑ 0.05 to <1 units/kg OR 3.04 (0.97–9.55) | | | | | |

| Author | Polypharmacy | Intensive therapy | Insulin | SU | Oral antidiabetic other than SU | Cardiac | CNS | Antibiotics |
|---|---|---|---|---|---|---|---|---|
| | | | ↑ > 1 units/kg OR 4.57 (1.45-14.41) ↑ 4 TO < 8 units/kg OR 2.76 (0.80–9.51) ↑ > 8 units/kg OR 4.17 (1.18-14.75) | | | | | |
| (Geller et al., 2014) | | | ↑ RR 2.5 (1.5 - 4.3) | | | | | |
| (Rubin et al., 2011) | | | ↑ 0.6–0.8 units/kg OR 2.10 (1.08–4.09) ↑ > 0.8 units/kg: OR 2.95 (1.54–5.65) ↑ 0.2–0.4 units/kg OR 1.08 [(0.64–1.81) ↑ 0.4–0.6 units/kg OR 1.60 (0.90–2.86) | | | | | |
| **(Davis et al., 2010)** | | | ↑ Risk of long-acting insulin HR 4.29 (2.44–7.55) | ↑ HR 1.15 (0.65–2.0) | | ↑ Anticoagulant OR 2.93 (1.06–8.1) | | |
| (Wohland et al., 2017) | | | ↑ NPH Insulin OR 3.68 (1.64, 8.91) | | | | | |
| (Mantovani et al., 2016) | | | | ↑ OR 1.61 (0.32–8.02) | | | | |
| (Tschope et al., 2011) | | | | ↑ OR 2.58 (2.03-3.29) | ↓ Metformin OR 0.64 (0.50-0.82) ↓ DDP-4 OR 0.34 (0.16-0.70) | | | |

| Author | Polypharmacy | Intensive therapy | Insulin | SU | Oral antidiabetic other than SU | Cardiac | CNS | Antibiotics |
|---|---|---|---|---|---|---|---|---|
| | | | | | ↓Thiazolidinedione OR 0.50 (0.28-0.89) | | | |
| | | | | ↑ OR 2.25 (2.06–2.70) | ↓ Metformin 0.62 (0.53–0.73) | ↑ beta blocker OR 1.20 (1.78 –2.26) | | ↑fluoroquinolones OR 2.59 (3.82–5.77)<br>↑ Trimethoprim 1.97 ( 2.68–5.41) |
| (Rathmann et al., 2013) | | | | ↓ OR 0.21 (0.08–0.57) | | | | |
| (McCoy et al., 2016) | | ↑ OR 3.04 (1.9 - 4.18) | | | | | | |
| (Allen et al., 2001) | | ↑ OR 1.6 (1.3–1.9) | | | | | | |
| (Roumie et al., 2016) | | ↑ OR 1.39 (1.12–1.72) | | | | | | |
| (Eriksson et al., 2016) | | ↑ HR 2.07 (1.11–3.86) | | | | | | |
| (Durán-Nah et al., 2008) | ↑ OR 4.9 (0.7 - 35.1) | | | | | | | |
| (Lin et al., 2010) | ↑ OR 2.93 (1.63 - 5.28) | | | | | ↑ beta blocker OR 4.48 (2.33 - 8.61)<br>↓ CCB OR 0.19 (0.08-0.46) | | |
| (Derijks et al., 2008) | | | | | | | ↑ antidepressant OR 2.75 (1.31–5.77) | |
| (Thamer et al., 1999) | | | | | | ↑ ACEI 1.5 (0.8 to 2.8)<br>↑ BB 2.3 (0.9 to 6.1)<br>↑ CCB 1.1 (0.5 to 2.6)<br>↑ Diuretic 1.4 (0.7 to 2.7) | | |
| (Morris et al., 1997) | | | | | | ↑ OR 4.3 (1.2-16.0) | | |

| Author | Polypharmacy | Intensive therapy | Insulin | SU | Oral antidiabetic other than SU | Cardiac | CNS | Antibiotics |
|---|---|---|---|---|---|---|---|---|
| (Romley et al., 2015) | | | | | | ↑ Anticoagulant OR 1.22 (1.05 - 1.42) | | |
| (Nam et al., 2018) | | | | | | ↑ Glimepiride + Warfarin 1.47 (1.07-2.02). ↑ Glimepiride + Warfarin 1.20 (0.98-1.46). ↑ Glimepiride + Warfarin 1.09 (0.88-1.35) . ↑ Glimepiride + Warfarin 1.73 (1.38-2.16) | | |
| (Bramlage et al., 2012) | | | | ↑ OR 1.71 (1.17-2.49) | | | | |
| (Leonard et al., 2016) | | | | | | ↑ Risk of gemfibrozil (fibrates) OR 1.57 (1.22-2.03) ↑ Risk of fenofibrate (fibrates) OR 1.63 (1.29-2.06) No risk of atorvastatin OR 0.92 (0.77-1.09) ↓ Risk of simvastatin OR 0.83 (0.70-0.99) No Risk of lovastatin OR 0.89 (0.69-1.16) No risk of rosuvastatin OR 0.87 (0.67-1.13) | | |
| (Van Keulen et al., 2015) | | | | | | | ↑ Antipsychotic OR 2.27 (1.46-3.54) | |

| Author | Polypharmacy | Intensive therapy | Insulin | SU | Oral antidiabetic other than SU | Cardiac | CNS | Antibiotics |
|---|---|---|---|---|---|---|---|---|
| (Holstein et al., 2011) | | | ↑ OR 1.61 (0.84-3.09) | | | | | |
| (Takeishi et al., 2016) | | | ↑ OR 1.40 (0.55-3.59) | | ↓ Metformin OR 0.67 (0.28-1.61) ↓ DDP-4 OR 2.11 (0.85-5.24) ↓Thiazolidinedione OR 0.50 (0.28-0.89) | | | |
| (Corsonello et al., 1999) | | | | | | No risk Beta blocker OR 0.95 ( 0.13-7.20) No risk ACEI OR 0.5 (0.19-1.55 ) | | |
| (Lundkvist et al., 2005) | | | ↑ OR 5.55 | | | | | |
| (Jick et al., 1990) | | | ↑ RR 1.3 ( 0.5, 3.5) | | | | | |
| (Sämann et al., 2013) | | | ↑ (OR= 3.43 (1.31, 8.96) | | | | | |
| (Bruderer et al., 2014a) | | | ↑ OR 11.83 (9.00–15.54) | ↑ OR 4.45 (3.53–5.60) SU + CYP substrates ↓ OR 0.72 (0.39 - 1.34) | | | | |
| (Muller et al., 2017) | | | ↑ OR 14.613.3–15.9) | | | | | |
| (Tschope et al., 2012) | | | ↑ OR2.99 (2.27-3.95) | | | | | |
| (Freathy et al., 2006) | | | ↑ OR 2.77 (1.36-5.62) | | | | | |
| (Vlckova et al., 2010) | | | ↑ HR = 3.11 (CI 1.64 -5.88) | ↑ HR = 4.15 (CI 1.74- 9.91) | | | | |
| (ter Braak et al., 2000) | | | ↑ (OR1.3 (1.0–1.6) | | | ↑ beta blocker OR 14.9 (2.1–107.4) | | |
| (Ishtiak-Ahmed et al., 2017) | | | ↑ OR 2.17 (1.16–4.08) | | | | | |

| Author | Polypharmacy | Intensive therapy | Insulin | SU | Oral antidiabetic other than SU | Cardiac | CNS | Antibiotics |
|---|---|---|---|---|---|---|---|---|
| (Deusenberry et al., 2012) | | | ↑ OR 3.01 | | | | | |
| (Ragia et al., 2012) | | | | ↑ OR 3.218 (1.116–9.285) | | | | |
| (Pedersen-Bjergaard et al., 2003) | | | | | | ↑ ACEI RR 2.9 (1.0–8.2) | | |
| (Herings et al., 1995) | | | | | | ↑ ACEI OR 2.8 ( 1.4-12.2) | | |
| (Tan et al., 2015) | | | | | | | | ↑ Co-trimoxazole OR 3.89 (2.29–6.60) |
| (Chou et al., 2013) | | | | | | | | ↑ Moxifloxacin OR 2.13(1.44–3.14) ↑ Levofloxacin OR 1.79 (1.33–2.42 ) ↑ Ciprofloxacin OR 1.45 1.07–2.00) |

**OR** odds ratio, **HR** hazard ratio, **RR** relative risk, **SU** sulfonylureas, **BB** beta blockers, **CCB** calcium channel blockers, **ACEI** angiotensin-converting enzyme inhibitor,

**CNS** central nervous system, **CYP** cytochrome P45.

### 2.5.6.3 Comorbidities

A total of 24 studies investigated the risk of hypoglycaemia associated with comorbidities. The most frequently reported disease was chronic kidney diseases (CKD). 10 studies reported an increased risk of hypoglycaemia was associated with CKD and the highest odds ratio at OR 6.0 (3.8–9.5) reported by Weir et al. (Weir et al., 2011). 7 studies included in this review highlighted the association between the cardiovascular disease (CVD) and the risk of hypoglycaemia in DM patients, with. Endo et al. demonstrated that the risk of hypoglycaemia is increased by 7-fold in cardiovascular patients with DM (Endo et al., 2000), while Dendy et al. reported that the risk of hypoglycaemia in patients with cardiovascular disease and DM was OR 1.25 (0.76 - 2.10) (Dendy et al., 2014). Cerebrovascular accidents (CVA) were reported by 5 studies in this review, with all of the studies demonstrating that CVA can increase the risk of hypoglycaemia in diabetes patients. 7 citations studied the risk of hypoglycaemia associated with dementia. This association was highlighted by Bruce et al., where the authors examined the relationship between dementia and risk of hypoglycaemia by recruiting study sample through postcode-defined urban Australian community in Australia. The study was an observational over 302 DM patients with and without dementia. The authors found a significant cross-sectional increase by 3-fold HR 3.00 (1.06–8.48) in the risk of hypoglycaemia in DM patients with dementia compared to DM patients without dementia (Bruce et al., 2009). In addition, another prospective cohort study in the US on DM patients aged 70 to 79 years, enrolled in the Health, Aging, and Body Composition reported a similar increased risk of hypoglycaemia with dementia in DM patients (Yaffe et al., 2013). In the UK nested case-control analysis Bruderer et al. reported that dementia was associated with

twofold OR 2.0 (1.37–2.91) increase in the risk of severe hypoglycaemia among patients with T2DM newly treated (patients with at least one prescription of antidiabetic medication and the first prescription record) with antidiabetic medications using the UK-based General Practice Research Database(Bruderer et al., 2014a). In a cross-sectional analysis, Kim et al. found that dementia was strong risk factors for hypoglycaemia OR 1.93 (1.76–2.12) among older T2DM Korean population using the Health Insurance Review & Assessment services (HIRA) database (Kim et al., 2016).

Lee et al reported the risk of hypoglycaemia associated with dementia in DM patients, HR 1.57 (1.33–1.84). This study was a prospective cohort analysis recruited 1,206 DM patients from four US communities (Lee et al., 2017). Feil et al. also reported similar results of the association between dementia and the risk of hypoglycaemia in DM patients OR 1.58 (1.53–1.62). This study was a cross-sectional analysis using 497,900 patients' data from the Veterans Health Administration in the US (Feil et al., 2011). The lowest risk of hypoglycaemia associated with dementia was OR 1.32(1.02-1.72) reported by Borzi et al. among T2DM Italian patients (Borzi et al., 2016).

depression was also reported to increase the risk of hypoglycaemia, 5 studies demonstrated that depression can increase the risk of hypoglycaemia and one study reported that depression is a protective factor for hypoglycaemia with OR 0.14 (0.02-0.51) (Wohland et al., 2017).

Similar results were also reported among other comorbidities in increasing the risk of hypoglycaemia, including diabetes microvascular complications and cirrhosis. For further details on comorbidities as risk factors of hypoglycaemia see **Table 14**.

**Table 14 Studies Reported Comorbidities Risk Factors of Hypoglycaemia in DM Patients**

| Author | CKD | Depression | Dementia | CVD | CVA | Cirrhosis | Microvascular complication |
|---|---|---|---|---|---|---|---|
| (Lee et al., 2017) | | | ↑ HR 1.57; 95% CI 1.33–1.84 | | | | |
| (Kim et al., 2016) | ↑ OR 2.52 | | ↑ OR 1.93 | ↑ OR 1.7 (1.57-1.83) | ↑ OR 1.78 (1.64-1.94) | | |
| **(Davis et al., 2010)** | ↑ OR 2.90 (1.68–5.00) | | | | | | |
| (Wohland et al., 2017) | | ↓ OR 0.14 (0.02- 0.51) | | | | | |
| (Mantovani et al., 2016) | ↑ OR 2.42 (1.11– 8.09) | | | | | ↑ OR 6.76 (1.24–36.8) | |
| (Tschope et al., 2016) | | | | ↑ OR 1.77 (1.28-2.45) | ↑ OR 1.72 (1.08-2.72) | | |
| (Quilliam et al., 2011) | ↑ OR 2.22 (6.49 –10.81) | | | ↑ OR 2.33 (8.86–13.64) | ↑ 2.78 (6.37–14.52) | | |
| (Borzi et al., 2016) | ↑ OR 1.32 (1.02-1.72) | | ↑ OR 1.32(1.02-1.72) | | | | |
| (Dendy et al., 2014) | ↑ OR 1.64 (0.96 - 2.80) | | | ↑ OR 1.25 (0.76 - 2.10) | | ↑ OR 1.51 (0.73-3.12) | |
| (Endo et al., 2000) | | | | ↑ OR 7.0 (1.0-47) | | | |
| (Durán-Nah et al., 2008) | ↑ OR 3.0 (1.2 - 7.7) | | | | | | |
| (Kostev et al., 2015) | | | | | ↑ OR 1.90 (1.03-3.50) | | |
| (Lin et al., 2010) | | | | ↑ OR 3.38 (1.91-6.01) | | | |
| (Bramlage et al., 2012) | | ↑ OR 4.24 (2.35-7.65) | | ↑ OR 1.61 (1.02-2.53) | ↑ OR 1.94 (1.04-3.59) | | |
| (Bruderer et al., 2014a) | ↑ OR 1.34(1.04–1.71) | | ↑ OR 2.00 (1.37–2.91) | | | | |
| (Tschope et al., 2012) | | ↑ (OR= 1.81; 1.14-2.88) | | | | | ↑ diabetic retinopathy OR |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 3.27 (1.07-30.02) |
| (ter Braak et al., 2000) | | | | | | | ↑ nephropathy OR 3.9 (1.5–10.4) |
| (Deusenberry et al., 2012) | ↑ OR 3.64 | | | | | | |
| (Lin et al., 2010) | | | | | | | ↑ neuropathy RR (1.89) |
| (Honkasalo et al., 2011) | | ↑ (OR 1.6 (1.0–2.6) | | | | | |
| (Weir et al., 2011) | ↑ OR 6.0 (3.8–9.5) | | | | | | |
| (Katon et al., 2013) | | ↑ HR 1.42 (1.03-1.96) | | | | | |
| (Bruce et al., 2009) | | | ↑ HR 3.00 (1.06–8.48) | | | | |
| (Feil et al., 2011) | | | ↑ OR=1.58 (1.53–1.62) | | | | |
| (Yaffe et al., 2013) | | | ↑ HR=3.00 (1.06–8.48) | | | | |

**OR** odds ratio, **HR** hazard ratio, **RR** relative risk, **CVA** cerebrovascular accident, **CVD** cardio vascular disease, **CKD** chronic kidney disease

#### 2.5.6.4 Other risk factors

Citations included in this review also studied other risk factors in increasing the risk of hypoglycaemia. Some of these risk factors have been reported with high odds, for example, the association between previous hypoglycaemia and the risk of hypoglycaemia was highlighted by 10 studies and the highest odd ratio was OR 38.7 (95% CI, 20.4 – 73.3) reported by Dendy et al. (Dendy et al., 2014). Missing meals, impaired awareness and fasting were all demonstrated to increase the risk of hypoglycaemia. For further details on the risk factors of hypoglycaemia see **Table 15**.

**Table 15 Studies Reported Other Risk Factors of Hypoglycaemia in DM Patients**

| Author | Previous hypoglycaemia | Impaired awareness | Missing meals | Smoking | Care of patients | Low socioeconomic | Post dinner dietary intake | Biomarkers |
|---|---|---|---|---|---|---|---|---|
| **(Lee et al., 2017)** | | | | | | | | ↑ HR microalbuminuria (HR 1.95; 95% CI 1.23–3.07) |
| **(Davis et al., 2010)** | ↑ HR 6.59 (2.62–16.60) | | | | | | | |
| **(Wohland et al., 2017)** | | ↑ OR 2.06 (1.09- 3.93) | | | ↑ No monitoring OR 4.88 (1.41 - 22.63). | | | |
| **(Quilliam et al., 2011)** | ↑ OR 9.48 (4.95–18.15) | | | | | | | |
| **(Loke et al., 2010)** | | | ↑ RR of 1.60 (1.05-2.43) | | | | | |
| **(Ishtiak-Ahmed et al., 2017)** | ↑ HR 3.19 (2.62–3.88) | | | ↑ HR 1.11(0.89-1.39) | | | | |
| **(Barkai et al., 1998)** | | ↑ OR 5.8 (2.3-13.2) | | | | | | |
| **(Ganz et al., 2014)** | ↑ OR 8.08 (5.99-10.91) | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **(Dendy et al., 2014)** | ↑ OR 38.7 (20.47-73.33) | | | | | | | |
| **(Endo et al., 2000)** | ↑ OR 15 (0.77 - 297) | | ↑ OR 81 (3.6-1 84) | | | | | |
| **(Durán-Nah et al., 2008)** | ↑ OR 2.9 (1.3 - 6.5) | | ↑ OR 19.8 (9.1-43.1) | | | ↑ OR 3.7 (1.4-10.0) | | |
| **(Muhlhauser et al., 1998)** | ↑ HR 2.73 (1.7-4.25) | | | | | | | ↑ C-peptide level HR 4.0, CI 1.2-12.7 |
| **(Jeon et al., 2016)** | ↑ OR 22.0 (6.05 – 80.0) | | | | ↑ No monitoring OR 4.43 (1.30–15.1) | | | |
| **(Kostev et al., 2015)** | ↑ OR 11.27 (6.6 - 18.99) | | | | | | | |
| **(Lin et al., 2010)** | | | ↑ OR 3.50 (1.97 - 6.22) | | | | | |
| **(Faerch et al., 2011)** | | | | | | | | ↑ Serum ACE activity RR 1.32 (1.14 - 1.55) |
| **(Pedersen-Bjergaard et al., 2003)** | | | | | | | | ↑ Serum ACE activity RR 1.4 (1.2-1.6) |
| **(Davis et al., 2011)** | | | | | | | | ↑ Serum ACE activity HR 2.35 (1.13–1.53) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **(Sarkar et al., 2010)** | | | ↑ Fasting OR 1.4 (1.1–1.7) | | | | | |
| **(Seewi et al., 2008)** | | | | | | | | ↑ Insulin binding OR 4.8 (1.5-15.2) |
| **(Berkowitz et al., 2012)** | | | | | | ↑ Risk of low income OR 1.51(1.19-1.91) | | |
| **(Basu et al., 2017)** | | | | | | ↑ OR 1.07 (1.02–1.12) | | |
| **(Seligman et al., 2010)** | | | | | | ↑ OR 2.95 (1.48-5.91) | | |
| **(Desjardins et al., 2014)** | | | | | | | ↑ OR 1.16 (1.04–1.29) | |
| **(Sato et al., 2010)** | | | | | | | ↑ OR: 1.65 | ABCC gene Ser Allele ↑ OR 1.65 |
| **(Ren et al., 2016)** | | | | | | | | ↑ Uric acid OR 3.03 (2.13–4.32) |
| **(Holstein et al., 2009)** | | | | | | | | No risk KCNJ11(E23K) OR 0.68 (0.34 – 1.35) |
| **(Deusenberry et al., 2012)** | | ↑ OR 2.06 (1.09- 3.93) | | | ↑ Nursing home OR 4.88 (1.41 - 22.63). | | | |
| **(Li et al., 2014)** | | | | ↑ RR 1.48 | | ↑ RR 2.09 | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **(Honkasalo et al., 2011)** | | | ↑ Fasting RR of 1.60 (1.05-2.43) | | | | | |
| **(Feil et al., 2011)** | | ↑ OR 5.8 (2.3-13.2) | | | | | | |
| **(Sreenan et al., 2014)** | ↑ T1D OR 2.21 [1.51- 3.22] ↑ T2D OR = 16.65 (8.66-32.02) | | | | | | | |
| **(Seligman et al., 2010)** | | | ↑ OR 19.8 (9.1-43.1) | | | ↑ OR= 2.95 (1.48-5.91) | | |
| **(Weinstock et al., 2013)** | | | | | | ↑ Low socioeconomic OR 2.23 (1.53 - 3.26) ↑ No insurance OR=2.08 (1.58-2.74) ↑ Learning problems OR 3.72 (2.28-6.05) | | |
| **(Alonso-Moran et al., 2015)** | | | ↑ OR 3.50 (1.97 - 6.22) | | | | | |
| **(Hirai et al., 2007)** | | | | ↑ OR 2.40 (CI 1.30–4.40) | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **(Chu et al., 2017)** | ↑ HR 1.19 (1.18-1.32) | | | | | | | |
| **(Jabbar et al., 2017)** | ↑ OR 7.80; 95% CI 5.31–11.4 | | | | | | | |

**T1DM** type 1 diabetes mellitus, **T2DM** type 2 diabetes mellitus, **OR** odds ratio, **IR** incidence rate, **HR** hazard ratio, **RR** relative risk, **ACE** angiotensin-converting enzyme

## 2.6 Discussion

This systematic review demonstrated the high prevalence and incidence of hypoglycaemia and that hypoglycaemia is a very common complication that many DM patients, both T1DM and T2DM, may experience in real life across different countries and different treatment regimens. RCT studies were excluded as they were unlikely to be able to represent the general population since hypoglycaemia is an acute event and RCT studies usually select patients based on a certain condition.

### 2.6.1 Prevalence and incidence of hypoglycaemia

#### 2.5.7.1 Summary of findings

The pooled estimate of the overall prevalence of hypoglycaemia among the DM population was 11.0% (95%CI, 7.0–17.0). The pooled estimate of the overall incidence rate of hypoglycaemia was 64.1 episodes per 1,000 person-years (95% CI, 29.4–139.7). In addition, this review highlighted that the prevalence and incidence of hypoglycaemia were higher among T1DM patients compared to T2DM patients. The prevalence was 14.0% (95% CI 7.0–24.0) and 11.0% (95% CI, 6.0–21.0), respectively, and the incidence was 156.5 episodes per 1,000 person-years (95% CI, 61.6–397.6) and 40.9 episodes per 1,000 person-years (95% CI, 9.5–174.9), respectively. Hypoglycaemia was more common in insulin-treated DM patients compared to patients treated with sulfonylureas.

#### 2.5.7.2 Comparison to other literature

Previously published systematic reviews investigating the prevalence and incidence among T1DM and T2DM patients in observational studies are limited. Only two systematic reviews have examined the prevalence and incidence of mild/moderate

and moderate hypoglycaemia among only T2DM patients. However, there was no overall estimate of the prevalence and incidence of hypoglycaemia reported and T1DM patients were excluded from the reviews (Bloomfield et al., 2012b, Edridge et al., 2015). It is important to mention that the risk of hypoglycaemia is different according to the DM type (UK Hypoglycaemia Study Group, 2007); this was highlighted in my results. T1DM patients were at higher risk of hypoglycaemia compared to T2DM patients.

In terms of treatment regimens, DM patients who were on insulin treatment had higher prevalence rates of hypoglycaemia compared to DM patients who were on sulfonylurea-based treatment. A previous meta-analysis of clinical trials investigated the prevalence of hypoglycaemia in sulfonylurea-treated T2DM patients; the pooled estimate of the prevalence of hypoglycaemia was 10.1 % (95% CI, 7.3–13.8), which was likely to be higher compared to my results of 8.0 % (95% CI, 3.0–18.0) (Schopman et al., 2014). In addition, in three clinical trials that were included in the above review, it was reported that the proportion of hypoglycaemia in insulin-treated T2DM patients ranged from 8.0 % to 56.0 %. My estimate for the prevalence of hypoglycaemia in insulin-treated DM patients was in the same range as these studies (Schopman et al., 2014). Insulin- and sulfonylurea-based antidiabetic therapies are commonly associated with hypoglycaemic events, compared to other antidiabetic therapies (Cryer, 2004, Umpierrez and Korytkowski, 2016b). The higher risk of hypoglycaemia associated with the use of insulin or sulfonylurea therapies among DM patients is due to their mechanisms of action, which is either by administration of exogenous insulin formulations or by triggering pancreatic cell secretion of insulin (Proks et al., 2002b), while other antidiabetic therapies increase sensitivity to insulin and limit the absorption of glucose, leading to a lower risk of hypoglycaemic events (Luna and Feinglos, 2001).

Regarding the data sources, there was considerable variation in the prevalence of hypoglycaemia. The prevalence rates of hypoglycaemia in studies in which hypoglycaemia was self-reported were higher compared to studies in which hypoglycaemia data were obtained from health record databases. These high numbers could be due to the tendency to report even mild hypoglycaemia. Self-reported hypoglycaemia is dependent on the patient's ability to perceive hypoglycaemia when it happens, which may be restricted by impaired awareness of hypoglycaemia, and to distinguish it accurately from irrelevant symptoms (Naser et al., 2019). On the other hand, hypoglycaemia events reported by health record databases are more likely to be objective and confirmed by healthcare professionals. Health record databases report more severe cases of hypoglycaemia that require either emergency visits or hospital admission.

#### 2.5.7.3 Quality of included studies

There was a large variation in the quality of the included studies. Studies that reported hypoglycaemia as self-reported were more likely to be poor in quality and biased towards milder forms of hypoglycaemia and to overestimate or underestimate its prevalence, since these mild hypoglycaemic symptoms could be experienced by patients who were unaware of them and therefore did not report them. However, studies that reported hypoglycaemia from health record databases were better in quality compared to self-reported studies. They were more likely to be accurate because they mainly used the ICD system or hospital codes for hypoglycaemia diagnosis entered by either physicians or healthcare professionals; however, it is important to mention that the ICD system or hospital codes are subject to misreporting or under-reporting bias (Leong et al., 2013).

## 2.6.2 Risk factors of hypoglycaemia

Our study also reviewed the risk factors of hypoglycaemia among DM patients although the literature available in this area is sparse. I did not identify any other systematic reviews that evaluated risk factors for severe hypoglycaemia in both types of DM patients. Comparing my results of the risk factors of hypoglycaemia with previous reviews showed that my results are more comprehensive, although the findings are generally consistent with what has been reported previously.

### 2.5.8.1 Demographic characteristics

A total of 26 studies identified demographic risk factors and their association with hypoglycaemia. The demographic risk factors reported in this review are age, gender, HbA1c, diabetes duration, race and body mass index (BMI).

The majority of the studies included in this review reported that older age, female gender, low levels of HbA1c and longer diabetes duration are associated with a significant increase in the risk of hypoglycaemia. However, the remaining characteristics' results were controversial.

### 2.5.8.2 Drug-induced hypoglycaemia

A total of 50 studies investigated different medications as a risk factor of hypoglycaemia, including antidiabetic medications and other medications.

Insulin- and sulfonylurea-based therapies were the most common antidiabetic medications associated with a risk of hypoglycaemia and almost all of the studies demonstrated that both medications were independent risk factors for hypoglycaemia.

Furthermore, intensive antidiabetic therapy was found to be a risk factor for hypoglycaemia in DM patients in this review. This result is in line with the recent guidelines that recommended intensifying diabetes therapy to achieve optimal

glycaemic control and to prevent macrovascular and microvascular complications, which may result in an increased risk of hypoglycaemia (Nathan et al., 1993). Moreover, in previous literature, it was reported that intensive antidiabetic therapy increases the risk of hypoglycaemia fivefold compared to patients on antidiabetic monotherapy (Naser et al., 2018).

Besides antidiabetic medications, other medications were examined in this review. Cardiac medications were the most common medications reported by the included studies to be associated with high risk of hypoglycaemia, including BB, ACEI, CCB and anticoagulants. Antidepressants, antipsychotics and co-trimoxazole antibiotic were found to be associated with a higher risk of hypoglycaemia among DM patients. Finally, it is important to highlight that other risk factors, such as polypharmacy, can also increase the risk of hypoglycaemia.

#### 2.5.8.3 Comorbidities

A total of 24 included studies examined multiple comorbidities and disease complications. CKD was the most common comorbidity reported in this review with the highest risk associated with hypoglycaemia among DM patients (Weir et al., 2011).

Several potential risk factors have not been adequately evaluated, including cognitive impairment/dementia. A total of seven studies investigated the association between dementia and hypoglycaemia in DM patients, of which four cross-sectional studies were conducted to examine the relationship between the risk of hypoglycaemia and dementia among the older population with DM (Kim et al., 2016, Feil et al., 2011, Bruce et al., 2009, Borzì et al., 2016). However, there are multiple limitations due to the descriptive nature of the study design; the smaller sample size and shorter study duration limited the study's ability to investigate the association between incident

hypoglycaemia and dementia. The authors were also unable to adjust for confounding variables, which may have biased their results.

Out of the seven studies, one prospective observational study was carried out in relation to older patients with DM and dementia participating in the prospective population-based Health, Aging, and Body Composition Study, to examine the bidirectional association between hypoglycaemia and dementia in the USA (Yaffe et al., 2013). Another observational study was conducted in the USA to examine the risk factors of hypoglycaemia among the older population with diabetes (Lee et al., 2017).

Only one observational study was conducted in the UK using the General Practice Research Database to identify the risk factors and comorbidities (including dementia) for incident severe hypoglycaemia in T2DM patients newly treated with antidiabetic medications (Bruderer et al., 2014b). However, several limitations were mentioned by the study's authors: (1) the study population included only to T2DM patients newly treated with antidiabetic medications with a history of three years recorded in the database before the follow-up period; (2) the definition of hypoglycaemia was restricted only to severe hypoglycaemic events that were reported to the GP by the hospital or with a specific Read code for third-party assistance or hypoglycaemic coma, excluding any other form of hypoglycaemic events.

These findings suggest that the likelihood of DM-related complications, such as hypoglycaemia, may be increased in the dementia population. A possible explanation is that patients with DM who have dementia experience progressive physical and mental deterioration, leading to their dependence on others. Therefore, they are less able to recognise hypoglycaemia, avoid hypoglycaemia by initiating appropriate responses and communicate their needs for assistance in managing the symptoms of hypoglycaemia. Furthermore, these patients are likely to take drug overdoses and

hypoglycaemic events may occur repeatedly. Despite this, there is evidence that a substantial proportion of older adults are potentially overtreated (Lipska et al., 2015, Sinclair et al., 2011).

#### 2.5.8.4 Other risk factors

A total of 38 studies reported different variables as risk factors of hypoglycaemia in this review. The most frequent risk factor with the highest risk reported by 10 included studies was previous hypoglycaemia. Patients who had experienced previous hypoglycaemic events were at a 38 times increased risk of experiencing future hypoglycaemia compared to patients who had never experienced hypoglycaemia (Dendy et al., 2014). However, only one study reported that nursing home patients with low patient care were at a 4.88 times higher risk of developing hypoglycaemia (Deusenberry et al., 2012).

### 2.6.3 Strengths

This systemic review has several strengths. Firstly, to the best of my knowledge, this is the first systematic review and meta-analysis to review the incidence, prevalence and risk factors of hypoglycaemia in the DM population. Secondly, only observational studies that reported the prevalence, incidence rates and/or risk factors of hypoglycaemia in the diabetes population were included and, therefore, I assume that my results will reflect the real-life situation in the general population. RCTs are considered the gold standard for demonstrating clinical efficacy (Elliott et al., 2016). However, large RCTs generally include patients who are restricted to their suggested regimens, subjected to close monitoring and support, rather than patients in routine clinical practice. In addition, RCTs do not include patients with a history of severe hypoglycaemia, the elderly or those with a poor health status (Elliott et al., 2016). Therefore, the rates and nature of hypoglycaemic events reported from clinical trials

may not be generalised for real-world practice. Thirdly, this systematic review and meta-analysis reviewed a large number of studies covering the topics: incidence, prevalence and risk factors of hypoglycaemia. The data extracted in this review covered a wide range of information previously published in the literature. Finally, two independent reviewers assessed the quality of the evidence and extracted the data in this review, and a third reviewer was involved for any disagreement between the two authors.

### 2.6.4 Limitations

This systematic review also has limitations. Firstly, the heterogeneity between the studies was high; therefore, my results should be interpreted with caution. The high heterogeneity could not be explained by any of the study level covariates considered in the subgroup analysis, and it is likely to be due to study characteristics that were not measured or reported by the original articles. Secondly, it was not possible to stratify my results based on the severity of hypoglycaemia because the definition of hypoglycaemia varied across the studies. Thirdly, due to the differences in study designs between the studies included in this review (questionnaire/interview/medical records/database) and because a biochemical definition of hypoglycaemia was rarely used except in hospital-based studies, it should be recognised that this may cause difficulties when combining results across studies, resulting in under- or over-reporting of hypoglycaemia.

## 2.7 Research rationale

This chapter has systematically reviewed the relevant literature on the rate of hypoglycaemia and its risk factors and explained the rationale for this research. The findings from the systematic review have shown that hypoglycaemic events are

prevalent among patients with DM (including T1DM and T2DM) and increase significantly with advancing age. Additionally, studies on antidiabetic medication use revealed that elderly patients were frequently prescribed antidiabetics and are intensively controlled compared to other age groups and that hypoglycaemia was one of the most common side effect of intensive diabetes therapy in the elderly population, and in the dementia population in particular.

Despite the advances in the knowledge and understanding of various aspects of the relationship between dementia and DM in elderly patients, and of the challenges and higher burden associated with managing them, the effect of dementia on glycaemic level control remains unclear and has not been studied in a population-wide perspective in the UK setting. Therefore, is a lack of in-depth data around hypoglycaemia within this population, which deserves to be highlighted and explored.

An exploration of the prevalence and the risk of hypoglycaemic events associated with dementia through pharmacoepidemiological research can provide insights into the burden of hypoglycaemia and the importance of cognitive function and preventing hypoglycaemia in the clinical management of DM among the elderly. Furthermore, healthcare professionals should be careful in managing DM and offer appropriate education or treatment modification advice for the patients and relatives/carers to prevent future events, which may help to support and improve the patient's quality of life.

This PhD project has filled this gap and addressed the association between hypoglycaemia and dementia in patients with DM from a clinical perspective.

## 2.8 Conclusion

In conclusion, hypoglycaemia is very common among DM patients. The rate of hypoglycaemia among T1DM patients and among patients treated with insulin is higher compared to those treated with other antidiabetic medications and T2DM patients. However, the quality of information available in the literature varied greatly. Over the last 10 years of the study period, the quality of evidence has improved compared to previously published studies. However, this cannot be generalised across all citations. Studies using data from health records databases were much better in recording the incidence and prevalence of hypoglycaemia.

The findings from this review are limited in providing strong evidence for the association between dementia and the risk of hypoglycaemia among patients with DM and dementia. These preliminary findings demonstrate a gap in the knowledge and a need for further exploration in this area to improve medication management for those with complex needs due to diabetes and dementia.

The next chapter describes the research aim and objectives and studies conducted in this thesis to fill these gaps.

# 3 CHAPTER THREE: Thesis Aim and Objectives

## Aim

The overall aim of this PhD thesis was to study the rate of hypoglycaemia and its association with dementia in patients diagnosed with diabetes mellitus (DM) and dementia from clinical perspective.

## Objectives

The following objectives of this PhD thesis were identified to achieve the aim:

To estimate the annual prevalence and incidence of dementia in DM patients in primary care settings.

To describe the prescribing of antidiabetic medication annually among patients diagnosed with DM and dementia.

To estimate the annual rate of hypoglycaemia in patients with DM and dementia in primary care settings.

To investigate the association between dementia and the risk of hypoglycaemia among patients with DM and dementia.

To examine and compare the glycaemic control and the rate of hypoglycaemia among DM patients before and after dementia diagnosis.

The main themes of this PhD project are highlighted below: refer to **Figure 17**.

1. The descriptive population-based study estimated the prevalence and incidence of dementia in patients diagnosed with DM during the recent years (Chapter five).

2. The drug utilisation study examined the prescribing rate of antidiabetic medication and the rate of hypoglycaemia experienced by patients diagnosed with DM and dementia, basing the exploration on the findings of the systematic review (Chapter six).

3. The retrospective cohort study explored the primary research question of this PhD project by investigating the association of dementia and the risk of hypoglycaemia in diabetes and dementia population (Chapter seven).

4. The pre-post, observational study assessed the glycaemic control and the rate of hypoglycaemia before and after dementia diagnosis among DM patients (Chapter eight).

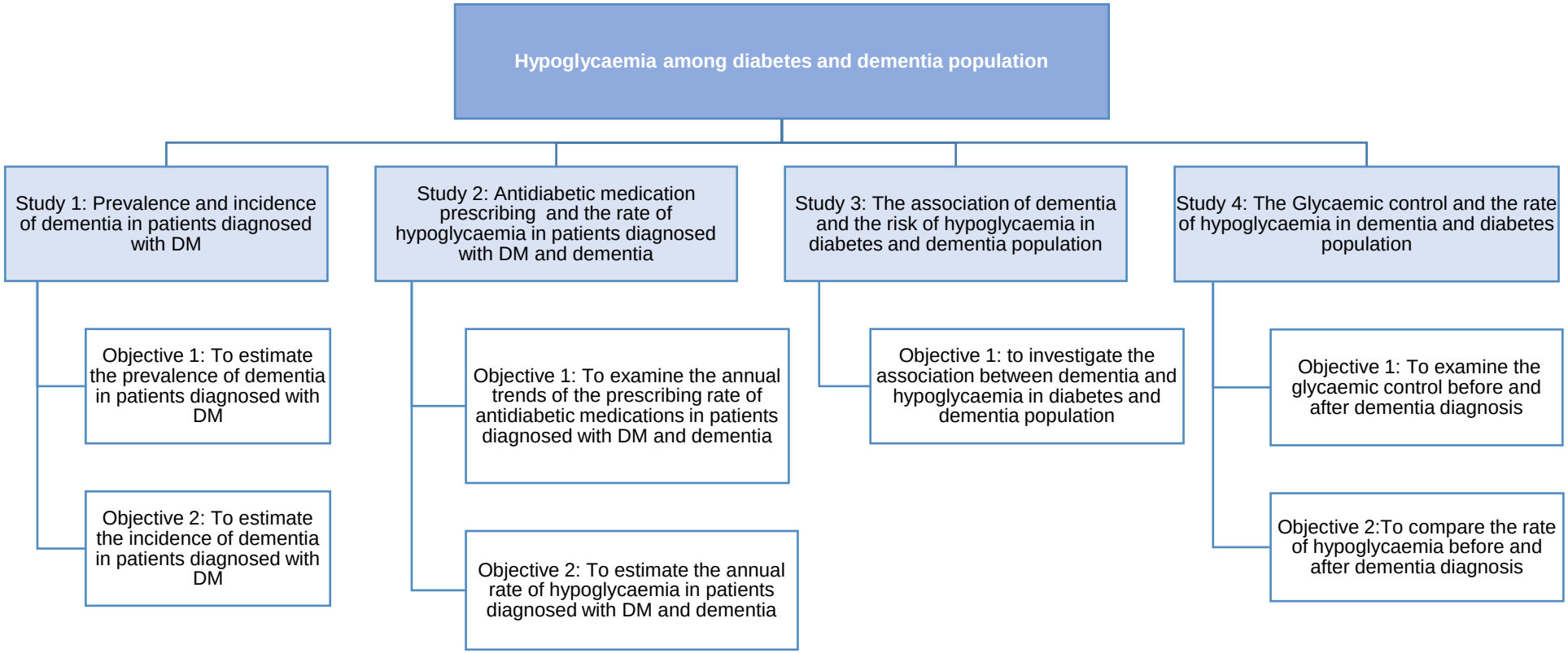



**Figure 17 PhD Thesis Theme**

# 4 CHAPTER FOUR: Introduction to UK Primary Care Database

This chapter provides an overview of real-world databases and specifically the UK primary care database used in this research. In the next section, the IMRD-UK database is described and the rationale behind its selection explained, then the data structure of IMRD-UK is outlined. The chapter then goes on to define the missing data and how to handle this issue. The reason for following this structure was to provide the reader with an overview of some important aspects of the database used and the nature of the data collected before describing the research methodology.

## 4.1 Overview of UK databases

Randomised clinical trials (RCTs) are considered the “gold standard” for providing treatment effectiveness, but they are insufficient to guide clinical practice due to their limitations such as using small populations under tightly controlled conditions (Trojano et al., 2009). As a result, evidence from observational studies and real-world data have become important for understanding disease epidemiology, treatment efficacy and safety, as well as providing insight into patterns of care (Takahashi et al., 2012).

The Association of the British Pharmaceutical Industry has defined real-world data as data collected without the controlled constraints of conventional randomised clinical trials to evaluate what is happening in routine clinical practice (The Association of the British Pharmaceutical Industry, 2011).

Over the past decades, electronic medical records (EMR) databases have been introduced to medical practice (Takahashi et al., 2012). The routine implementation of electronic medical records has provided unique opportunities for healthcare professionals, researchers and decision makers to gather and use real-world data for planning and monitoring different healthcare services and measuring the quality of services and care provided (McDonald et al., 2016). Currently, available EMR

databases normally contain patients' administrative and clinical data. The data collected from primary care practices have many unique advantages. First and most important, they are population representative, that is, longitudinal data of normal clinical care have been developed to capture patients' related data. Second, a large population of patients can be followed over long time periods (retrospectively) at low cost in a relatively short time span. Third, the accuracy of diagnostic coding for chronic conditions is high and therefore, the validity of the diagnosis data is better compared to other types of databases. Fourth, these data sources can answer a variety of research questions, including the study of rare outcomes (Schneeweiss and Avorn, 2005). However, there are also unique disadvantages, especially the presence of missing data from some general practitioners (GPs) and the wide variability between GPs in the coding and recording of the data needed (Khan et al., 2010, Kang, 2013).

In the UK, there are several EMR databases available in GP surgeries, such as the CPRD, IMRD-UK, QResearch and MEMO. These are considered the largest databases in the UK and are widely used in a substantial number of scientific studies and publications (Vezyridis and Timmons, 2016).

However, data from IMRD are available for use at the School of Pharmacy, University College London, and hence this dataset will be described in more detail in the next section.

## 4.2 IMRD-UK database

IMRD-UK, formerly known as The Health Improvement Network (THIN) is one of the well-known databases in the UK. The IMRD-UK database was used to carry out the studies in this thesis. It contains longitudinal, electronic patient data recorded by GPs during routine clinical practice and was extracted from the VISION practice

management software, which provides timely medical information for research purposes (IQVIA, 2018).

The IMRD-UK is broadly representative of the UK population. It contains data from over 744 general practices across the UK and currently has anonymised clinical data for more than 17 million patients, covering around 5% of the UK population (**Figures 18 & 19**) (launched in 1996 up to 26 September 2017) (IQVIA, 2018). Approximately 3 million patients are actively registered with the practices and historical data are available for the remaining patients who have either left the practice or died (IQVIA, 2018). **Table 16** provides the strengths and limitations of the IMRD-UK database.

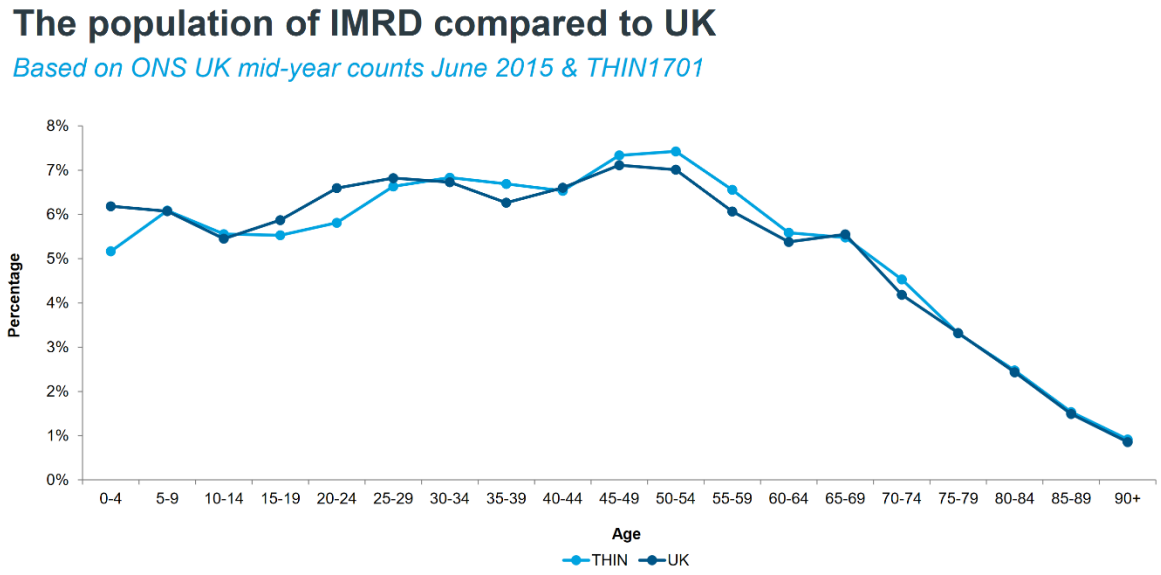



**Figure 18 Comparison between IMRD-UK Population and UK General Population (IQVIA, 2018)**

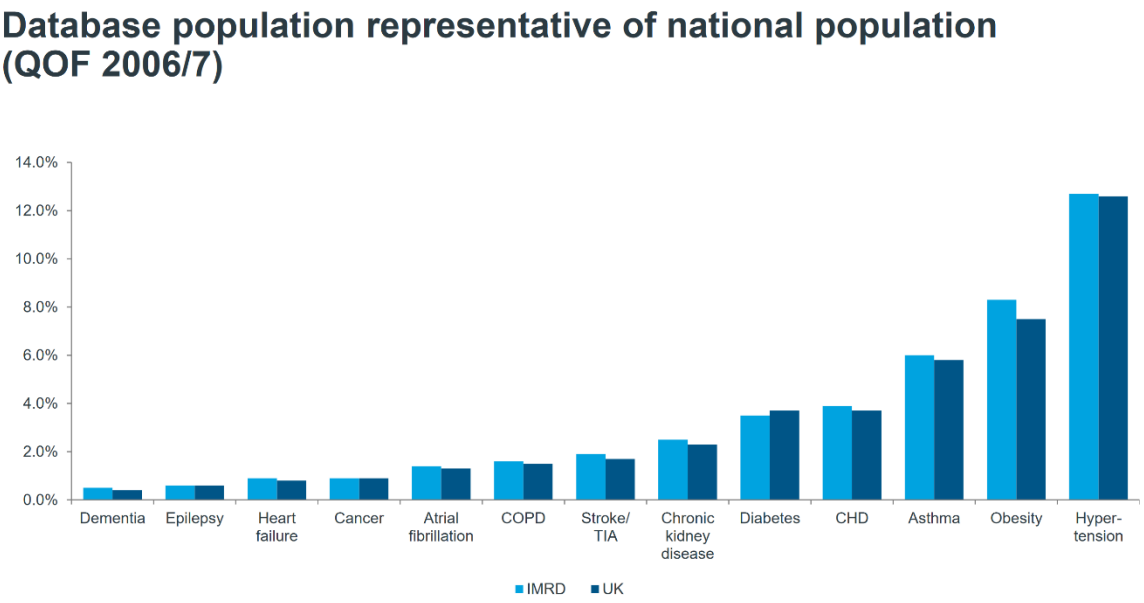



**Figure 19 Comparison between IMRD-UK Population and UK General Population by Disease (IQVIA, 2018)**

IMRD-UK has been widely used for over 1,000 published peer-reviewed articles and epidemiological research, particularly for the population diagnosed with DM and dementia (THIN®, 2020, Brauer et al., 2019, Mongkhon et al., 2020, Alwafi et al., 2020a, Alwafi et al., 2020b).

Access to the latest version of IMRD-UK data can be obtained from IQVIA via academic collaboration or by paying a fee (IQVIA, 2018). Each study using IMRD data is required to submit an application to the Scientific Review Committee (SRC) for ethical/scientific review and approval. All studies included in this PhD thesis have obtained SRC ethical approval. Refer to **Appendix 10.**

**Table 16 Strengths and Limitations of the IMRD Database in the UK**

| Database | Diagnoses/ clinical code | System | Strengths | Limitations |
|---|---|---|---|---|
| **THIN** | Read code | Collaboration between two companies: In Practice Systems (INPS) and Cegedim Healthcare Software | - Data are broadly representative of the UK population<br>-The database contains useful 'Acceptable Mortality Recording' provides a natural filter to avoid the danger of "immortal period" bias<br>-Reliable<br>-Additional service are offered such as questionnaires to GPs to obtain further information<br>-Data linked to HES<br>-Data have been widely used by researchers and over 1,000 articles published in peer-review journals | - Data are primarily collected for clinical management not for research purpose<br>- NO records on hospital tests, length of stay and prescriptions.<br>-There may be misclassification or coding errors<br>- Incomplete records of some patient's characteristics e.g. (weight, height, smoking).<br>- OTC prescriptions records are limited<br>- Ethnicity is not recorded<br>- No direct link between prescriptions and diagnoses<br>- Only issued prescriptions are recorded<br>- Medication adherence is not recorded<br>- Expensive |

**OTC** over-the-counter; **HES** Hospital Episode Statistics (Lewis et al., 2007, IQVIA, 2018, Blak et al., 2011, THIN®, 2020)

## 4.3 Data structure of IMRD-UK

The IMRD-UK database contains data on patients' medical history, prescription history, referrals and hospitalisations (if recorded by the GP), free text comments of GPs, lab tests and results, screening for disease, and socioeconomic status linked to the patients' postcode. The data collection frequency varies by practice (weekly, fortnightly and monthly), and an updated dataset is created at least three times per year. These datasets are provided in SAS data format. The data in each practice are split into four main files: patient, medical, therapy and additional health data (AHD) (IQVIA, 2018).

Patient file: The information recorded on the patient file contains patient characteristics and registration details. These include a patient ID, patient flag, year of birth, gender, patient's registration date and registration status, date of transfer or death, marital status and prescription exemptions.

Medical file: This includes a record of symptoms, diagnoses and interventions that are recorded by the GP, as well as information transcribed from hospital discharge summaries or letters sent by specialists. Medical diagnoses are coded using Read codes (Read codes, the standard clinical coding system used by the UK's National Health Service). The medical file contains the variable patient ID, event date (diagnosis date), end of event date, medcode (Read code), source of record and priority (for life-threatening conditions).

Therapy file: This contains details of prescriptions issued to the patients. Each medication is generated as a new record, including repeat prescriptions, and contains the formulation, strength, dose and quantity of the medication prescribed. Medication information is coded through the BNF. Therapy file variables consist of the patient ID,

prescription date, the medication code, the dose code, the quantity prescribed, the duration of the prescription, whether it is a private or NHS prescription, if it is for acute or repeat prescription and other details.

Additional health data: This includes a range of data types, including information on BMI, immunisation, smoking status, alcohol consumption and test results, as well as free text. The variables include the patient ID, the event date, medcode (Read code) and anonymised free text comments.

As IMRD-UK data is organised by practice ID and patient ID, this means the patient ID is only unique to the practice. Thus, combining all the practices together into one dataset results in one patient ID for different patients. Therefore, I created a unique patient ID by combining the practice ID and patient ID to ensure that each patient had a unique patient ID that was used to link the patient file with other files in the IMRD-UK database. The database also provided us with medical and drug dictionaries in an Excel sheet format to identify and obtain the Read codes. The medical dictionary contains all information about diseases' diagnoses and their Read code, while the drug dictionary contains all information about medications, which are determined using relevant drug codes from the BNF. It also includes the medication's generic name, formulation, strength and unit.

## 4.4 Missing data

This section outlines the problems and types of missing data, along with the techniques for handling missing data. The mechanisms by which missing data occur are illustrated and the methods for handling the missing data are discussed.

### 4.4.1 Definition of missing data

Missing data is defined as data values not being available for the variable in an observation, which would be meaningful if they were available (Kang, 2013). Having missing data is a common problem in almost all research using primary care databases and it can raise significant challenges for statistical analysis and interpretation for statistical power reduction, biased estimation and sample representativeness reduction (Graham, 2009, Kang, 2013).

### 4.4.2 Missing data mechanisms

To handle missing data, it is important to know the reasons why missing data may arise (the missingness mechanism). This was first described by Rubin and it has implications for how I perform the analysis (RUBIN, 1976). Missing data mechanisms generally fall into one of three main classifications.

**Missing completely at random (MCAR)** is defined as when the chance of missing data is independent of both the observed and unobserved data. In other words, the missing data are not systematically related to participants with missing data or those with complete data. Relatively common situations in which data are MCAR include if data are missing by design (e.g. random selection), or due to equipment failure or because the samples are lost. The statistical advantage of data that are MCAR is that restriction to complete records remains valid (Mack et al., 2018).

**Missing at random (MAR)** is when the chance of missing data depends on the set of observed data, but is not related to the missing data themselves. This means that other variables (but not the same variable itself) in the dataset can be used to predict missingness on a given variable that is MAR. In this case, the simple summary statistics using the observed values will be biased, but can be corrected by proper

accounting for the known factors using multiple imputation (Mack et al., 2018). **Missing not at random (MNAR)** is when the chance of missing data depends on the set of unobserved data, and the missingness is related to other factors or events not measured or controlled in the study design. When data are MNAR, this is problematic and cannot be ignored. The only way to overcome this problem and obtain an unbiased estimate is to model the missing data, which is a more complex way of estimating the missing values (Mack et al., 2018).

### 4.4.3 Methods for handling missing data

In this section, I will list and briefly discuss the most common methods for dealing with missing data.

There are several methods that can be applied to handle the missing data discussed in the literature. The most common methods can be grouped into two broad groups, which are data deletion and imputation analysis (Groenwold et al., 2012, de Goeij et al., 2013, Kang, 2013).

**a) Data deletion:** Listwise deletion and pairwise deletion.

**b) Imputation analysis:**

- Single imputation (mean imputation (substitution), last observation carried forward (LOCF))

- Adding an indicator to capture missing data (the missing-indicator method, multiple imputation). **Table 17** briefly describes the most common methods of handling missing data.

**Table 17 Methods for Handling Missing Data**

| Handling missing data | | | | | | |
|---|---|---|---|---|---|---|
| | Deletion | | Imputation | | | |
| | | | Single imputation | | The missing indicator | Multiple imputation |
| **Method's name** | Listwise (known as Complete Case Analysis) | Pairwise (known as Available Case Analysis) | Mean Imputation (known as Mean Substitution) | LOCF | Adding an indicator | Multiple imputation |
| **Strategy** | - All patients with missing data on one or more variables are deleted and excluded from analysis.<br>- Analysis is performed on the available | - All patients with missing data on one or more variables are ignored and the present values are included in the analysis<br>- Analysis performed on the observed variables in the dataset. | - All missing data on one or more variables are replaced by the mean value for the same variable.<br>- Analysis performed on full dataset. | - All missing data on one or more variables (with repeated measures) are replaced with the last observed value for each variable.<br>- Analysis performed on full dataset. | - All missing data on one or more variables are grouped in a new binary variable or category for each variable.<br>- Analysis performed on full dataset. | - All missing data on one or more variables are replaced with a multiple values estimated by the distribution of the observed data which reflect the uncertainty around the true value.<br>- Multiple datasets are created.<br>- Analysis performed on each imputed dataset and estimates are combined to produce single overall result. |
| **Missing data type** | MCAR | MCAR or MAR | MCAR | MCAR | MCAR | MCAR or MAR |
| **Advantages** | - Simple and easy to apply. | - Used all observed data<br>- Increase power in the analysis. | - Simple and easy to apply.<br>- Used the full dataset. | - easily understood.<br>- Appropriate for longitudinal or time-series data.<br>- Used the full dataset. | - Simple and easy to apply.<br>- Appropriate if proportion of patients with missing data is relatively high.<br>- Used the full dataset. | - Restore the natural variability of the missing data.<br>- Incorporate the uncertainty around the true values of the missing variables.<br>- Produce valid statistical inference.<br>- Good approach to handle missing data in large dataset. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Disadvantages** | - smaller sample size.<br>- Lower power of the analysis in small sample.<br>- Not appropriate if proportion of patients with missing data is relatively high. | - more likely to produce negative correlation in matrix.<br>- The analysis performed on different datasets (sample size) with different statistics (standard errors). | - Reduce the variance of the dataset<br>- Lead to inconsistent bias with missing data not at random.<br>- Underestimate the errors. | - Bias introduced for data with visible trend.<br>- Not recommended by the National Academy of Sciences | - Still need imputation.<br>- Produce the multi-collinearity and reduce linear model performance. | - Complex technique<br>- require appropriate software. |

**MCAR** missing completely at random, **MAR** missing at random, **LOCF** last observation carried forward (de Goeij et al., 2013, Kang, 2013, Groenwold et al., 2012)

In conclusion, listwise deletion, mean imputation, LOCF and multiple imputation are the four methods most commonly used in medical research to deal with missing data. In real-world data analysis, the missing data can be MCAR, MAR, or MNAR depending on the reasons that have led to the data being missing. When missing data are under the assumption of the MCAR mechanism, listwise deletion and multiple imputation methods perform equally well. Under the MAR assumption of missing data, multiple imputation has the least bias compared to other methods. Therefore, listwise deletion or the multiple imputation method are the appropriate methods to use when the data are MCAR, while the multiple imputation method is a more reliable and better statistical method to use when the data are MAR. The single imputation method, like LOCF, should not be carried out as a primary analysis because it produces biased estimates under both MCAR and MAR assumptions.

## 4.5 Summary

This chapter has described the real-world databases that are available in the UK. The IMRD-UK was used as a data source for this PhD project. As shown above, the database is representative of the UK population in terms of the age and gender of patients, allowing conclusions about the impact of my study results to be extrapolated to the whole population. Overall, data recorded in IMRD-UK are of good quality and it is considered an excellent source of data. Missing data is one of the disadvantages of primary care databases and is unavoidable in epidemiological research. However, there are several methods to overcome this issue. In this chapter, I have discussed the most common methods used to handle missing data, including some relatively simple approaches that can often yield reasonable results

# 5 CHAPTER FIVE: Prevalence and Incidence of Dementia in People with Diabetes Mellitus in the United Kingdom

The majority of the findings from this study in this chapter have been published in the Journal of Alzheimer's Disease (JAD) in May 2020 under the title: "Prevalence and Incidence of Dementia in People with Diabetes Mellitus".

## 5.1 Introduction

In 2020, DM in the UK had an estimated prevalence of 7% (Whicher et al., 2020), with 3.9 million patients currently diagnosed with DM (Diabetes UK, 2019a). In addition, approximately one million patients are unaware of their condition (Diabetes UK, 2019a). DM is a progressive disorder in nature, leading to major complications including microvascular complications, such as retinopathy, nephropathy, neuropathy, and macrovascular complications, such as CVDs, cognitive decline and death (Goff et al., 2007, Papatheodorou et al., 2018).

The link between diabetes and dementia among older people is controversial; some studies have found an association, while others have not (Biessels et al., 2006, MacKnight et al., 2002). Evidence from observational studies shows that DM is recognised as a major contributor of cognitive impairment and dementia and those with DM are at a twofold increased risk of dementia compared to those without DM (Gudala et al., 2013, Biessels et al., 2006). Dementia is a cognitive function deterioration syndrome resulting in disabilities and dependence that can be overwhelming, not only for the patient but also for their families/carers and healthcare systems (National Institute for Health and Care Excellence, 2018c). In 2020, the prevalence of dementia was estimated at 66% of the UK's older population aged 65+ years (alzheimer's Reasearch UK, 2020).

Patients with dementia are considered to be among the most vulnerable people due to the progressive nature of the disease, the life-threatening complications, increased mortality rate and the cost of diabetes and dementia care (Austin, 2016, Garcia-Ptacek

et al., 2014, Trikkalinou et al., 2017). Therefore, diabetes and dementia are major global health concerns (Hurd et al., 2013, Seuring et al., 2015). However, to the best of my knowledge, there are currently no data available on the prevalence and incidence of dementia in patients with diabetes in the UK. Therefore, in this study, I aimed to estimate the prevalence and incidence of dementia diagnosis in diabetes patients aged 18 or above in the UK primary care setting.

## 5.2 Aim and objectives

This study aimed to describe the annual trends of dementia diagnosis rate among patients diagnosed with DM. Additionally, this study estimated the rate of dementia diagnosis on study population subgroups based on diabetes type and gender.

The specific objectives were:

1. To estimate the annual prevalence rate of dementia diagnosis among patients diagnosed with DM.

2. To estimate the annual incidence rate of dementia diagnosis among patients with DM.

## 5.3 Methods

### 5.3.1 Study design

This was a retrospective population-based descriptive study using a primary care database in the UK.

### 5.3.2 Data source

The researcher extracted the data from IMRD-UK (previously known as THIN) database from 1st of January 2000 to 31st of December 2016. IMRD-UK database is one of the largest UK primary care databases (Lewis et al., 2007). It contains anonymised data from over 744 practices on more than 13 million individuals, covering

about 6% of the UK population, and is broadly representative in terms of demographic and health variables (Lewis et al., 2007, Blak et al., 2011, Bourke et al., 2004). IMRD-UK has information on diagnosis records issued by the GPs, which has been widely used to study various conditions including diabetes and dementia (Brauer et al., 2019, Mongkhon et al., 2020). Refer to **section 4.2 and 4.3** for more details about IMRD-UK database.

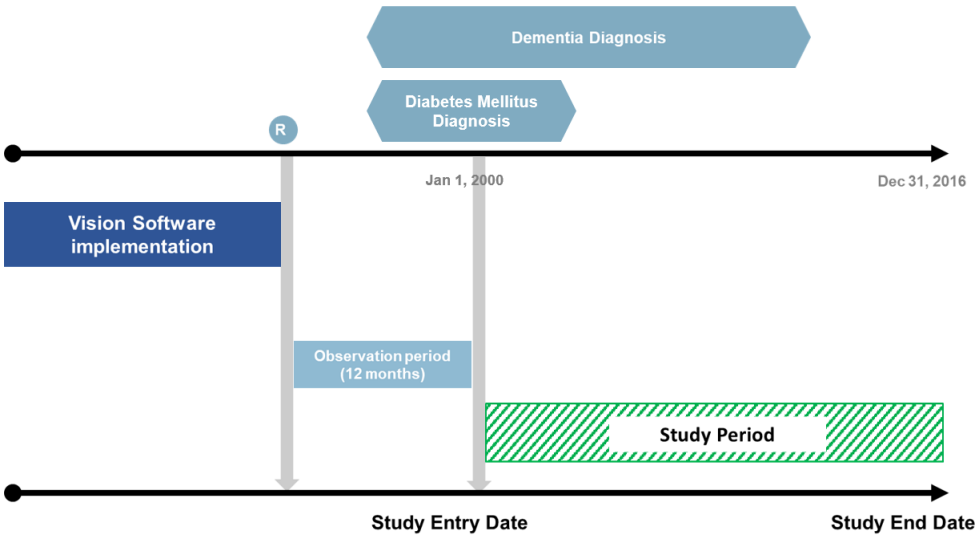
### 5.3.3 Data extraction

The target population for the present study was identified through Read codes. Initially, these codes were identified by searching into the medical dictionary for all DM and dementia diagnosis relevant codes. Once the Read codes identified, they were compared with the inclusion and exclusion criteria of the study. In terms of the codes validation and ensuring the desired population group is identified, I compared the identified codes with previously validated and used Read codes by other researchers, this included the code lists created by researchers at the London School of Hygiene & Tropical Medicine and The Department of Public Health and Primary Care Unit at the University of Cambridge (Cambridge, 2017, LSHTM, 2017). Moreover, the code list was compared to code lists used in other peer-reviewed articles published in medical journals (Springate et al., 2014, Brauer et al., 2019, Mongkhon et al., 2020). The final Read codes are listed in **Appendix 10**.

### 5.3.4 Inclusion criteria for study patients

The data of all patients aged 18 years or above who registered in the database and had a recorded diagnosis of DM during study period were identified by Read Codes. Among patients with DM records, I have identified those already diagnosed or developed dementia during study period. For each identified patient, the latest date of either the patient's registration at their general practice or the date that the general

practice began using the vision software system was defined as the patient's registration date. The date of first record of DM is defined as the study entry date. Only patients who had an observation period of at least twelve months available prior to their entry date were included. Patients with DM record within 12 months prior to study entry date, their entry date was defined as 1st January 2000. For dementia incident patients, the records were screened from the registration date to identify the incident patients throughout the study period. However, patients who had a record of dementia 12 months prior to 1st January 2000 were only included in the prevalence calculation. **Figure 20** illustrates the study population in this study**.**




**R** date of patient's registration in the GP

**Figure 20 Study Population**

## 5.3.5 Ethical considerations

No ethical approvals were required from UCL Research Ethics Committee as the study was exempt as the data involves anonymised records and appropriate permission has

been obtained. This study was approved by the SRC in July 2018 (reference: 18THIN054). Refer to **Appendix 11.**

### 5.3.6 Data quality and cross-check

To confirm the accuracy and the quality of the study findings, the data extraction and analyses were checked by a well-trained and experienced specialist in the field of pharmacoepidemiology and IMRD-UK data from the practice and policy department in the University College London (UCL), School of Pharmacy.

### 5.3.7 Statisical analysis

#### 5.3.6.1 Data Analysis

Data analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., 2019). Descriptive analyses of the study were carried out and presented to show the baseline characteristics and comorbidities of the population. Continuous data were reported as mean ± standard deviation (SD), and categorical data were reported as number (percentage), and were compared and tested for difference between participants by the independent t-test and the Chi-squared ($\chi 2$) test, respectively. P-values <0.05 were considered as statistically significant. The overall prevalence and incidence of dementia over the 17-year study period were calculated and expressed as rates per 100 persons with 95% confidence intervals estimated using the Poisson method.

#### 5.3.6.2 Criteria of measuring clinical outcomes

The annual prevalence of dementia was calculated using the number of all the prevalent diabetic patients with a diagnosis of dementia in a particular year (numerator), divided by the total number of diabetes patients available in the database in the same year (denominator) multiplied by 100.

$$\textbf{\textit{Prevalence of dementia}} = \frac{Number\ of\ diabetes\ patients\ diagnosed\ with\ dementia\ diagnosis\ in\ specific\ year}{Total\ diabetes\ population\ in\ the\ same\ year}\ X\ 100$$

The annual incidence of dementia diagnosis was estimated using the number of patients with a first record of dementia diagnosis in a particular year (numerator), divided by the number of patients at risk in the same year i.e. diabetes patients without records of dementia diagnosis prior to/at the beginning of that particular year (denominator) multiplied by 100.

$$\textbf{\textit{Incidence of dementia}} = \frac{Number\ of\ diabetes\ patients\ with\ first\ record\ of\ dementia\ diagnosis\ in\ specific\ year}{Number\ of\ patients\ at\ risk\ in\ the\ same\ year}\ X\ 100$$

Both annual prevalence and incidence were stratified by gender, age groups (18- 65 years old, 65-74 years old, 75-84 years old and ≥ 85 years old) and by diabetes types (T1DM and T2DM) by using the same formulas above.

## 5.4 Results

After applying the inclusion criteria, the researcher identified a study population of 544,162 DM patients, of which 28,772 patients had a record of dementia diagnosis during the 17-year period.

### 5.4.1 Study population characteristics

**Table 18** shows the baseline characteristics for the study population (DM patients with a diagnosis of dementia and those without), and **Table 19** shows the baseline characteristics of DM patients who developed dementia during the study period.

**Table 18 Study Population Characteristics**

| Characteristics | Total Diabetes mellitus 544,162 (100%) | Diabetes Mellitus without Dementia 515,390 (100%) | Diabetes Mellitus with Dementia 28,772 (100%) | P-value |
|---|---|---|---|---|
| **Mean age at first diabetes mellitus diagnosis (SD)** | 59.4 years (15.0) | 58.7 years ( 14.9) | 73.1 years (10.0) | <0.0001 |

| Characteristics | Total Diabetes mellitus 544,162 (100%) | Diabetes Mellitus without Dementia 515,390 (100%) | Diabetes Mellitus with Dementia 28,772 (100%) | P-value |
|---|---|---|---|---|
| **Mean age at first dementia diagnosis (SD)** | - | - | 80.76 years (7.8) | - |
| **Gender (%)** | | | | |
| **Male** | 300,157 (55.2) | 288,093 (55.9) | 12,064 (41.9) | <0.0001 |
| **Female** | 244,005 (44.8) | 227,297 (44.1) | 16,708 (58.1) | <0.0001 |
| **Comorbidities (%)** | | | | |
| **Chronic Kidney Disease** | 111,349 (20.5) | 100,824 (19.6) | 10,525 (36.6) | <0.0001 |
| **Hypertension** | 332,921 (61.2) | 313,811 (60.8) | 19,110 (66.4) | <0.0001 |
| **Arrhythmias** | 69,674 (12.8) | 63,479 (12.3) | 6,195 (21.5) | <0.0001 |
| **Myocardial Infarction** | 160,216 (29.4) | 149,583 (29.2) | 10,633 (37.0) | <0.0001 |
| **Stroke** | 52,174 (9.6) | 45,558 (8.8) | 6,616 (23.0) | <0.0001 |
| **Depression** | 160,093 (29.4) | 150,547 (29.2) | 9,546 (33.2) | <0.0001 |
| **Heart failure** | 52,216 (9.6) | 48,316 (9.3) | 3,900 (13.6) | <0.0001 |
| **Diabetic retinopathy** | 179,649 (33.0) | 170,735 (33.1) | 8,914 (31.0) | <0.0001 |
| **Diabetic nephropathy** | 4,563 (0.8) | 4,369 (0.8) | 194 (0.7) | 0.0014 |
| **Diabetic neuropathy** | 81,362 (14.9) | 77,150 (14.9) | 4,212 (14.6) | 0.5729 |
| **Diabetic foot** | 30,886 (5.7) | 28,791 (5.6) | 2,095 (7.3) | <0.0001 |
| **Types of diabetes (%)** | | | | |
| **Type 1 diabetes mellitus** | 22,668 (4.2) | 22,167 (4.3) | 980 (3.4) | <0.0001 |
| **Type 2 diabetes mellitus** | 521,494 (95.8) | 493,223 (95.7) | 27,792 (96.6) | <0.0001 |
| **Types of dementia (%)** | | | | |

| Characteristics | Total Diabetes mellitus 544,162 (100%) | Diabetes Mellitus without Dementia 515,390 (100%) | Diabetes Mellitus with Dementia 28,772 (100%) | P-value |
|---|---|---|---|---|
| **Unspecified dementia** | - | - | 14,125 (49.1) | - |
| **Vascular Dementia** | - | - | 8,034 (27.9) | - |
| **Alzheimer's Disease** | - | - | 6,162 (21.4) | - |
| **Dementia with Lewy bodies** | - | - | 290 (1.0) | - |
| **Parkinson's Dementia** | - | - | 139 (0.5) | - |
| **Frontotemporal Dementia** | - | - | 22 (0.1) | - |

**Table 19 Baseline Characteristics of DM Patients Newly Diagnosed with Dementia**

| Characteristics | Diabetes Mellitus who developed dementia 19,046 (100%) |
|---|---|
| **Mean age at first diabetes mellitus diagnosis (SD)** | 72.5 years (10.1) |
| **Mean age at first dementia diagnosis (SD)** | 80.4 years (7.9) |
| **Gender (%)** | |
| **Male** | 8,191 (43.0) |
| **Female** | 10,855 (57.0) |
| **Comorbidities (%)** | |
| **Chronic Kidney Disease** | 7,538 (39.6) |
| **Hypertension** | 13,488 (70.8) |
| **Arrhythmias** | 4,332 (22.7) |
| **Myocardial Infarction** | 7,802 (40.9) |
| **Stroke** | 4,364 (22.9) |

| Characteristics | Diabetes Mellitus who developed dementia<br>19,046 (100%) |
|---|---|
| **Depression** | 6,807 (35.7) |
| **Heart failure** | 2,807 (14.7) |
| **Diabetic retinopathy** | 6,978 (36.6) |
| **Diabetic nephropathy** | 161 (0.8) |
| **Diabetic neuropathy** | 3,581 (18.8) |
| **Diabetic foot** | 1,557 (8.2) |
| **Types of diabetes (%)** | |
| **Type 1 diabetes mellitus** | 739 (3.9) |
| **Type 2 diabetes mellitus** | 18,307 (96.1) |
| **Types of dementia (%)** | |
| **Unspecified dementia** | 9,473 (49.7) |
| **Vascular dementia** | 5,178 (27.2) |
| **Alzheimer's disease** | 4,123 (21.6) |
| **Dementia with Lewy bodies** | 164 (0.9) |
| **Parkinson's dementia** | 92 (0.5) |
| **Frontotemporal dementia** | 16 (0.1) |

The next eight sections provide details about the annual prevalence and incidence of dementia in the DM population stratified by age, gender and DM type.

### 5.4.2 Prevalence of dementia in the DM population by calendar year

The overall annual prevalence estimates of dementia between 2000 and 2016 increased by around five times (497.6%) (from 0.42 [95% CI, 0.42–0.43] in 2000 to 2.51 [95% CI, 2.50–2.52] per 100 persons in 2016) (**Table 20 and Figure 21**).

**Table 20 Annual Prevalence of Dementia in Diabetes Population**

| Year | Total Patients with Dementia and Diabetes (numerator) | Total Patients with Diabetes (denominator) | Dementia Prevalence per 100 persons | 95% Confidence interval |
|---|---|---|---|---|
| **2000** | 631 | 148,822 | 0.42 | (0.42-0.43) |
| **2001** | 830 | 169,371 | 0.49 | (0.48-0.49) |
| **2002** | 1,087 | 190,860 | 0.57 | (0.56-0.57) |
| **2003** | 1,335 | 211,072 | 0.63 | (0.62-0.64) |
| **2004** | 1,596 | 229,774 | 0.69 | (0.68-0.70) |
| **2005** | 1,873 | 246,155 | 0.76 | (0.75-0.80) |
| **2006** | 2,373 | 261,446 | 0.90 | (0.90-0.91) |
| **2007** | 2,773 | 274,213 | 1.01 | (1.00-1.02) |
| **2008** | 3,033 | 285,674 | 1.06 | (1.05-1.07) |
| **2009** | 3,511 | 295,513 | 1.18 | (1.17-1.19) |
| **2010** | 3,984 | 300,175 | 1.32 | (1.31-1.33) |
| **2011** | 4,585 | 303,180 | 1.51 | (1.50-1.52) |
| **2012** | 5,191 | 305,749 | 1.69 | (1.68-1.70) |
| **2013** | 5,823 | 304,749 | 1.91 | (1.90-1.92) |
| **2014** | 6,267 | 287,330 | 2.18 | (2.16-2.19) |
| **2015** | 6,367 | 262,455 | 2.42 | (2.41-2.43) |
| **2016** | 5,502 | 219,366 | 2.50 | (2.49-2.52) |

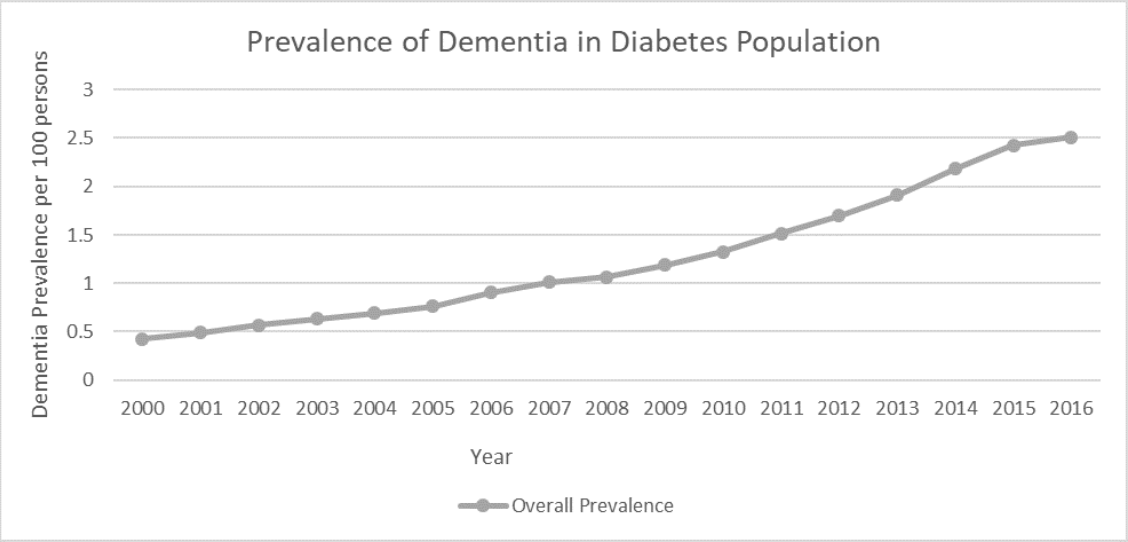



**Figure 21 Annual Prevalence of Dementia in Diabetes Population**

### 5.4.3 Prevalence of dementia in the DM population by age

The prevalence estimates of dementia increased with increasing age. Younger patients aged below 65 years had lower estimates compared to patients aged 65 years and above. The estimates increased for both age groups fourfold (400%) (from 0.03 [95% CI, 0.02–0.04] in 2000 to 0.15 [95% CI, 0.42–0.43] per 100 persons in 2016, and from 0.85 [95% CI, 0.84–0.87] in 2000 to 4.2 [95% CI, 0.14–0.16] per 100 persons in 2016, for patients aged below 65 years and above 65 years), respectively. However, the estimates were highest in elderly patients aged 85 years and above compared to other age groups (**Figure 22**).

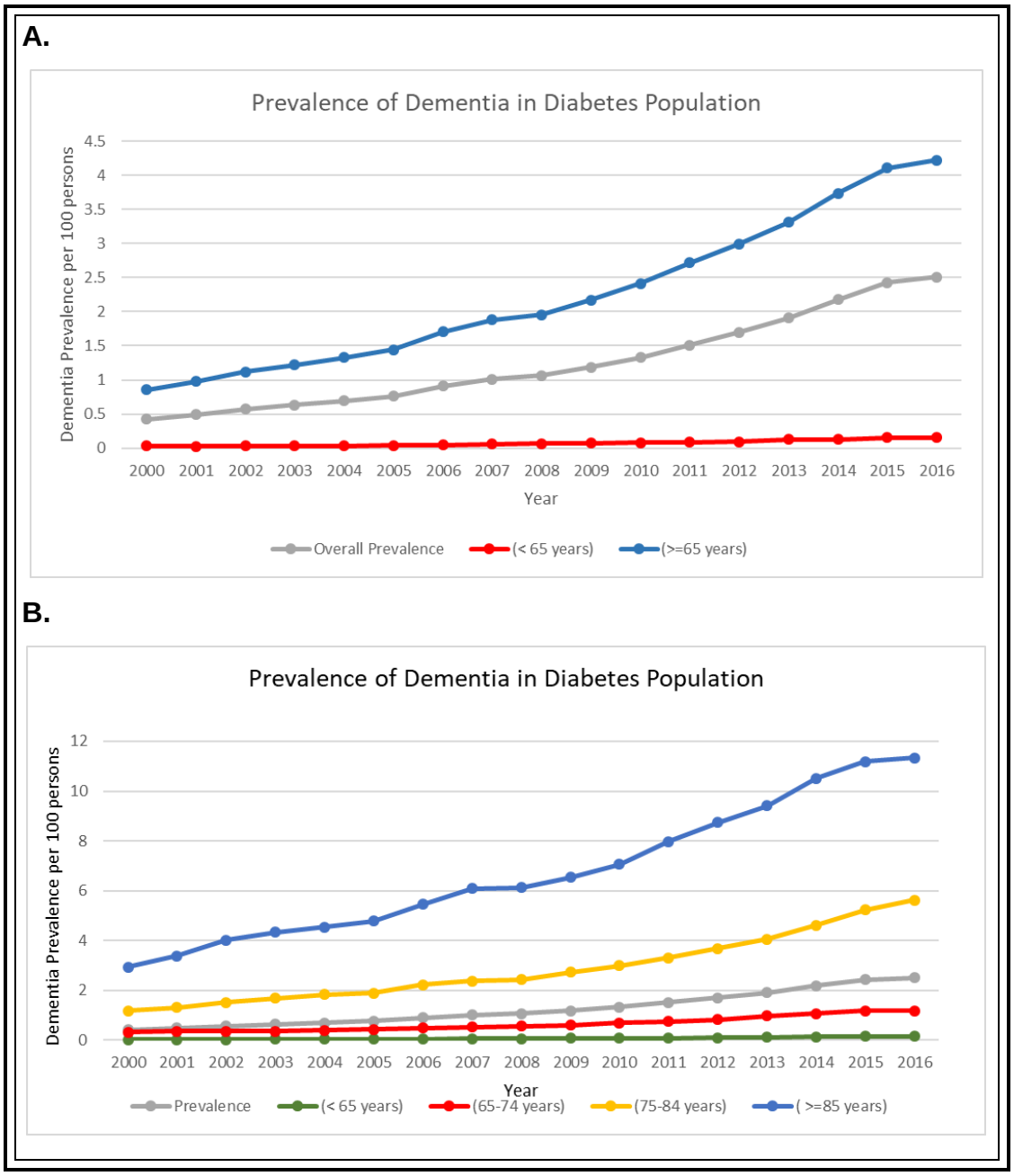



**Figure 22 Annual Prevalence of Dementia in Diabetes Population Stratified by Age Group A. Below and above 65 years B. All age groups**

## 5.4.4 Prevalence of dementia in the DM population by gender

Dementia prevalence estimates were statistically significantly higher in females than males ($p < 0.05$). In 2016, the prevalence of dementia in females was approximately 1.5 times higher compared to males, being 3.14 (95% CI, 3.12–3.15) and 2.01 (95% CI, 2.00–2.02) per 100 persons, respectively (**Figure 23**).

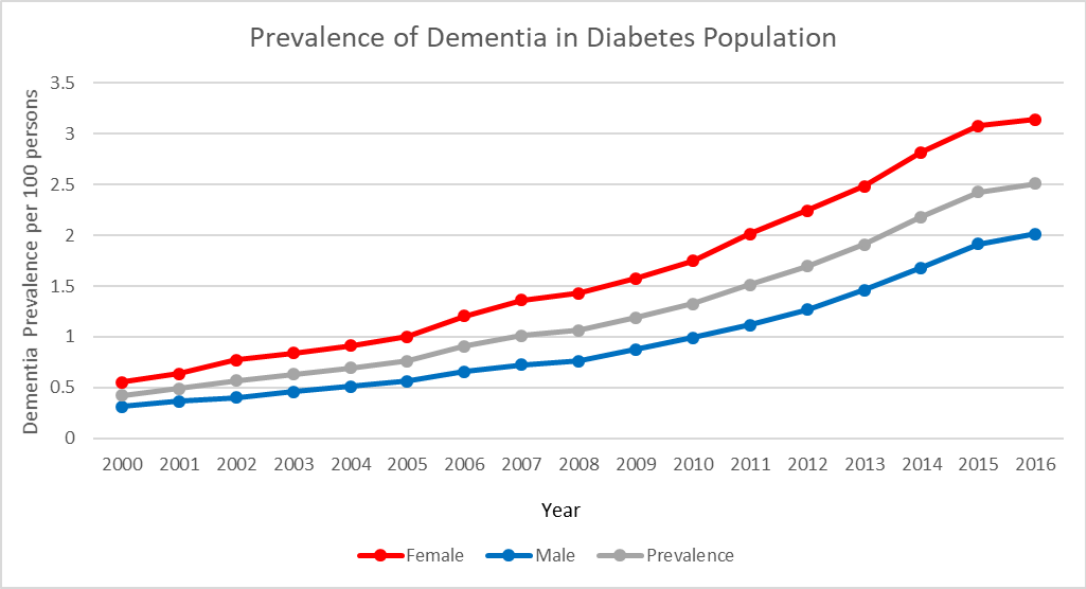



**Figure 23 Annual Prevalence of Dementia in Diabetes Population Stratified by Gender**

### 5.4.5 Prevalence of dementia in the DM population by DM types

There were statistically significant differences in dementia prevalence estimates between DM types ($p < 0.05$). The prevalence of dementia in 2016 was three times higher in patients diagnosed with T2DM (2.77 [95% CI, 2.76–2.82] per 100 persons) compared to the prevalence in patients diagnosed with T1DM (0.53 [95% CI, 0.52–0.54] per 100 persons). Refer to **Figure 24**.

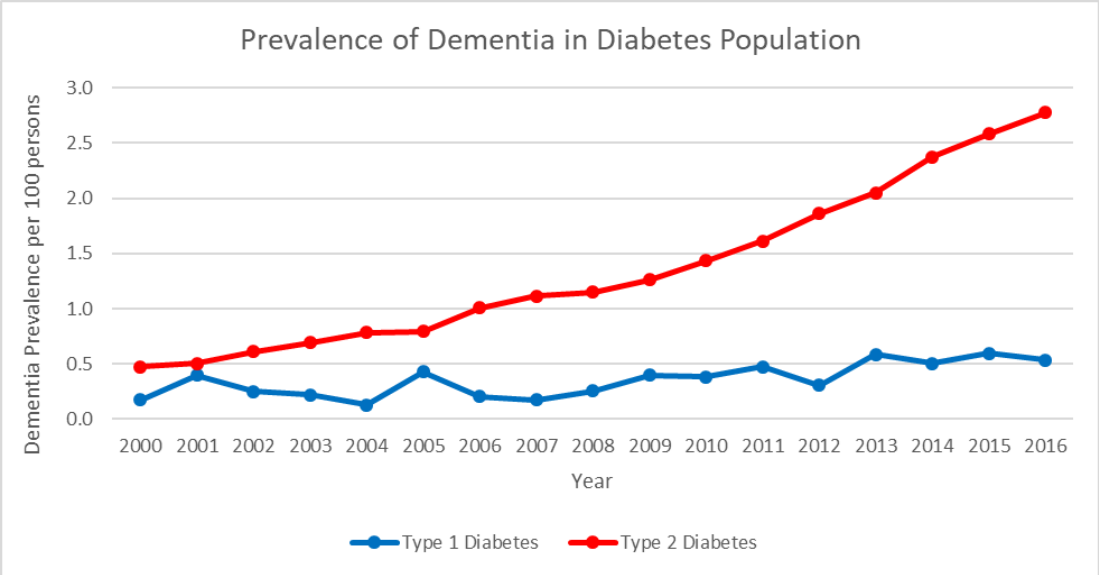



**Figure 24 Annual Prevalence of Dementia in Diabetes Population Stratified by Diabetes Type**

### 5.4.6 Incidence of dementia in the DM population by calendar year

**Table 21** shows the annual incidence rates of dementia in the diabetes population during the study period. Similar to the prevalence estimates, the overall incidence rates of dementia increased about threefold (277.8%) from 0.18 (95% CI, 0.17–0.18) in 2000 to 0.68 (95% CI, 0.67–0.69) per 100 persons in 2016 (**Figure 25).**

**Table 21 Annual Incidence of Dementia in Diabetes Population**

| Year | Total Dementia Incident Patients with Diabetes (numerator) | Total Patients with Diabetes (at risk population, denominator) | Dementia Incidence per 100 persons/year (%) | 95% Confidence interval |
|---|---|---|---|---|
| **2000** | 269 | 148,353 | 0.18 | (0.17-0.19) |
| **2001** | 350 | 168,740 | 0.21 | (0.20-0.22) |
| **2002** | 432 | 190,030 | 0.22 | (0.21-0.23) |
| **2003** | 527 | 209,985 | 0.25 | (0.24 -0.25) |
| **2004** | 597 | 228,439 | 0.26 | (0.25-0.26) |
| **2005** | 668 | 244,559 | 0.27 | (0.26-0.28) |
| **2006** | 907 | 259,573 | 0.34 | (0.34-0.35) |
| **2007** | 922 | 271,840 | 0.33 | (0.32-0.34) |
| **2008** | 943 | 282,901 | 0.33 | (0.31-0.35) |
| **2009** | 1,213 | 292,480 | 0.41 | (0.40-0.42) |
| **2010** | 1,340 | 296,664 | 0.45 | (0.44-0.46) |
| **2011** | 1,492 | 299,196 | 0.49 | (0.46-0.50) |
| **2012** | 1,654 | 301,164 | 0.54 | (0.53-0.55) |
| **2013** | 1,873 | 299,558 | 0.62 | (0.61-0.68) |
| **2014** | 1,971 | 281,507 | 0.70 | (0.69-0.71) |
| **2015** | 1,847 | 256,188 | 0.72 | (0.71-0.74) |
| **2016** | 1,454 | 212,999 | 0.68 | (0.67-0.69) |

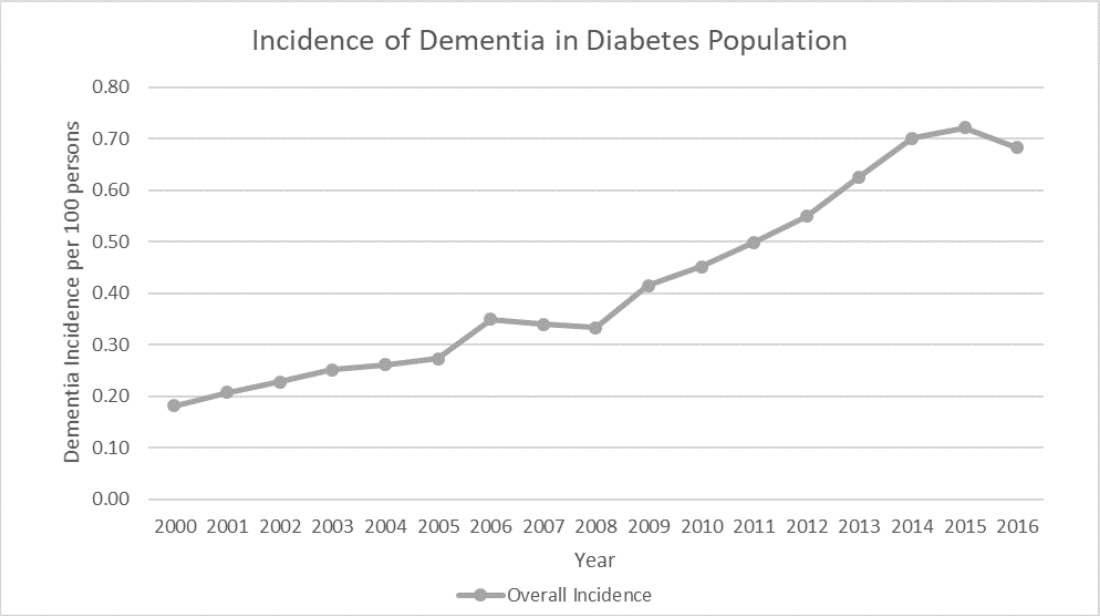



**Figure 25 Annual Incidence of Dementia in Diabetes Population**

### 5.4.7 Incidence of dementia in the DM population by age

Among all age groups, the incidence estimates of dementia between 2000 and 2016 were found to be higher in those patients aged 65 years and above compared to patients aged below 65 years. Among patients aged 65 years and above, the highest increase in dementia incidence rate was in elderly patients aged 75–84 years, which increased around twofold (205.5%) (from 0.54 [95% CI, 0.53–0.55] in 2000 to 1.65 [95% CI, 1.64–1.66] per 100 persons in 2016), followed by the 65–74 age group, which more than doubled (176.9%) (from 0.13 [95% CI, 0.12–0.14] to 0.36 [95% CI, 0.35–0.37] per 100 persons). In the 85 years and above age group, the incidence rate more than doubled (172.6%) (from 1.13 [95% CI, 1.11–1.16] to 3.08 [95% CI, 3.05–3.10] per 100 persons), and in the below 65 years age group it doubled (100%) (from 0.02 [95% CI, 0.018–0.03] to 0.04 [95% CI, 0.04–0.05] per 100 persons): refer to **Figure 26**.

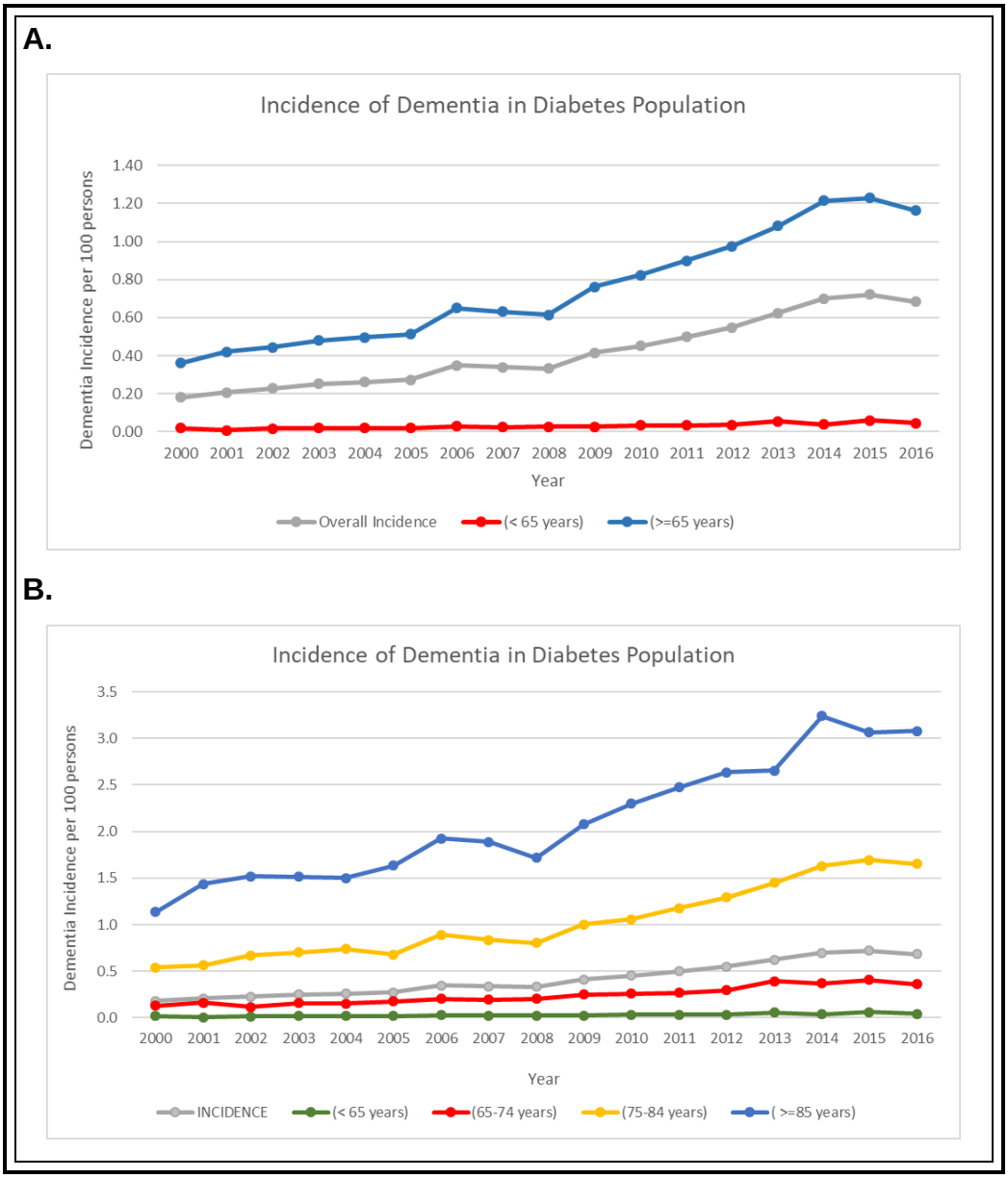



**Figure 26 Annual Incidence of Dementia in Diabetes Population Stratified by Age Groups A. Below and above 65 years B. All age groups**

## 5.4.8 Incidence of dementia in the DM population by gender

When the data were stratified by gender, dementia incidence rates were shown to be statistically significantly higher among females than males during the study period ($p < 0.05$). In 2016, the incidence rate reached 0.82 (95% CI, 0.81–0.83) and 0.58 (95% CI, 0.57–0.60) for females and males, respectively **(Figure 27**).

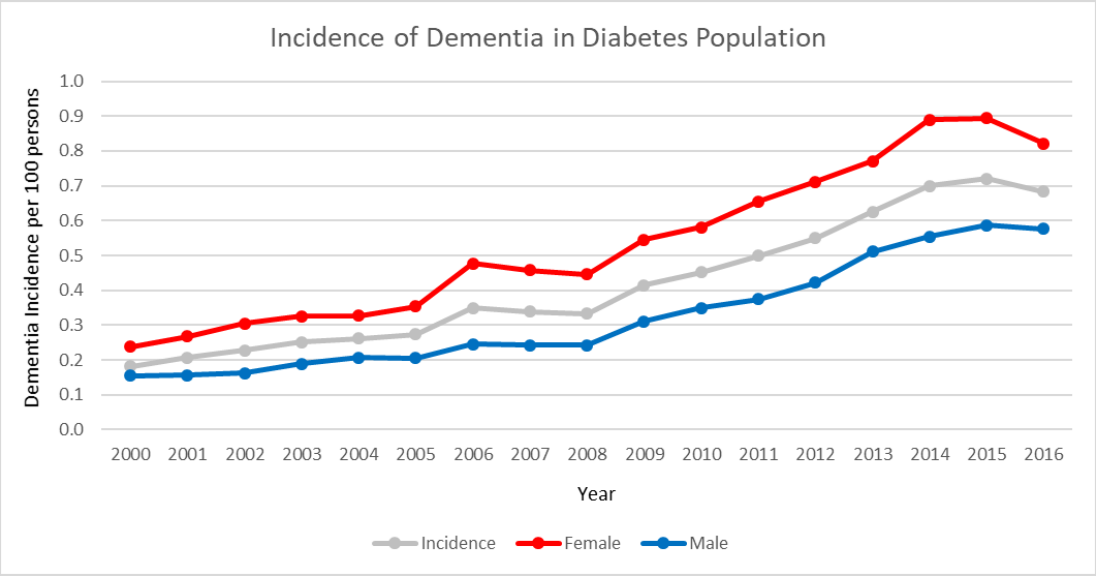



**Figure 27 Annual Incidence of Dementia in Diabetes Population Stratified by Gender**

### 5.4.9 Incidence of dementia in the DM population by DM type

Over the study period, dementia incidence rates were higher among T2DM patients compared to T1DM patients. In 2016, the incidence rate reached 0.74 (95% CI, 0.72–0.77), and 0.26 (95% CI, 0.24–0.28) per 100 persons for T2DM and T1DM, respectively (**Figure 28**). There were statistically significant differences in dementia incidence rates between diabetes types ($p < 0.05$).

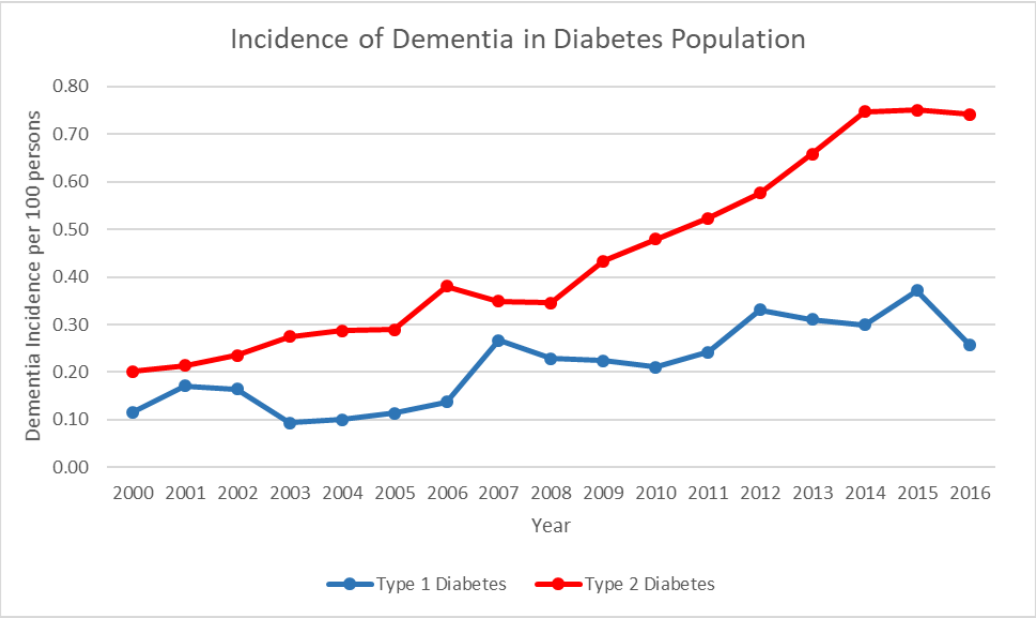



**Figure 28 Annual Incidence of Dementia in Diabetes Population Stratified by Diabetes Type**

## 5.5 Discussion

The findings of this study showed that there was a sharply rising trend of dementia prevalence and incidence in the UK from 2000 to 2016 among the DM population.

Previous literature found that the prevalence of DM and dementia increased worldwide from 1980 to 2018 (Wang et al., 2018, Weuve et al., 2015, Brookmeyer et al., 2018). However, the prevalence of dementia in the DM population has not been reported or estimated yet (Lee et al., 2018). However, the association between diabetes and dementia is now well established and multiple observational studies found that DM patients were at 73% increased risk of all types of dementia compared to patients without DM (Gudala et al., 2013). Various possible mechanisms may contribute to the development of dementia in DM patients, including brain vascular lesions, oxidative distress, insulin resistance, and hyperglycaemia causing inflammation (Lee et al., 2018).

### 5.5.1 Dementia prevalence and incidence trends

Direct comparison between my study and previous studies was not feasible as different populations were used. Possible explanations for the difference between the rates observed in this study and other studies (Matthews et al., 2016, Pham et al., 2018, Rait et al., 2010) are: 1) the study design - this study was a descriptive, population-based study, monitoring the trends of dementia incidence and prevalence using the IMRD-UK primary care database, which only provides information from the primary care setting, and therefore underestimation of the prevalence and incidence of dementia is possible; 2) different study population (general population versus DM population); 3) different age groups were studied; 4) different study period.

The current study estimates that the prevalence rate of dementia has increased during the 17 years of the study period. The increase in the prevalence rate of dementia may

reveal an increase in the prevalence of an elderly population (World Health Organization, 2015). However, there is a lack of data on the prevalence of dementia among the DM population.

The annual incidence rate of dementia in this study increased threefold between 2000 and 2016 from 0.18 to 0.68 per 100 persons in 2000 and 2016, respectively. This rising trend is similar to what was previously reported in another nationally representative study sample using THIN data, which stated that there was a 3.75 to 5.65 per 1,000 person-years risk between 2007 and 2015 (Pham et al., 2018). On the other hand, in a large, population-based cohort study conducted in the UK, the dementia incidence rate remained stable over the study period from 3 per 1,000 persons in 1997 to 4 per 1,000 persons per year in 2007 (Rait et al., 2010).

This study has found that there is a difference in the incidence of dementia among patients from different genders, different age groups and diabetes type. Females and elderly patients aged 60 and above had a higher incidence rate of dementia, which confirms the findings of previous studies (Matthews et al., 2016, Lee et al., 2019, Rait et al., 2010).

This study suggests that the proportion of DM patients who were diagnosed with dementia rose significantly over the study period. These findings may reflect the effects of the National Dementia Strategy drives to improve dementia awareness and provide higher quality care services by introducing a new dementia toolkit, resulting in an increase in the dementia diagnosis rate (Department of Health, 2015). Between 2014 and 2015, additional services were provided by GPs aiming to further increase the dementia diagnosis rate up to 67% in 2015 (Department of Health, 2015, Black et al., 2015). I believe this had a major impact on the increase in known cases of dementia in the primary care setting (Mukadam et al., 2014).

### 5.5.2 Strengths and limitations

The strengths of this study are as follows: a) to the best of my knowledge, this is the first study to estimate the prevalence and incidence of dementia among the diabetes population in a nationally representative sample in the UK; b) this study has monitored the trends of prevalence and incidence of dementia over a 17-year period, which has enabled us to do longitudinal monitoring of the trends and quantify the problem of dementia; c) a large, UK-representative study sample has been used, which is a particularly suitable database for chronic disease prevalence work (Blak et al., 2011); d) there were no restrictions on the age of the patients, which has been limited to specific age groups in previous studies.

The limitations of this study include: a) the study findings did not apply to patients with suspected dementia or with symptoms of dementia and without confirmed dementia diagnosis; b) based on the literature, dementia tends to be under-recorded in primary care settings (Boustani et al., 2003, Turner et al., 2004); c) in addition, the medcodes of dementia entered were non-specific and I was not able to do data stratification based on dementia types.

## 5.6 Conclusion

Increased prevalence and incidence rate of dementia in the DM population were observed during the study period. Further studies are required to identify the reasons that lie behind these two conditions, to estimate the workload and costs of dementia, and evaluate the effect of dementia on health and social care services.

# 6 CHAPTER SIX: Antidiabetic medication prescribing and the hypoglycaemia rate in patients with diabetes mellitus and dementia: a population-based study in the United Kingdom

The findings of the descriptive study in Chapter Five suggest that dementia is prevalent among the diabetes mellitus (DM) population in the UK. The systematic review results indicate a gap in studies describing the use of antidiabetic medications and the frequency of hypoglycaemic events in DM patients with dementia. The purpose of this chapter is to present the drug utilisation study that was conducted in a large UK primary care database (IMRD-UK) to describe the DM pharmacotherapy provided to DM patients with dementia and to bridge the research gap that was highlighted in the systematic review (Chapter Two).

## 6.1 Introduction

In the UK, antidiabetic medication accounts for a high proportion of prescriptions in primary care settings and drug expenditure among healthcare costs (Hex et al., 2012). According to the National Health Service (NHS), during the year 2019/20, patients with DM in England were prescribed 57 million items, of which antidiabetic medications contributed to 85.0%, with 41.9 million and 7.6 million of these items accounting for antidiabetic medications and insulin, respectively (National Health Services, 2020). The goal of antidiabetic medication use is to achieve adequate glycaemic control, measured by glycated haemoglobin (HbA1c) levels. Adequate glycaemic control is important to reduce the complications associated with DM (National Institute for Health and Care Excellence, 2015a). Clinical guidance for the management of DM has been provided by National Institute for Health and Care Excellence (NICE) and American Diabetes Association (ADA). After lifestyle modifications, both NICE and ADA recommend starting with metformin monotherapy, followed by a series of intensification steps by adding

antidiabetic medication (National Institute for Health and Care Excellence, 2016b). In 2007, major developments in DM pharmacological treatment occurred in the UK. NICE recommended intensive regimens together with tighter glycaemic control (HbA1c level < 6.5%) to prevent long-term complications (National Institute for Health and Care Excellence, 2007, American Diabetes Association, 2007). However, a U-shaped association was found in a UK study between HbA1c level and all-cause mortality in older patients, which means an increased risk of mortality was associated with the lowest and the highest mean HbA1C (Currie et al., 2010). Furthermore, intensified regimens and tighter glycaemic control have been associated with an increased risk of hypoglycaemia, which is a serious side effect of antidiabetic medication, resulting in increased morbidity and mortality (Umpierrez and Korytkowski, 2016a).

In the elderly, DM and dementia are interrelated, as DM patients are at a 1.6 times higher risk of developing dementia compared to patients without DM (Cukierman et al., 2005). Among DM patients aged above 65 years, 15.5% have been diagnosed with dementia (Thorpe et al., 2012, Feil et al., 2011).

Dementia by definition is an irreversible, progressive cognitive impairment syndrome characterised by psychiatric and behavioural symptoms, including loss of memory, self-expressive difficulties, self-neglect, disorientation and changes in personality (Prince, 2014a). These symptoms cause a loss of executive functions that may impact on the management of DM and worsen glycaemic control (Amar Puttanna, 2017).

The evidence of diabetes care in the elderly population is not sufficient because the majority of landmark clinical trials do not include them due to their comorbid diseases and

multiple medication treatments (Cruz-Jentoft et al., 2013). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, elderly participants aged 80 years or more were excluded (Buse et al., 2007), and the UK Prospective Diabetes Study (UKPDS) only included patients who were aged < 65 years at diabetes diagnosis (UKPDS, 1991). Therefore, recommendations for diabetes care for older populations are largely based on expert opinions applied from younger and healthier patient samples, which may not be generalisable for the elderly (Kirkman et al., 2012). For this reason, it is important to examine the prescribing of antidiabetic medication and describe the rate of hypoglycaemia in patients with DM and dementia.

## 6.2 Aim and objectives

This study aimed to describe the prescribing patterns of antidiabetic medication for patients with DM and dementia. The primary objective of this study was to determine the annual prescribing patterns of antidiabetic medication stratified by therapeutic class. The secondary objective was to evaluate the annual hypoglycaemic episode rate.

## 6.3 Methods

### 6.3.1 Study design

This study was a retrospective, longitudinal drug utilisation study. It was designed to identify the annual prescribing patterns of antidiabetic medication. The benefit of this study design is that all the results and outcomes can be described and calculated in order to generate new hypotheses and in-depth analytical studies in the future. In addition, it is

cost-effective to perform and only requires the use of routinely accessible data. However, this study design does not allow for inferences to be drawn about causal associations.

### 6.3.2 Data source

The study used data from the IMRD-UK database as a source of patients' diagnosis and prescription data. The database contained anonymised patient records from 744 practices and more than 13 million patients distributed all over the UK, covering about 6% of the UK population (Lewis et al., 2007, Bourke et al., 2004). Refer to **sections 4.2 and 4.3** for more details about the IMRD-UK database.

### 6.3.3 Data extraction

Data were retrieved from the IMRD-UK database for a 17-year period from 1 January 2000 to 31 December 2016. Extracted data included: patients' demographics, such as age and gender; DM-specific information including DM diagnosis, type of DM, duration of the disease and antidiabetic medication use with the date of initiating therapy; dementia-specific information including dementia diagnosis and type of dementia; data of any hypoglycaemic episodes.

The antidiabetic prescribing data were determined by therapeutic classes using relevant drug codes for insulin and other antidiabetic medications: biguanides (metformin), sulfonylureas, meglitinides, thiazolidinedione, dipeptidyl peptidase-4 inhibitors (DDP-4), sodium-glucose cotransporter-2 inhibitors (SGLT-2), glucagon-like peptide-1 receptor agonists (GLP-1), and acarbose from the BNF (**Table 22**) and the drug dictionary provided by the database (British Medical Association, 2009). The Read codes used in

this study were obtained from the official website of the University of Cambridge (University of Cambridge) and published studies (Khunti et al., 2015, Brauer et al., 2019, Springate et al., 2014, Mongkhon et al., 2020). The final codes are listed in **Appendix 10**.

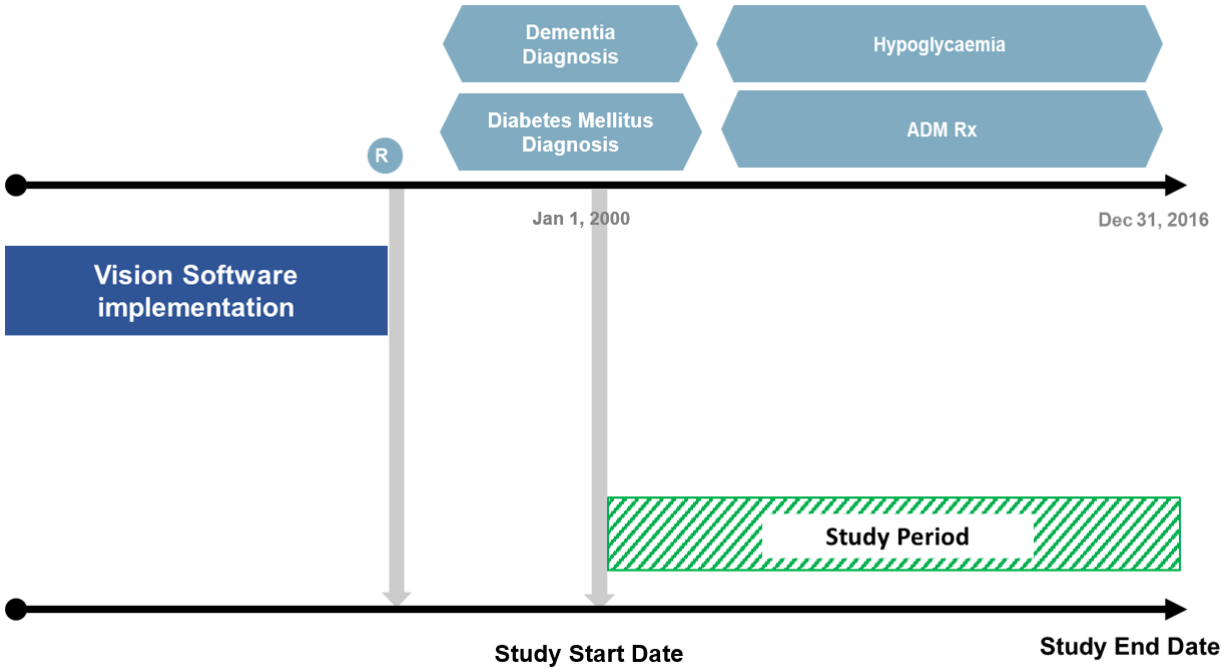
**Table 22 BNF codes and their description for antidiabetic medications**

| BNF drug code | Description |
|---|---|
| **6.1.1** | Insulins |
| **6.1.2** | Antidiabetic drugs |
| **6.1.2.1** | Sulfonylureas |
| **6.1.2.2** | Biguanides |
| **6.1.2.3** | Other antidiabetic drugs |

**BNF** British National Formulary

### 6.3.4 Inclusion criteria for study patients

The data of all patients aged 40 years and above who had a diagnosis record of DM (T1DM and T2DM) and dementia were included. For each patient, the latest date of DM diagnosis and dementia diagnosis was considered the patient's start date (coexistence of both diseases). The study end date was determined by the patient's death, their transferral out of the practice or the end of the study. The study population is shown in **Figure 29**.




**R** date of patient's registration in the GP, **ADM Rx** Antidiabetic medication prescription.

**Figure 29 Study Population**

### 6.3.4.1 Antidiabetic prescriptions

Records of patients with DM and dementia receiving at least one prescription of antidiabetic medications were included. For each patient, the prescriptions for the study medications recorded after their start date and during the study period were identified, and the annual prescribing rates of the study population using antidiabetic medications were calculated for each antidiabetic therapeutic class.

### 6.3.4.2 The rate of hypoglycaemic episodes

Each treated patient with a record of a hypoglycaemic episode (one or more episode) on or after their start date and during the study period was included. The annual rates of hypoglycaemic episodes were calculated during the study period.

### 6.3.5 Ethical considerations

Ethical approval was granted by the research ethics committee of the IMRD-UK (THIN) database before the study commenced. IMRD-UK data are available as anonymised data. Therefore, there was no need to obtain ethical approval for the study through the UCL Research Ethics Committee (SRC reference number: 18THIN011): refer to **Appendix 11**.

### 6.3.6 Data quality and cross-check

Two investigators, including myself and my colleague, extracted the study Read code list separately. Following that, the data analyses were fully cross-checked to assess the accuracy and quality.

### 6.3.7 Statistical analysis

#### 6.3.6.1 Data analysis

Data analyses were performed using the Statistical Analysis System (SAS V.9.4) (SAS Institute Inc., 2019). Continuous data are reported as mean (μ) ± standard deviation (SD), and categorical data as frequencies (n) and percentages (%). Descriptive statistics were used to describe the patients' characteristics, medication use and comorbidities. The prescribing and hypoglycaemia rates were presented as rates per 100 persons with 95% confidence intervals (CIs) calculated using the Poisson method. The Pearson correlation coefficient was used to assess the correlation between antidiabetic medication prescribing and the rate of hypoglycaemia. P-values of less than 0.05 were considered statistically significant.

### 6.3.6.2 Criteria for measuring clinical outcomes

1) The frequency of each class of antidiabetic prescription issued during the study period was calculated using the number of prescriptions issued for each antidiabetic medication therapeutic class divided by the overall number of all antidiabetic medication prescriptions issued.

$$\textbf{\textit{Frequency of Each Antidiabetic Class Prescriptions}} = \frac{Antidiabetic\ prescriptions\ issued\ for\ each\ therapeutic\ class}{Total\ number\ of\ antidiabetic\ prescriptions\ issued} \text{ X } 100$$

2) The annual prescribing rates for each class of antidiabetic medication users were calculated over the study period using the number of patients issued with a particular antidiabetic medication class in a specific year (as the numerator) divided by the total number of patients with DM and dementia in that calendar year (as the denominator) multiplied by 100. The change in the prescribing rate between 2000 and 2016 was presented as a percentage.

$$\textbf{\textit{Annual Prescribing Rate of Each Antidiabetic Class}} =$$

$$\frac{Number\ of\ patients\ issued\ with\ a\ particular\ antidiabetic\ medication\ class\ in\ year\ x}{Total\ population\ in\ the\ same\ year} \text{ X}100$$

3) The annual rates of hypoglycaemic episodes during the study period were calculated by dividing the number of patients who experienced hypoglycaemic episodes in a specific year (as the numerator) by the total number of treated diabetes and dementia patients in that calendar year (as the denominator) multiplied by 100.

$$\textbf{\textit{Annual Hypoglycaemia Rate}} = \frac{Number\ of\ patients\ experienced\ hypoglycaemic\ episodes\ in\ year\ x}{Total\ population\ in\ the\ same\ year} \text{X}100$$

## 6.4 Results

A total of 544,162 patients aged ≥ 40 years and diagnosed with DM were identified, of which 28,772 patients (52.9%) were diagnosed with dementia during the study period. Of these 19,282 (67.0%) patients with both DM and dementia had at least one antidiabetic medication prescription.

### 6.4.1 Study population characteristics

Out of 28,772 patients who were identified and included in the analysis, 12,064 (41.9%) were males. The mean patient age at the start date was 80.76 (SD 7.80) years. The majority of the study population were T2DM (n = 27,792, 96.6%), while 980 (3.40%) patients were T1DM. The mean duration of DM was 10.2 (SD = 6.7) years. The mean HbA1c was 7.46 (SD 1.95). The most common type of dementia was vascular dementia contributing to 27.9% (n = 8,034), while Alzheimer's disease contributed to 21.4% (n = 6,162) and other dementia types accounted for < 2%; 49.1% (n = 14,125) of patients had no specific dementia type code. Full details on study population characteristics are presented in **Table 23**.

**Table 23 Study Population Characteristics**

| Characteristics | Diabetes Mellitus with Dementia 28,772 (100%) |
|---|---|
| **Mean age at start date (SD)** | 80.76 years (7.8) |
| **Gender** | |
| **Male** | 12,064 (41.9) |
| **Female** | 16,708 (58.1) |
| **Mean HbA1c (SD)** | 7.46 (1.95) |

| Characteristics | Diabetes Mellitus with Dementia 28,772 (100%) |
|---|---|
| **Diabetes types** | |
| **Type 1 diabetes mellitus** | 980 (3.4) |
| **Type 2 diabetes mellitus** | 27,792 (96.6) |
| **Dementia types** | |
| **Unspecified dementia** | 14,125 (49.1) |
| **Vascular dementia** | 8,034 (27.9) |
| **Alzheimer's disease** | 6,162 (21.4) |
| **Dementia with Lewy bodies** | 290 (1.0) |
| **Parkinson's dementia** | 139 (0.5) |
| **Frontotemporal dementia** | 22 (0.1) |
| **Comorbid conditions** | |
| **Chronic kidney disease** | 10,525 (36.6) |
| **Hypertension** | 19,110 (66.4) |
| **Arrhythmias** | 6,195 (21.5) |
| **Myocardial infarction** | 10,633 (37.0) |
| **Stroke** | 6,616 (23.0) |
| **Depression** | 9,546 (33.2) |
| **Heart failure** | 3,900 (13.6) |
| **Diabetic retinopathy** | 8,914 (31.0) |
| **Diabetic nephropathy** | 194 (0.7) |
| **Diabetic neuropathy** | 4,212 (14.6) |
| **Diabetic foot** | 2,095 (7.3) |

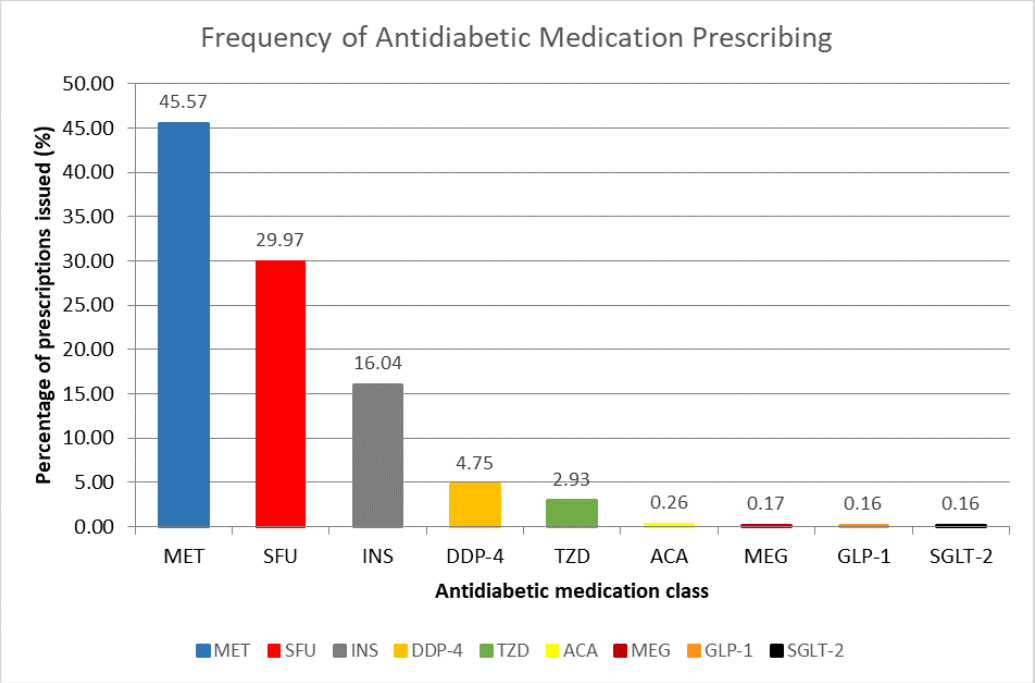
**SD** standard deviation

### 6.4.2 Antidiabetic medication prescribing

There was a total of 19,282 patients (67.01% of the cohort) who received 889,515 antidiabetic prescriptions between 2000 and 2016. There was a statistically significant difference in antidiabetic medication prescribing between males and females and between T1DM and T2DM patients ($p < 0.05$). Of the patients treated, (n = 10,836, 56.2%) were females and (n = 8,446, 43.8%) were males, and 94.9% were T2DM (n = 18,302) and 5.1% were T1DM (n = 980).

#### 6.4.2.1 Frequency of antidiabetic medication prescription

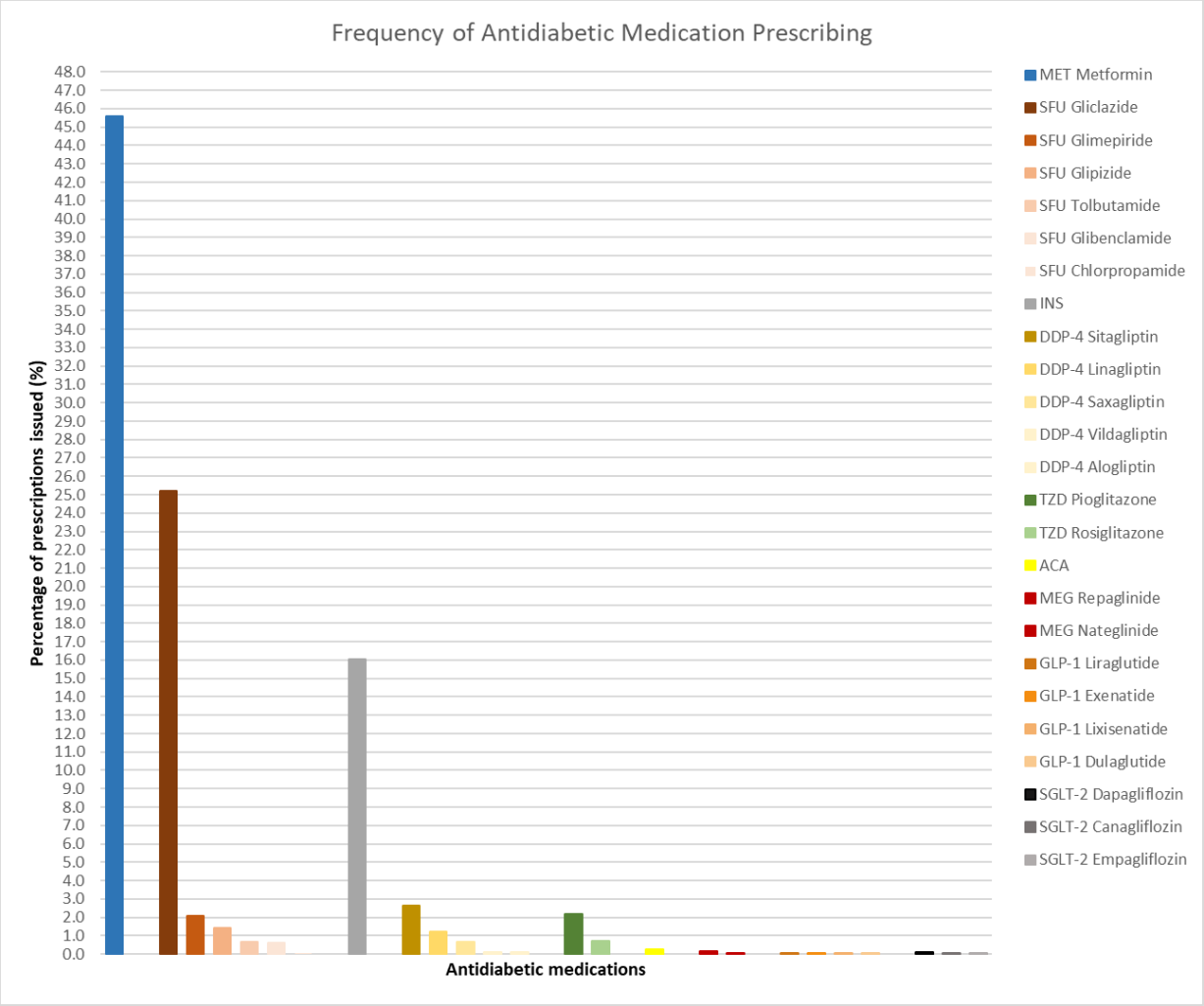
The most commonly prescribed antidiabetic medication class in the study population throughout the study period was metformin (405,375 prescriptions, 45.57% of all antidiabetic medication prescriptions), followed by sulfonylureas (266,560 prescriptions, 29.97%) and insulin (142,652 prescriptions, 16.0%). There were 42,268 (4.75%) prescriptions for DDP-4, and meglitinides prescriptions accounted for 1,495 prescriptions (0.17%) of all antidiabetic prescriptions issued to the cohort. The least prescribed antidiabetic medication classes were GLP-1 (1,417 prescriptions, 0.16%) and SGLT-2 (1,408 prescriptions, 0.16%) (**Figure 30).**




**MET** metformin, **SFU** sulfonylureas, **MEG** meglitinides, **TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **GLP-1** glucagon-like peptide-1 receptor agonists, **ACA** acarbose.

**Figure 30 Frequency of Antidiabetic Medication Prescriptions by therapeutic class among Study Population**

The highest number of sulfonylurea prescriptions was issued for gliclazide (224,278 prescriptions, 84.1%). Sitagliptin was the most frequently prescribed of the DDP-4 class (23,471 prescriptions, 55.5%). Repaglinide accounted for 1,323 prescriptions (88.5 %) of all meglitinides prescriptions issued to the cohort. The most commonly prescribed GLP-1 was liraglutide (669 prescriptions, 47.2%) and the most commonly prescribed SGLT-2 was dapagliflozin (1,021 prescriptions, 72.5%) (**Figure 31**).




**MET** metformin, **SFU** sulfonylureas, **MEG** meglitinides, **TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **GLP-1** glucagon-like peptide-1 receptor agonists, **ACA** acarbose.

**Figure 31 Frequency of Antidiabetic Medication Prescriptions by antidiabetic agent among Study Population**

### 6.4.2.2 Antidiabetic medication prescribing as monotherapy

A total of 8,346 (43.28%) patients were prescribed monotherapy during the study period. Of those patients, 86.04% (n = 7,181) were prescribed metformin monotherapy; 6.43%

(n = 537), 3.56% (n = 297) and 3.27% (n = 273) of patients were on sulfonylureas monotherapy, insulin monotherapy and DDP-4 monotherapy, respectively. Other antidiabetic medication classes were rarely prescribed as monotherapy (< 0.3%) (**Table 24**).

**Table 24 Antidiabetic Medication Class Prescribed as Monotherapy Among the Study Population**

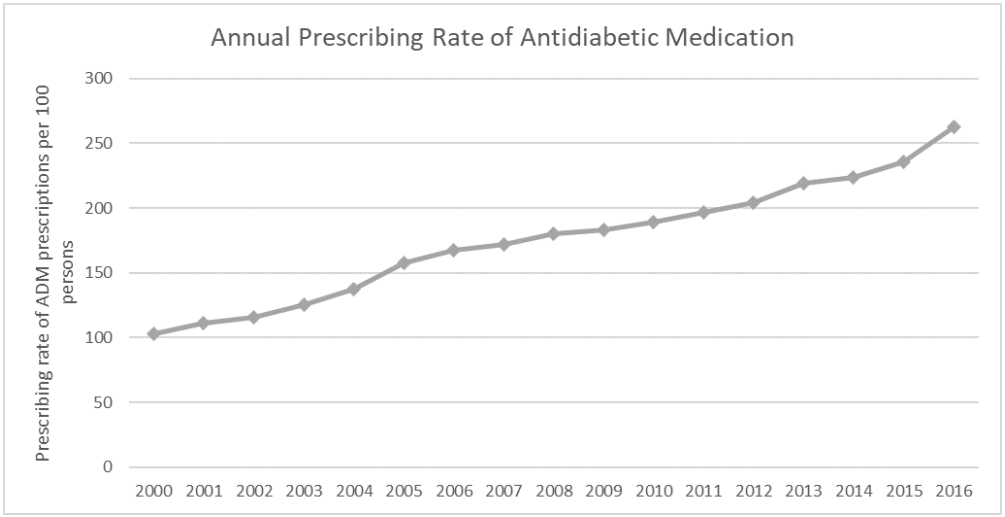
| Monotherapy ( antidiabetic medication class) | Number of patients n= 8346 (100%) |
|---|---|
| **Metformin** | 7,181 (86.0) |
| **Sulfonylurea** | 537 (6.43) |
| **Insulin** | 297 (3.55) |
| **Dipeptidyl peptidase-4 inhibitors** | 273 (3.27) |
| **Acarbose** | 20 (0.24) |
| **Thiazolidinedione** | 20 (0.24) |
| **Glucagon-like peptide-1 receptor agonists** | 17 (0.20) |
| **Meglitinides** | 1 (0.01) |

### 6.4.2.3 Annual prescribing rates of antidiabetic medications

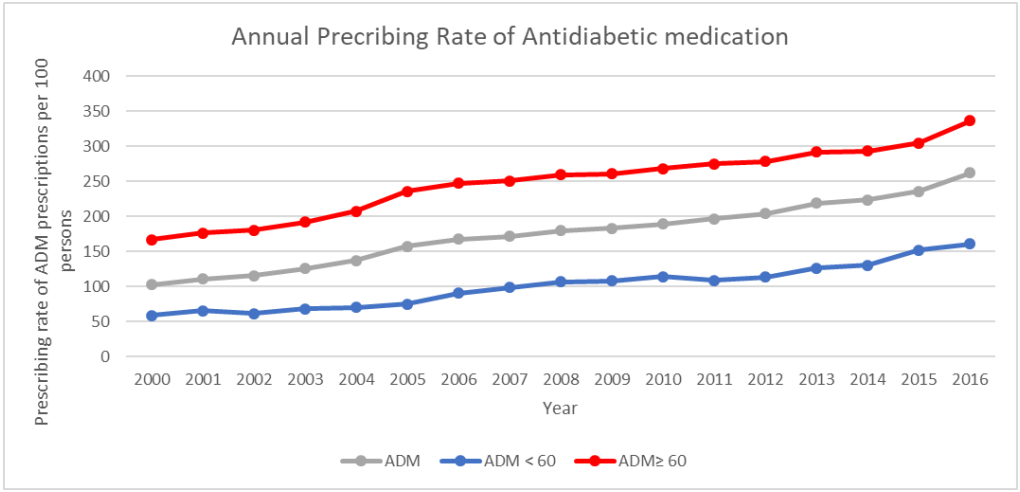
The prescribing rate of all antidiabetic medications between 2000 and 2016 among DM patients with dementia increased by over 1.5 times (155.0%) (from 102.9 [95% CI, 100.4–104.5] to 262.5 [95% CI, 255.2–269.9] prescriptions per 100 persons) with an average increase of 9.1% per year (**Figure 32A**). Antidiabetic prescribing rate during the study period among DM patients with dementia aged ≥ 60 years (166.9 [95% CI 155.7–170.2] in 2000 and 336.9 [95% CI 330.5–340.9] in 2016 prescriptions per 100 persons) was higher compared to patients aged < 60 years, (58.9 [95% CI 55.7–62.2] in 2000 and 160.5

[95% CI 151.5–168.9] in 2016 prescriptions per 100 persons) (**Figure 32B**). There was a continuous increase in the prescribing of antidiabetic medications in all therapeutic classes except sulfonylureas, meglitinides and acarbose: refer to **Figure 33 A.**

**A.**




**B.**




**ADM** antidiabetic medications

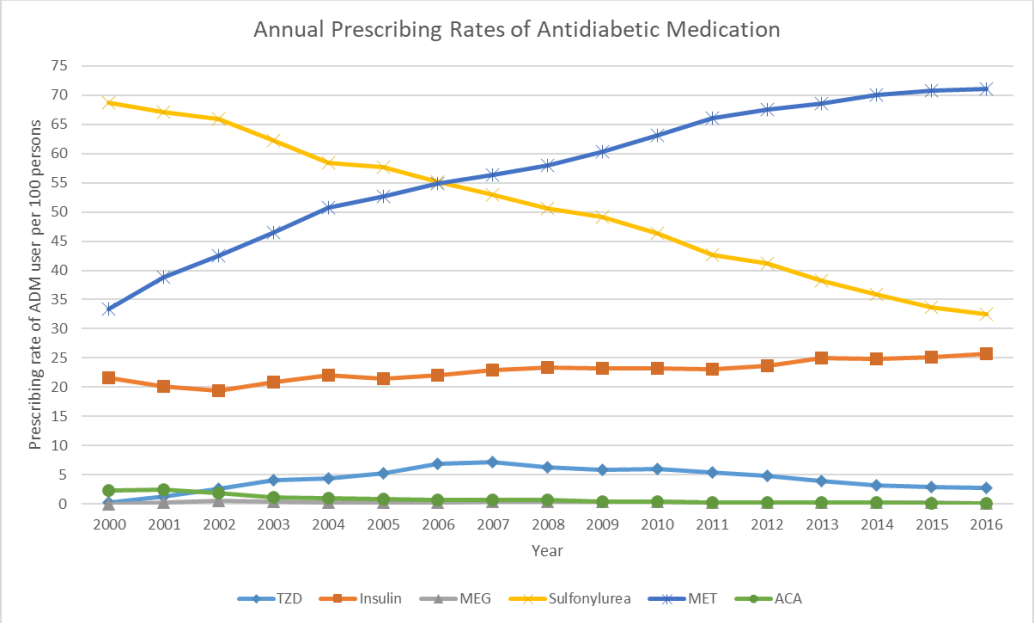
**Figure 32 Annual Prescribing Rate of Antidiabetic Medications Among Treated Study Population. A. Overall antidiabetic prescribing rate. B. Antidiabetic prescribing rate stratified by age groups.**

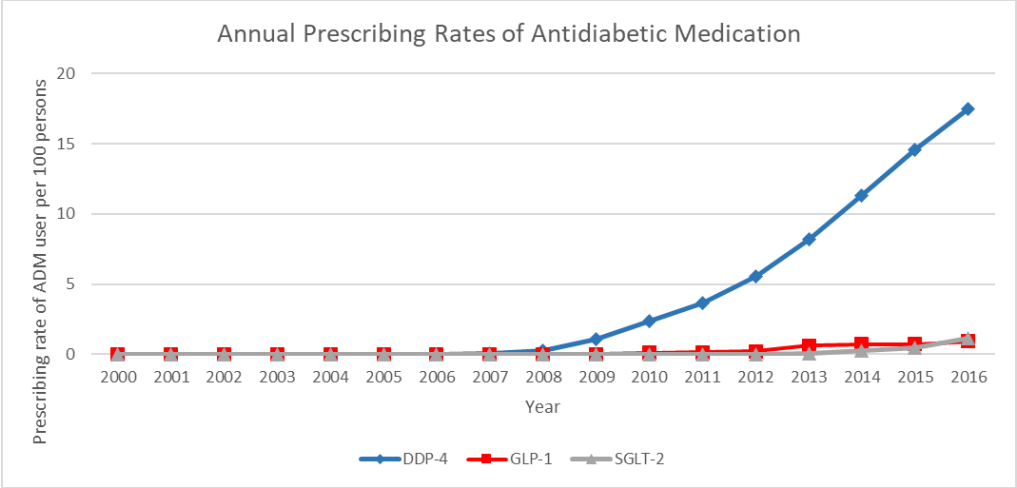
During these years, the prescribing rate of metformin, thiazolidinedione, GLP-1, SGLT-2, and DDP-4 increased. The rate of metformin prescribing doubled (from 33.4 [95% CI, 28.7–38.8] in 2000 to 71.0 [95% CI, 68.7–72.9] in 2016 per 100 persons), while the rate of thiazolidinedione increased twelvefold (1200%) (from 0.2 [95% CI, 0.03–1.4] to 2.7 (95% CI 2.3–3.2] per 100 persons), and the prescribing rate of GLP-1 increased thirtyfold (3000%) (from 0.03 [95% CI, 0.02–0.05] to 0.93 [95% CI, 0.19–1.3] per 100 persons). The prescribing rate of SGLT-2 increased about fortyfold (3900%) (from 0.04 [95% CI, 0.01–0.2] to 1.6 [95% CI, 1.2–2.1] per 100 persons). Finally, the rate of DDP-4 prescribing increased from 0.04 (95% CI, 0.01–0.3) to 17.5 (95% CI, 16.4–18.7) per 100 persons. However, the prescribing rate of sulfonylureas, meglitinides and acarbose showed a downward trend in DM patients with dementia. There was an overall decrease in the prescribing of sulfonylureas by half (-52.8%) (from 68.8 [95% CI, 61.9–76.4) to 32.5 [95% CI, 30.9–34.1) per 100 persons). The rate of meglitinides prescribing also decreased by more than half (-60%) (from 0.3 [95% CI, 0.07–1.1] to 0.12 [95% CI, 0.05–0.3] per 100 persons). Finally, the prescribing rate of acarbose declined by almost double (-93.33%) (from 2.4 [95% CI, 1.3 – 4.2] to 0.16 [95% CI, 0.08 - 0.3] per 100 persons) over the study period. The rates of insulin prescribing remained relatively steady with an overall slight increase by 18.9% from 21.6 (95% CI, 17.9–26.1) to 25.7 (95% CI, 24.3–27.2) per 100 persons.

Between 2000 and 2016, the highest rate of antidiabetic medication prescribing among all therapeutic classifications was for metformin, with an average increase of 2.2% per

year. The DDP-4 prescribing rate increased less sharply in comparison, with an average of 1.7% per year during the same duration. The overall increase in insulin prescribing rate was similar to thiazolidinedione and SGLT-2 with an average of 0.2% per year. Looking at the thiazolidinedione prescribing data in detail shows that the prescribing rate peaked in 2007 at 7.2 (95% CI, 6.3–8.3) per 100 persons, and then decreased to 2.7 (95% CI, 2.3–3.2) per 100 persons in 2016.

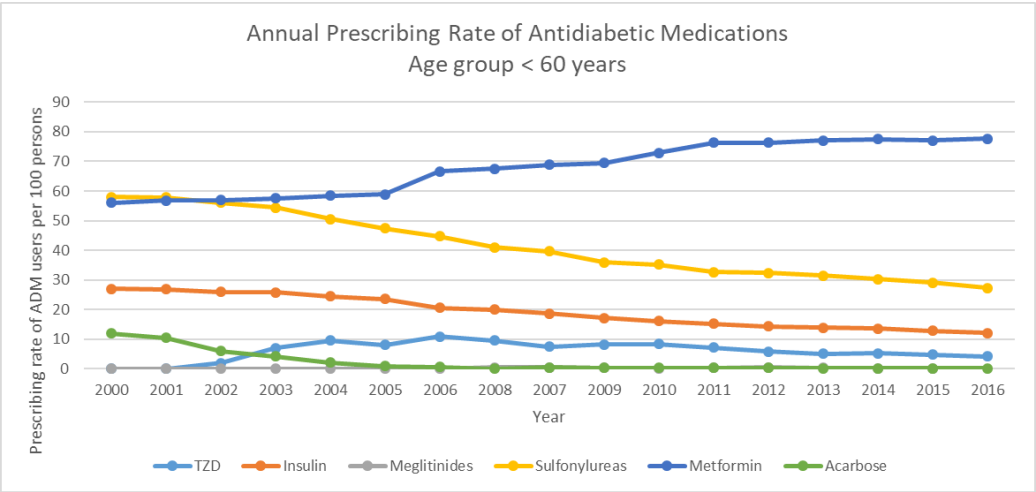
**A.**

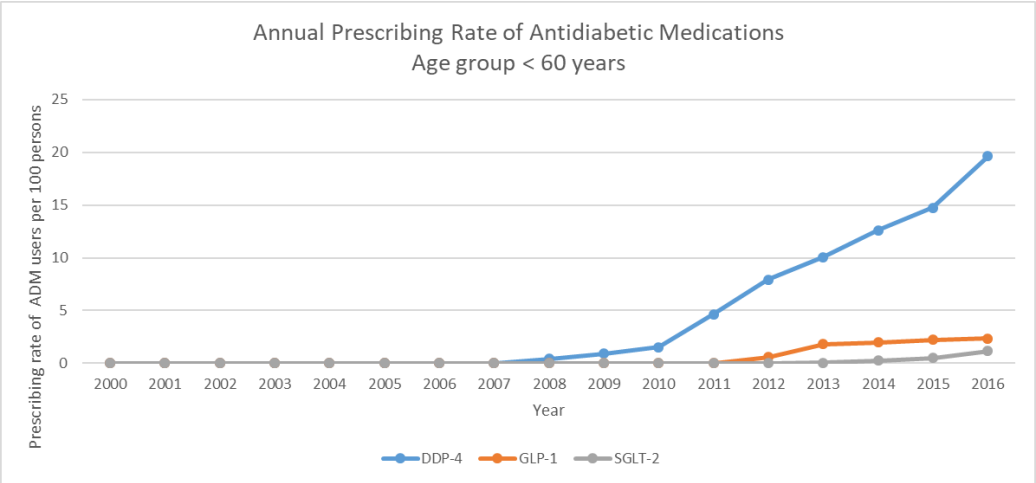



**ADM** antidiabetic medication **MET** metformin, **SFU** sulfonylureas, **MEG** meglitinides, **TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **GLP-1** glucagon-like peptide-1 receptor agonists, **ACA** acarbose.

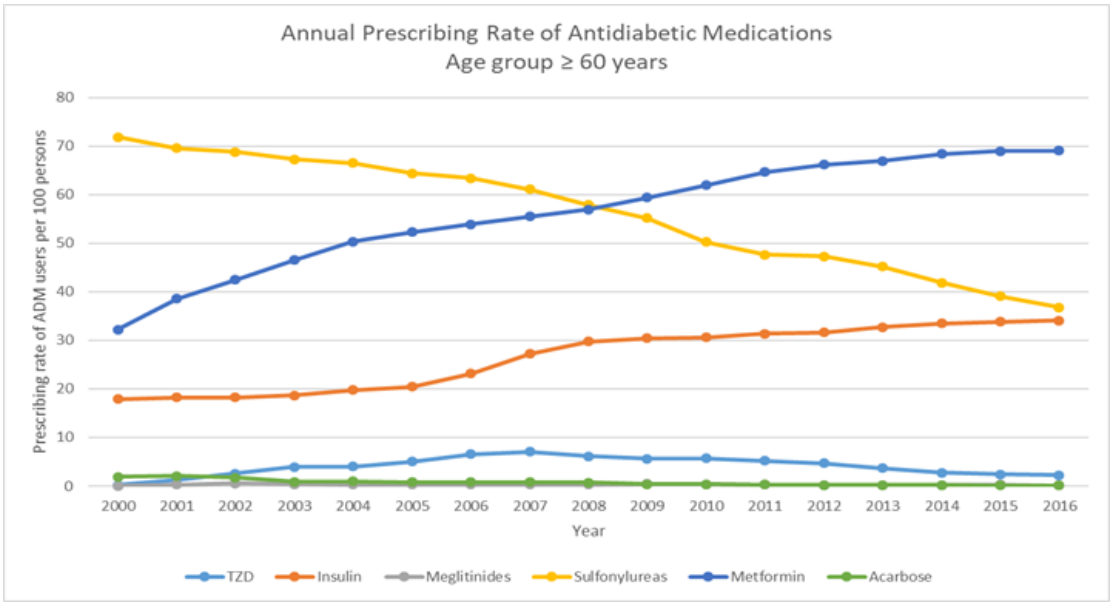
**B.**

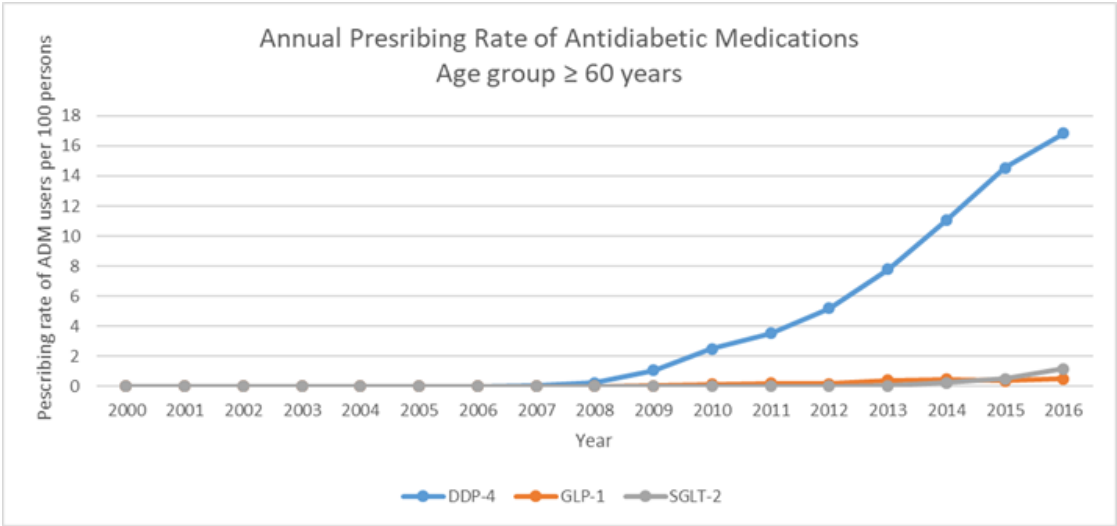



**TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **GLP-1** glucagon-like peptide-1 receptor agonists.

**C.**




**TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **GLP-1** glucagon-like peptide-1 receptor agonists.

**Figure 33 The Annual Prescribing Rates of Antidiabetic Medication among the Treated Study Population A. Overall prescribing rate stratified by antidiabetic therapeutic class. B. Prescribing rate stratified by Age group (< 60 years). C. Prescribing rate stratified by age group (≥ 60 years).**

Furthermore, I stratified the study population based on age into two age groups (< 60 years and ≥ 60 years) and a similar rate of all antidiabetic classes was found across both age groups. However, an increase in the prescribing rate of insulin was found among patients aged 60 years and above from 17.8% (95%CI 17.1%–25.4%) in 2000 and 34.07% (95% CI 33.5%–37.1%) in 2016 and there was a decreased prescribing rate of insulin among patients aged below 60 years from 27% (95% CI 25%–32.1%) in 2000 and 12.05% (95% CI 8.9%–14.3%) in 2016. The prescribing rate of sulfonylureas during the study period was also significantly higher among patients aged 60 years and above compared to patients aged below 60 years (p-value < 0.001). (**Figure 33 C&B**)

### 6.4.3 The rate of hypoglycaemic episodes

A total of 1,148 (5.95%) treated patients experienced 1,671 hypoglycaemic episodes between 2000 and 2016. The annual rate of hypoglycaemia among patients with DM and dementia increased eightfold (830.3%) from 0.92 (95% CI, 0.34–2.5) in 2000 to 8.6 (95% CI, 7.7–9.3) per 100 persons in 2016, with an average increase of 0.5% per year (**Figure 34A**). Of the patients who developed hypoglycaemia, 57.75% (n = 663) were females. The majority of hypoglycaemic episodes (91.38%, n=1,527) were experienced by T2DM patients and 8.62% (n = 144) of hypoglycaemic episodes were experienced by T1DM patients. Insulin was the most frequent antidiabetic medication prescribed for those patients (50%) who experienced hypoglycaemia during the study period.

Furthermore, I stratified the study population who experienced hypoglycaemia by age into two groups: those below 60 years and those above 60 years. The results revealed that the rate of hypoglycaemia experienced by patients aged 60 years and above significantly increased from 1.5% (95% CI, 1.1–1.9) in 2000 and 11.1% (95% CI, 10.6–11.9) in 2016, which was higher compared to patients aged below 60 years, for whom the rates was 0.07% (95% CI, 0.04–0.13) in 2000 and 0.5% (95% CI, 0.3–0.9) in 2016 (**Figure 34B**).

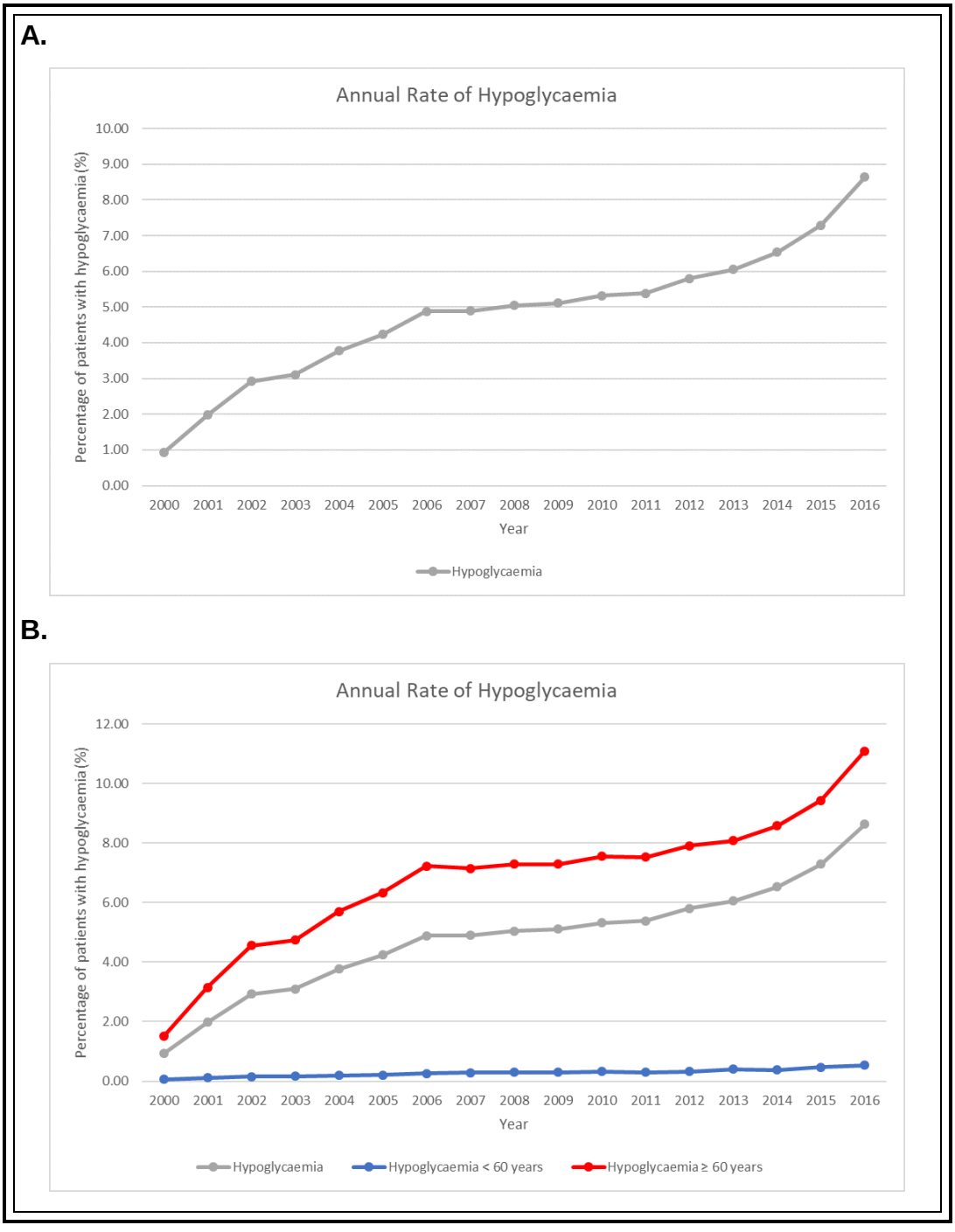



**Figure 34 The Annual Rate of Hypoglycaemia Among Treated DM Patients with Dementia A. An Overall hypoglycaemic rate, B. Hypoglycaemic rate stratified by age groups.**

### 6.4.4 Antidiabetic medication prescribing trends and hypoglycaemia rate

By comparing the trends of antidiabetic medication prescribing with the rate of hypoglycaemia during the same study period, I found a synchronised constant increase in their prescribing accompanied by an increase in hypoglycaemia episodes, with a strong positive correlation coefficient of 0.96 (**Figure 35**).

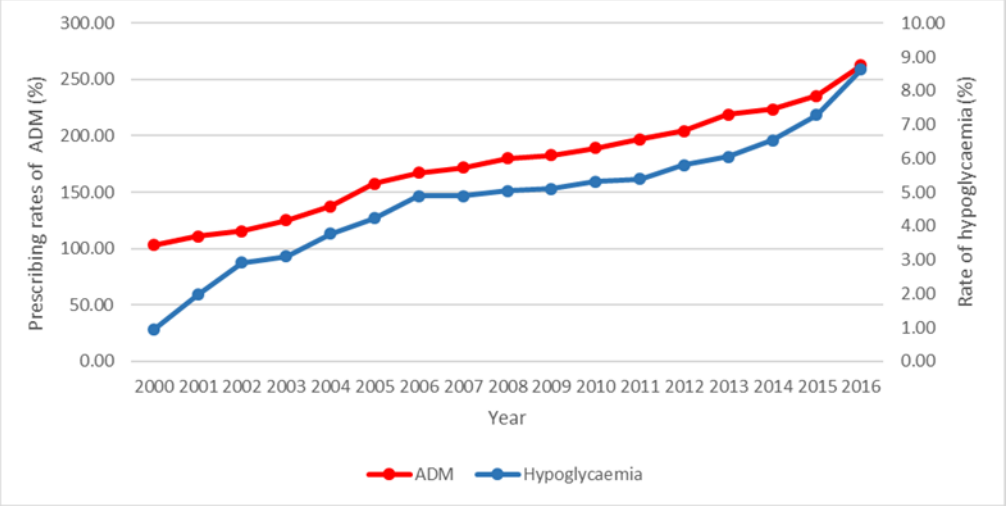



**Figure 35 Trends of Antidiabetic Medication Prescribing, and Hypoglycaemia Rates**

## 6.5 Discussion

The findings of this study showed that there was a rapidly rising trend in the prescribing of antidiabetic medications in the UK during the 17 years of the study period, accompanied by an increase in the rate of hypoglycaemia among DM patients with dementia during the same period.

The current study shows that 57% (n = 10,936) of patients were prescribed more than one antidiabetic medications. The overall prescribing rate of antidiabetic medications

increased by 1.5 times (155.1%) and the hypoglycaemia rate by eight times (830.3%). The increase in the prescribing of antidiabetic medications may reflect an increase in the DM population or an increase in the use of combination antidiabetic medications due to intensified treatment regimens to achieve better glycaemic control.

### 6.5.1 Antidiabetic medication prescribing trends

Previous studies investigating the trend of antidiabetic medication prescribing and estimating the rate of hypoglycaemia in patients with DM and dementia are limited. Most of the published studies were restricted to patients with DM without dementia. Therefore, I was unable to make a direct comparison with previous studies as they used different populations.

Available data show that the overall trends in the prescribing of antidiabetic medications for the DM population and wider age groups in the UK with a different study period were generally consistent with the results observed in the present study (Sharma et al., 2016, Hamada and Gulliford, 2015, Datta-Nemdharry et al., 2017, Curtis et al., 2018). Similar to my study findings, all previous studies showed that over the two study periods from 1990 to 2013 and from 2000 to 2017, the three most commonly prescribed classes of antidiabetic medications remained the same: metformin, sulfonylureas and insulin (Hamada and Gulliford, 2015, Wilkinson et al., 2018). Furthermore, they found that the prescribing rate was higher among females than males (Hamada and Gulliford, 2015, Datta-Nemdharry et al., 2017, Wilkinson et al., 2018).

The increased rate was not consistent across different antidiabetic therapeutic classes. The most commonly prescribed antidiabetic medication class was metformin, with a

sharp increase in their prescribing between 2000 and 2016 with an average increase of 2.2% per year. This was in accordance with the recommendations from the NICE guidelines for diabetes management (National Institute of Clinical Excellence, published 2015). Since 2005, metformin was the recommended first-line treatment for diabetes management due to its long-term benefits in reducing cardiovascular risks and organ damage without significant weight gain or hypoglycaemic episodes (Inzucchi et al., 2015, Holman et al., 2008).

I observed a slight increase in the percentage of insulin use with an overall increase by 19%, which confirms previous studies' findings (Sharma et al., 2016). The observed increase in the prescribing of insulin may reflect the recommendations of two landmark trials, suggesting possible benefits of intensive glycaemia control in reducing microvascular complications and cardiovascular events, which can be achieved by earlier initiation of insulin (UKPDS group, 1998, Nathan et al., 1993). However, intensive glycaemic control was found to be associated with more frequent hypoglycaemic episodes particularly in the elderly population and this becomes a barrier for diabetes management (Ober et al., 2006). Therefore, current guidance does not support the early introduction of insulin to achieve tight glycaemic control (The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008).

As noticed and supported by previous studies, the prescribing of sulfonylureas, thiazolidinedione and acarbose fell during the study period (National Institute of Clinical Excellence, published 2015, Inzucchi et al., 2015). This is due to the risk of hypoglycaemic episodes associated with sulfonylureas and safety alerts regarding

cardiovascular complications related to thiazolidinedione, mainly with rosiglitazon and highlighted by the FDA in 2007 (Nathan, 2007) and by the European Medicines Agency (EMA) in 2008 (EMEA., 2008). In addition, the availability of safer and new treatment options may explain the decline in their use despite their efficacy (Genuth, 2015). My study results were consistent with the global warning and showed that the prescribing rate of TZD increased from 0.19% (95% CI, 0.02–1.4) in 2000 to 7.22% (95% CI, 6.3–8.3) in 2007, but then fell to 2.7% (95% CI, 2.3–3.2) in 2016. Acarbose use was restricted by NICE guidelines for patients who cannot tolerate other oral agents, resulting in a decline in its use (National Institute of Clinical Excellence, published 2015).

Meglitinides were used by less than 1% of patients with DM and dementia annually in my study compared to less than 2% of DM patients annually between 2000 and 2013 (Sharma et al., 2016). Due to the high risk of hypoglycaemia, the requirement for multiple daily dosing and the fact that it is more expensive than sulfonylureas, the use of meglitinides is limited (National Institute of Clinical Excellence, published 2015). Repaglinide was the most commonly prescribed meglitinide compared to nateglinide, perhaps due to its better glycaemic control and safety profile (Li et al., 2009, Rosenstock et al., 2013).

Prescribing of new classes of antidiabetic medications, including DDP-4s, GLP-1 agonists and SGLT-2 inhibitors, increased. In the DDP-4 group, sitagliptin was the most commonly prescribed active ingredient, which confirms what has been reported in other studies (Hampp et al., 2014, Clemens et al., 2015). However, DDP-4 has rarely been used as monotherapy since its emergence in 2006 (Sharma et al., 2016). A recent study

also suggested that DPP-4 may be a better option for add-on therapy for patients with DM on a combination of metformin and sulfonylureas, due to the associated lower risk of mortality, microvascular and macrovascular complications (Wong et al., 2019).

In 2009, GLP-1 analogues were introduced as antidiabetic medication by NICE (National Institute for Health and Care Excellence, 2009, National Institute for Health and Care Excellence, 2010). I have shown that the prescribing of GLP-1 analogues in UK primary care remains low with an average increase of 0.1% per year. However, it increased from 0.03% (95% CI, 0.004–0.21) in 2009 to 0.93 % (95% CI, 0.70–1.20) in 2016 with a thirtyfold (3078%) overall change during the study period. NICE guidelines recommended the use of GLP-1 in patients who are on two other classes of antidiabetic medications, for who at least three classes of antidiabetic medication are contraindicated or who are obese. These recommendations may explain the lower use of GLP-1 in the UK (National Institute for Health and Care Excellence, 2015b).

The overall prescribing of SGLT-2 inhibitors increased by 0.3% per year. This class is the newest class of antidiabetic medication; it was licensed for use in the UK by NICE in 2012 (National Institute for Health and Care Excellence, 2016a). The prescribing of GLP-1 and SGLT-2 inhibitors in my study was similar to the rate of prescribing these drugs in other UK studies of the DM population without dementia between 2000 and 2013 using the same database (Sharma et al., 2016).

The overall prescribing patterns reflect NICE guidelines in particular (National Institute for Health and Care Excellence, 2019). Metformin emerged as the most commonly prescribed medication. Further, the prescribing rate of sulfonylureas declined over the

study period. This is because the elderly population is at higher risk of developing hypoglycaemia. However, insulin, despite its limitations, remained the second most common therapy prescribed, which may reflect the disease progress. Finally, the latest NICE updates encourage greater use of the new antidiabetic medications for DM patients, which are associated with fewer hypoglycaemic events.

### 6.5.2 Hypoglycaemic episode rates

The annual rate of hypoglycaemia increased during the study period, reaching 8.63% (95% CI, 7.7–9.3) per 100 persons in 2016, representing an overall eightfold increase (830.3%) over the study period. Further, the annual rate of hypoglycaemia was higher in patients aged above 60 years compared to patients aged below 60 years. Similar trends were observed in the studies by Naser et al. and Zaccardi et al., which covered the period from 1999 to 2016 and from 2005 to 2014, respectively, in patients with DM only (Naser et al., 2018, Zaccardi et al., 2016). However, the increase in the rate of hypoglycaemia in patients with DM from 1999 to 2016 was much lower in Naser's study (17.2 and 47.1 per 100,000) compared to my study population (Naser et al., 2018). This could be attributed to the difference in the aggregate data and individual level data used.

### 6.5.3 Antidiabetic medications prescribing trends and hypoglycaemia rate

The findings of this study demonstrate that there is a parallel increase in the rate of antidiabetic medication prescribing and the rate of hypoglycaemia in the UK. The increased prescribing trend of all antidiabetic medications supports the hypothesis that aggressive antidiabetic treatments (using insulin, sulfonylureas or multiple antidiabetic

medications) is associated with the increased risk of hypoglycaemia in patients with DM and dementia. The Correlation coefficient between hypoglycaemia and antidiabetic medication prescribing rates was 0.96, which reflects a strong positive linear relationship.

Based on this, I can assume that elderly patients with dementia were treated with an intensified antidiabetic regimen, which may be associated with the increased risk of hypoglycaemia. Elderly patients with dementia were substantially more likely to develop hypoglycaemia due to multiple comorbidities, undernutrition, polypharmacy, long disease duration, and kidney or liver failure (Abdelhafiz et al., 2015, Meneilly and Tessier, 2016). With this in mind, I hypothesise that dementia in elderly patients with diabetes using antidiabetic medications is a factor that is associated with the increased rate of hypoglycaemia. The previous literature has explored this assumption and reported that dementia and the use of insulin- or sulfonylurea-based antidiabetic therapy in T2DM patients newly treated with antidiabetic therapy were associated with more hypoglycaemia events (Bruderer et al., 2014b).

Based on the study findings, clinicians should carefully monitor antidiabetic medications among elderly patients with DM and dementia (Bruce et al., 2009). If appropriate, individualised care and treatment strategies should be provided by regular review of antidiabetic regimens, either switching and/or de-intensifying of antidiabetic medications (Leung et al., 2018).

### 6.5.4 Strengths and limitations

This study has some strengths. Firstly, to my knowledge this is the first study to detail changes in the prescribing of antidiabetic medications and the rate of hypoglycaemia in patients with diabetes and dementia between 2000 and 2016 using the IMRD-UK database. Secondly, the information recorded in the IMRD-UK database is broadly representative of the UK population and it provides great insight into real-world clinical practice (Blak et al., 2011).

This study has also limitations. Firstly, antidiabetic medication prescribing may be underestimated as the IMRD database only contains information from primary care settings. The record of prescriptions in the IMRD-UK database is not systematically generated in non-primary healthcare settings. Therefore, it was not possible to include patients who were treated in specialised centres (secondary, tertiary, private). However, it is well established that the majority of antidiabetic medication prescribing for DM patients is done in primary care (Willens et al., 2011). Therefore, I would not expect my study results to be affected significantly. Secondly, due to the nature of the descriptive study design, I did not investigate the factors associated with the trends in the prescription of antidiabetic medications and hypoglycaemia including patients' biological profile (such as their renal and liver function), socioeconomic status or ethnicity. Moreover, antidiabetic medication costs may also influence the trend of prescribing as antidiabetic medication costs account for approximately 10% of the total cost of National Health Service primary care spending (Hex et al., 2012). Thirdly, almost half of the study population was recorded with non-specific codes of dementia subtypes, which did not allow me to stratify the

antidiabetic medications prescribing by dementia subtype. Fourthly, information on patient compliance and adherence to the prescribed medications was not available in the database, which may significantly affect glycaemic control and in turn can affect the rate of hypoglycaemia. Finally, data on non-severe asymptomatic hypoglycaemic events were not collected and only symptomatic hypoglycaemia documented by GPs was included. Under-reporting of hypoglycaemia by patients or poor clinical documentation by GPs may lead to an underestimation of the frequency of true hypoglycaemic events (Östenson et al., 2014).

## 6.6 Conclusion

This study demonstrates that there were parallel increases in the rate of antidiabetic prescriptions and the rate of hypoglycaemia in patients with diabetes and dementia, particularly for those on insulin therapy. Therefore, further analytical studies are encouraged to investigate the association between individual antidiabetic medications and other risk factors of hypoglycaemic episodes among patients with diabetes and dementia.

# 7 CHAPTER SEVEN: The Association between Dementia and the Risk of Hypoglycaemia Events among Patients with Diabetes Mellitus: A Propensity Score Matched Cohort Analysis

The findings of the drug utilisation study in Chapter Six suggest that diabetes patients with dementia are at an increased risk of experiencing hypoglycaemia. The systematic

review in Chapter Two highlights that there is limited evidence on the association between dementia and the risk of hypoglycaemia, with no study having investigated the association between dementia and the risk of hypoglycaemia in terms of the occurence of hypoglycaemia among the diabetes and dementia population in the UK in general, without restricting the definition of hypoglycaemia to specific severity. This chapter presents a cohort study that was conducted to test the hypothesis drawn in Chapter Six, and to bridge the research gap that was highlighted in the systematic review (Chapter Two).

## 7.1 Introduction

Hypoglycaemia is defined as a condition where blood glucose falls below normal levels, less than 70 mg/dL (American Diabetes Association, 2019). It is the most common side effect in DM management and becomes a barrier for effective glycaemic control (Morales and Schneider, 2014, Östenson et al., 2014). Several factors may participate in developing hypoglycaemia. They can be categorised into three categories: medications use, comorbid diseases and individual factors.

Drug-induced hypoglycaemia is frequently experienced by diabetic patients, particularly those who are using insulin analogues and sulfonylureas compared to other classes of antidiabetic medications (Frier, 2014, Amiel et al., 2008, Edridge et al., 2015). Other medications are also associated with hypoglycaemia, including quinolones, pentamidine, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (Murad et al., 2009). Comorbid diseases are considered to be the second risk factor that may contribute to the occurrence of hypoglycaemia. These include dementia, cardiovascular disease, renal failure and depression (Morales and Schneider, 2014, Rubin and Golden, 2013). Finally, individual factors that play a role in the occurrence of hypoglycaemia are

patient's age, female gender, low BMI, DM type, history of hypoglycaemia, glycaemic control and malnutrition (Rubin and Golden, 2013, Morales and Schneider, 2014).

Cognitive impairment, including dementia or milder forms of cognitive dysfunction, may delay recognition of the warning symptoms of hypoglycaemia, which is fundamental to effective self-management and to prevent progression in severity (McAulay et al., 2001, Bremer et al., 2009).

The results of the systematic review in Chapter Two showed that there are limited studies that discuss the association between dementia and the risk of hypoglycaemic events. The majority of these studies looked at the association between dementia and the risk of hypoglycaemia with a different study population and study design. However, it is important to determine the influence of dementia diagnosis on the risk of developing hypoglycaemia in a large and representative diabetic population for predicting severe hypoglycaemia and forming a strategy to prevent its complications in patients with dementia and to improve their quality of life.

The first two studies in this PhD project showed synchronised trends of the prevalence and incidence of dementia and the rate of hypoglycaemia. The current study in this chapter has enabled me to explore the primary hypothesis of this PhD project: diabetes patients with dementia diagnosis using antidiabetic medications have a higher risk of hypoglycaemia than diabetes patients without dementia.

## 7.2 Aim and objective

This study aimed to determine the impact of the diagnosis of dementia on the risk of hypoglycaemic events. The specific objective was to determine whether the risk of hypoglycaemic events in patients with diabetes is increased by dementia.

## 7.3 Methods

### 7.3.1 Study design

A population-based, retrospective cohort study was conducted. Patients with DM and dementia recorded in their medical records during the period of January 2000 to September 2017 in the IMRD-UK database were identified and included in the study.

Observational studies using real-world databases have a very large sample size and aim to be more population representative than RCTs; they include the unselected patients in the RCTs (e.g. elderly patients or those with comorbid conditions) and provide information on treatment practices in these specific populations (Cohen et al., 2015). The retrospective cohort design is a type of observational study, which is a useful technique for investigating disease occurrence and its association with exposure retrospectively. It is also called a historical cohort study (Song and Chung, 2010). Thus, it is considered a suitable technique to reveal the temporal sequence between exposure and outcomes (Song and Chung, 2010). The retrospective cohort design is a convenient study design commonly used in pharmacoepidemiology to investigate the association between the risk factors and the outcome of interest and it has the advantage of studying multiple outcomes with the same exposure and is efficient at investigating rare exposures (Song and Chung, 2010). Additionally, a retrospective cohort design is relatively inexpensive, quick and easy to perform compared to a prospective cohort design because of the availability of data (Song and Chung, 2010).

### 7.3.2 Data source

The IMRD-UK database is a large electronic patient data recorded by GPs during routine clinical practice and currently has anonymised clinical data for 13 million patients (covering approximately 6% of the UK population) registered with 744 general practices

across the UK (Blak et al., 2011). Refer to **sections 4.2 and 4.3** for more details about IMRD-UK database.

### 7.3.3 Data extraction

Data were extracted from IMRD-UK using Read codes from 1 January 2000 to 26 September 2017 (**Appendix 10**). Extracted data include: patients' demographics, such as age, gender, BMI, smoking status, alcohol consumption status; medical history (coexisting disease); DM-specific information, including records of DM diagnosis including T1DM and T2DM, duration of the disease and DM complications; medication use history, including antidiabetic medications and other prescribed medications; dementia-specific information, including records of dementia diagnosis and records of anti-dementia medication; all records of hypoglycaemic events. The Read codes used in this cohort were obtained from previously published code lists (University of Cambridge) and published studies (Doran et al., 2011, Mongkhon et al., 2020).

### 7.3.4 Inclusion criteria for study patients

The inclusion criteria for this study were:

1. Patients aged 50 years or over.
2. Patients had prevalent DM at baseline or developed DM during the follow-up period, including both T1DM and T2DM.
3. Patients who had at least two antidiabetic prescriptions and registered in IMRD-UK were identified and followed up from January 2000 onwards.

Follow-up ended at the earliest on the following points: the date the patient left the practice, the date of death, the date the patient experienced hypoglycaemia (the outcome of interest after index date), or the last date of data collection.

#### 7.3.4.1 Exposure group

Patients who met the above-mentioned inclusion criteria were identified. Exposure was determined by dementia diagnosis. All identified patients who had dementia at baseline or developed dementia were included and placed in the dementia group and defined as the exposed group. The index date for each exposed patient was defined as the date of the latest first record between DM diagnosis and dementia diagnosis (coexistence of both diseases).

#### 7.3.4.2 Selection of the comparison group

Patients with DM and dementia diagnosis were compared to patients diagnosed with DM only; the latter formed the non-exposed group (comparison group). To remove immortal time bias, the index date for patients in the non-exposed group was assigned randomly based on the index date of the exposed group by incidence density sampling method. Patients who had the follow-up date before the assigned index date were excluded from the study.

### 7.3.5 Confounding factors

Confounding factors are external influences that may change the effect of both dependent and independent research variables, leading to invalid results (Nørgaard et al., 2017). Non-randomised epidemiological research is susceptible to bias due to confounding factors. This commonly occurs in observational studies of associations between a specific exposure and outcome of interest using large databases (Nørgaard et al., 2017). The confounding factors include age (< 65 years and ≥ 65 years), sex, BMI (categorised into 5 categories: BMI < 18.5, BMI = 18.5–24.9, BMI = 25–29.9, BMI = 30–39.9, BMI ≥ 40), smoking status (categorised into three categories: non-smoker, ex-smoker and smoker), alcohol consumption (categorised into three categories: non-drinker, ex-drinker and drinker), HbA1c (categorised into 5 categories: HbA1c < 4, HbA1c = 4–5.7, HbA1c = 5.7–

6.4, HbA1c = 6.5–13.9, HbA1c ≥ 14), diabetes duration (≤ 5 years and > 5 years) and history of hypoglycaemic events at baseline or prior to the study entry date. Chronic comorbidities history in the last 12 months included diabetes microvascular complications (including neuropathy, nephropathy, retinopathy and diabetic foot), hypertension (HTN), myocardial infarction (MI), arrhythmias, heart failure (HF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), depression, cerebrovascular disease (CeVD) and obesity. Finally, medication use in the last six months included antidiabetic medications classified based on the BNF (24) according to their therapeutic class: insulin, biguanides (metformin), sulfonylureas, meglitinides, thiazolidinedione (TZD), dipeptidyl peptidase-4 inhibitors (DDP-4), sodium-glucose cotransporter-2 inhibitors (SGLT-2), glucagon-like peptide-1 receptor agonists (GLP-1), and acarbose. Other prescribed medications included angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta blockers (BBs), calcium channel blockers (CCBs), antiarrhythmic medication, statins, aspirin, antidepressants and anti-dementia medications (i.e. study entry date).

### 7.3.6 Ethical considerations

Ethical approval was granted by the research ethics committee of the database before the study commenced in July 2018 (SRC reference number: 18THIN054): refer to **Appendix 11**.

### 7.3.7 Data quality and cross-check

To confirm the accuracy and the quality of the study findings, the data analyses were checked by (K.M.) and (W.L.) well-trained and experienced specialists in the field of pharmacoepidemiology methodologies in medication research with clinical large

databases, including IMRD-UK data from the School of Pharmacy at University College London (UCL).

## 7.3.8 Statistical analysis

### 7.3.8.1 Data analysis

Data were analysed using statistical software (SAS, version 9.4). Descriptive statistics were used to describe the patients' demographic characteristics, medication use and comorbidities. Data are presented as mean ± SD for continuous variables and as frequencies (%) for categorical variables.

Incidence density sampling is a method used to produce unbiased results by selecting the non-exposed group without replacement from all persons at risk at the time of exposure occurrence (Richardson, 2004). This method was used to assign an index date to the non-exposure group by matching the exposed to a sample of the non-exposed who were at risk at the exposure index date. Therefore, the immortal bias is eliminated.

The multiple imputation technique was conducted to handle missing data. It included BMI, HbA1c, smoking and alcohol consumption, and these variables were used in the final analysis with 25 imputations to produce imputed data. For more details about the multiple imputation technique, refer to **section 4.4.3.**

In the primary analysis, Cox proportional hazards regression was used to estimate the hazards ratios (HR) of hypoglycaemic events for whole patients. The Cox proportional hazards assumption was checked by Kaplan-Meier curves.

The HR estimated the risk of hypoglycaemia associated with dementia by comparing DM patients with dementia (exposed) with DM patients without dementia (non-exposed). The full model was adjusted for all above-mentioned covariates.

A PS matched analysis was also carried out as the secondary analysis. To balance the distribution of observed baseline covariates between the exposed and non-exposed group, I matched each exposed patient with up to two non-exposed patients by the propensity score (PS) matching method. Propensity scores were estimated by logistic regression with the confounding variables, including baseline variables, chronic comorbidities history, which was measured over a 12-month period prior to the index date and medication use, which was assessed over a six-month period preceding the index date (all variables are presented in **Table 25**). The balance achieved by matching PS was assessed using standardised differences; an absolute standardised difference between study groups < 0.1 was considered negligible.

The statistical significance level was set at 95% CI and p-value < 0.05 was considered statistically significant.

#### 7.3.8.1 Sensitivity analyses

Four sensitivity analyses were conducted: (1) performing a complete case analysis; (2) the missing-indicator method by creating a new category to indicate the missing data (vs the multiple imputation method for the missing data in the final analysis), refer to **section 4.4.3** for more details about complete case analysis and the missing-indicator method; (3) an inverse probability of treatment weighting (IPTW) using the PS method was applied (vs PS matching in my secondary analysis). IPTW is a statistical analysis that uses PS to create weights, forming a pseudo-population in which there is no longer an association between the measured confounders and exposure (Austin, 2011); (4) an additional sensitivity analysis was conducted to assess the robustness of my results against any unmeasured confounding using the E-value method (VanderWeele and Ding, 2017). The E-value method estimates the minimum strength of the association that would be required between an unmeasured confounder and both dementia diagnosis and risk of

hypoglycaemia, conditional on the measured covariates, to explain away an observed association (VanderWeele and Ding, 2017).

## 7.4 Results

A total of 3,919,518 patients aged 50 years and older were in the IMRD-UK, of which 376,601 patients (9.6%) were diagnosed with DM (including T1DM and T2DM) and had two or more consecutive prescriptions of antidiabetic medications identified. Of these, 133,664 (35.5%) patients met the inclusion criteria during the study period. Among the study population, 15,470 (11.6%) patients had dementia diagnosis, compared to 118,194 (88.4%) patients diagnosed with DM only. The distribution of patients according to the inclusion criteria is shown in **Figure 36**.

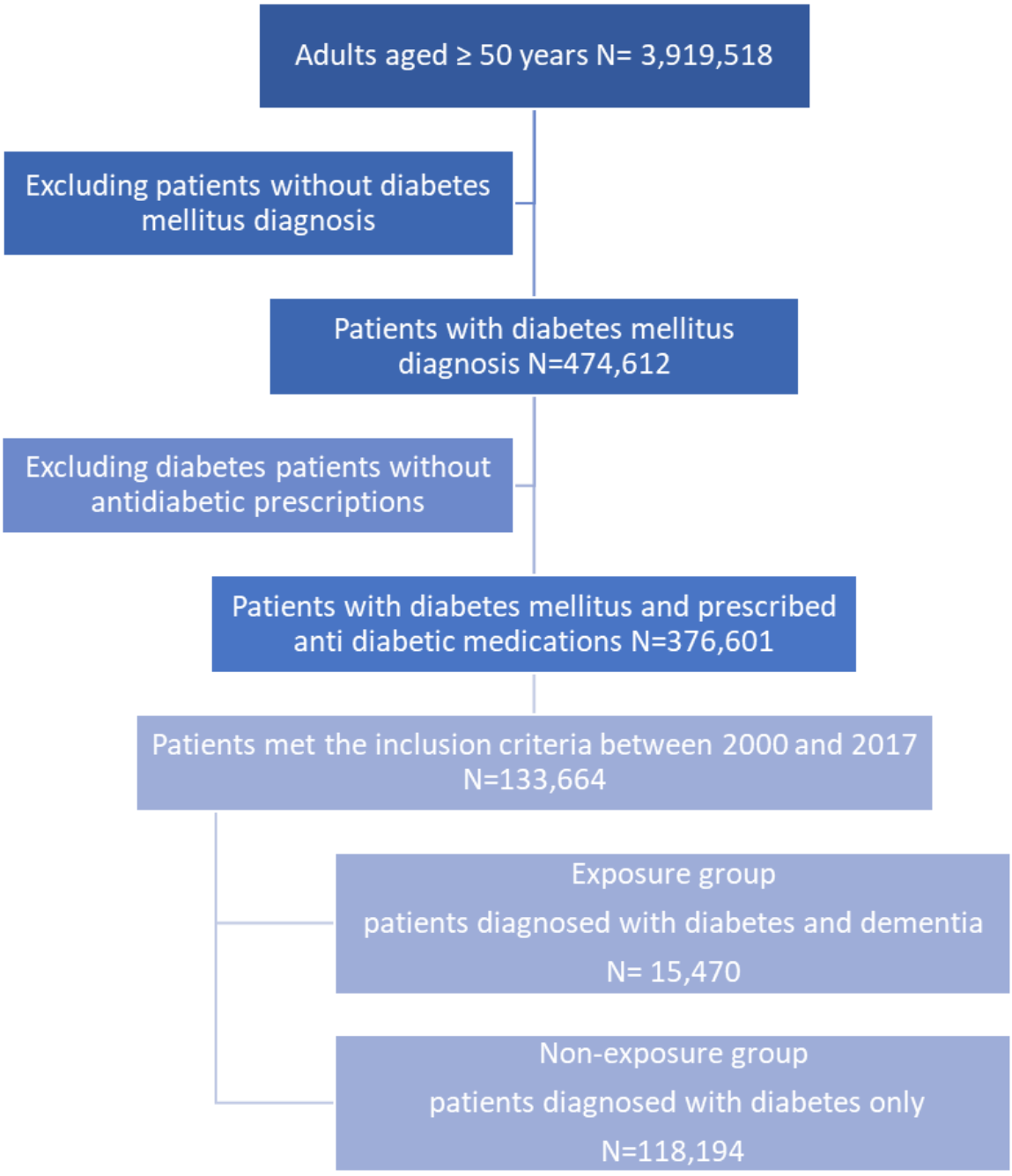



**Figure 36 Flowchart of the Study Population Included in the Cohort Study**

### 7.4.1 Study population characteristics

A total of 133,664 patients were identified and included in the study with mean follow-up period of 6.11 (SD = 4.11) years. Of these, 73,405 (54.92%) were males and 60,259 (45.08%) were females. The mean age of the patients at the index date was 66.91 (SD, 11.4) years old. The average BMI of the patients was 27.7 (SD, 11.3) kg/m$^2$. Around

33.73% (n = 45,088) of the patients were non-smokers, 42.60% (n = 56,947) were ex-smokers and only 15.50% (n = 20,724) were smokers. Of the patients, 60.25% (n = 80,538) reported alcohol consumption in their daily life, 13.81% (n = 18,461) were ex-drinkers and 12.1% (n = 16,137) were non-drinkers. The most common type of diabetes was T2DM, consisting of 98.5% (n = 131,650) of the study population. The average duration of DM was 7.09 (SD = 5.4) years and the average HbA1c of the patients was 7.0 (SD = 1.95) mmol/mol. A total of 11.57 % (n = 15,470) of the patients had a confirmed diagnosis of dementia during the study period. Data on dementia subtypes recorded were available for 8,994 patients (58.1%). These showed that 31.6% of the patients were diagnosed with vascular dementia and 24.9% of the patients were diagnosed with Alzheimer's disease. However, 41.9% of the patients had non-specific codes of dementia subtype. Full details on sample characteristics are presented in **Table 25**.

**Table 25 Study Population Characteristics**

| Characteristics | Exposure N= 15,470 (100%) | Non-exposure N= 118,194 (100%) | P-value |
|---|---|---|---|
| **Age at index date, Mean (SD)** | | | |
| | 80.42 (7.5) | 65.14 (10.6) | < 0.001 |
| **Gender** | | | |
| **Male** | 6,922 (44.74) | 66,483 (56.25) | <0.001 |
| **Follow-up time, person-years, Mean (SD)** | | | |
| | 3.091 (2.06) | 6.51 (4.14) | < 0.001 |
| **BMI kg/m$^2$** | | | |
| | 24.8 ( 9.4) | 27.7 (11.5) | < 0.001 |
| **Smoking** | | | < 0.001 |
| **Non-smoker** | 5,850 (37.82) | 39,238 (33.19) | |
| **Ex-smoker** | 7,592 (49.08) | 49,355 (41.26) | |
| **Smoker** | 1,445 (9.34) | 19,279 (16.31) | |
| **Alcohol consumption** | | | < 0.001 |
| **Non-drinker** | 2,736 (17.69) | 13,401 (11.34) | |
| **Ex-drinker** | 3,471 (22.44) | 14,990 (12.68) | |

| Characteristics | Exposure N= 15,470 (100%) | Non-exposure N= 118,194 (100%) | P-value |
|---|---|---|---|
| **Drinker** | 7,394 (47.79) | 73,144 (61.88) | |
| **Diabetes types** | | | < 0.001 |
| **Type 1 diabetes mellitus** | 549 (3.55) | 1,465 (1.24) | |
| **Type 2 diabetes mellitus** | 14,921 (96.45) | 116,729 (98.76) | |
| **Diabetes duration, Mean (SD)** | | | |
| | 12.59 (9.1) | 6.37 (4.2) | < 0.001 |
| **HbA1c, mmol/mol, Mean (SD)** | | | |
| | 6.9 (1.94) | 7.3 (1.95) | < 0.001 |
| **Dementia Types** | | | |
| **Vascular dementia** | 4,891 (31.62) | - | - |
| **Alzheimer's disease** | 3,846 (24.86) | - | - |
| **Parkinson's disease dementia** | 75 (0.48) | - | - |
| **Lewy Body Disease** | 155 (1) | - | - |
| **Frontotemporal dementia** | 25 (0.1) | - | - |
| **Posterior cortical atrophy** | 2 (0.01) | - | - |
| **Unspecified** | 6,476 (41.86) | - | - |
| **Diabetes microvascular complications** | | | |
| **Diabetic neuropathy** | 3,062 (19.79) | 16,007 (13.54) | < 0.001 |
| **Diabetic nephropathy** | 138 (0.89) | 361 (0.31) | < 0.001 |
| **Diabetic retinopathy** | 6,145 (39.72) | 36,111 (30.55) | < 0.001 |
| **Diabetic foot** | 1,267 (8.19) | 2,999 (2.54) | < 0.001 |
| **Chronic comorbidities** | | | |
| **Chronic obstructive pulmonary disease** | 1,555 (10.05) | 13,143 (11.12) | < 0.001 |
| **Cerebrovascular disease** | 4,258 (27.52) | 11,816 (10.0) | < 0.001 |
| **Arrhythmias** | 3,536 (22.86) | 15,913 (13.46) | < 0.001 |
| **Myocardial infarction** | 6,133 (39.64) | 35,833 (30.32) | < 0.001 |
| **Hypertension** | 11,253 (72.74) | 80,548 (68.15) | < 0.001 |
| **Chronic kidney disease** | 6,198 (40.06) | 24,339 (20.59) | < 0.001 |
| **Obesity** | 2,124 (13.73) | 26,221 (22.2) | < 0.001 |
| **Depression** | 5,827 (37.67) | 37,388 (31.63) | < 0.001 |
| **Antidiabetic medication** | | | |
| **Insulin** | 3,962 (25.61) | 14,905 (12.61) | < 0.001 |
| **Sulfonylurea** | 8,979 (58.04) | 47,581 (40.26) | < 0.001 |
| **Metformin** | 12,406 (80.19) | 110,686 (93.65) | < 0.001 |
| **GLP-1** | 189 (1.22) | 4,025 (3.41) | < 0.001 |
| **SGLT-2** | 107 (0.69) | 5,483 (4.64) | < 0.001 |

| Characteristics | Exposure N= 15,470 (100%) | Non-exposure N= 118,194 (100%) | P-value |
|---|---|---|---|
| **Meglitinides** | 193 (1.25) | 795 (0.67) | < 0.001 |
| **TZD** | 2,021 (13.06) | 10,397 (8.80) | < 0.001 |
| **DDP-4** | 1,903 (12.30) | 22,902 (19.38) | < 0.001 |
| **Acarbose** | 298 (1.93) | 392 (0.33) | < 0.001 |
| **Chronic medications** | | | |
| **Beta blockers** | 7,397 (47.82) | 55,320 (46.80) | 0.02 |
| **ACEI-ARBS** | 11,233 (72.61) | 84,803 (71.75) | 0.03 |
| **Calcium channel blockers** | 7,432 (48.04) | 56,023 (47.40) | 0.13 |
| **Statins** | 2,335 (15.09) | 23,345 (19.75) | <0.001 |
| **Anti-dementia** | 4,746 (30.68) | - | - |
| **Antidepressants** | 3,807 (24.61) | 24,113 (20.40) | <0.001 |
| **Aspirin** | 11,596 (74.96) | 62,652 (53.01) | < 0.001 |
| **History of hypoglycaemia** | 1,131 (7.31) | 1,367 (1.16) | < 0.001 |

**BMI** Body mass index, **SD** Standard deviation, **GLP-1** glucagon-like peptide-1 receptor agonists, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors, **ACEI-ARBs** angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

The majority of the patients in this study (n = 124,695; 93.28%) were diagnosed with more than one chronic disease, and only 6.71% of patients were free from comorbid conditions (n = 8,969). Hypertension and depression were the two most common chronic conditions, affecting around 68.7% and 32.3% of the patients, respectively. Moreover, 31.6% and 31.4% of the patients in the study reported retinopathy and MI, respectively. Furthermore, 22.8% of the patients were suffering from CKD. For full details about the prevalence of chronic comorbidities across the study sample: refer to **Figure 36.**

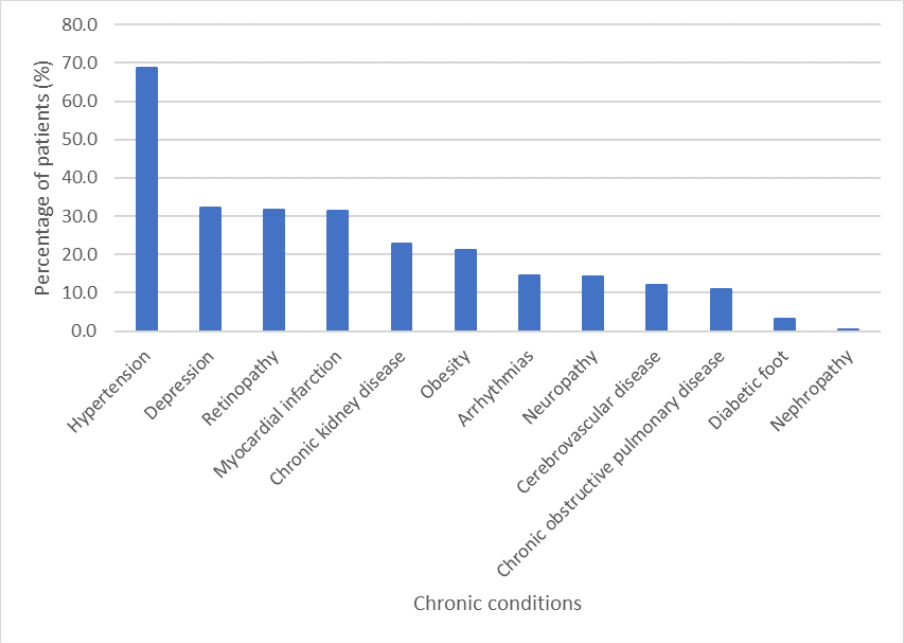
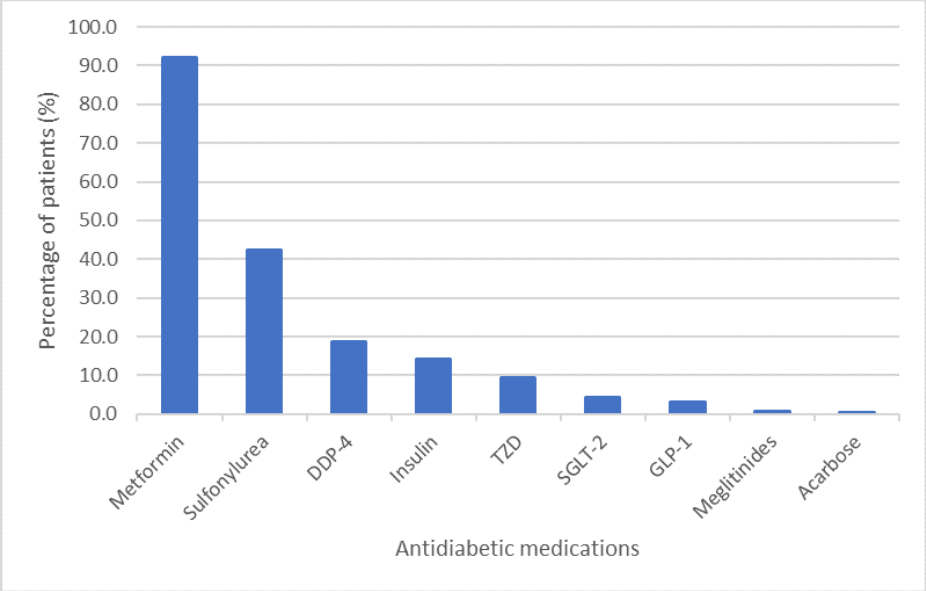



**Figure 36 Distribution of Chronic Diseases Among the Study Sample in the Cohort Study**

## Antidiabetic medications

During the study period, the majority (n = 114,797; 85.9%) of the patients were using oral antidiabetic medications (whether as monotherapy or combination therapy); only 1.96% (n = 2,620) were using insulin by itself while 12.2% (n = 16,247) were using insulin in combination with other antidiabetic medications. The most common oral antidiabetic medication was metformin, which contributed 92.1% (n = 123,092), followed by sulfonylureas at 42.3% (n = 56,560). DDP-4 was the third most common antidiabetic medication prescribed for 18.6% (n = 24,805): refer to **Figure 37**.




**GLP-1** glucagon-like peptide-1 receptor agonists, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors

**Figure 37 Percentage of Patients Using Antidiabetic Therapy in the Cohort Study**

In general, monotherapy was used by around 49.9% (n = 66,695) of the patients, followed by 30.7% (n = 41,005) for the use of dual antidiabetic therapy, and 13.2% (n = 17,680) for the use of triple antidiabetic therapy. On the other hand, quadruple antidiabetic therapy was used by only 6.2% (n = 8,284) of the patients: refer to **Figure 38**.

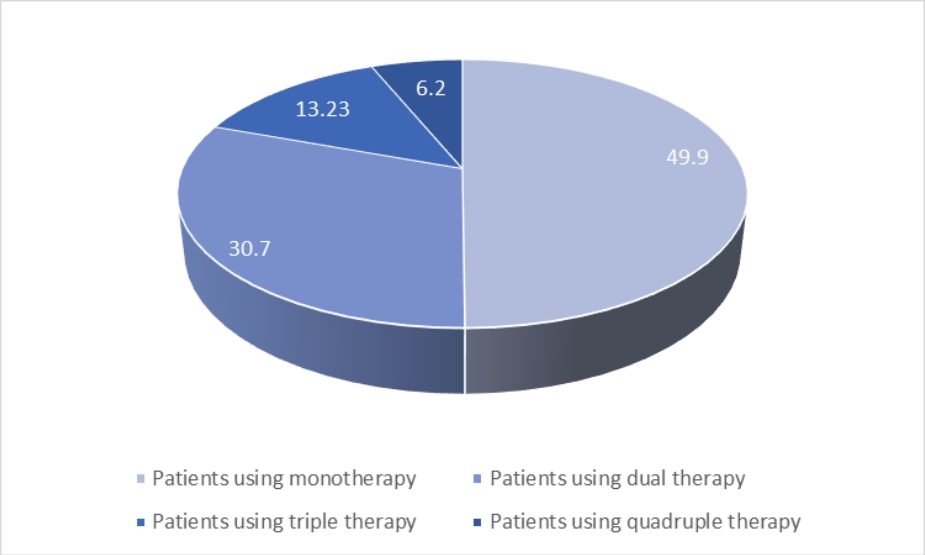
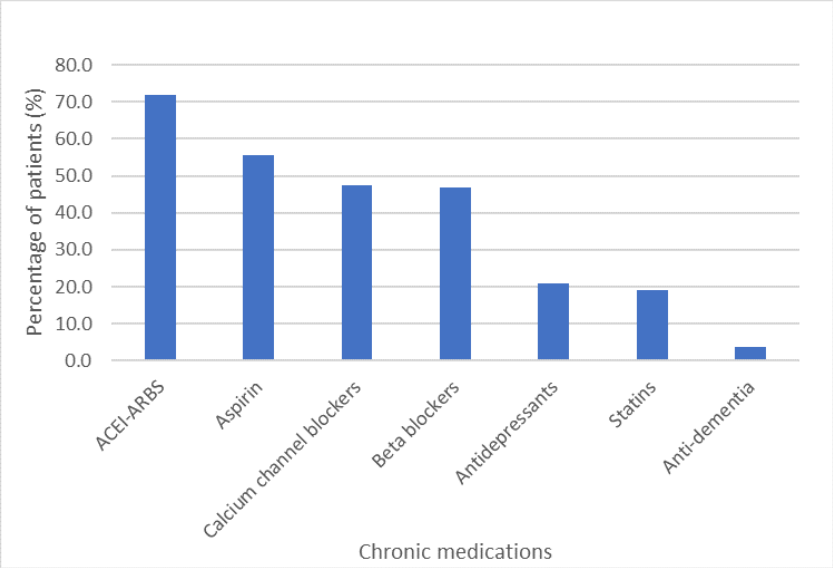



**Figure 38 Percentage of Patients Using Monotherapy and Different Combination Therapies in the Cohort Study**

## Other medications

Cardiovascular system medication use was prevalent among the patients. ACEIs/ARBs and aspirin were the most commonly used chronic medications, contributing to 71.8% (n = 96,036) and 55.5% (n = 74,248), respectively. For further details on the percentage of patients using different chronic medications: refer to **Figure 39**.




**ACEI-ARBs** angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Figure 39 Percentage of Patients Using Different Chronic Therapies among the diabetes patients

### 7.4.2 Distribution of missing data

Most of the patients' records were complete and included all clinical data relevant to patients' medical history and medication use history. However, for some variables there were some missing data. **Table 26** shows the percentage of missing data regarding each variable in the study.

**Table 26 Percentage of Missing Data in the Cohort Study**

| Variables | Number of patients with missed data | Percentage from total patients (%) |
|---|---|---|
| **BMI, Kg/m$^2$** | 14,939 | 11.2% |
| **Smoking status** | 10,905 | 8.2% |
| **Alcohol consumption** | 18,528 | 13.9% |
| **HbA1c, mmol/mol** | 44,716 | 33.5% |

The majority of missing data were for patients' characteristics, with percentages ranging from 8.2% to 33.5%. Multiple imputation was used in the main analysis, while complete case analysis and the missing-indicator method were used in the sensitivity analyses. The three methods yielded similar results.

### 7.4.3 Risk of hypoglycaemic events

A total of 24,442 hypoglycaemic episodes were experienced by 4.2 % (n = 5,589) of the patients during the follow-up period. **Table 27** shows the results of the retrospective cohort analyses for the risk of hypoglycaemia due to dementia in the primary, secondary and sensitivity analyses.

**Table 27 Cohort Results for the Risk of Hypoglycaemia Patients with Dementia Vs Patients without Dementia in the Primary, Secondary, and Sensitivity Analyses**

| | Multivariable analysis Primary analysis | | PS Matching Secondary analysis | IPTW Sensitivity analysis |
|---|---|---|---|---|
| | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) | Adjusted HR (95% CI) | Adjusted HR (95% CI) |
| **Multiple imputation** | 2.34 (2.3 – 2.4) | 2.25 (2.2 -2.3) | 2.04 (1.6 -2.7) | 1.97 (1.9 -2.0) |
| **Complete case Analysis** | 1.98 (1.8 – 2.2) | 1.88 (1.7 -2.1) | 1.90 (1.7 - 2.2) | 1.90 (1.6 - 2.1) |
| **Missing-indicator method** | 2.2 (2.0– 2.3) | 2.1 (1.9 -2.2) | 1.95 (1.7 - 2.2) | 1.95 (1.8 -2.2) |

**PS** propensity score, **IPTW** inverse probability of treatment weighting, **HR** hazards ratio, **CI** confidence interval

* For multivariable analysis, adjusted for baseline characteristics (age, gender, body mass index, smoking status, alcohol consumption, HbA1c, diabetes duration and history of hypoglycaemic events), chronic comorbidities (diabetes microvascular complications (including neuropathy, nephropathy, retinopathy and diabetic foot), hypertension, myocardial infarction, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, depression, cerebrovascular disease, lipoedema and obesity), and medication use.

All primary, secondary and sensitivity analyses confirmed an increased risk of hypoglycaemia among dementia patients.

## Primary analysis of risk of hypoglycaemia (multivariable analysis)

Unadjusted result from the Cox proportional hazards regression models revealed a two-fold (HR, 2.34; 95% CI, 2.32–2.39) increased risk for hypoglycaemia among diabetic patients diagnosed with dementia compared to those who did not develop dementia. Adjustment for patient's baseline characteristics, chronic comorbidities and medication use produced a similar result (the multivariate-adjusted HR, 2.25; 95% CI, 2.22–2.32). **Table 28** illustrates the statistically significant results of unadjusted and adjusted Cox proportional hazards regression models.

**Table 28 Cox Proportional Hazards Ratio Models and 95% Confidence Intervals for the Risk of Hypoglycaemia Associated with Dementia (multivariable analysis)**

| Variables | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) | P-Value |
|---|---|---|---|
| **Non-Dementia** | 1.00 | 1.00 | |
| **Dementia** | 2.34 (2.32–2.39) | 2.25 (2.22–2.32) | <.0001 |
| **Age** | | | |
| **< 65 years** | 1.00 | 1.00 | |
| **≥ 65 years** | 1.90 (1.17 – 2.99) | 1.87 (1.15 – 2.80) | <.0001 |
| **Gender** | | | |
| **Female** | 1.00 | 1.00 | |
| **Male** | 1.16 (1.10 – 2.04) | 1.10 (1.06 – 2.01) | <.0001 |
| **Diabetes type** | | | |
| **Type 2 diabetes mellitus** | 1.00 | 1.00 | |
| **Type 1 diabetes mellitus** | 1.68 (1.06 – 2.01) | 1.60 (1.03 – 2.00) | <.0001 |
| **HbA1c (mmol/mol)** | | | |
| **HbA1c=4-5.7** | 1.00 | 1.00 | |
| **HbA1c < 4** | 2.1 (1.8 -3.4) | 1.9 (1.4 -3.0) | <.0001 |
| **HbA1c=5.7-6.4** | 1.8 (1.3 – 2.0) | 1.7 (1.6 – 1.9) | 0.001 |
| **HbA1c =6.5-14** | 1.7 (1.0 – 2.4) | 1.5 (0.9 – 2.1) | 0.060 |
| **HbA1c ≥ 14** | 2.0 (1.5 – 3.0) | 2.0 (1.2 – 3.3) | 0.031 |
| **Smoking** | | | |
| **Non-smoker** | 1.00 | 1.00 | |
| **Smoker** | 1.10 (1.02 – 2.01) | 1.07 (1.001 – 1.91) | <.0001 |
| **Ex- smoker** | 1.1 (0.8 – 1.3) | 1.0 (0.9 – 1.1) | 0.671 |
| **BMI (kg/m$^2$)** | | | |
| **18.5 - 24.9** | 1.00 | 1.00 | |
| **< 18.5** | 1.3 (1.1 – 2.04) | 1.28 (1.08 – 1.99) | <.0001 |
| **25 - 29.9** | 1.2 (1.1 – 1.5) | 1.3 (1.1 - 1.8) | 0.356 |

| Variables | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) | P-Value |
|---|---|---|---|
| **30 – 39.9** | 0.8 ( 0.5 - 0.9) | 0.5 (0.1 – 0.9) | 0.012 |
| **≥ 40** | 1.1 (1.01 – 1.7) | 0.8 (0.5 - 0.9) | 0.024 |
| **History of Hypoglycaemia** | | | |
| **No history of hypoglycaemia** | 1.00 | 1.00 | |
| **History of hypoglycaemia** | 3.55 (3.2 – 5.64) | 3.40 (3.00 – 5.59) | <.0001 |
| **Diabetes duration** | | | |
| **Diabetes duration ≤ 5 years** | 1.00 | 1.00 | |
| **Diabetes duration > 5 years** | 1.8 (1.2 – 2.0) | 1.6 ( 1.2 – 2.0) | <.0001 |
| **Comorbid conditions** | | | |
| **No history of hypertension** | 1.00 | 1.00 | |
| **Hypertension** | 1.9 (1.3 -2.0) | 1.6 (1.3 -1.8) | <.0001 |
| **No history of depression** | 1.00 | 1.00 | |
| **Depression** | 1.7 (1.2 - 1.9) | 1.4 (1.2 - 1.7) | <.0001 |
| **No history of chronic kidney disease** | 1.00 | 1.00 | |
| **Chronic Kidney disease** | 1.5 (1.1 - 1.7) | 1.3 (1.1 - 1.5) | <.0001 |
| **Antidiabetic medication** | | | |
| **Non- metformin** | 1.00 | 1.00 | |
| **Metformin** | 0.9 (0.8 - 0.99) | 0.8 (0.5 - 0.9) | <.0001 |
| **Non-Insulin** | 1.00 | 1.00 | |
| **Insulin** | 2.14 (1.63 – 2.96) | 2.09 (1.59 – 2.75) | <.0001 |
| **Non-Sulfonylurea** | 1.00 | 1.00 | |
| **Sulfonylurea** | 1.96 (1.29 – 3.01) | 1.89 (1.19 – 2.97) | <.0001 |
| **Non- meglitinides** | 1.00 | 1.00 | |
| **Meglitinides** | 1.8 (1.1 – 2.2) | 1.6 (1.1 – 1.9) | 0.030 |
| **Non- GLP-1** | 1.00 | 1.00 | |
| **GLP-1** | 0.9 (0.4 - 0.9) | 0.6 (0.3 - 0.8) | <.0001 |

| Variables | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) | P-Value |
|---|---|---|---|
| **Other medications** | | | |
| **Non- beta blockers** | 1.00 | 1.00 | |
| **Beta blockers** | 0.9 (0.8 – 0.9) | 0.8 (0.6 – 0.9) | <.0001 |
| **Non- aspirin** | 1.00 | 1.00 | |
| **Aspirin** | 1.3 (1.1–1.5) | 1.2(1.1–1.5) | <.0001 |

## Secondary analysis of risk of hypoglycaemia (Propensity score matching analysis)

After PS matching, a total of 20,706 matched patients were identified; 7,762 (37.48%) patients comprised the exposed group and were matched with 12,944 (62.51%) non-exposed participants. The baseline characteristics of the matched groups are shown in **Table 29**; all variables with absolute values of standardised differences were < 0.1. The mean follow-up period of the matched pairs was 4.09 years. The adjusted HR for hypoglycaemic events for the exposed patients was 2.04 (95% CI, 1.63–2.66) compared to non-exposed patients. In addition to dementia, I found other predictors of hypoglycaemia were age ≥ 65 years, male gender, T1DM, smoking, HbA1c measurements, BMI, history of hypoglycaemic events, diabetes duration > 5 years. The use of insulin and sulfonylureas also had a statistically significant effect on hypoglycaemia risk (P-value < 0.05). (**Table 30**)

**Table 29 Study Population Characteristics after Propensity Score Matching**

| Characteristics | Exposure N= 7,762 (100%) | Non-exposure N= 12,944 (100%) | Standardised mean difference |
|---|---|---|---|
| **Age at index date, Mean (SD)** | | | |
| | 79.1 ± 7.8 | 78.7 ± 8.4 | 0.07 |
| **Gender** | | | |

| Characteristics | Exposure N= 7,762 (100%) | Non-exposure N= 12,944 (100%) | Standardised mean difference |
|---|---|---|---|
| **Male** | 3,643 (46.9) | 6,246 (48,25) | -0.03 |
| **Follow-up time, person-years, Mean (SD)** | | | |
| | 3.0 ± 2.1 | 4.8 ± 3.4 | |
| **BMI Kg/m$^2$, Mean (SD)** | 27.9 ± 5.5 | | |
| | 27.7 ± 5.6 | 28.1 ± 5.4 | 0.07 |
| **Smoking** | | | 0.02 |
| **Non-smoker** | 2,932 (37.78) | 4,780 (36.93) | |
| **Ex-smoker** | 3,953(50.93) | 6,670 (51.53) | |
| **Smoker** | 877 (11.30) | 1,494 (11.54) | |
| **Alcohol consumption** | | | 0.03 |
| **Non-drinker** | 1,528 (19.68) | 2,392 (18.48) | |
| **Ex-drinker** | 1,909 (24.59) | 3,153 (24.36) | |
| **Drinker** | 4,325 (55.73) | 7,399 (57.16) | |
| **Diabetes types** | | | -0.02 |
| **Type 1 diabetes mellitus** | 170 (2.19) | 251 (1.94) | |
| **Type 2 diabetes mellitus** | 7,592 (97.80) | 12,693 (98.06) | |
| **Diabetes duration, Mean (SD)** | | | |
| | 9.6 ± 6.3 | 9.2 ± 4.7 | -0.02 |
| **HbA1c, mmol/mol, Mean (SD)** | 7.2 ± 1.9 | | |
| | 7.2 ± 1.9 | 7.2 ± 1.9 | 0.01 |
| **Dementia Types** | | | |
| **Vascular dementia** | 3,095 (39.88) | - | |
| **Alzheimer's disease** | 1,264 (16.28) | - | |
| **Parkinson's disease dementia** | 41 (0.52) | - | |
| **Lewy Body disease** | 50 (0.64) | - | |
| **Frontotemporal dementia** | 18 (0.24) | - | |
| **Posterior cortical atrophy** | 2 (0.03) | - | |
| **Unspecified** | 3,292 (42.41) | - | |
| **Diabetes microvascular complications** | | | |
| **Neuropathy** | 1,472 (18.96) | 2,409 (18.61) | 0.01 |
| **Nephropathy** | 53 (0.68) | 85 (0.66) | 0.003 |
| **Retinopathy** | 2,844 (36.64) | 4,706 (36.36) | 0.01 |
| **Diabetic foot** | 560 (7.21) | 828 (6.39) | -0.06 |
| **Chronic comorbidities** | | | |

| Characteristics | Exposure N= 7,762 (100%) | Non-exposure N= 12,944 (100%) | Standardised mean difference |
|---|---|---|---|
| **Chronic obstructive pulmonary disease** | 908 (11.70) | 1,566 (12.10) | -0.02 |
| **Cerebrovascular disease** | 2,084 (26.85) | 3,307 (25.55) | 0.03 |
| **Arrhythmias** | 1,884 (24.27) | 3,140 (24.26) | 0.003 |
| **Myocardial infarction** | 3,050 (39.29) | 5,155 (39.83) | -0.01 |
| **Hypertension** | 5,646 (72.74) | 9,477 (73.21) | -0.02 |
| **Chronic kidney disease** | 3,033 (39.07) | 5,039 (38.93) | 0.01 |
| **Obesity** | 1,120 (14.43) | 1,910 (14.76) | -0.01 |
| **Depression** | 2,771 (35.70) | 4,615 (35.65) | 0.001 |
| **Antidiabetic medications** | | | |
| **Insulin** | 1,565 (20.16) | 2,524 (19.50) | 0.03 |
| **Sulfonylurea** | 4,383 (56.47) | 7,172 (55.41) | 0.04 |
| **Metformin** | 6,403 (82.50) | 10,653 (82.30) | 0.04 |
| **GLP-1** | 176 (2.27) | 295 (2.28) | 0.03 |
| **SGLT-2** | 140 (1.80) | 243 (1.88) | 0.06 |
| **Meglitinides** | 80 (1.03) | 168 (1.30) | 0.04 |
| **TZD** | 1,030 (13.27) | 1,716 (13.26) | 0.01 |
| **DDP-4** | 1,443 (18.59) | 2,416 (18.67) | -0.06 |
| **Acarbose** | 93 (1.20) | 155 (1.19) | -0.02 |
| **Chronic medications** | | | |
| **Beta blockers** | 3,879 (49.97) | 6,669 (51.52) | -0.03 |
| **ACEI-ARBS** | 5,743 (73.99) | 9,717 (75.07) | -0.02 |
| **Calcium channel blockers** | 3834 (49.39) | 6,512 (50.31) | -0.02 |
| **Statins** | 1,210 (15.59) | 2,087 (16.12) | -0.01 |
| **Anti-dementia** | 298 (3.84) | - | - |
| **Antidepressants** | 1,782 (22.96) | 2,934 (22.67) | 0.01 |
| **Aspirin** | 5,712 (73.50) | 9,514 (73.50) | -0.001 |
| **Hypoglycaemia** | | | |
| **History of hypoglycaemia** | 329 (4.24) | 509 (3.93) | 0.02 |

**BMI** Body mass index, **SD** Standard deviation, **GLP-1** glucagon-like peptide-1 receptor agonists, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **TZD** thiazolidinedione, **DDP-4** dipeptidyl peptidase-4 inhibitors, **ACEI-ARBs** angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

**Table 30 Cox Proportional Hazards Ratio Model and 95% Confidence Intervals for the Risk of Hypoglycaemia Associated with Dementia for PS matched patients**

| Variables | Propensity score matched<br>Adjusted HR (95% CI) | P-value |
|---|---|---|
| **Non-Dementia** | 1.00 | |
| **Dementia** | 2.04 (1.63–2.66) | <.0001 |
| **Age** | | |
| **< 65 years** | 1.00 | |
| **≥ 65 years** | 1.74 (1.03 -3.04) | <.0001 |
| **Gender** | | |
| **Female** | 1.00 | |
| **Male** | 1.07 (1.01 -2.22) | <.0001 |
| **Diabetes type** | | |
| **Type 2 diabetes mellitus** | 1.00 | |
| **Type 1 diabetes mellitus** | 1.64 (1.01 -2.64) | <.0001 |
| **HbA1c (mmol/mol)** | | |
| **HbA1c= 4-5.7** | 1.00 | |
| **HbA1c < 4** | 2.1 (1.7 -3.1) | <.0001 |
| **HbA1c=5.7-6.4** | 1.2 (1.02 – 1.9) | 0.001 |
| **HbA1c =6.5-14** | 1.2 (0.8 – 1.9) | 0.07 |
| **HbA1c ≥ 14** | 1.7 (1.2 – 2.3) | 0.04 |
| **Smoking** | | |
| **Non-smoker** | 1.00 | |
| **Smoker** | 1.07 (1.07 -2.11) | <.0001 |
| **Ex- smoker** | 1.1 (0.8 – 1.5) | 0.84 |
| **BMI (kg/m$^2$)** | | |
| **18.5 - 24.9** | 1.00 | |
| **< 18.5** | 1.3 (1.1 -1.6) | <.0001 |
| **25 - 29.9** | 1.2 (1.0 - 1.8) | 0.42 |
| **30 – 39.9** | 0.5 (0.2 – 0.9) | 0.002 |
| **≥ 40** | 0.8 (0.4 - 0.9) | 0.024 |
| **Hypoglycaemia** | | |
| **No history of hypoglycaemia** | 1.00 | |
| **History of hypoglycaemia** | 3.2 (2.27 -4.01) | <.0001 |
| **Diabetes duration** | | |
| **Diabetes duration ≤ 5 years** | 1.00 | |
| **Diabetes duration > 5 years** | 2.4 (2.2 – 2.7) | <.0001 |
| **Comorbid conditions** | | |

| Variables | Propensity score matched<br>Adjusted HR (95% CI) | P-value |
|---|---|---|
| **No history of hypertension** | 1.00 | |
| **Hypertension** | 1.5 (1.3 -1.7) | <.0001 |
| **No history of depression** | 1.00 | |
| **Depression** | 1.3 (1.2 - 1.5) | <.0001 |
| **No history of chronic kidney disease** | 1.00 | |
| **Chronic Kidney disease** | 1.2 (1.04 - 1.3) | <.0001 |
| **Antidiabetic medications** | | |
| **Non- metformin** | 1.00 | |
| **Metformin** | 0.8 (0.8 - 0.9) | <.0001 |
| **Non- Insulin** | 1.00 | |
| **Insulin** | 2.07 (1.46 -3.61) | <.0001 |
| **Non- Sulfonylurea** | 1.00 | |
| **Sulfonylurea** | 1.87 (1.03 -2.98) | <.0001 |
| **Non- meglitinides** | 1.00 | |
| **Meglitinides** | 1.5 (1.1 – 2.2) | 0.027 |
| **Non- GLP-1** | 1.00 | |
| **GLP-1** | 0.5 (0.3 - 0.8) | <.0001 |
| **Other medications** | | |
| **Non- beta blockers** | 1.00 | |
| **Beta blockers** | 0.9 (0.8 – 0.9) | <.0001 |
| **Non- aspirin** | 1.00 | |
| **Aspirin** | 1.3 (1.1–1.5) | <.0001 |

## Sensitivity analysis

**Table 31** presents the results of the sensitivity analyses. A complete case analysis and the missing-indicator method were used to address the missing data and yielded similar results to the primary and secondary analyses. An IPTW analysis of the study outcome was not significantly different from the primary and secondary analyses. The E-value for the point estimate and upper confidence bound for the risk of hypoglycaemia were 3.41 and 2.64, respectively.

**Table 31 Sensitivity Analyses on Propensity Score Matched and IPTW Patients**

| | Complete Case Analysis | | New Category for missing data | | Multiple imputation | |
|---|---|---|---|---|---|---|
| | **Patients included** | **HR (95% CI)** | **Patients included** | **HR (95% CI)** | **Patients included** | **HR (95% CI)** |
| **PS matched** | 15,894 | 1.90 (1.70-2.20) | 20,414 | 1.95 (1.75-2.20) | 20,706 | 2.00 (1.60-2.66) |
| **IPTW method** | 22,981 | 1.90 (1.60-2.10) | 26,617 | 1.95 (1.76-2.20) | 28,248 | 2.00 (1.90-2.10) |

## 7.5 Discussion

This population-based, retrospective cohort study confirmed that dementia was significantly associated with the risk of experiencing hypoglycaemia. I found that dementia increased the risk of hypoglycaemia twofold compared to diabetes patients without dementia. Moreover, the association remained even after adjustment for age, sex, BMI and other covariates. These results were confirmed using two different PS methods: the first was PS matching and the second one was IPTW.

Previous trials and observational studies in different countries have explored the epidemiological associations between dementia and the risk of hypoglycaemia (Yaffe et al., 2013, Bruce et al., 2009, de Galan et al., 2009, Punthakee et al., 2012, Feil et al., 2011, Bruderer et al., 2014b), which are consistent with my findings of an increased risk of hypoglycaemia among dementia patients. To the best of my knowledge, this is the first pharmacoepidemiological study to investigate the association between dementia and the risk of hypoglycaemia among patients diagnosed with both DM and dementia in the UK healthcare database, without restricting the comparison to a specific diabetes type or hypoglycaemia severity.

### 7.5.1 Dementia and hypoglycaemic events

The findings of this study confirmed the hypothesis of an earlier study (Chapter Six) and found a strong positive association between dementia and the risk of hypoglycaemia in patients using antidiabetic medications. Likewise, in a nested case-control study in the UK using the CPRD database, there were similar results of a twofold increase in the risk of severe hypoglycaemia associated with dementia among newly treated T2DM (adjusted OR, 2.10; 95% CI, 1.35–3.25) (Bruderer et al., 2014b). However, there are differences between the present study and the previous study. First, Bruderer et al. assessed the incidence rates and identified the risk factors for incident severe hypoglycaemia in T2DM patients newly treated with antidiabetic medications. Second, the study population included only to T2DM patients newly treated with antidiabetic medications with a history of three years recorded in the database before the follow-up period; this restriction led to a number of T2DM patients being missed. Third, the definition of hypoglycaemia was restricted only to severe hypoglycaemic events reported to the GP by the hospital or with a specific Read code for third-party assistance or hypoglycaemic coma and excluded any other form of hypoglycaemic events.

In another prospective population-based Health, Aging, and Body Composition Study, the risk of hypoglycaemia was assessed and a threefold increased risk of hypoglycaemia was found to be significantly associated with severe cognitive dysfunction (HR 3.1; 95% CI, 1.5–6.6). I found that the HR for risk of hypoglycaemia was twofold higher among patients with diabetes and dementia compared to diabetes patients only. Possible justifications for varied results could be the difference in: (1) population characteristics - they included only patients aged 70 to 79 years; (2) sample size - they involved only 783 elderly patients who had DM diagnosis, which is a relatively small sample size; (3) study design and analyses - this study was a prospective cohort study over a 12-year follow-up

period, and the analyses were adjusted only for age, sex, education, insulin use, race/ethnicity prevalent DM, baseline score of the Modified Mini-Mental State Examination (3MS) and three comorbidities (MI, stroke, and hypertension) (Yaffe et al., 2013).

### 7.5.2 The role of patient's characteristics, comorbidities and medication use

Hypoglycaemia is the most frequent side effect associated with DM medication management, and the risk increases with age (Shorr et al., 1997). My study showed that the age (≥ 65 years) of patients diagnosed with both DM and dementia was significantly associated with increased risk of hypoglycaemia (HR, 1.74; 95% CI,1.03–3.04). Patients with cognitive impairment or dementia may experience a higher rate of hypoglycaemia due to several factors including unawareness or unrecognition of the warning symptoms of hypoglycaemic events, reduced secretion of glucagon and altered psychomotor performance resulting in inability to make decisions and control hypoglycaemia correctly (Meneilly et al., 1994, Bremer et al., 2009). In addition to age and dementia diagnosis, other predictors were found to be significantly associated with the risk of hypoglycaemia, including male gender, T1DM, BMI, smoking, HbA1c level, diabetes duration > 5 years and history of hypoglycaemia. The history of hypoglycaemia was associated with a threefold increased risk of experiencing hypoglycaemia in patients diagnosed with DM and dementia. A history of hypoglycaemia could induce a reversible pathophysiological state called hypoglycaemia unawareness state with hypoglycaemia-associated autonomic failure (an inefficient homeostatic glucose compensatory mechanism leading to neurogenic responses) (Segel et al., 2002). These results were also in line with a previous study where the authors reported that these factors are likely to influence the occurrence of hypoglycaemia in patients diagnosed with DM only (Kajiwara et al., 2015,

Vlckova et al., 2010, Sämann et al., 2013, Lipska et al., 2013b, Durán-Nah et al., 2008, Amiel et al., 2008, Zoungas et al., 2010, Emanuele et al., 1998).

The existence of other chronic diseases with DM and the extensive use of other chronic medications (polypharmacy) among my study cohort could be another independent risk factor that has played a role in increasing the risk of hypoglycaemia. Hypertension and depression were the most commonly coexisting diseases with diabetes. It has been established that comorbidities such as cardiovascular diseases and depression increase the risk of hypoglycaemia in the DM population (Katon et al., 2013, Kim et al., 2016). Consistent with my study results, patients who had a history of hypertension (adjusted HR, 1.5; 95% CI, 1.3–1.7), depression (adjusted HR, 1.3; 95% CI, 1.2–1.5), and CKD (adjusted HR, 1.2; 95% CI, 1.04–1.3) were significantly associated with a higher risk of experiencing hypoglycaemia. Furthermore, the use of CVD medications, such as aspirin, beta blockers, ACEIs/ARBs and calcium channel blockers was common among the study cohort and could have contributed to increasing the risk of hypoglycaemia (Murad et al., 2009). My study found that patients who had a history of using aspirin were significantly associated with a higher risk of hypoglycaemia (adjusted HR, 1.3; 95% CI, 1.1–1.5). In contrast, having a history of beta blockers use was associated with a lower risk of developing hypoglycaemia (adjusted HR, 0.9; 95% CI, 0.8–0.9).

It is clear from the mechanism of action of antidiabetic medications that all have a hypoglycaemic effect. However, hypoglycaemia was a common side effect of certain classes. SFU and insulin users tended to have a higher risk of hypoglycaemia (Zammitt and Frier, 2005). In addition to insulin and sulfonylureas, meglitinides were more likely to be associated with hypoglycaemia, while use of metformin and GLP-1 were protective factors against hypoglycaemia (adjusted HR, 0.8; 95% CI, 0.8–0.9 and 0.5; 95% CI, 0.3–

0.8, respectively). Nevertheless, the impact of other medications on hypoglycaemia among the DM and dementia population was not statistically significant.

Based on the study findings, a significant risk of hypoglycaemia was associated with dementia in this cohort of DM patients treated with antidiabetic medications; those diagnosed with dementia were especially vulnerable. Healthcare professionals who provided care for elderly patients diagnosed with DM are advised to pay more attention to dementia and hypoglycaemia in the clinical management of diabetes and make an effort to reduce hypoglycaemia and promote patient safety through self-management support and education for patients with dementia and their family/carers.

### 7.5.3 Strengths and limitations

This study has several strengths. Firstly, this is the first retrospective population-based observational study design with a long follow-up period and a large cohort using the IMRD-UK database to test the hypothesis of dementia associated with increased risk of hypoglycaemia in DM patients compared to DM patients without dementia. Secondly, unlike previous studies that focused on severe incident cases of hypoglycaemia or self-reported hypoglycaemia, this study included hypoglycaemic events with no restriction of hypoglycaemia definition and was based on diagnostic codes (Read codes), which is a more objective measure than self-reported events. Thirdly, for valid statistical inferences, there is no acceptable cut-off proportion of missing data from previous literature. Some reported that a missing data rate of 5% or below is insignificant, while others reported that statistical analysis is likely to be biased when the missing rate is more than 10% (Schafer, 1999, Bennett, 2001). The percentage of missing data is not the only factor will impact the study results; the mechanism and the missing patterns have a greater impact (Tabachnick BG, 2019). In accordance with Rubin, I assumed that the mechanism of the

missing data was missing at random (MAR) or missing completely at random (MCAR) (RUBIN, 1976). Refer to **section 4.4.2** for more details about the mechanisms of missing data. Therefore, I applied multiple imputation for the missing data, which is considered to be a good approach when analysing large datasets with missing data in the literature (Leyrat et al., 2019). Fourthly, I was also able to achieve a balanced distribution of confounders across study groups using PS matching and IPTW techniques. IPTW has an advantage compared to PS matching in that IPTW results are representative of the patient characteristics in the overall population rather than only matched patients (Austin, 2011). Therefore, the studies using PS matching and IPTW methods are more robust and at low risk of bias (Glynn et al., 2006).

However, this study has limitations that should also be considered. Firstly, this study used the IMRD-UK primary care database, which provides a definition of dementia and hypoglycaemia by clinically important measures (Read codes including diagnostic codes or medication use). I was unable to examine the effects of subclinical outcomes, such as patients with milder or moderate hypoglycaemia. Furthermore, the dementia definition for the exposed group was likely a very specific clinical diagnosis and probably insensitive to mild cases of cognitive impairment. Moreover, most diagnostic codes of dementia entered were non-specific and did not allow us to differentiate between subtypes. Secondly, due to the observational design nature, unmeasured confounding may have persisted. However, the sensitivity analysis using E-value methodology suggested that the observed HR of 2.00 for hypoglycaemia could only be explained by an unmeasured confounder that was associated with both dementia and a risk of hypoglycaemia by a risk ratio of more than 3.41 above and beyond that of the confounders that were measured in this study (upper confidence bound = 2.64). Given that the unmeasured confounders risk ratio is much greater than any observed for known hypoglycaemia risk factors examined

in the present study, such as age, diabetes duration, chronic comorbidities, antidiabetic medications and history of hypoglycaemia, it is unlikely that an unmeasured or unknown confounder exists that would have a substantially greater effect on hypoglycaemia than these observed well-known risk factors with a relative risk exceeding 3.41.

## 7.6 Conclusion

Based on the study results, reduced cognitive function and dementia diagnosis among DM patients may increase the risk of hypoglycaemic events. Further studies are needed to identify effective management strategies for preventing and reducing the frequency of hypoglycaemia among the elderly diagnosed with DM and dementia, as well as in those with milder forms of cognitive impairment. Healthcare professionals, patients and relatives/carers should be extra vigilant when patients with dementia and on antidiabetic therapy have risk factors, including age ≥ 65 years, male gender, low BMI, smoking, diabetes duration and previous hypoglycaemia.

# 8 CHAPTER EIGHT: The Glycaemic Control and Rate of Hypoglycaemia in Dementia and Diabetes Population: Population-based study

The findings of Chapter Seven showed that dementia increases the risk of hypoglycaemia in patients with DM. This chapter presents a population-based study to assess the glycaemic control and the rate of hypoglycaemia in patients with DM before and after diagnosis of dementia.

## 8.1 Introduction

Comorbidities, cognitive impairment, diet habits and social factors make diabetes management in elderly patients complicated and challenging for healthcare providers, compared to the care given to younger and relatively healthier patients with diabetes (Kirkman et al., 2012). Diabetes and dementia are interrelated in the elderly (MacKnight et al., 2002). They need to be treated efficiently to prevent the development of complications. In previous cohort study, 52% of DM patients with dementia are intensively controlled (HbA1c <7) and managed with medications for which hypoglycaemia is considered one of the main adverse effects (Thorpe et al., 2015).

Patients with dementia might be less able to appropriately manage complex diabetes medications, to recognise hypoglycaemia symptoms and to respond adequately (Alzheimer's Association, 2013). Furthermore, they might underestimate the frequency of hypoglycaemia, potentially resulting in more frequent episodes of severe hypoglycaemia (Bruce et al., 2009). Recent evidence has suggested that hypoglycaemic events are common complications among elderly patients receiving antidiabetic medications, which result in greater hospitalisation and healthcare costs (Greco et al., 2010).

Hypoglycaemic events vary in their severity. They may cause acute, potentially fatal events that cannot be managed easily at home by patients themselves or by family members/carers (Seaquist et al., 2013a).

Hypoglycaemia not only impacts a patient's daily activities but also may cause serious morbidity, increase the risk of falls, cognitive impairment and cardiovascular and cerebrovascular complications, which can lead to death (Matsuhisa and Kuroda, 2019).

Therefore, assessing the glycaemic control and estimating the rate of hypoglycaemia is critical for developing individualised and effective management strategies to improve disease management and patient care.

## 8.2 Aim and objectives

The primary aim of this study was to assess the glycaemic control and estimate the rate of hypoglycaemia among DM patients before and after dementia diagnosis in a primary care setting in the UK.

The specific objectives were:

1. To compare the glycaemic control of DM patients before and after dementia.
2. To estimate and compare the rate of hypoglycaemia six months before and after dementia diagnosis among patients with DM.

## 8.3 Methods

### 8.3.1 Study design

This was a retrospective pre-post exposure study to examine the glycaemic control and investigate the rate of hypoglycaemia pre- and post-dementia diagnosis in patients with DM. The study design was similar to self-controlled studies, which are based on cases only (exposed patients). The comparison is performed within-individual over different time periods; therefore, the most potentially confounding characteristics that are stable over the time frame are effectively controlled (Gault et al., 2017).

The glycaemic control and the rate of hypoglycaemia experienced by patients were studied in different time windows (i.e. exposed period and non-exposed period) for the same patients. I compared the glycaemic control and the rate of hypoglycaemia after exposure to dementia diagnosis (the index date) during a defined exposed period (or risk period) with the period before exposure (non-exposed period). Only DM patients with dementia were included in the study and they served as their own controls.

### 8.3.2 Data source

The electronic health records from the IMRD-UK database (formerly known as THIN) was used in the present study. Detailed information about this database is described in previous studies (Alsharif et al., 2020, Brauer et al., 2019). In short, IMRD-UK is one of the largest databases in the UK containing anonymous information from electronic medical records collected in primary care settings since 1994, covering approximately 744 practices and over 13 million patients, which accounts for approximately 6% of UK population (Blak et al., 2011, Lewis et al., 2007, Bourke et al., 2004). This database is representative of the UK population and has been used for several epidemiological studies of DM and dementia in the UK (Alsharif et al., 2020, Brauer et al., 2019, Lewis et al., 2007, Blak et al., 2011).

### 8.3.3 Data extraction

Data were extracted using the medical and drug dictionary provided by IMRD-UK. Read codes were used to identify the diagnosis of DM, dementia and hypoglycaemia. All diagnostic codes for DM, including T1DM or T2DM, or a record of any prescribed antidiabetic medications, were used to identify diabetic patients. Dementia diagnosis or records of any prescribed anti-dementia medications were used to identify dementia. To identify the glycaemic control, I used the Read codes of HbA1c. I included all patients

who were recorded as experiencing hypoglycaemic events during the study period. I obtained the Read codes from the official website of the University of Cambridge (University of Cambridge, 2017) and published studies (Doran et al., 2011, Mongkhon et al., 2020). Extracted data included: patients' demographics, such as age, gender, BMI, smoking status, alcohol consumption status; chronic comorbidities history (coexisting diseases); DM-specific information, dementia-specific information, medication use, and all records of hypoglycaemic events.

### 8.3.4 Inclusion criteria for study patients

The inclusion criteria for this study were:

1. Patients aged 50 years or over.
2. Patients had prevalent DM at baseline or who developed DM during the follow-up period.
3. Patients who had at least two antidiabetic prescriptions and registered in IMRD-UK were identified and followed up from January 2000 onwards.
4. Patients who developed dementia after their DM diagnosis were included.

Patients who met the above inclusion criteria formed the study cohort. The first record of dementia diagnosis during the follow-up was defined as the index date. Patients diagnosed with dementia before the diagnosis of DM were excluded. Follow-up ended at the earliest at the following points: the date the patient left the practice, the date of death, or the last date of data collection. **Figure 40** presents the study population.

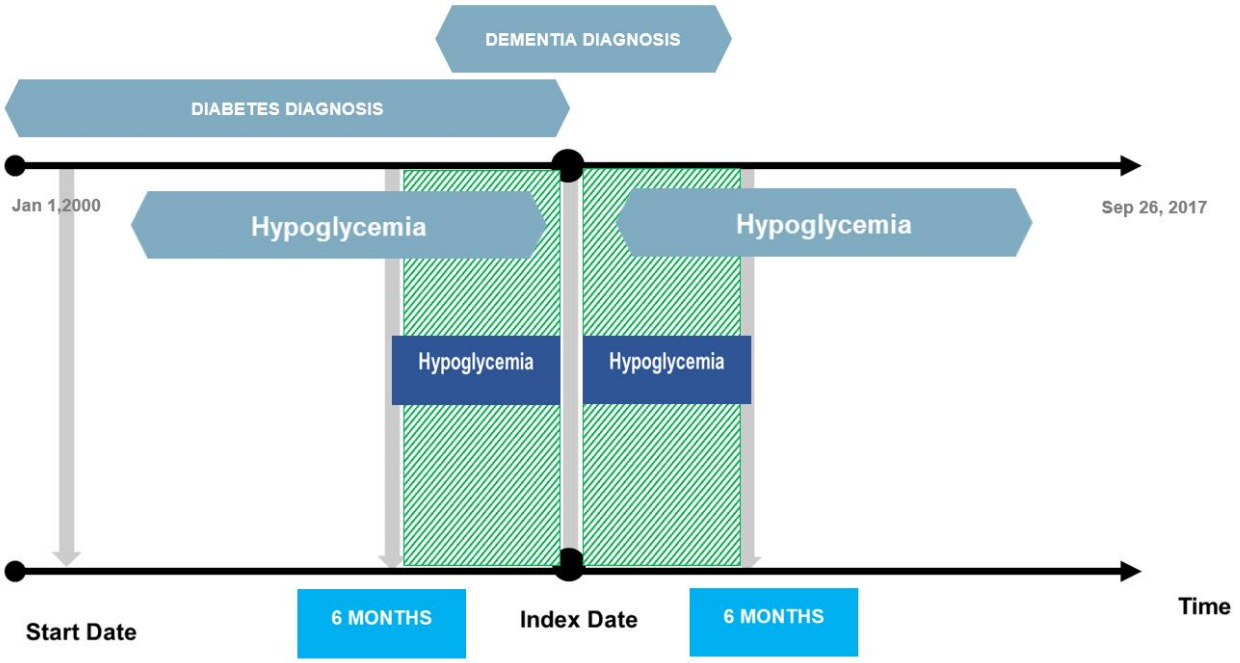



**Figure 40 Study Population**

## 8.3.5 Study variables

Similar to the self-controlled study design, this design allows for eliminating the effects of measured and unmeasured time stable confounding variables, since the cases serve as controls for themselves (Gault et al., 2017). Therefore, confounding factors bias due to patients' characteristics, such as age and gender, type of diabetes, is cancelled before and after the diagnosis of dementia. I have categorised the study variables into three groups: 1) The baseline characteristics included age, gender, BMI, smoking status (non-smoker, ex-smoker and current smoker), alcohol consumption (non-drinker, ex-drinker and current drinker), HbA1c, and diabetes duration; 2) The chronic comorbidities were measured at baseline and over the 12-month period preceding the index date, including diabetes microvascular complications (including neuropathy, nephropathy, retinopathy and diabetic foot), HTN, MI, arrhythmias, HF, COPD, CKD, depression, cerebrovascular disease (CeVD) and obesity; and 3) The medications included chronic medications and

antidiabetic medications. Antidiabetic medications were classified according to the BNF (British National Formulary (BNF), 2017) based on their therapeutic classes. Medications were assessed at baseline and over the six-month period preceding the index date. I included ACEIs or ARBs, BBs, CCBs, statins, aspirin, antidepressants and anti-dementia medications, as chronic medications.

### 8.3.6 Ethical considerations

Approvals for this study were obtained from the IMRD-UK database research ethics committee in July 2018 (reference: 18THIN054). IMRD-UK contains patients' anonymous information from electronic medical records, and therefore no further approvals are needed.

### 8.3.7 Data quality and cross-check

To confirm the accuracy and the quality of the study findings, the data analyses were checked by (K.M.) and (W.L.) a well-trained and experienced specialist in the field of pharmacoepidemiology.

### 8.3.8 Statistical analysis

Data analyses were performed using Statistical Analysis Software (SAS, version 9.4) (SAS Institute Inc., 2019). Continuous data is reported as a mean ± SD, and categorical data as frequencies (n) and percentages (%). I compared the categorical variables using chi-squared analysis ($\chi 2$). Descriptive statistics were carried out to describe patients' characteristics, prescribed medications and chronic comorbidities.

The rate of hypoglycaemia six months pre- and post-dementia diagnosis was presented per 100 persons with 95% CIs using the Poisson method. This was calculated by dividing the number of all DM patients who developed hypoglycaemia six months pre-/post-

dementia diagnosis over the population of patients with DM who were available in the same period during the study period.

$$\boldsymbol{The\ Rate\ of\ Hypoglycaemia} = \frac{Number\ of\ patients\ experienced\ hypoglycaemia\ 6\ months\ (prior\ or\ post)\ dementia\ diagnosis}{Total\ number\ of\ patients\ in\ the\ same\ period} \text{ X100}$$

## 8.4 Results

During the study period of 2000 and 2017, a total of 133,664 patients diagnosed with DM aged 50 years and above were identified, of whom only 13,863 patients with DM and dementia were included. The distribution of patients according to the inclusion criteria is shown in **Figure 41**.

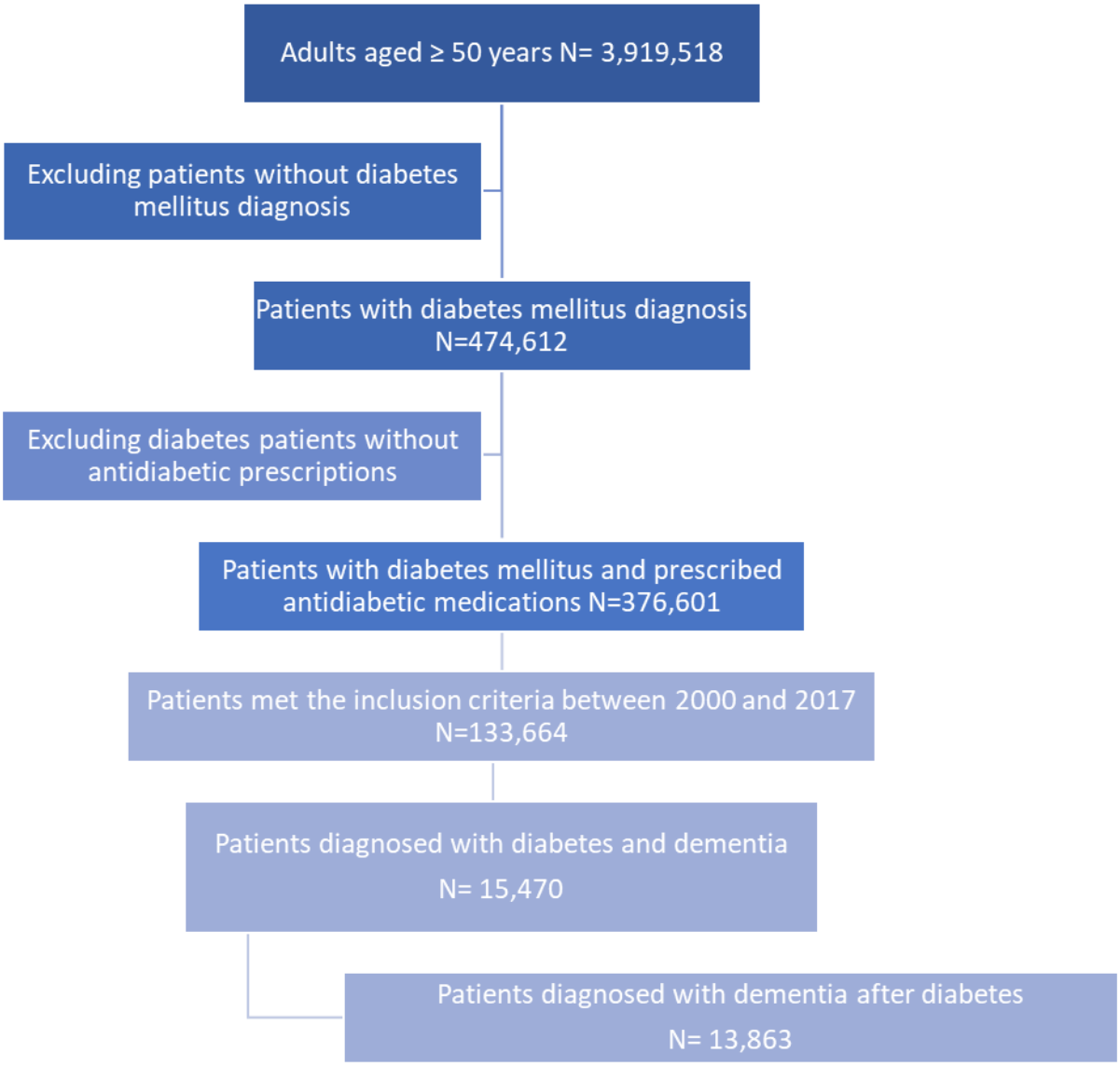



**Figure 41 Flowchart of the Patients Included in the Study**

### 8.4.1 Study population characteristics

Out of 13,863 patients who were identified and included in the present study, 6,282 (45.3%) were males. The average patient age at the index date was 80.4 (SD = 7.4) years old. The average BMI of the patients was 27.2 (SD = 5.4) kg/m2. Around 37.0% (n = 5,131) of the patients were non-smokers, 50.72% (n = 7,032) were ex-smokers, and only 9.4% (n = 1,310) were smokers. Almost half of the patients reported alcohol consumption during in daily life. The most common type of diabetes was T2DM, contributing to 96.4% (n = 13,360) of the sample. The average duration of DM was 13.8 (SD = 8.9) years. The

average patient HbA1c was 7.3 mmol/mol (SD = 1.9). Data on dementia subtypes were available for 9,356 patients (67.9%), and they showed that 4,507 (32.5%) patients had a record of vascular dementia and 3,378 (24.4%) patients were recorded with Alzheimer's disease. Other dementia subtypes were recorded in ≤ 1% of the study sample. The characteristics of study population are summarised in **Table 32**.

**Table 32 Study Population Characteristics**

| Characteristics | Study population (N=13,863 (100%)) |
|---|---|
| **Age at index date, mean (SD)** | 80.4 ± 7.4 |
| **Gender (%)** | |
| **Male** | 6,282 (45.31) |
| **Female** | 7,581 (54.69) |
| **BMI, Kg/m$^2$** | 27.2 ± 5.4 |
| **Smoking (%)** | |
| **Never smoker** | 5,131 (37.01) |
| **Ex-smoker** | 7,032 (50.72) |
| **Current smoker** | 1,310 (9.44) |
| **Missing data** | 390 (2.81) |
| **Alcohol consumption (%)** | |
| **Never drinker** | 2,424 (17.48) |
| **Ex-drinker** | 3,225 (23.26) |
| **Current drinker** | 6,813 (49.15) |
| **Missing data** | 1,401 (10.11) |
| **Diabetes type (%)** | |
| **Type 1 diabetes mellitus** | 503 (3.63) |
| **Type 2 diabetes mellitus** | 13,360 (96.37) |
| **Diabetes duration, mean (SD)** | 13.8 ± 8.9 |
| **HbA1c, mmol/mol** | 7.3 ± 1.9 |
| **Dementia type (%)** | |
| **Vascular dementia** | 4,507 (32.51) |
| **Alzheimer's disease** | 3,378 (24.37) |
| **Parkinson's disease dementia** | 69 (0.50) |
| **Lewy Body Disease** | 143 (1.03) |
| **Frontotemporal dementia** | 18 (0.13) |
| **Posterior cortical atrophy** | 2 (0.01) |

| Characteristics | Study population (N=13,863 (100%)) |
|---|---|
| **Unspecified** | 5,746 (41.45) |
| **Chronic comorbidities (%)** | |
| **Cerebrovascular disease** | 3,864 (27.87) |
| **Arrhythmias** | 3,193 (23.03) |
| **Myocardial infarction** | 5,651 (40.76) |
| **Hypertension** | 10,369 (74.80) |
| **Chronic kidney disease** | 5,721 (41.27) |
| **Depression** | 5,281 (38.09) |
| **Chronic obstructive pulmonary disease** | 1,401 (10.11) |
| **Obesity** | 2,030 (14.64) |
| **Diabetes microvascular complications** | |
| **Diabetic neuropathy** | 2,961 (21.36) |
| **Diabetic retinopathy** | 4,676 (33.73) |
| **Diabetic nephropathy** | 137 (0.99) |
| **Diabetic foot** | 1,181 (8.52) |
| **Medications (%)** | |
| **Insulin** | 3,826 (27.59) |
| **Metformin** | 11,312 (81.60) |
| **Sulfonylureas** | 8,468 (61.08) |
| **DDP-4** | 1,846 (13.32) |
| **GLP-1** | 222 (1.60) |
| **SGLT-2** | 139 (1.00) |
| **Thiazolidinedione** | 2,033 (14.66) |
| **Meglitinides** | 226 (1.63) |
| **Acarbose** | 329 (2.37) |
| **Beta blockers** | 6,804 (49.08) |
| **Calcium channel blockers** | 6,884 (49.66) |
| **ACEI-ARBs** | 10,463 (75.47) |
| **Statins** | 2,189 (15.79) |
| **Aspirin** | 10,590 (76.39) |
| **Antidepressant** | 3,485 (25.14) |
| **Anti-dementia** | 4,183 (30.17) |

**SD** standard deviation, **DDP-4** dipeptidyl peptidase-4 inhibitors, **GLP-1** glucagon-like peptide-1 receptor agonists, **SGLT-2** sodium-glucose cotransporter-2 inhibitors, **ACEI-ARBs** angiotensin-converting enzyme inhibitors - angiotensin receptor blockers

All study patients were diagnosed with at least one chronic comorbidity, and the majority of the patients in this study (n = 12,885; 92.9%) were diagnosed with more than one chronic disease. Hypertension, CKD and myocardial infarction were the three most common chronic conditions, affecting around 74.8%, 41.27% and 40.8% of the patients, respectively. Moreover, 38.09% of the patients in the study reported depression. For full details about the prevalence of chronic conditions across the study sample: refer to **Figure 42**.

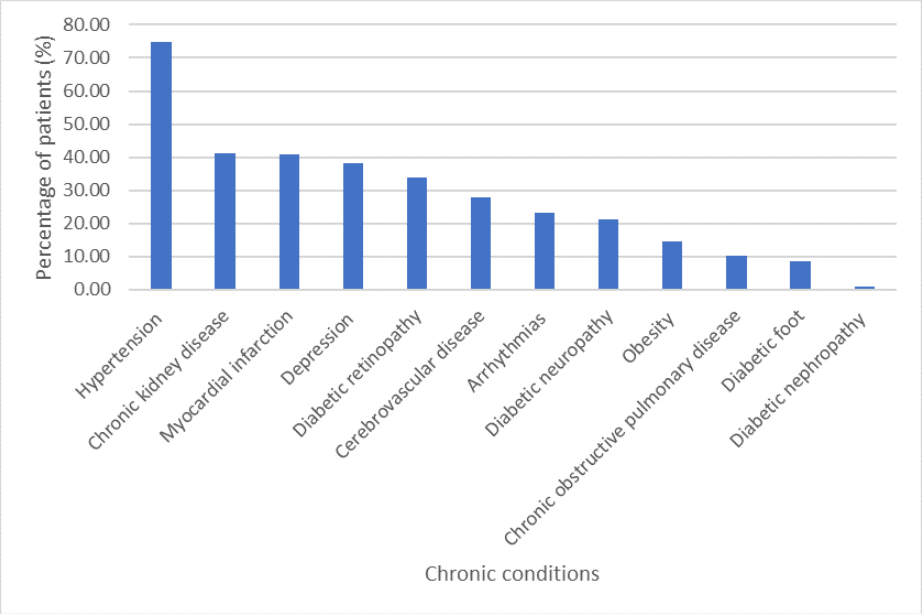



**Figure 42 Distribution of Chronic Comorbidities among the Study patients**

## Antidiabetic medications

The most common antidiabetic medication prescribed was metformin, which contributed to 81.4% (n = 11,279), followed by sulfonylureas at 60.8% (n = 8,435). For further details on the percentage of patients using different therapeutic classifications of antidiabetic therapy: refer to **Figure 43**.

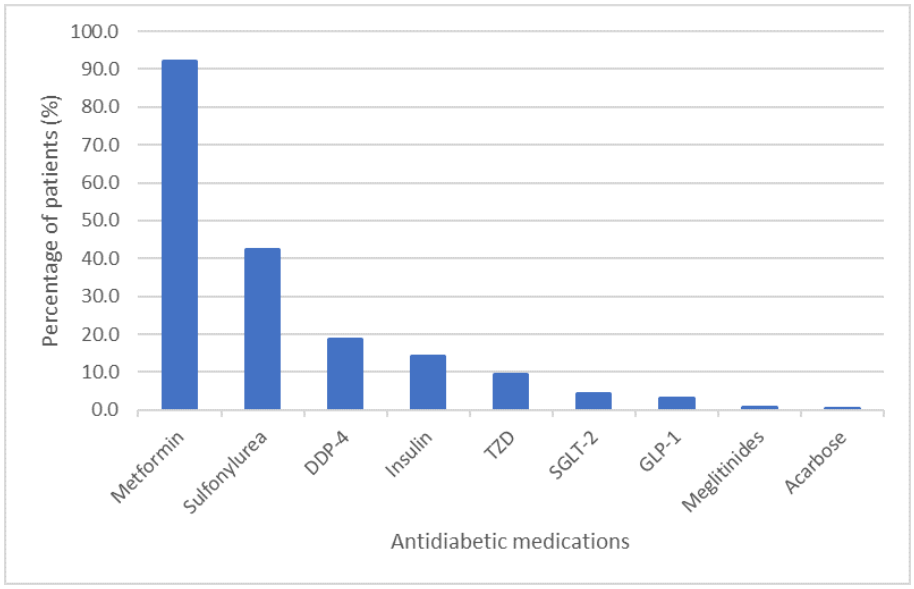



**Figure 43 Percentage of Patients Using Antidiabetic Therapy in the Study**

In general, antidiabetic monotherapy was used by around 39.2% (n = 5,438) of the patients, followed by 36.0% (n = 4,986) for the dual antidiabetic therapy and 16.8% (n = 2,325) for the use of triple therapy. On the other hand, quadruple antidiabetic therapy was used by only 8.0% (n = 1,114) of the patients: refer to **Figure 44**.

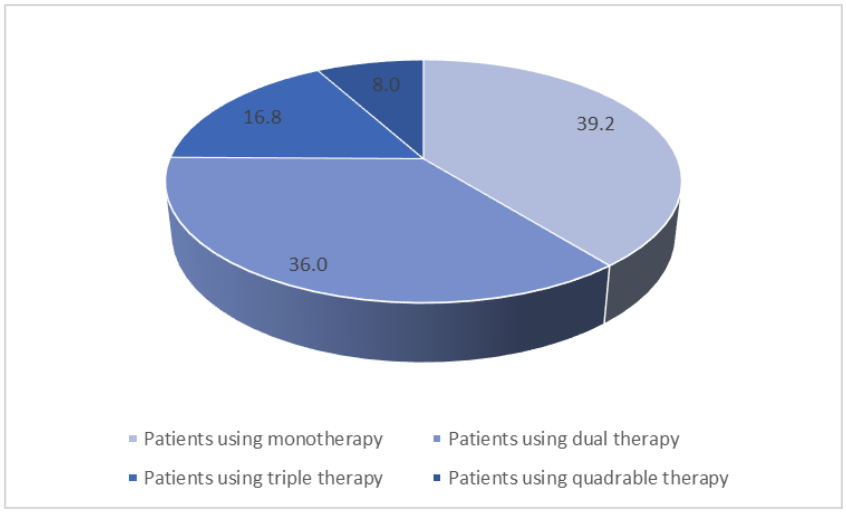



**Figure 44 Percentage of Patients using Monotherapy and Different Combination Therapies in Study**

### 8.4.2 Distribution of patients' missing data

Most of the patients' data were complete and included all clinical data relevant to the patients' medical history and medication use history. However, for some patients there were some missing data. **Table 33** shows the percentage of missing data regarding each variable in the study.

**Table 33 Percentage of Missing Data in this Study**

| Variable | Number of patients with missed data | Percentage from total patients (%) |
|---|---|---|
| **BMI, Kg/m$^2$** | 961 | 6.9% |
| **Smoking status** | 390 | 2.8% |
| **Alcohol consumption** | 1,401 | 10.1% |
| **HbA1c, mmol/mol** | 2,932 | 21.1% |

The majority of missing data were for patients' characteristics, with low percentages ranging from 2.8% to 10.1%. However, a considerable percentage of the patients did not have their HbA1c measurements (21.1%).

### 8.4.3 Glycaemic control pre- and post-dementia

A total of 10,931 patients had at least one record of HbA1c during the study period. The majority of patients prior to dementia diagnosis had a high HbA1c level at 88.94%. only 8% of the patients had a normal level of HbA1c, while less than 1% of patients with below normal HbA1c level (0.87%). Thus, patients prior to dementia diagnosis had poor glycaemic control based on the HbA1c measurements. After dementia diagnosis, the number of patients with high HbA1c level reduced to 34.63%. The majority of patients

post-dementia diagnosis had a normal HbA1c level at 54.06%. The percentage of patients with extremely high HbA1c level was the lowest at 0.8%.

Comparing the measurements of HbA1c pre- and post-dementia diagnosis I found that the proportion of patients with a normal and below normal level of HbA1c increased, which reflects tighter and better control of DM after the diagnosis of dementia. However, the proportion of patients with below normal HbA1c level after dementia increased significantly and the number of patients with a high HbA1c after dementia diagnosis significantly decreased compared to the HbA1c level prior to dementia. **Table 34** presents the measurements of HbA1c pre- and post-dementia diagnosis.

**Table 34 HbA1c Measurements Pre and Post Dementia Diagnosis**

| HbA1c level | Pre dementia N=10,931 (100%) | Post dementia N=10,931 (100%) | P-value |
|---|---|---|---|
| **Below normal level (< 4)** | 95 (0.87) | 1,151 (10.53) | <.0001 |
| **Normal level (4 - 5.6)** | 876 (8.01) | 5,910 (54.06) | <.0001 |
| **High level (5.7-14)** | 9,722 (88.94) | 3,785 (34.63) | <.0001 |
| **Extremely high level (> 14)** | 238 (2.17) | 85 (0.8) | <.0001 |

### 8.4.4 The rate of hypoglycaemia in diabetic patients with dementia

A total of 1,782 (12.85%) patients experienced 3,373 hypoglycaemic episodes during the study period. Before dementia diagnosis, 297 (16.67%) patients experienced 497 (14.73%) hypoglycaemic episodes and 1,485 (83.33%) patients experienced 2,876 (85.27%) hypoglycaemic episodes after dementia diagnosis. The rate of hypoglycaemia in diabetic patients six months before dementia diagnosis calculated by person time was 2.18 (95% CI, 2.15–2.21) per 100 persons, which was significantly lower compared to the rate of hypoglycaemia six months after dementia diagnosis at 3.06 (95% CI, 3.02–3.09) per 100 persons, $p < 0.0001$: refer to **Table 35.**

Among the patients who had hypoglycaemic events, majority of patients had a hypoglycaemic episode within six months prior to the dementia diagnosis, 273 out of 297 (91.91%). However, only 23.23% of patients (345 out of 1485) had a hypoglycaemic episode in the first six months after dementia diagnosis.

**Table 35 Hypoglycaemia Rate Pre and Post Dementia Diagnosis in Patients with Diabetes Mellitus**

| | Pre dementia N=13,863 (100%) | Post dementia N=13,863 (100%) | P-value |
|---|---|---|---|
| **No. of patients experienced hypoglycaemia** | 297 (2.14) | 1,485 (10.71) | <.0001 |
| **Hypoglycaemia by diabetes Type** | | | |
| **Type 1 diabetes mellitus** | 35 (0.25) | 167 (1.2) | <.0001 |
| **Type 2 diabetes mellitus** | 262 (1.88) | 1,318 (9.51) | <.0001 |

## 8.5 Discussion

In this population-based study, I investigated the glycaemic control and the rate of hypoglycaemia in diabetic patients pre- and post-dementia diagnosis over a 17-year period. The key findings were: 1) a tighter glycaemic control was demonstrated post-dementia diagnosis compared to pre-dementia, 2) the rate of hypoglycaemia was significantly higher within six months post-dementia diagnosis compared to six months pre-dementia diagnosis, 3) the proportion of patients who experienced hypoglycaemia six months pre-/post-dementia diagnosis was 273 (91.91%) and 345 (23.23%), respectively.

### 8.5.1 Glycaemic control pre- and post-dementia

Optimal glycaemic control is the main goal of diabetes management to prevent and minimise microvascular and macrovascular complications, which can be achieved by targeting HbA1c levels less than 6.5 or 7% (Holman et al., 2008, Reaven et al., 2009). However, intensive glycaemic control contributes to a higher burden of therapy, is expensive, and has more side effects, particularly an increased risk of hypoglycaemia (Chatterjee et al., 2013, Group, 2008). Previous research has indicated that patients with DM and comorbid dementia are intensively controlled (HbA1c < 7), resulting in an increased risk of hypoglycaemia (Thorpe et al., 2015). Similarly, my study found that glycaemic control post-dementia diagnosis was better and tighter compared to pre-dementia diagnosis. Approximately 54% of patients post-dementia were at a normal level of HbA1c (4–5.6) compared to 8% of patients prior to dementia diagnosis. On the other hand, 10.5 % of patients post-dementia diagnosis were at a below normal HbA1c level (< 4) compared to only 0.8% of patients prior to dementia.

### 8.5.2 The rate of hypoglycaemia

In addition to tight glycaemic control, impaired hypoglycaemia awareness and difficulties with self-management of diabetes faced by this population due to their cognitive decline can explain the higher rate of hypoglycaemia (Abdelhafiz et al., 2015). As highlighted in the previous chapter, DM patients with dementia were at a twofold increased risk of developing hypoglycaemia compared to DM patients only without dementia. My results showed a significant higher rate of hypoglycaemia experienced six months post-dementia diagnosis. There are several possible explanations for why DM patients have a higher rate of hypoglycaemic events after dementia diagnosis. First, DM patients with dementia were aggressively glycaemic controlled and more prone to experience hypoglycaemia (Thorpe et al., 2015). Second, dementia could lead to patient errors in timing or dosage

of diabetes therapy, leading to poor compliance with therapy (Amar Puttanna, 2017). Third, dementia could interfere with proper adjustment of diabetes medication in response to changes in nutritional intake or weight loss (Ikeda et al., 2002). Fourth, patients with dementia may not recognise their hypoglycaemia or misinterpret it and not correctly respond to the blood glucose levels obtained through self-monitoring (Hopkins et al., 2016).

On the other hand, 92% of patients who experienced hypoglycaemia prior to dementia had the hypoglycaemic episodes six months pre-dementia. This could be explained by the fact that dementia is a progressive neurodegenerative disease where a patient's cognitive functions will decline gradually from their normal baseline cognitive abilities to brain dysfunction and inability to perform daily activities, owing to cognitive deficits (Mayeux, 2010). Dementia has three different stages: 1) the preclinical stage is defined by amyloid accumulation with subtle cognition changes, 2) the prodromal stage is defined by amyloid accumulation with obvious symptoms of brain dysfunction and mild cognitive impairment, and 3) the dementia stage is defined by severe symptoms of cognitive and functional impairment, which eventually impairs the patient's ability to perform daily activities that they were previously able to perform (Albert et al., 2011, Sperling et al., 2011, McKhann et al., 1984).

Based on my study findings, DM patients were on tighter glycaemic control and experienced more hypoglycaemic episodes after dementia diagnosis compared to the period before dementia diagnosis. It is important to remind healthcare professionals to highlight the cognitive decline and diagnosis of dementia and take a proactive role in meeting these patients to ensure their safety and well-being. Regular monitoring, discussions and clear instructions to the patient or family/carers are needed to define roles and goals of treatment for preventing these episodes and better outcomes.

### 8.5.3 Strengths and limitations

To the best of my knowledge, this is the first study that has examined glycaemia control and the rate of hypoglycaemia in DM patients six months before and after dementia diagnosis over a 17-year period. This study used a primary care database, which is representative of the UK general population. My study design was based only on cases, which then act as their own control (i.e. they consist of within-patient comparisons at different periods of time), which allows us to control the confounders (including unmeasured or unknown) that are stable over time. However, there are some limitations to my study. Firstly, the IMRD-UK database only provides information in primary care settings, and therefore underestimation of the rate of hypoglycaemia is possible as IMRD-UK was not able to include milder forms of hypoglycaemia. Secondly, patients were identified using relevant Read code lists and algorithms; patients with memory loss or suspected dementia and no diagnosis would not have been included in my study population and my results would not apply to these groups.

## 8.6 Conclusion

In conclusion, the results suggest that DM patients after dementia diagnosis experience a higher rate of hypoglycaemic episodes and are managed intensively. Efforts should be made to support individualised patient care by considering dementia diagnosis in the clinical management of diabetes, loosening glycaemic control and providing suitable counselling to the patient or patient's family members/carers on safe use of antidiabetic and other medications that can help in early detection, prevention and management of hypoglycaemia in patients with dementia.

# 9 CHAPTER NINE: Overall Discussion and Conclusion

This PhD work investigated the association between hypoglycaemia and dementia in patients with DM from a clinical perspective. Firstly, a systematic review was conducted to explore the available literature on the prevalence and incidence rate of hypoglycaemia in patients with diabetes in addition to other outcomes of interest (Chapter Two). This was followed by an examination of the epidemiology of dementia in the DM population over the 17-year period of 2000–2016 in the UK (Chapter Five). Thirdly, an investigation into medication use was conducted by exploring the prescribing pattern of antidiabetic medications and the rate of hypoglycaemia. Fourthly, I examined the association between hypoglycaemia and dementia among DM patients (Chapters Six and Seven). Fifthly, I aimed to evaluate the glycaemic control and hypoglycaemia in DM patients before and after dementia diagnosis (Chapter Eight). This chapter provides the key findings of this PhD project, in addition to explaining the contribution to the existing knowledge and the implications for clinical practice. The main strengths and limitations of the studies conducted are also discussed. Recommendations for future research are also provided in this chapter.

## 9.1 Summary of research key findings

This thesis has described four linked studies to examine the epidemiology and the risk of hypoglycaemia in patients with DM and dementia from a clinical perspective, using the IMRD-UK database (formerly known as THIN) primary care database:

1. The findings presented in Chapter Five, a population-based, descriptive study to estimate the prevalence and incidence of dementia among the DM population in the UK over 17 years suggest an increasing trend in the prevalence and incidence of dementia in elderly patients with DM.

2. The drug utilisation study results found an increase in the trend of antidiabetic medication prescribing for patients with DM and dementia and that the rate of hypoglycaemia increased over the 17-year study period (Chapter Six).

3. To examine the primary research question of this project, an analytical, retrospective cohort study design was employed. A significant association was found between dementia and the risk of experiencing hypoglycaemia (Chapter Seven).

4. A pre-post observational study design was employed to identify the glycaemic control and the rate of hypoglycaemia among DM patients with dementia at the individual level (Chapter Eight). Tighter glycaemic control and a higher rate of hypoglycaemia were found in DM patients after dementia diagnosis than before dementia diagnosis.

## 9.2 Overall discussion

As highlighted in Chapter Two, previous reviews that have been conducted to explore the prevalence, incidence and risk factors of hypoglycaemia in patients with DM have focused on T2DM patients only (Bloomfield et al., 2012b, Edridge et al., 2015). None of the mentioned studies focused on exploring the prevalence, incidence and risk factors among the DM population in the general population and specifically in terms of an overall estimate of the prevalence and incidence of hypoglycaemia regardless of its severity. Thus, the aim of the systematic review (refer to Chapter Two) was to fill this gap in the knowledge by conducting a systematic review and meta-analysis that focused on studies examining the frequency and the risk factors associated with hypoglycaemia in the general DM population. This systematic review highlighted that hypoglycaemia is a very common complication that many DM patients, both T1DM and T2DM, may experience in real life. At the same time, it showed that hypoglycaemia is associated with several risk factors. A number of evidence gaps were identified from the reviewed literature and bibliographies in the existing knowledge of the epidemiology of hypoglycaemia in DM

patients with dementia and of GPs' prescribing of antidiabetic medication for elderly patients with DM and dementia in the UK. Furthermore, limited evidence was found on the association between dementia and the risk of hypoglycaemia among the DM population in the UK. This PhD project addressed these gaps in the knowledge by conducting different pharmacoepidemiological study designs in this project. The following section discusses the key findings from this PhD work.

Overall, dementia was found to be a common health condition in DM elderly patients in UK. The overall annual prevalence of dementia increased nearly fivefold (497%) between 2000 and 2016 from 0.42 (0.42–0.43) to 2.51 (2.50–2.5) per 100 persons, whereas incidence rates increased twofold (277%), from 0.18 (0.17–0.19) to 0.68 (0.67–0.69) per 100 persons during the same period. A slight elevation of incidence rate of dementia was observed in 2015, which may reflect the introduction of the National Dementia Strategy. The National Dementia Strategy aimed to improve diagnosis rates by providing higher quality care services between 2014 and 2015 and increased diagnosis rates up to 67% in 2015 (Department of Health, 2015, Black et al., 2015). Females had a higher incidence and prevalence rate of dementia compared to males. This could be explained by several reasons including; a) females live longer than males on average, and older age is the greatest risk of developing dementia (Mielke et al., 2014); b) oestrogen sex hormone is protecting brain cells and the reduced level of oestrogen hormone in older females can lead to brain cell damage (Alzheimer's Association, 2019); and c) genetic variation, some evidence showed that females carrying APOE-4 gene are at an increased risk of developing dementia compared to males (Alzheimer's Association, 2019). The prevalence of dementia increased with advancing age. Data showed that patients aged ≥ 65 years and diagnosed with T2DM were more likely to develop dementia compared to patients aged < 65 years who were diagnosed with T1DM. These results were consistent

with the trends of diabetes and dementia between 1980 and 2018 (Brookmeyer et al., 2018, Wang et al., 2018).

In term of medication management, this study found that metformin was among the most commonly prescribed antidiabetic drugs for DM patients with dementia, involving 45.57% of prescriptions, while the second most common antidiabetic medications prescribed were sulfonylureas (30%), followed by insulin (16.0%). The prescription rate for all antidiabetic medications increased by 155.1% (from 102.9 [95% CI, 100.4–104.5] to 262.5 [95% CI, 255.2–269.9] per 100 persons) among DM patients with dementia between 2000 and 2016. Furthermore, there was a parallel increase in the rate of antidiabetic medication prescriptions and hypoglycaemia during the same study period, with correlation coefficients of 0.96 for hypoglycaemia. The rate of hypoglycaemia increased by 830.3% from 0.92 (95% CI, 0.34–2.5) in 2000 to 8.6 (95% CI, 7.7–9.3) per 100 persons in 2016. The increased trend in antidiabetic prescribing might give valid justification to the idea that aggressive antidiabetic treatments (using insulin, sulfonylureas and multiple antidiabetic medications) were responsible for the increased trend in hypoglycaemia in patients with DM and dementia.

As was mentioned in section 7.1, many factors other than antidiabetic medication use could contribute to increasing the risk of experiencing hypoglycaemia, including other medications, comorbid diseases and individual factors (Rubin and Golden, 2013, Morales and Schneider, 2014). The cohort study (Chapter Seven) investigated the association between dementia and the risk of hypoglycaemia among the DM population. The study findings showed that dementia was associated with a higher risk of experiencing hypoglycaemia compared with DM patients who did not have a dementia (HR, 2.00; 95% CI,1.63–2.66). In addition to dementia, other predictors of hypoglycaemia were age ≥ 65 years, T1DM, smoking, BMI, history of hypoglycaemic events, diabetes duration > 5

years. Furthermore, male patients were at an increased risk of developing hypoglycaemia compared to females. Multiple factors are associated with this increased risk of hypoglycaemia in males such as skipping meals, increased alcohol consumption and cigarette smoking, excessive physical activity and increased glucose uptake by muscles (Chang et al., 2019, Thenmozhi Paluchamy, 2019).

Furthermore, the use of insulin and sulfonylureas also has a statistically significant effect on hypoglycaemia risk. The increased risk of hypoglycaemia associated with insulin and sulfonylureas in particular depends on their mechanism of action, pharmacodynamics and pharmacokinetics (Holstein and Egberts, 2003, Boyle and Zrebiec, 2008, Miller et al., 2001). Refer **to Chapter 1 section 1.1.4** for more details about the mechanism of action of antidiabetic medications.

To gain insights on the individual level and to cover this area, a retrospective, pre-post study (Chapter Eight) was conducted to explore glycaemic control and the rate of hypoglycaemia among the DM population before and after dementia. This study showed that the glycaemic control of patients with DM was tighter and better controlled after the diagnosis of dementia compared to the glycaemic control before dementia diagnosis, which may perhaps be attributed to the carer's support. The high rate of hypoglycaemia after dementia diagnosis could be due to better reporting by carers and intensive treatment to control blood sugar level.

## 9.3 Implications for clinical practice

The findings of this PhD project provided evidence on what could be addressed concerning the currently available healthcare practices for DM patients with dementia to minimise the possibility of providing unnecessary intensive antidiabetic therapy, and thus decrease the incidence of associated hypoglycaemic events. Clinical practice guidelines

could be updated by the study findings from this PhD work. Implications for clinical practice are provided below.

1. Healthcare professionals who intend to prescribe antidiabetic medications to elderly patients with uncontrolled diabetes must become adept at recognising the conditions commonly associated with diabetes, including the patient's cognitive level, or have other comorbidities. To avoid the harm of unrecognised cognitive impairment in the DM population, early screening for cognitive impairment and dementia should be provided to the elderly population. The purpose of screening is to identify marked clinically relevant stages of dementia likely to interfere with diabetes management. Healthcare professionals should be extra vigilant concerning patients with impaired cognitive function or those diagnosed with dementia as this is associated with a higher risk of hypoglycaemia.

2. Healthcare professionals are advised to create a treatment plan by individualising the diabetes management, placing greater emphasis on the patient's clinical profile (such as their cognitive function or being on polypharmacy) and being consistent with the patient's needs or his/her caregiver's healthcare preferences. For sufficient glycaemic control and to reduce the medical burden, it is reasonable to consider flexible glycaemic control strategies based on the patient's health status, and not on a standard, pre-defined HbA1c value that might not applicable to all patients.

3. Healthcare professionals are encouraged to educate patients and their relatives/carers on how to identify and self-manage their disease, and guide them on how to set goals for preventing or reducing associated adverse events (particularly hypoglycaemia). In addition, the diabetes education plan should consider the following: a) providing simple self-care regimens; b) avoiding medications with a high risk of hypoglycaemia, such as insulin analogues, sulfonylureas (Frier, 2014, Amiel et al., 2008, Edridge et al., 2015),

quinolones, pentamidine, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (Murad et al., 2009); c) improving the overall problem-solving perception of the patients towards hypoglycaemia, so that they can make relevant medication, dietary and physical activity behavioural changes in order to achieve better diabetes control; d) consideration of patient and carer preferences is an important aspect of treatment individualisation. This would be a suitable approach to improve the patients' and their carers' knowledge and ability to recognise their hypoglycaemia and consequently reduce the probability of experiencing further recurrent events in the future.

4. Healthcare professionals are recommended to review and assess their patient's clinical and medication profile on a regular basis to have better outcomes and to reduce any potential drug adverse events.

5. Healthcare professionals' knowledge about current practices should be updated through the arrangement of continual educational programmes conducted by an accredited medical organisation. These programmes should emphasise the importance of designing tailored care, revising patients' therapy on a regular basis, and an education plan that meets the needs of the patient/caregiver in order to reduce the potential harm due to adverse drug events, including hypoglycaemia.

## 9.4 Research strengths and limitations

The strengths and limitations for each study of my PhD project have been discussed at the end of Chapters Two, Five, Six, Seven and Eight. This section outlines the overall strengths and limitations of this PhD project.

**Strengths:**

The main strengths of this PhD project are as follows:

Firstly, all studies were based on the IMRD-UK, which is one of the world's largest electronic primary care databases and broadly representative of the UK population in

terms of patient demographics, practice size, geographical distribution and data quality (Blak et al., 2011). Secondly, the first study conducted to estimate the prevalence and incidence of dementia among the DM population in the UK. It has enabled the researcher to understand the burden of dementia, and showed that dementia is a very common comorbidity in older DM patients. Thirdly, the first study conducted to monitor the trend of antidiabetic medication prescribing and the pattern of hypoglycaemia in patients with DM and dementia in the UK. It revealed a strong positive linear relationship between the trends of hypoglycaemia and antidiabetic medication prescribing. Moreover, the findings showed that other factors may be associated with hypoglycaemia among this population. Fourthly, the first study conducted to investigate the association between dementia and the risk of hypoglycaemia in the UK. It has enabled the researcher to explore the primary research question of this project, and the results showed that dementia is associated with an increased risk of hypoglycaemia.

Finally, the first study to have been conducted in the UK to examine glycaemic control and to estimate the rate of hypoglycaemia among DM patients before and after dementia diagnosis to assess the research question at the individual level and found that glycaemic control was tighter and better in DM patients after dementia diagnosis and the rate of hypoglycaemia was significantly higher after dementia diagnosis.

**Limitations:**

The main limitations of the studies included in this PhD project are as follows:

Firstly, as with any computerised database, misclassification or imprecise use of the disease classification system may have occurred during data entry by the GPs, which in turn may have resulted in incomplete capture of all cases or measuring of GPs' adherence. Secondly, patients were identified using relevant Read code lists and algorithms; thus, patients with suspected dementia or asymptomatic dementia without diagnosis would not have been included in my study sample, which could mean that the

true burden of dementia was underestimated. In addition, I was not able to do data stratification based on dementia type due to lack of subtype coding. Thirdly, I was not able to access data on patient compliance and adherence to the prescribed medication from the database, which may significantly affect the diabetes control and the rate of hypoglycaemia. Fourthly, the IMRD-UK database only provides information from primary care settings, and therefore, underestimation of the rate of hypoglycaemia is possible as IMRD-UK may not be able to include all events of hypoglycaemia, especially the milder forms of hypoglycaemia. Fifthly, due to the descriptive nature of the drug utilisation study, I could not investigate the factors that may influence the trends of the prescription of antidiabetic medications and hypoglycaemia.

Finally, the residual confounding may have persisted despite PS or multivariable analyses or E-value analysis.

## 9.5 Contribution to the knowledge

The work presented in this thesis contributes to the current body of knowledge concerning the epidemiology of dementia and hypoglycaemia in the DM population.

**Information in this research area**

- No previous systematic review and meta-analysis to review the prevalence, incidence and risk factors of hypoglycaemia in both T1DM and T2DM patients.
- No previous studies that have estimated the prevalence and incidence of dementia among the DM population in the UK using primary care data.
- There is a lack of studies that have examined the prescribing rate of antidiabetic medications and the rate of hypoglycaemia among DM patients with dementia.
- The use of antidiabetic medications is associated with more hypoglycaemic events among DM patients with dementia.

- There is a lack of studies that have investigated the association between dementia and hypoglycaemia among the DM population in the UK. Only one study has been conducted in the UK to identify risk factors for incident severe hypoglycaemia in patients with T2DM newly treated with antidiabetic medications.
- No previous studies have been conducted in the UK to investigate glycaemic control and to estimate the rate of hypoglycaemia on the patient level.

**PhD project contribution to current knowledge**

- First systematic review and meta-analysis to provide a pooled estimate of the overall prevalence and incidence of hypoglycaemia among the DM population representing real-life situations.
- First study to estimate the prevalence and incidence of dementia among the DM population in the UK. The findings showed that dementia was prevalent among the DM population over the 17 years of the study period.
- First study to examine antidiabetic medication prescribing trend and the rate of hypoglycaemia among DM patients with dementia in the UK, which showed a concurrent increase in trend during the 17 years of the study period.
- First cohort study in the UK that has revealed the increased risk of hypoglycaemia associated with dementia among the DM population.
- First study to explore glycaemic control and the rate of hypoglycaemia at an individual level in the UK. It showed that DM patients were aggressively glycaemic controlled after the diagnosis of dementia compared to glycaemic control before dementia diagnosis. The rate of hypoglycaemia was estimated to be significantly higher after dementia diagnosis compared to the rate of hypoglycaemia before dementia diagnosis.

## 9.6 Recommendations for future research

The findings from this PhD project serve as a foundation for further investigation and have highlighted many thoughts and ideas in need of further investigation in the area of dementia and hypoglycaemia in the UK. It is recommended that further research be undertaken in the following areas:

1. Further work is needed to explore the risk factors underlying the diagnosis of dementia, and understanding the relationship between diabetes and dementia will be important in discovering the risks and causes that lie behind these two conditions.

2. The findings of this project can assist future studies in estimating the workload and costs associated with patients with dementia and exploring the national burden and long-term consequences of dementia in the UK by linking existing EMR databases to the Hospital Episode Statistics (HES) database. EMR databases contain countless valuable pieces of information that can be utilised for further studies on DM patients with dementia in the context of GP surgeries.

3. Further analytical studies should be conducted to examine the safety of the use of newer oral antidiabetic medications, such as GLP-1 and SGLT-2, and their effect on hypoglycaemia among the dementia population. Future studies should also identify antidiabetic combination regimens that are associated with a higher risk of hypoglycaemia among the DM population, and specifically in patients with dementia.

4. It is recommended that further research be undertaken to identify other factors (such as the clinical profile of the patient, history of comorbidities and history of hypoglycaemia) that should be considered by healthcare professionals when initiating antidiabetic medications. These studies should inform the physicians about the most significant factors that should be taken into account and given priority when managing their patients.

5. As qualitative research is becoming routine in healthcare studies, future studies should be conducted to explore the hypoglycaemia problem-solving ability of patients who have DM and dementia by investigating their attitudes and perceptions towards their previous events. This may help to determine their abilities in solving any expected recurrent hypoglycaemic events and improving patient safety and disease outcomes.

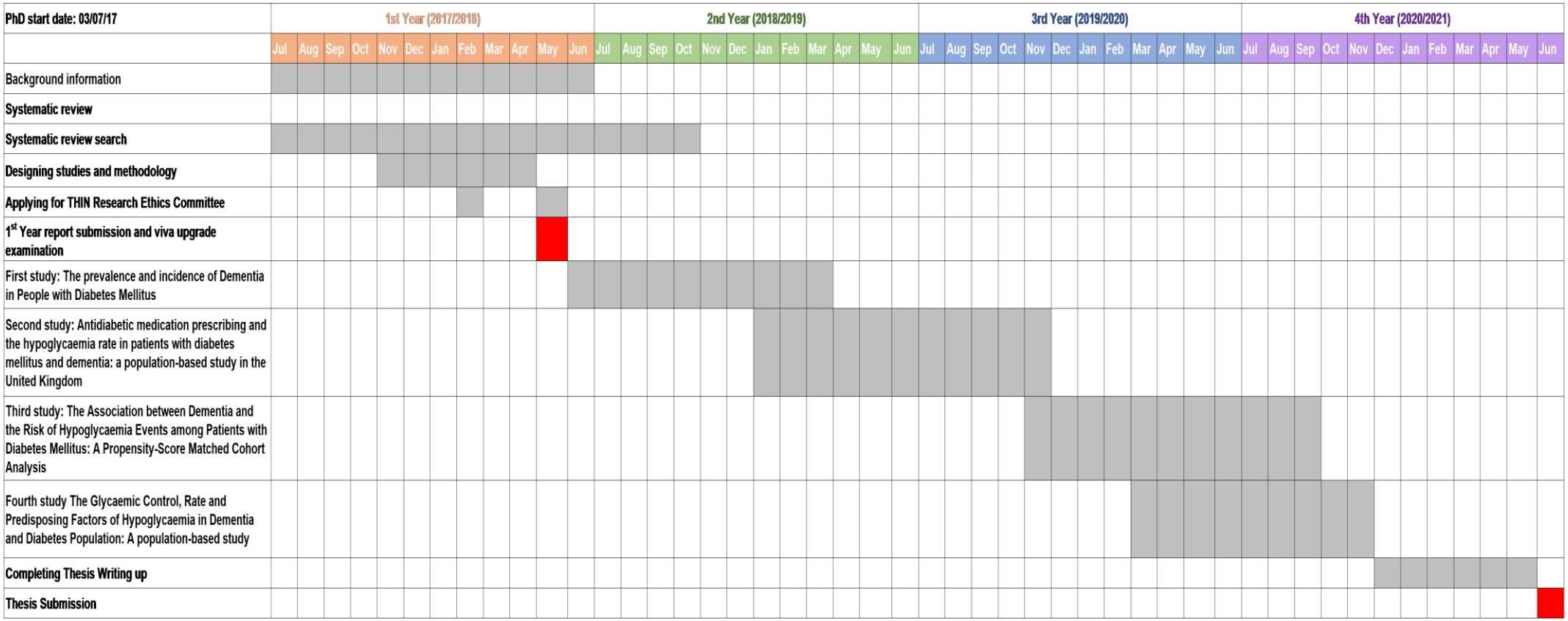
6. Further qualitative studies are needed to understand the physicians' perspective regarding antidiabetic therapy de-intensification and factors that affect their prescribing for DM patients with dementia. This will provide a better understanding of healthcare professional practices and help in identifying sub-optimal practices that may increase the risk of hypoglycaemia. In addition, factors influencing physicians' prescribing are important issues that enable us to have a better understanding of their practices and thus to improve overall healthcare practices and decrease the risk of diabetes overtreatment.

## 9.7 Conclusion

This PhD project has filled multiple gaps in the area of knowledge concerning the association between dementia and hypoglycaemic events in patients with DM. This PhD thesis has used different pharmacoepidemiological methods to address the epidemiology of dementia and hypoglycaemic events in patients with DM. Dementia is prevalent among the DM population, and hypoglycaemia is a common adverse outcome experienced by DM patients with dementia. Dementia is associated with a higher risk of hypoglycaemia in patients with DM, and the majority of patients are on tight glycaemic control. Healthcare professionals should initiate their antidiabetic therapy choice based on several factors other than patients' clinical data and should consider treatment individualisation based on the patient's health status. By considering these factors, the management of patients with DM will be associated with better outcomes.

A detailed timetable for this PhD project is showed in **Table 36**.

**Table 36 PhD Timeline**



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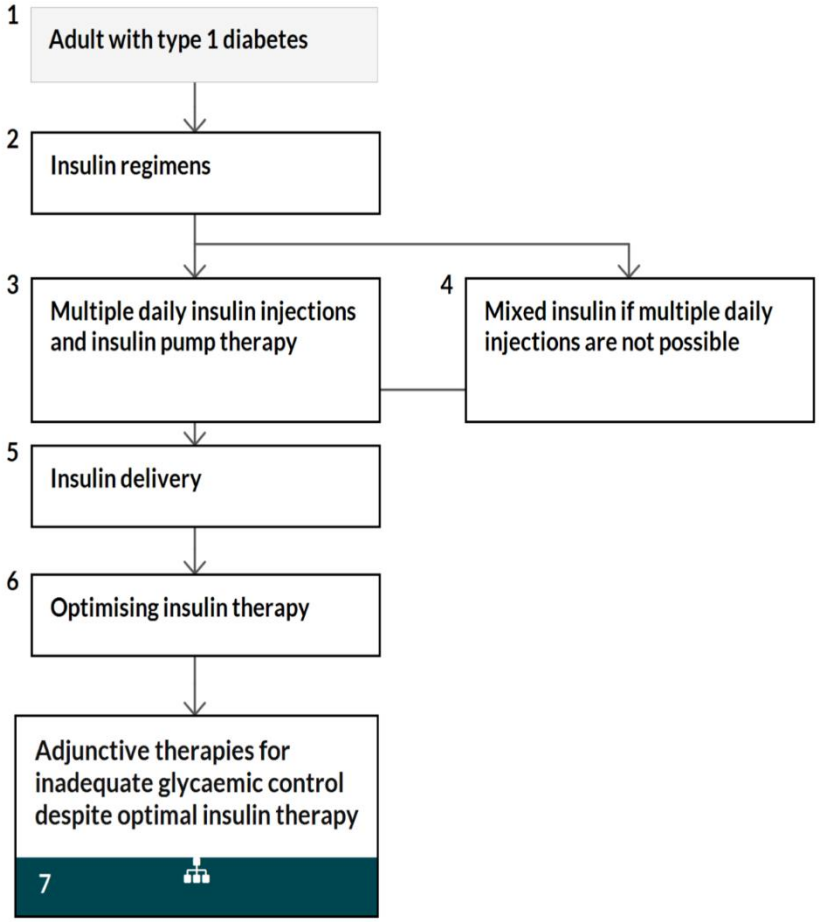
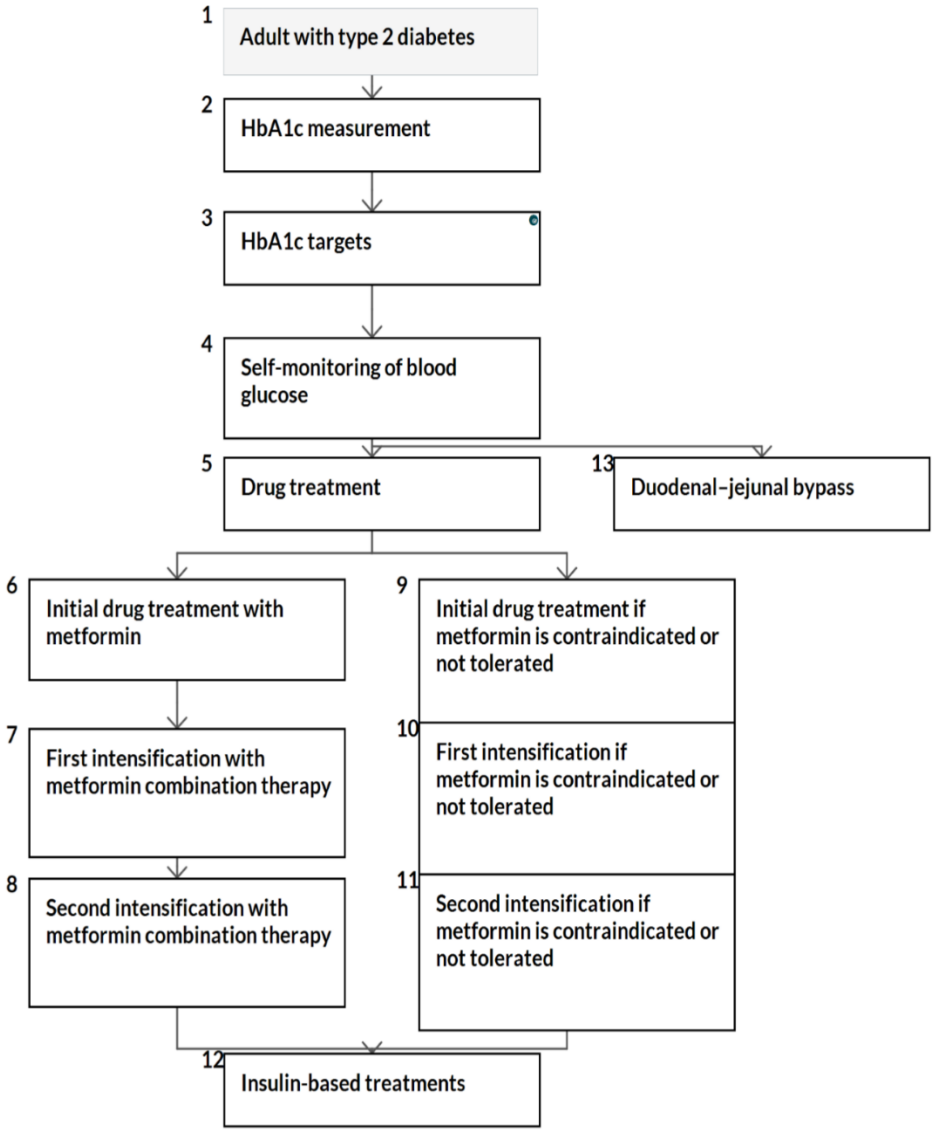
# Appendices

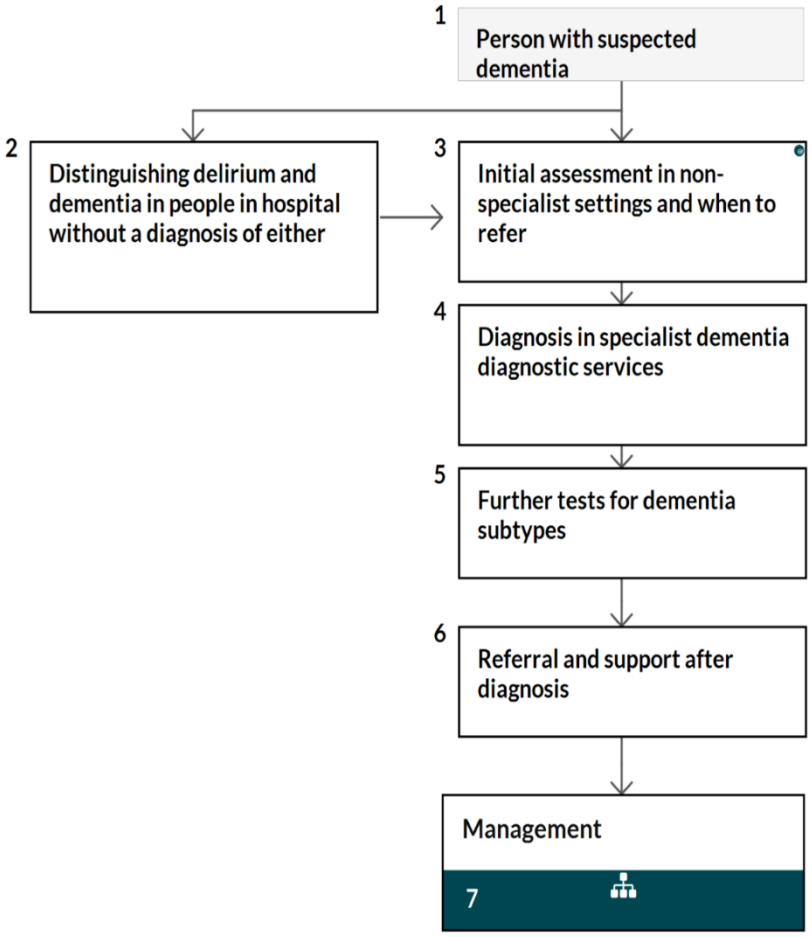
## Appendix 1 NICE's pathway in managing T1DM patients (National Institute for Health and Care Excellence, 2016c)



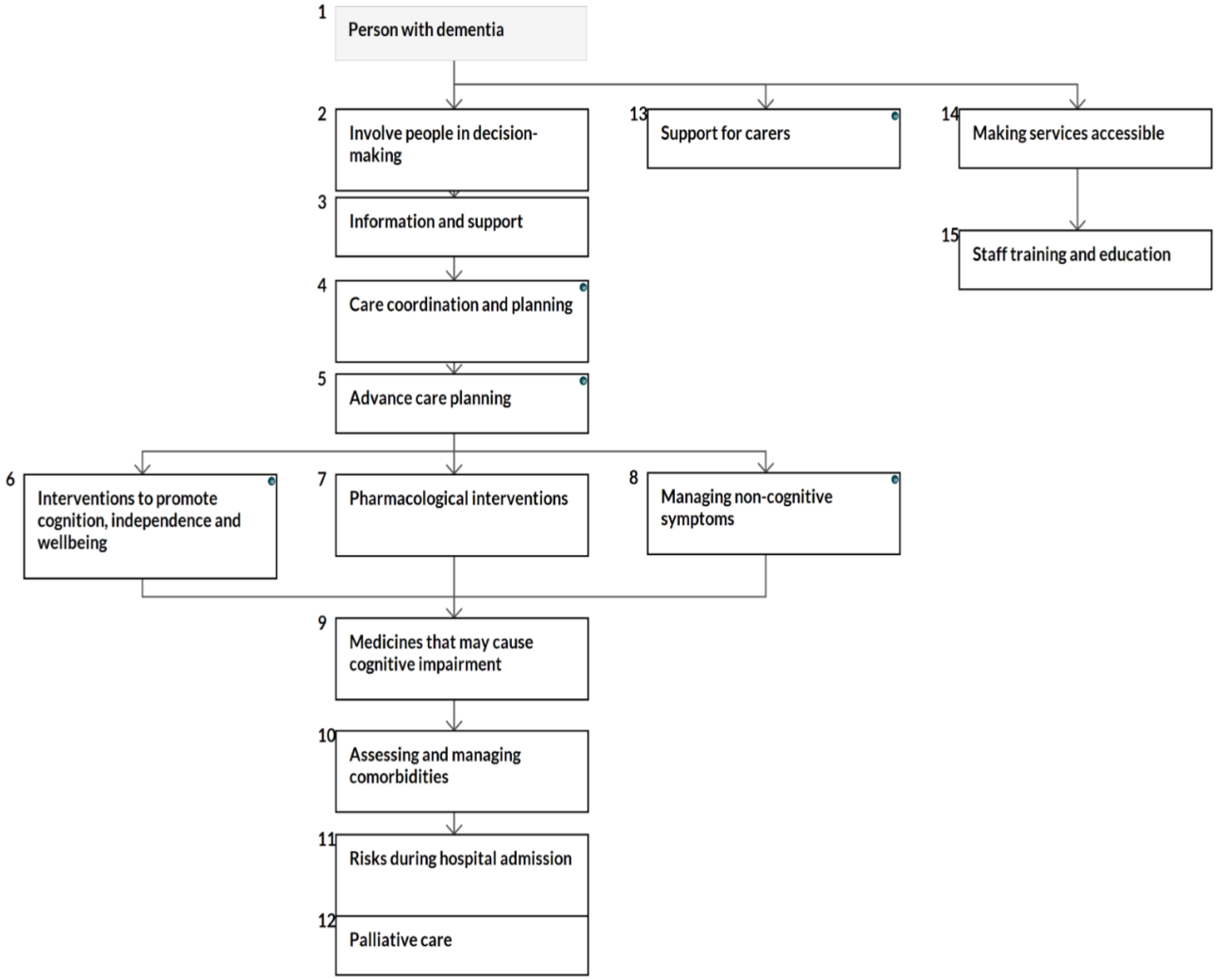
## Appendix 2 NICE's pathway in managing T2DM patients (National Institute for Health and Care Excellence, 2016b)



## Appendix 3 NICE's pathway in diagnosing patients with dementia (National Institute for Health and Care Excellence, 2018a)



## Appendix 4 NICE's pathway in managing patients with dementia (National Institute for Health and Care Excellence, 2018b)



# Appendix 5 PROSPERO Approval

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Print | PDF

**Incidence, prevalence and risk factors of hypoglycemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycemic agents; a systematic review**

*Hassan Alwafi, Alaa Al sharif, Abdullah Naser, Li Wei, Simon Bell, Jenni Ilomak, Gang Fang, Mansour Al Metwazi, Ian Wong*

**Citation**

Hassan Alwafi, Alaa Al sharif, Abdullah Naser, Li Wei, Simon Bell, Jenni Ilomak, Gang Fang, Mansour Al Metwazi, Ian Wong. Incidence, prevalence and risk factors of hypoglycemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycemic agents; a systematic review. PROSPERO 2017 CRD42017077013 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017077013

**Review question**

What are the incidence, prevalence and risk factors of hypoglycemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycemic agents?

**Searches**

PubMed, Embase and Cochrane Library will be searched for observational studies looking at hypoglycemia in humans with type I and type II diabetes mellitus.

**Types of study to be included**

1- Observational studies will be included. 2- Published as full-text papers.

**Condition or domain being studied**

We will study hypoglycemia in type I and type II diabetes mellitus individuals.

**Participants/population**

Inclusion criteria
1- The study population is in type I, type II or mixed type I and II diabetes mellitus individuals, sampled from any primary, secondary or tertiary care settings, without any restrictions on the ethnic groups or sociodemographic characteristics.
2- Reported hypoglycemia as primary/secondary objective (an outcome of interest).
Exclusion criteria:
1. Interventional studies, case reports, case series, narrative reviews, commentary, editorial, book chapters, other summaries, and duplicate publications.
2. Gestational diabetes
3. Animal studies.

**Intervention(s), exposure(s)**

Anti-diabetic medications and/or non-pharmacological treatment, if applicable.

**Comparator(s)/control**

No control group.

**Main outcome(s)**

Hypoglycaemia incidence / prevalence.

**Additional outcome(s)**

Hypoglycaemia risk factors.

**Risk of bias (quality) assessment**

The Newcastle-Ottawa Scale (NOS) for the assessment of the methodological quality of the included studies and minimization of bias will be used. Two independent reviewers (H.A and A.A) will assess the studies selection. Two independent reviewers (H.A and A.A) will undertake quality assessment and allocate stars for adherence to the pre-specified criteria. We will classify studies into a low, medium and high risk of bias. We will consider the risk of bias in the study while synthesizing available evidence. We will perform the sensitivity analysis by including and excluding studies with high risk of bias.

**Strategy for data synthesis**

If studies are sufficiently homogeneous in terms of design, we will conduct meta-analyses. Study results will be summarized using prevalence and incidence rates and the association of risk factors with hypoglycemia will be reported as relative risk or odds ratio at 95% confidence interval. If required, sensitivity analysis will be conducted to assess heterogeneity by patient characteristics (age, gender) and publication type (risk of bias).
A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies.

**Analysis of subgroups or subsets**

None planned.

**Contact details for further information**

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### Organisational affiliation of the review

University College London

### Review team members and their organisational affiliations

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### Anticipated or actual start date

24 July 2017

### Anticipated completion date

01 December 2017

### Funding sources/sponsors

None

### Conflicts of interest

None known





### Language

English

### Country

England

### Stage of review

Ongoing

### Subject index terms status

Subject indexing assigned by CRD

### Subject index terms

Diabetes Mellitus, Type 2; Humans; Hypoglycemia; Hypoglycemic Agents; Incidence; Insulin; Prevalence; Risk Factors

### Date of registration in PROSPERO

16 October 2017

### Date of publication of this version

15 September 2017

### Versions

15 September 2017

### Stage of review at time of this submission

| Stage | Started | Completed |
|---|---|---|
| Preliminary searches | No | Yes |
| Piloting of the study selection process | Yes | Yes |
| Formal screening of search results against eligibility criteria | Yes | No |
| Data extraction | No | No |
| Risk of bias (quality) assessment | No | No |
| Data analysis | No | No |

## Appendix 6 Databases searching strategy

Database: Pubmed

Accessed from: Wiley Online Library

Search date: 01/10/2018

Search strategy:

| | Key words | MeSH terms | Terms as free text | Search |
|---|---|---|---|---|
| **A** | Incidence | Incidence | Incidences | ("Incidence"[MeSH]) OR incidence* |
| **B** | Prevalence | Prevalence | Prevalences | ("Prevalence"[MeSH]) OR prevalence* |
| **C** | Risk factor | Risk factor | Factor, Risk, Factors, Risk Risk Factor, Population at Risk, Risk, Population at Populations at Risk Risk, Populations at | (((((((("Risk Factors"[MeSH]) OR risk factor*)) OR Factor, Risk) OR Factors, Risk) OR Risk Factor) OR Population at Risk) OR Risk, Population at) OR Populations at Risk) OR Risk, Populations at |
| **D** | Rate risk | | Rate risks | Rate risk OR rate risks |
| **E** | Relative risk | | Relative risks | (relative risks) OR relative risk |
| **F** | Odds ratio | | Odds ratios | (odds ratios) OR odds ratio |
| **G** | hypoglycaemia | Hypoglycaemia | Postprandial Hypoglycaemia Hypoglycaemia, Postprandial Reactive Hypoglycaemia Hypoglycaemia, Reactive Fasting Hypoglycaemia Hypoglycaemia, Fasting Postabsorptive Hypoglycaemia Hypoglycaemia, Postabsorptive | (((((((("Hypoglycaemia"[MeSH]) OR hypoglyc*) OR Postprandial Hypoglycaemia ) OR Hypoglycaemia , Postprandial) OR Reactive Hypoglycaemia ) OR Hypoglycaemia , Reactive) OR Fasting Hypoglycaemia ) OR Hypoglycaemia , Fasting) OR Postabsorptive Hypoglycaemia ) OR Hypoglycaemia , Postabsorptive |
| **H** | episode | | | episode* |
| **I** | event | | | event* |
| **J** | diabetes | Diabetes mellitus | | (diabet*) OR "Diabetes Mellitus"[MeSH] |

1- (A) OR (B) OR (C) OR (D) OR (E) OR (F) OR (H) OR (I)

2- G AND 1

3- J AND 2

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Database: EMBASE

Classic + Embase1947 to 01/10/2018

Accessed from: Ovid

Search date: 01/10/2018

Search strategy:

| Key word | MeSH terms | Terms as free text |
|---|---|---|
| **Diabetes** | Diabetes mellitus | Diabetes<br>Diabetes Complications [MeSH Descriptor]<br>Diabetic |
| **Diabet*** | | |
| **Hypoglycaemia** | Experimental hypoglycaemia | Experimental hypoglycaemia, Experimentally induced hypoglycaemia, Experimentally induced hypoglycaemia |
| | hypoglycaemia | conditioned hypoglycaemia, conditioned hypoglycaemia, hypoglycaemia, hypoglycaemic reaction , hypoglycaemic reaction, insulin reaction, ketotic hypoglycaemia, ketotic hypoglycaemia , late hypoglycaemic syndrome, reactive hypoglycaemia, reactive hypoglycaemia , spontaneous hypoglycaemia, spontaneous hypoglycaemia |
| | Insulin hypoglycaemia | hypoglycaemia,insulin, hypoglycaemia,insulin dependent, hypoglycaemia ,insulin, hypoglycaemia ,insulin dependent, insulin hypoglycaemia |
| | Nocturnal hypoglycaemia | Nocturnal hypoglycaemia |

1- Diabetes,

2- Diabetes mellitus,

3- Diabetes Complications,

4- Diabetic,

5- Diabet*

6- 1 OR 2 OR 3 OR 4 OR 5

7- Hypoglycaemia,

8- Experimental hypoglycaemia

9- Experimental hypoglycaemia

10- Experimentally induced hypoglycaemia

11- Experimentally induced hypoglycaemia

12- Hypoglycaemia

13- Conditioned hypoglycaemia

14- Conditioned hypoglycaemia

15- hypoglycaemic reaction

16- Hypoglycaemic reaction

17-insulin reaction

18- ketotic hypoglycaemia

19- ketotic hypoglycaemia

20- Late hypoglycaemic syndrome

21- Reactive hypoglycaemia

22- Reactive hypoglycaemia

23- Spontaneous hypoglycaemia

24- Spontaneous hypoglycaemia

25- Insulin hypoglycaemia

26- hypoglycaemia, insulin

27- hypoglycaemia, insulin dependent

28- hypoglycaemia, insulin

29- hypoglycaemia, insulin dependent

30- Insulin hypoglycaemia

31- Nocturnal hypoglycaemia

32- 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31

33- Incidence, 34- Incidence rate, 35- Rate, incidence

36- 33 OR 34 OR 35

37- Prevalence,

38- Prevalence study

39- 37 OR 38

40- Risk factor,

41- Relative risk,

42- Risk factors

43- 40 OR 41 OR 42

44- 43 OR 36 OR 39

45- odds ratio,

46- rate risk

47- 45 OR 46

48- 44 OR 47

49- 6 AND 32 AND 48

---

Database: Cochrane library

Accessed from: Wiley Online Library

Search date: 01/10/2018

Search strategy:

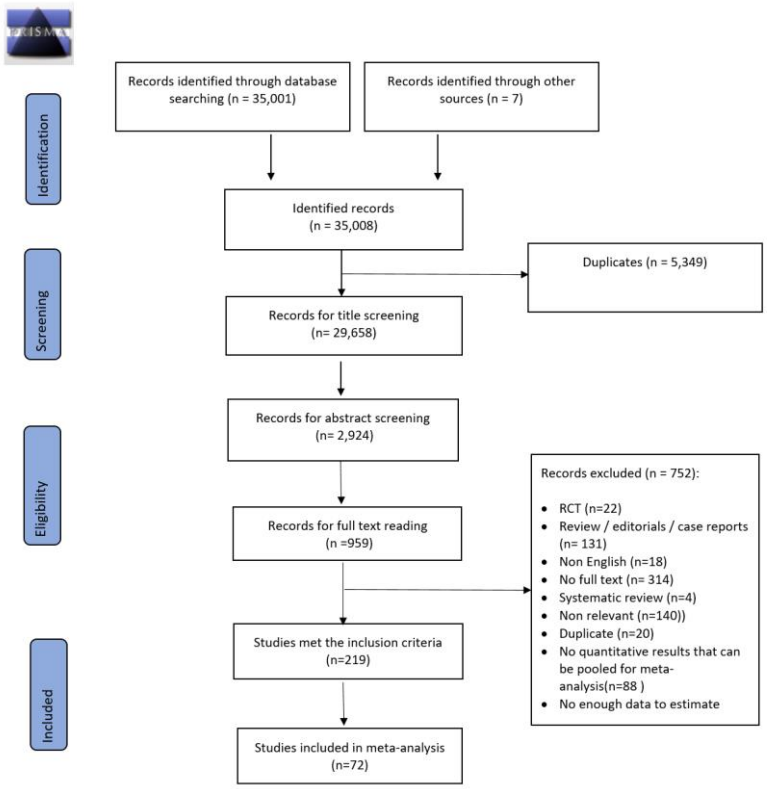
| | Key word | MeSH terms | Free text |
|---|---|---|---|
| **A** | Diabetes mellitus | Diabetes mellitus | Diabet* |
| **B** | hypoglycemia | Hypoglycemia | • hypoglyc*<br>• Postprandial Hypoglycemia<br>• Reactive Hypoglycemia<br>• Fasting Hypoglycemia<br>• Postabsorptive Hypoglycemia |
| **C** | Incidence | Incidence | Incidences |
| **D** | Prevalence | Prevalence | Prevalences |
| **E** | Risk factor | Risk factors | • Factors, Risk<br>• Population at Risk |
| **F** | event | | |
| **G** | episode | | |

1- C OR D OR E OR F OR G

2- B AND 1

3- A AND 2

## Appendix 7 PRISMA Flow Diagram for Studies Selection' Process included in the Meta-Analysis



## Appendix 8 Characteristics of studies included in the Systematic Review (Data Extraction Table)

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **(Jabbar et al., 2017)** | Multinational | Retrospective | 3250 | Self-reported | T2DM | 54.7 | M48.5% | NA | NA | Yes | No | No | **NA** |
| **(Akirov et al., 2018)** | NA | Prospective | 5301 | Self-reported | Both types ofdiabetes | 73 ± 13 | M 51% | 12 ± 11 | A combination of oral or Insulin | Yes | No | No | **Hypoglycaemia and serious hypoglycaemia were defined as at least one blood glucose measurement ≤ 70 and < 54 mg/dl.** |
| **(Lee et al., 2017)** | North America | Prospective | 1206 | Self-reported | T2DM | 64 | 54% | NA | NA | No | No | Yes | **ICD codes** |
| **(Allen et al.,2001)** | North America | Retrospective | 415 | Self-reported | T1DM | NA | M 51.3% F 48.7 % | NA | Insulin | No | No | Yes | **Frequent hypoglycaemia was definedas approximately two to four times per week or more, and severe hypoglycaemia was defined as loss of consciousness during an insulin reaction.** |
| **(Aung et al.,2012)** | Europe | Retrospective | 1066 | Self-reported | T2DM | 67.9 ± 4.2 | M 51% | 8.1 SD ±6.5 | A combination of oral and insulin | Yes | No | No | **Severe hypoglycaemia was definedas self-reported episodes of hypoglycaemia requiring external help.** |
| **(Barkai et al.,1998)** | Europe | Prospective | 130 | Self-reported | T1DM | NA | M 52.3 % | NA | Insulin | No | Yes | No | **A hypoglycaemic event was defined as an episode which was accompanied by typical common symptoms of hypoglycaemia and which was corrected by oral carbohydrate, parenteral glucose orglucagon therapy, irrespective of whether hypoglycaemia had been demonstrated by blood glucose measurement. Severe hypoglycaemia** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **was defined as any event requiring the assistance of another person for treatment** |
| **(Basu et al.,2017)** | North America | Retrospective | 560,503 | Database | NA | 49.7 | M 48.7%, F 51.3% | NA | NA | No | No | Yes | **ICD codes** |
| **(Berkowitz et al.,2012)** | North America | Retrospective | 14,357 | Self-reported | T2DM | 58 SD ±10 | M 51%, F 49 % | 10 SD ± 8 | A combination of oral and insulin | No | No | Yes | **Severe hypoglycaemia was defined as an event that required assistance from another person who actively administered carbohydrate, glucagonor other resuscitative actions and was associated with either a blood glucose level less than 3.9 mmol l (< 70mg dl) or prompt recovery after restoring normoglycaemia** |
| **(Birkebaek et al.,2017)** | Europe | Retrospective | 8806 | Database | T1DM | 11 | M 52% | 5.1±3.1 years | NA | No | Yes | No | **SH was defined in accordance with the guidelines of the International Society of Pediatric and Adolescent Diabetes as an event associated with severe neuroglycopenia resulting incoma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)** |
| **(Pedersen-Bjergaard et al.,2003)** | Europe | Prospective | 171 | Self-reported | T1DM | 44 ± 12 | M 54% | 19 ±11 years | Insulin | No | Yes | Yes | **Severe hypoglycaemia was definedas hypoglycaemic episodes with a need for assistance from other persons in order to restore glucose levels.** |
| **(Blasetti et al.,2011)** | Europe | Prospective | 195 | Database | T1DM | 13.9 ± 6.6 | M 51.79 % | NA | Insulin | No | Yes | No | **< 50 mg/dl associated with altered status of consciousness including seizure or coma or** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **confessional state** |
| **(Bognetti et al.,1997)** | Europe | Retrospective | 187 | Self-reported | NA | NA | M 56.1% | NA | Insulin | Yes | Yes | No | **NA** |
| **(Borzi et al.,2016)** | Europe | Retrospective | 3,167 | Self-reported | T2DM | 75.2 SD ±11.2 | M 50.7%,F 49.3 % | NA | NA | No | No | Yes | **Hypoglycaemic episodes had to besymptomatic with a blood glucose level <3.89 mmol/L and/or specific treatment for hypoglycaemia.** |
| **(ter Braak et al.,2000)** | Europe | Retrospective | 195 | Self-reported | T1DM | Uncomplicated hyop 39 ± 12 Hypoglycaemic coma 44 ± 14 | NA | Uncomplicated hyop 22 SD ± 10 Hypoglycaemic coma 24 SD ± 13 | Insulin | No | No | Yes | **SH was defined as all episodes for which help from others was requireddivided into uncomplicated SH (i.e., SH episodes not complicated by coma, seizure, or treatment with glucagon or intravenous dextrose) and hypoglycaemic coma (i.e., SH complicated by coma, seizure, or treatment with glucagon or intravenous dextrose)** |
| **(Bramlage et al.,2012)** | Europe | Retrospective | 3810 | Self-reported | T2DM | NA | M 48.9% | NA | A combination of oral only | Yes | No | No | **Patients with mild hypoglycaemia were defined as being with or withoutspecific symptoms but manageable without help. These were usually detected by self-measurements of blood glucose (<2.22 mmol/l; 40 mg/dl in any case; 2.22-2.78 mmol/l or 50 mg/dl in case of symptoms) . Patients with moderate hypoglycaemia experienced symptoms of hypoglycaemia and required assistance from a second person (e.g. a relative or friend), but no attention of a medical professionalwas necessary. Patients** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **with severe hypoglycaemia were seeking medical attention or were admitted to hospital because of hypoglycaemia** |
| **(Bron et al.,2012)** | Europe | Retrospective | 212061 | Database | T2DM | 53.9 ±10.6 | M 56 % | NA | A combination of oral and insulin | No | Yes | No | **ICD codes** |
| **(Bruce et al.,2009)** | Australia | Retrospective | 302 | Database | NA | NA | NA | NA | NA | No | No | Yes | **Severe hypoglycaemia required EDvisit or hospitalisation** |
| **(Bruderer et al.,2014)** | Europe | Retrospective | 130,761 | Database | T2DM | 61.7 | NA | NA | A combination of oral and insulin | No | No | Yes | **To define severe hypoglycaemia, we required one of the following records: (i) a code for hypoglycaemia requiring third-party assistance; (ii) a code for hypoglycaemic coma; (iii) a code for hypoglycaemia or a blood glucose level <3.0 mmol/l followed by emergency admission to hospital orby death within 30** |
| **(Buyken et al.,1998)** | Europe | Retrospective | 2065 | Self-reported | T1DM | 32.7± 10.2 | M 50.9 | 14.8 ±9.5 years | Insulin | Yes | No | No | **Severe hypoglycaemia (requiring thehelp of another person)** |
| **(Cherubini et al.,2013)** | Europe | Retrospective | 2025 | Self-reported | T1DM | 12.4 ± 3.8 | M 53 % | 5.6 ± 3.5 years | Insulin | Yes | Yes | No | **Hypoglycaemia was defined as any episode leading to hospitalisation or requiring the administration of glucagon because the patient was unconscious or had seizures** |
| **(Chou et al.,2013)** | Asia | Retrospective | 78, 433 | NA | NA | NA | NA | NA | NA | No | No | Yes | **Severe hypoglycaemia required EDvisit or hospitalisation** |
| **(Alexiu et al.,2017)** | North America | Retrospective | 232898 | Database | Both types ofdiabetes | NA | NA | NA | A combination of oral and insulin | No | Yes | No | **Mild, moderate, and severe hypoglycaemia severity is typicallydefined on the basis of service use, medical setting, and/or hospitalisation** |
| **(Conceicao** | Europe | Retrospective | 425706 | Self- | T2DM | NA | NA | NA | A combination | Yes | No | No | **ER admissions** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| etal., 2017) | | | | reported | | | | | of oral and insulin | | | | |
| (Corsonello etal., 1999) | Europe | Retrospective | 3,477 | Database | Both types ofdiabetes | 71.4 | NA | NA | A combination of oral and insulin | No | No | Yes | NA |
| (Davis et al.,2011) | Australia | Retrospective | 602 | Database | T2DM | 66.5 SD ±9.9 | M 51.8% | NA | NA | No | No | Yes | An episode in which a patient with a subnormal blood/plasma/ serum glucose required documented health service use (ambulance attendance, emergency department attendance, or hospitalisation) and hypoglycaemia was the primary diagnosis |
| (Davis et al.,2010) | Australia | Retrospective | 616 | Database | T2DM | 6.7 ± 9.8 | M 52.3% | 7.7 years | NA | No | Yes | No | NA |
| (Davis et al.,1998) | Australia | Prospective | 709 | Self-reported | T1DM | 12.3 ±4.4 | M 52 % | 4.9 years | Insulin | No | Yes | No | Moderate hypoglycaemia defined as hypoglycaemia requiring the assistance of another person for treatment and severe hypoglycaemia as an eventresulting in coma or convulsion. |
| (Deusenberry etal., 2012) | North America | Retrospective | 692 | Database | T2DM | NA | M 51.3 % | NA | Sulfonylureas | Yes | No | No | Glucose <70 mg/dl |
| (Dendy et al., 2014) | North America | Retrospective | 5,026 | Database | Both types ofdiabetes | 67.6 SD±13.2 | M 62%, F 38% | NA | NA | No | No | Yes | Hypoglycaemia was defined as a glucose measuremen‹70 mg/dL. |
| (Derijks et al.,2008) | North America | Retrospective | 2,446 | Database | Both types ofdiabetes | 69 | NA | NA | A combination of oral and insulin | No | No | Yes | NA |
| (Desjardins etal., 2014) | North America | Retrospective | 108 | Self-reported | T1DM | 46.4 | M 53% | NA | Insulin | No | No | Yes | NA |
| (Duran-Nah etal., 2008) | North America | Retrospective | 282 | Hospital based | T2DM | NA | M 67.6% , F 32.4% | 13.7 SD ±8.3 | NA | No | No | Yes | Defined as glucose concentration less than or equal to 4 mmol/L (72 mg/dL) |
| (Donnelly et al.,2005) | Europe | Prospective | 267 | Database | Both types ofdiabetes | NA | NA | NA | Insulin | No | Yes | No | Patients were encouraged to use their own glucose meter to take their recording), together with the nature ofthe remedial action taken and whether |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **the episode required assistance of a third party (i.e. severe hypoglycaemia** |
| **(Egger et al.,1991)** | Europe | Retrospective | 155 | Self-reported | T1DM | 12.6 SD±4.6 | NA | 5.5 SD ±4.0 | NA | No | No | Yes | **Grade 1, minor signs, self-management possible; grade 2, moderate signs, patient dependent on external help but no loss of consciousness; grade 3, unconscious-ness with documented low blood glucose and/or immediate response to glucose or glucagon** |
| **(Elwen et al.,2015)** | Europe | Retrospective | 1,156 | Self-reported | Both types ofdiabetes | 61 | M 60 %, F40 % | NA | A combination of oral and insulin | No | No | Yes | **Capillary blood glucose (CBG) levelswere less than 4 mmol/L at attendance of the emergency crew.** |
| **(Endo et al.,2000)** | North America | Retrospective | 38 | Database | T2DM | 6.9+ SD ± .1 | M 78%, F 28% | 22 SD ±7.7 | Sulfonylureas | No | No | Yes | **glucose 54 mg/dL requiring intravenous glucose administration with or without concurrent therapy forlonger than 12 hours were included as case patient** |
| **(Eriksson et al.,2016)** | Europe | Retrospective | 52,760 | Database | T2DM | 64.4 SD ± 11.8 | M 59.8 %, F 40.1 % | NA | A combination of oral only | No | No | Yes | **ICD codes** |
| **(Fang et al.,2015)** | Asia | Retrospective | 291 | Hospital based | T2DM | 75.7 | NA | 16.7 SD ±9.6 | A combination of oral only and insulin | No | No | Yes | **NA** |
| **(Faerch et al., 2011)** | Europe | Prospective | 128 | Self-reported | T1DM | 45± 12 years | M 56.2% | 19±11 years | Insulin | Yes | No | No | **Severe hypoglycaemia was definedas an episode at which the patient needs assistance from another person to restore the blood glucose level** |
| **(Feher et al., 2016)** | Europe | Retrospective | 1569 | Self-reported | T2DM | NA | M 66% | NA | A combination of oral and insulin | Yes | No | No | **As: feeling hungry, sweating, dizziness, tiredness (fatigue), blurredvision, trembling or shakiness, fast pulse or palpitations,** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **tingling lips, irritability, difficulty concentrating, confusion, and disorderly or irrationalbehaviour, which may be mistaken for drunkenness. 'Mild hypoglycaemia ' was defined as any of the above symptoms where a thirdparty was not required, and 'severe hypoglycaemia was defined as the above symptoms with third-party involvement or where there was loss of consciousness** |
| **(Farmer et al., 2012)** | Europe | Retrospective | 3562 | Self-reported | NA | NA | NA | NA | NA | Yes | No | No | **NA** |
| **(Feil et al., 2011)** | North America | Retrospective | 497900 | Database | NA | NA | NA | NA | NA | No | No | Yes | **ICD codes** |
| **(Freathy et al.,2006)** | Europe | Retrospective | 308 | Self-reported | T2DM | 54 .5 | M 54 .5/ 45.5% | 10 (5-14) | A combination of oral only and insulin | No | No | Yes | **Definitions of mild (self-treated) and severe (requiring help from another person to effect recovery)** |
| **(Fu et al., 2014)** | North America | Retrospective | 887,182 | Database | T2DM | NA | M 52.25%, F 47.75% | NA | A combination of oral only and insulin | No | No | Yes | **NA** |
| **(Ganz et al.,2014)** | North America | Retrospective | 7,235 | Database | T2DM | 60.82 SD11.65 | M 49.3 %,F 50.70 % | NA | Insulin | No | No | Yes | **SH events were defined as events requiring medical attention with the appropriate SH diagnosis codes attached to outpatient, inpatient, or emergency department visits or by arecorded glucose level of 40 mg/dL. + ICD CODES** |
| **(Geller et al.,2014)** | North America | Retrospective | 8,100 | Self-reported | NA | NA | M 49.6% , F 50.4% | NA | Insulin | No | No | Yes | **(1) Clinical documentation of related clinically relevant hypoglycaemia (BG<70mg/dL (2) "insulin overdose" or "insulin reaction," or (3) An error in** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | insulin use (e.g: administration of the wronginsulin dose) |
| (Green et al., 2012) | North America | Retrospective | 3000 | Self-reported | T2DM | NA | NA | NA | NA | Yes | No | No | Hypoglycaemia was based on self-reported low blood sugar |
| (Gu et al., 2016) | Asia | Retrospective | 6,633 | Self-reported | T2DM | 56.31 SD ± 10.57 | M 56% ,F43% | NA | NA | No | No | Yes | Mild hypoglycaemia was defined as having one or more episodes of hypoglycaemia with symptoms (e.g., palpitations, hunger,sweating, tremulousness, weakness, fatigue, dizziness, and anxiety) in one month prior to thesurvey |
| (Guisasola et al.,2008) | Europe | Retrospective | 1709 | Self-reported | T2DM | 62.9 ±10.6 | M 54.9% | 7.8 SD ±5.1 | A combination of oral only | Yes | No | No | NA |
| (Henderson etal., 2003) | Europe | Retrospective | 215 | Self-reported | T2DM | 68 | NA | NA | Insulin | Yes | Yes | No | Mild hypoglycaemia was defined bythe ability to have self-treated the episode and severe hypoglycaemiaas having required external assistance to effect recovery. |
| (Herings et al.,1995) | Europe | Retrospective | 748 | Database | NA | NA | NA | NA | A combination of oral only | No | No | Yes | ICD codes |
| (Hirai et al.,2007) | North America | Retrospective | 537 | Self-reported | T1DM | 45.3 ± 9.9 | M 50.1% | 31.3 ± 7.9 years | Insulin | Yes | No | No | Severe hypoglycaemia required EDvisit or hospitalisation |
| (Holstein et al.,2009) | Europe | Retrospective | 97 | Hospital based | T2DM | 75.2 SD ±10.4 | M 53%, F47 % | 8.6 SD ±11.3 | Sulfonylureas | No | No | Yes | symptomatic event requiring treatment with intravenous glucoseand was confirmed by a blood glucose measurement of < 50 mg /dl ( < 2.8 |
| (Holstein et al.,2011) | Europe | Prospective | 264 | Hospital based | T2DM | NA | NA | NA | Sulfonylureas | No | No | Yes | Defined by the requirement for intravenous glucose or |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | glucagon injection and blood glucose value of <2.8 mmol/l |
| (Honkasalo etal., 2011) | Europe | Retrospective | 1776 | Self-reported | Both types ofdiabetes | 61.6± 13.5 years | NA | 12.8 ±11.0 years | insulin | Yes | No | Yes | SH was defined as a condition forwhich the patient needs the assistance of another person to recover from a hypoglycaemic episode as used by the UK Hypoglycaemia Study Group |
| (Ishikawa et al.,2017) | Asia | Retrospective | 170 | Database | T2DM | 74.1 | NA | NA | A combination of oral and insulin | No | No | Yes | NA |
| (Ishtiak-Ahmed et al., 2017) | Europe | Retrospective | 17230 | Database | T1DM | NA | M 57.3 % | NA | Insulin | Yes | Yes | No | Defined as an event when it requiredan outpatient, inpatient, or emergency care visit with the previously mentioned corresponding diagnostic code to icd codes-10 for HH |
| (Jeon et al.,2016) | Asia | Retrospective | NA | Database | NA | 66.3 SD ± 10.0 | M 59 %, F 41% | 14.1 SD ±8.8 | NA | No | No | Yes | Severe hypoglycaemia is defined asa state of low blood glucose that requires the assistance of another person |
| (Jick et al., 1990) | Europe | Retrospective | 121 | Database | NA | NA | NA | NA | A combination of oral only | No | No | Yes | ICD codes |
| (Yun et al., 2018) | Asia | Retrospective | 1366692 | Database | T2DM | 57.7± 11.7 | M 59.3% | NA | NA | Yes | No | | ICD codes |
| (Johansen et al.,2015a) | Europe | Retrospective | 3320 | Database | T1DM | NA | M 52.4% | NA | Insulin | No | Yes | No | Severe hypoglycaemia was defined according to ISPAD guidelines; a hypoglycaemic event leading to loss of consciousness and/or seizure |
| (Johnston et al.,2012) | North America | Retrospective | 361210 | Database | T2DM | NA | NA | NA | A combination of oral and insulin | Yes | No | No | ICD codes |
| (Karges et al., 2015) | Europe | Retrospective | 31330 | Database | NA | 12.7 ±9.2 | M 52.8 % | NA | Insulin | No | Yes | No | NA |
| (Karter et al.,2017) | North America | Retrospective | NA | Database | NA | 61.4± SD 13.7 | M 52.8 %, F 47.2 % | NA | A combination of oral and insulin | No | No | Yes | ICD codes |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **(Katz et al.,2012)** | North America | Prospective | 255 | Self-reported | T1DM | 12.2 | M 49% | 4.4years | Insulin | No | Yes | No | **hypoglycaemia requiring assistancefrom another person for oral treatment and hypoglycaemia with seizure/coma (altered consciousness) as determined by report of seizure or coma, requirement for parenteral therapy (i.e., glucagon or intravenous dextrose), or use of emergency services** |
| **(Katon et al.,2013)** | North America | Retrospective | 4,117 | Hospital based | T2DM | 63.4 (13.4) | M/F 51.9/48.1 | 9.6 (9.4) | NA | No | No | Yes | **ICD codes** |
| **(Kajiwara et al.,2015)** | Asia | Retrospective | 2,119 | Self-reported | NA | 68.4 SD ± 11.6 | NA | NA | NA | No | No | Yes | **NA** |
| **Kim et al (2016) (Kim et al., 2016a)** | Asia | Retrospective | 307107 | Database | T2DM | NA | M 41.7% | NA | A combination of oral and insulin | No | Yes | No | **ICD codes** |
| **Kostev et al(2014) (Kostev et al., 2014)** | Europe | Retrospective | 32545 | Database | T2DM | 70.2 | M 50.3% | NA | Insulin | Yes | No | No | **NA** |
| **(Kostev et al.,2015)** | Europe | Retrospective | 10,842 | Database | T2DM | 70.2±11.2 years | NA | NA | Insulin | No | No | Yes | **ICD codes** |
| **(Leckie et al., 2005)** | Europe | Prospective | 243 | Self-reported | NA | NA | NA | NA | Insulin | No | Yes | No | **Mild hypoglycaemia was defined as any symptomatic episode that was self-treated. Severe hypoglycaemia was defined as an episode that required treatment by another person and was associated either with a blood glucose concentration of ↨2.8 mmol/l or with prompt recovery after administration of oral carbohydrate, or the parenteral administration of dextrose or glucagon** |
| **(Leese et al.,2003)** | Europe | Retrospective | 977 | Database | T1DM | NA | NA | NA | Insulin | Yes | Yes | No | **Episodes of severe hypoglycaemia were defined as blood glucose <3.5 mmol/l associated with the need for treatment with** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **glucagon or intravenous dextrose to effect recovery or paramedic confirmation of hypoglycaemia with rapid recovery following treatment** |
| **(Leonard et al.,2016)** | North America | Retrospective | 592872 | Database | T2DM | NA | NA | NA | Sulfonylureas | No | Yes | No | **ICD CODES** |
| **(Li et al., 2014)** | Asia | Retrospective | 611 | Hospital based | T1DM | NA | M 47.3/ F 53.7% | NA | NA | No | No | Yes | **NA** |
| **(Lin et al., 2010)** | Asia | Retrospective | 233 | Database | T2DM | 74.1 SD ±9.8 | M 41 %, F59 % | NA | NA | No | No | Yes | **Defined severe hypoglycaemia usingthe American Diabetes Association criteria as an event requiring assistance of anotherperson to actively administer carbohydrate, glucagon, or other resuscitative action.** |
| **(Lipska et al.,2013)** | North America | Retrospective | 9094 | Database | T2DM | 59.5± 9.8 | NA | 10.6± 8.4 years | A combination of oral and insulin | Yes | No | No | **History of hypoglycaemia was basedupon at least one emergency department or inpatient visit for hypoglycaemia during the pre-observation period identified using previously validated ICD CODES-9codes** |
| **(Lipska et al.,2014)** | North America | Retrospective | 33952331 | Database | NA | NA | NA | NA | NA | No | Yes | No | **ICD codes** |
| **(Loke et al.,2010)** | Asia | Prospective | 61 | Self-reported | T2DM | NA | NA | NA | NA | No | No | Yes | **Severe hypoglycaemia was definedas a hypoglycaemic episode severe enough to require the assistance of another person** |
| **(Lundkvist et al.,2005)** | Europe | Retrospective | 309 | Hospital based | T2DM | 65 SD ±11 | M 60 /F40% | NA | A combination of oral and insulin | No | Yes | Yes | **Symptomatic hypoglycaemia was considered biochemically verified by a blood glucose concentration less than 3.3 mmol/l. Severe hypoglycaemia was de fined as a hypo glycaemic event for** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **which the patient required as assistance from another per son to re solve the situation. Mild hypoglycaemia was defined as manageable by the patient (e.g., by eating a sandwich)** |
| **Ly et al (2009)(Ly et al., 2009)** | Australia | Retrospective | 656 | Self-reported | T1DM | 12.8 ±4.0 | M 48.3% | 5.4 ± 3.9 years | Insulin | No | Yes | No | **Severe hypoglycaemia was defined as an event leading to loss of consciousness or seizure. Recurrent hypoglycaemia was defined as the occurrence of 2 episodes of severe hypoglycaemia in the preceding year.** |
| **(Maltoni et al.,2013)** | Europe | Retrospective | 269 | Self-reported | T1DM | NA | M 50.2% | NA | Insulin | No | Yes | No | **Hypoglycaemic episode as severe, we used ISPAD guidelines 2011 defining SH as an event of coma, seizures and/or altered mental statusrequiring third-party assistance** |
| **(Mauricio et al.,2015)** | Multinational | Retrospective | 40,627 | Database | T2DM | 63.3 | NA | NA | A combination of oral and insulin | No | No | Yes | **ICD codes** |
| **(Mantovani et al.,2016)** | Europe | Retrospective | 520 | Hospital based | Both types ofdiabetes | 72 SD ±16 | M 55 % ,F 45 % | 22 SD ±11 | A combination of oral and insulin | No | No | Yes | **We electronically searched for the terms "hypoglycaemia " or "hypoglycaemic event" in the discharge diagnosis from the hospital, or for recorded blood glucose levels less than 3.8 mmol/L.** |
| **(McCoy et al., 2016)** | North America | Retrospective | 31,542 | Database | T2DM | 58.0 SD | M 51.9%, F 49.1% | NA | A combination of oral only | No | No | Yes | **ICD codes** |
| **(Miller et al.,2001)** | North America | Retrospective | 1,055 | Self-reported | T2DM | 60.9 SD ±0.4 | M 28.2%, F 71.8% | 10.8 SD ±0.3 | A combination of oral and insulin | No | No | Yes | **Hypoglycaemia was defined as typical symptoms relieved by eating, and/or blood glucose level of** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **less than 60 mg/dL (<3.3 mmol/L)** |
| **(Alonso-Moranet al., 2015)** | Europe | Retrospective | 134413 | Database | T2DM | NA | M 53.9% | NA | NA | No | Yes | No | **ICD codes** |
| **(Morris et al., 1997)** | Europe | Retrospective | 504 | Database | Both types ofdiabetes | NA | NA | NA | A combination of oral only | No | No | Yes | **NA** |
| **(Muhlhauser etal., 1985)** | Europe | Retrospective | 384 | Self-reported | T1DM | 30±13 years | NA | 12±9 years | Insulin | Yes | No | No | **hypoglycaemia with loss of consciousness treated with glucagonor intravenous glucose,as** |
| **(Muhlhauser etal., 1998)** | Europe | Prospective | 684 | Self-reported | T1DM | 36 SD ±11 | M 59% , F41 % | NA | NA | No | No | Yes | **NA** |
| **(Muller et al.,2017)** | Europe | Retrospective | 7900000 | Database | T2DM | NA | NA | NA | A combination of oral and insulin | No | Yes | No | **ICD codes** |
| **(Murata et al., 2005)** | North America | Prospective | 344 | Database | T2DM | 65.5±9.7 years | M 96.5% | 14.7 ± 9.9 years | A combination of oral and insulin | Yes | Yes | No | **Glucose <60 mg/dl** |
| **(Nam et al.)** | North America | Retrospective | 3467 | Database | T2DM | NA | NA | NA | A combination of oral only | No | No | Yes | **ICD codes** |
| **(Nunes et al., 2017)** | North America | Retrospective | 143635 | Database | T2DM | NA | NA | NA | Sulfonylureas | Yes | No | No | **ICD codes** |
| **(Nunes et al., 2016)** | North America | Retrospective | 844683 | Database | T2DM | NA | M 48.5 % | NA | A combination of oral only | No | Yes | No | **NA** |
| **(Odawara et al.,2014)** | Asia | Retrospective | 4219 | Self-reported | T2DM | 62.8 ±12.1 | M 58.9% | 5.7 years | A combination of oral and insulin | No | Yes | No | **Severe hypoglycaemia included hypoglycaemic episodes satisfying any of the following serious AEs criteria; 1) resulted in death, 2) life-threatening, 3) required or prolongedinpatient hospitalisation, 4) persistently or significantly disabling/ incapacitating, 5) a congenital anomaly, and/or 6) medically important.** |
| **(Olsen et al.,2014)** | Europe | Retrospective | 440 | Self-reported | T1DM | NA | M 51.0% | NA | Insulin | Yes | No | No | **NA** |
| **(Yu et al., 2018)** | Europe | Retrospective | 14012 | Database | T2DM | NA | NA | NA | A combination of oral and insulin | No | No | Yes | **Read codes** |
| **(Ooi et al., 2011)** | Asia | Retrospective | 170 | Self-reported | T2DM | 67.32 +5.45 | M41.2% | 9.00 ±6.77 | A combination of oral and insulin | Yes | No | No | **NA** |
| **(Pathak et al., 2016)** | North America | Prospective | 917440 | Database | NA | 57.9 ±13.2 | M 52.1% | NA | NA | No | Yes | No | **ICD CODES** |
| **(Lyngsie et al.,2016)** | Europe | Retrospective | 307016 | Database | NA | NA | NA | NA | NA | No | Yes | No | **ICD codes** |
| **(Pedersen-** | Europe | Retrospective | 1076 | Self- | T1DM | NA | M 55.5% | NA | Insulin | Yes | No | Yes | **Mild hypoglycaemic** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bjergaard et al.,2004)** | | | | reported | | | | | | | | | **events were reported for the previous week, defined as episodes with symptoms of hypoglycaemia manageable by the patient. Severe hypoglycaemic events were defined as episodes where assistance from others was needed to restore blood glucose and were reported for the preceding one- and two-year periods.** |
| **(Pilemann-Lyberg et al.,2015)** | Europe | Prospective | 161 | Database | T2DM | 76±12 years | M 54 % | NA | Sulfonylureas | No | Yes | No | **We defined a severe hypoglycaemic event as an episode requiring external help** |
| **(Pirags et al.,2012)** | Multinational | Prospective | 991 | Self-reported | T2DM | 57.9±10.1 | M 52.2% | 9.2± 5.9 years | Insulin | Yes | Yes | No | **Severe hypoglycaemia was defined as an event that required assistance from another person who actively administered carbohydrate, glucagonor other resuscitative actions and was associated with either a blood glucose level less than 3.9 mmol l (< 70mg dl) or prompt recovery after restoring normoglycaemia** |
| **(Quilliam et al.,2011b)** | North America | Retrospective | 14,729 | Database | T2DM | 56.4 SD ±7.0 | M 51%, F 49 % | NA | NA | No | No | Yes | **ICD codes** |
| **(Radosevich etal., 2015)** | North America | Retrospective | 122 | Database | NA | 59.5 SD ±17.8 | M 43 %, F 53% | NA | Insulin | No | No | Yes | **Hypoglycaemia was defined as a glucose measuremen<70 mg/dL.** |
| **(Rajendran et al.,2015)** | Asia | Retrospective | 132 | Database | Both types ofdiabetes | 59±20 | M 52.2% | NA | A combination of oral and insulin | Yes | No | No | **NA** |
| **(Ragia et al., 2012)** | Europe | Retrospective | 176 | NA | T2DM | NA | NA | NA | Sulfonylureas | No | No | Yes | **NA** |
| **(Raju et al.,2016)** | North America | Retrospective | 11536 | Database | T2DM | 55.7 ±10.1 | M 58.8% | NA | A combination of oral only | No | Yes | No | **NA** |
| **(Rathmann et al.,2013)** | Europe | Retrospective | 50,294 | Database | T2DM | NA | NA | NA | A combination of oral only | No | No | Yes | **ICD codes** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **(Ren et al., 2016)** | Asia | Retrospective | 6,713 | Self-reported | T2DM | 56.38+-10 | M 56 %, F 44% | NA | NA | No | No | Yes | **Asymptomatic hypoglycaemia was defined as plasma glucose ≤3.9 mmol/L but without any symptoms in1 month before hospitalisation. Mild hypoglycaemia was defined as having one or more episodes of hypoglycaemia with symptom in 1 month prior to the hospitalisation. Severe hypoglycaemia was definedas having one or more episodes of hypoglycaemia that needed assistance from other people in 3 months before hospitalisation** |
| **(Romley et al.,2015)** | North America | Retrospective | 465, 918 | Database | T2DM | 74.6 SD ±7.5 | M 42.2%, F 57.8 % | NA | Sulfonylureas | No | No | No | **ICD codes** |
| **(Rubin et al.,2011)** | North America | Retrospective | 1,990 | Database | NA | NA | NA | NA | Insulin | No | No | No | **Defined by a POC glucose ,70 mg/dL after the first 24 h of admission** |
| **(Roumie et al.,2016)** | North America | Retrospective | 178,341 | Database | NA | NA | NA | NA | A combination of oral and insulin | No | No | No | **Hypoglycaemia was defined as hospital admission or an emergency department visit for hypoglycaemia, or an outpatient blood glucose valueof less than 3.3 mmol/L / ICD CODES** |
| **(Sako et al.,2015)** | Asia | Retrospective | 25071 | Database | NA | 73.4 ±13.1 | M 53.3% | NA | NA | No | Yes | No | **ICD codes** |
| **(Sarkar et al., 2010)** | North America | Retrospective | 14357 | Self-reported | T2DM | 58 ± 10 | M 51 % | 10 ± 8 years | A combination of oral and insulin | Yes | No | No | **We asked participants in the past year, how many times have you had a severe low blood sugar reaction, such as passing out or needing help to treat the reaction?** |
| **(Samann et** | Europe | Retrospective | sample of | Hospital | Both types | T1D 49 | T1D M 58/F | T1D 20 | A combination | Yes | No | Yes | **SH was defined as** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **al.,2013)** | | | participants with type 1 (n = 373) and type 2 diabetes (n = 4,481) Total =4,854 | based | ofdiabetes | SD ± 16 T2d 66 SD ± 10 | 42% T2D M 56 / F 44% | SD +13 T2D 8 SD ± 7 | of oral and insulin | | | | **hypoglycaemia with coma or the need for intravenous glucose or intramuscular glucagon injection** |
| **(Sato et al.,2010)** | Asia | Retrospective | 32 | Hospital based | T2DM | 74.8 SD ±8.5 | M 37% , F 63% | 14.9 SD ± 10.2 | Sulfonylureas | No | No | Yes | **Symptoms + < 50 mg/dl (2.8 mmol/l) + I.V glucose administration** |
| **(Schloot et al.,2016)** | Europe | Retrospective | 29485 | Database | T2DM | NA | M 51.1% | NA | Sulfonylureas | Yes | No | No | **NA** |
| **(Seligman et al.,2010)** | North America | Retrospective | 711 | Self-reported | T2DM | NA | NA | NA | NA | Yes | No | No | **NA** |
| **(Seewi et al.,2008)** | Europe | Retrospective | 73 | Self-reported | T1DM | NA | NA | NA | Insulin | No | No | Yes | **History, and potential explanation of severe hypoglycaemia (grade 2: requiring external help because of diminished consciousness, and grade3: coma, seizure, loss of consciousness** |
| **(Shriraam et al.,2017)** | Asia | Retrospective | 366 | Self-reported | T2DM | NA | M 23.5% | 10.9± 5.9 years | A combination of oral and insulin | Yes | No | No | **Severe hypoglycaemia required EDvisit or hospitalisation** |
| **(Solomon et al.,2013)** | North America | Retrospective | 8,626 | Database | T2DM | 56.4 | M 50.9 %, F 49.1% | NA | Insulin | No | No | Yes | **NA** |
| **(Sreenan et al.,2014)** | Europe | Retrospective | T1DM (*n* = 7,420 ) or T2DM(*n* = 12,98 1) | NA | Both types ofdiabetes | T1D 41.4 SD ± 16.8 T2D 60.6 SD ± 10.8 | NA | T1D 16.4 SD ± 12.5 T2D 11.2 SD ± 7.5 | Insulin | | | No | **SHEs were defined as an episode with symptoms of neuroglycopenia, in which the patient was unable to treat himself/herself and third-party intervention was needed, and where the patient had one of the following characteristics: (i) blood glucose <2.8 mmol/L (<50 mg/dL) or (ii)reversal of symptoms after food intake, glucagon or** |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | intravenous glucose administration. |
| (Stuart et al.,2017) | North America | Retrospective | 9584 | Self-reported | NA | NA | NA | NA | A combination of oral and | Yes | No | No | Glucose <4 mmol/L |
| (Strandberg etal., 2015) | Europe | Retrospective | 16,985 | Database | Both types ofdiabetes | NA | NA | NA | Insulin | No | No | Yes | ICD codes |
| (Takeishi et al.,2016) | Asia | Retrospective | 106 | Hospital based | T2DM | 66.6 SD ± 11.0 | M 52.8, F 47.2 % | 14.7 SD ± 10.7 | A combination of oral and insulin | No | No | Yes | Nocturnal hypoglycaemia was defined as a blood glucose level of <70 mg/dL occurring from 0 am to 8 am. |
| (Tan et al., 2015) | North America | Retrospective | 37,086 | Database | NA | NA | NA | NA | Sulfonylureas | No | No | Yes | NA |
| (Thamer et al.,1999) | North America | Retrospective | 1,779 | Database | NA | NA | M 41.8 % , female 58.2 % | NA | A combination of oral and insulin | No | No | Yes | NA |
| (Tschope et al.,2012) | Europe | Retrospective | 3347 | Self-reported | T2DM | 68.6 | M 51.7 % | NA | NA | Yes | No | Yes | NA |
| (Tschope et al.,2011) | Europe | Retrospective | 3,808 | Self-reported | T2DM | NA | M 53.1 % | NA | NA | No | No | Yes | NA |
| (Van Keulen etal., 2015) | Europe | Retrospective | 4,732 | Database | NA | 79.4 SD ±6.5 | NA | NA | NA | No | No | Yes | NA |
| (Vlckova et al.,2010) | Europe | Retrospective | 12 ,772 | Database | NA | 60.9 | M 53/ F47% | NA | NA | No | No | Yes | Hypoglycaemia was defined as an event recorded by GPs on the green forms. blood glucose or low blood sugar. |
| (Wang et al., 2015) | North America | Retrospective | 63972 | Database | NA | M 48.4% | NA | NA | NA | No | Yes | No | ICD codes |
| (Weinstock et al.,2013) | North America | Retrospective | 4973 | Database | T1DM | NA | M 46% | NA | NA | Yes | No | No | SH was defined as an episode in which the assistance of another individual was needed or glucagon was given. |
| (Weir et al.,2011) | North America | Retrospective | 364 | Self-reported | NA | NA | M 50.5 / F 49.5% | NA | A combination of oral and insulin | No | No | Yes | Severe hypoglycaemia required EDvisit or hospitalisation |
| (Williams et al.,2014) | North America | Retrospective | 24,751 | Hospital based | Both types ofdiabetes | 63.7 (12.1) | M 49.5/ F 51.5% | NA | NA | No | No | Yes | ICD codes |
| (Wohland et al.,2017) | Europe | Retrospective | 92,794 | Database | T1DM | 48.2 SD ± 19.1 | M 55.8%, F 44.2% | 24.9 SD ± 15.7 | Insulin | No | No | Yes | SH was defined as an event requiring treatment with intravenous glucose or glucagon |

| Author | Country | Study design | Sample size | Sample Source | Diabetes type | Mean age | Sex M/F | Diabetes duration | Treatment regimens | Prevalence data | Incidence data | Risk factors | Definition of hypoglycaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **administration and being confirmed by a blood glucose measurement of <2.8 mmol/l.** |
| **(Chu et al., 2017)** | Asia | Retrospective | 20845 | Database | Both types ofdiabetes | NA | NA | NA | NA | Yes | No | Yes | **ICD codes** |
| **(Cho and Cho,2018)** | Asia | Retrospective | 5693 | Database | T2DM | NA | 53.1% | NA | A combination of oral and insulin | No | No | Yes | **ICD codes** |
| **(Yu et al., 2016)** | Multinational | Retrospective | 4,399 | Self-reported | T2DM | 59.5 | M 52 %, F48 % | NA | A combination of oral only | No | No | Yes | **NA** |
| **(Ikeda et al.,2018)** | Asia | Retrospective | 166806 | Database | T2DM | 66.2 ±11.8 | M 62.1% | NA | A combination of oral and insulin | No | Yes | No | **ICD codes** |
| **(Yun et al., 2013)** | Asia | Retrospective | 878 | Database | T2DM | 55.3 ± 9.8 | NA | 9.8 6 ± 6.5 years | A combination of oral and insulin | No | Yes | No | **Hypoglycaemia episodes requiring the assistance of another person to actively administer carbohydrate, other resuscitative actions, hospitalisation, or medical care in an emergency department.** |
| **(Yun et al., 2015)** | Korea | Prospective | 624 | Hospital based | T2DM | 61.2 SD ±10.2 | M 48/ F42 % | 12.9 SD ±7.6 | A combination of oral and insulin | No | No | Yes | **Hypoglycaemic episodes requiring the assistance of medical care in an emergency department or hospitalisation** |
| **(Zaccardi et al.,2017)** | Europe | Retrospective | 405900 | Database | Both types ofdiabetes | NA | 52.5% | NA | NA | No | No | Yes | **ICD codes** |
| **(Zhong et al.,2017)** | **Europe** | **Retrospecti ve** | **23246** | **Database** | **T1DM** | **NA** | **NA** | **NA** | **NA** | **No** | **Yes** | **No** | **ICD codes** |

**Appendix 9 Modified Newcastle – Ottawa quality assessment scale**

| Legend |
| --- |
| 0 = Definitely no (high risk of bias) |
| 1 = Mostly no |
| 2 = Mostly yes |
| 3 = Definitely yes (low risk of bias) |

*** Domain of evaluation: Methods for selecting study participants (i.e. Selection bias)**

Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?

0 (high risk of bias) 1 2 3 (low risk of bias)

**Example of low risk of bias:** A consecutive sample or random selection from a population that is representative of the condition under study.

**Example of moderate risk of bias:** A consecutive sample or random selection from a population that is not highly representative of the condition under study.

**Example of high risk of bias:** The source population cannot be defined or enumerated (i.e. volunteering or self-recruitment).

*** Domain of evaluation: Methods to control confounding (i.e. Performance bias)**

Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?

0 (high risk of bias) 1 2 3 (low risk of bias)

**Example of low risk of bias**: Sample size was adequate and there was sufficient power to detect a difference in the outcome.

**Example of high risk of bias:** Sample size was small and there was not enough power to test outcome of interest.

Did the study identify and adjust for any variables or confounders that may influence the outcome?

0 (high risk of bias) 1 2 3 (low risk of bias)

**Example of low risk of bias:** The study identified and adjusted for all possible confounders that may influence estimates of association between exposure and outcome

(i.e. was the patient being treated for a medical condition such as chronic pain and was being prescribed opioids while on methadone treatment?).

**Example of moderate risk of bias:** The study identified and reported possible variables that may influence the outcome but did not explore the interaction.

**Example of high risk of bias:** The study either did not report any variables of influence or acknowledge variables of influence when it was clear they were present.

*** Domain of evaluation: Statistical methods (i.e. Detection bias)**

Did the study use appropriate statistical analysis methods relative to the outcome of interest?

0 (high risk of bias) 1 2 3 (low risk of bias)

**Example of low risk of bias:** The study reported use of appropriate statistical analysis as required (i.e. adjusting for an unbalanced distribution of a specific covariate among sexes, or correcting for multiple testing error).

**Example of moderate risk of bias:** The study either used correct statistical methods but did not report them well, or used the incorrect methods but reported them in detail.

**Example of high risk of bias:** The study did not use appropriate statistical analysis as required (i.e. did not adjust for an unbalanced distribution of a specific covariate among

sexes, or correct for multiple testing error when necessary) or did not report them adequately.

Is there little missing data and did the study handle it accordingly?

0 (high risk of bias) 1 2 3 (low risk of bias)

**Example of low risk of bias:** The study acknowledged missing data to be less than 10% and specified the method of handling it.

**Example of moderate risk of bias:** The study either had greater than 15% but they specified the method they used to handle it.

**Example of high risk of bias:** The study had greater than 15% missing data and did not handle it at all.

* **Domain of evaluation: Methods for measuring outcome variables (i.e. Information bias)**

Is the methodology of the outcome measurement explicitly stated and is it appropriate?

0 (high risk of bias) 1 2 3 (low risk of bias)

**Example of low risk of bias:** The study provides a detailed description of the outcome measure(s) which are appropriate for the outcome of interest.

**Example of moderate risk of bias:** The study provides a somewhat complete description of outcome measurements and they are justified.

**Example of high risk of bias:** The study provides limited information on the methods of measuring the outcome and the measure is not appropriate considering the outcome.

Is there an objective assessment of the outcome of interest?

0 (high risk of bias) 1 2 3 (low risk of bias)

**Example of low risk of bias:** The study used objective methods to discern the outcome status of participants (i.e. laboratory measurements, medical records).

**Example of moderate risk of bias:** The study relied on subjective data as the primary method to discern outcome status of participants (i.e. self-report).

**Example of high risk of bias:** The study had limited reporting about assessment of outcomes.

## Appendix 10 IMRD-UK Read codes dictionary

### 1- Diabetes codes

| Med code | Med term | Med code | Med term | Med code | Med term |
|---|---|---|---|---|---|
| **C10yy00** | Other specified diabetes mellitus with other spec comps | C108J12 | Type 1 diabetes mellitus with neuropathic arthropathy | C10FP00 | Type 2 diabetes mellitus with ketoacidotic coma |
| **C10ED00** | Type 1 diabetes mellitus with nephropathy | C109J12 | Insulin-treated Type II diabetes mellitus | C108511 | Type I diabetes mellitus with ulcer |
| **C10EM00** | Type 1 diabetes mellitus with ketoacidosis | C109J00 | Insulin-treated Type 2 diabetes mellitus | C108300 | Insulin-dependent diabetes mellitus with multiple complicatn |
| **C10E.11** | Type I diabetes mellitus | C10E700 | Type 1 diabetes mellitus with retinopathy | Cyu2.00 | [X]Diabetes mellitus |
| **C10FC00** | Type 2 diabetes mellitus with nephropathy | C10FM00 | Type 2 diabetes mellitus with persistent microalbuminuria | C10A.00 | Malnutrition-related diabetes mellitus |
| **C10F500** | Type 2 diabetes mellitus with gangrene | C10FB00 | Type 2 diabetes mellitus with polyneuropathy | C108200 | Insulin-dependent diabetes mellitus with neurological comps |
| **66AI.00** | Diabetic - good control | C10F600 | Type 2 diabetes mellitus with retinopathy | C109000 | Non-insulin-dependent diabetes mellitus with renal comps |
| **C104y00** | Other specified diabetes mellitus with renal complications | C108.11 | IDDM-Insulin-dependent diabetes mellitus | C101000 | Diabetes mellitus, juvenile type, with ketoacidosis |
| **C100100** | Diabetes mellitus, adult onset, no mention of complication | C10EH00 | Type 1 diabetes mellitus with arthropathy | C10F911 | Type II diabetes mellitus without complication |
| **C100111** | Maturity onset diabetes | C10E500 | Type 1 diabetes mellitus with ulcer | C10EJ00 | Type 1 diabetes mellitus with neuropathic arthropathy |
| **C103.00** | Diabetes mellitus with ketoacidotic coma | C10F000 | Type 2 diabetes mellitus with renal complications | C10E412 | Unstable insulin-dependent diabetes mellitus |
| **C106.00** | Diabetes mellitus with neurological manifestation | C102.00 | Diabetes mellitus with hyperosmolar coma | C101100 | Diabetes mellitus, adult onset, with ketoacidosis |
| **C106.13** | Diabetes mellitus with polyneuropathy | C108012 | Type 1 diabetes mellitus with renal complications | C109F11 | Type II diabetes mellitus with peripheral angiopathy |
| **C104.00** | Diabetes mellitus with renal manifestation | 66AJz00 | Diabetic - poor control NOS | C109411 | Type II diabetes mellitus with ulcer |
| **13L4.11** | Diabetic child | C10N.00 | Secondary diabetes mellitus | C10EQ00 | Type 1 diabetes mellitus with gastroparesis |

| Med code | Med term | Med code | Med term | Med code | Med term |
|---|---|---|---|---|---|
| **C109600** | Non-insulin-dependent diabetes mellitus with retinopathy | C106z00 | Diabetes mellitus NOS with neurological manifestation | L180X00 | Pre-existing diabetes mellitus, unspecified |
| **C108F11** | Type I diabetes mellitus with diabetic cataract | C10EP00 | Type 1 diabetes mellitus with exudative maculopathy | C109200 | Non-insulin-dependent diabetes mellitus with neuro comps |
| **C108.12** | Type 1 diabetes mellitus | C10F.11 | Type II diabetes mellitus | C109D11 | Type II diabetes mellitus with hypoglycaemic coma |
| **C109.12** | Type 2 diabetes mellitus | C108.13 | Type I diabetes mellitus | C108A00 | Insulin-dependent diabetes without complication |
| **66AL.00** | Diabetic-uncooperative patient | C109711 | Type II diabetes mellitus - poor control | C107400 | NIDDM with peripheral circulatory disorder |
| **C109G11** | Type II diabetes mellitus with arthropathy | C100000 | Diabetes mellitus, juvenile type, no mention of complication | C10F011 | Type II diabetes mellitus with renal complications |
| **C109012** | Type 2 diabetes mellitus with renal complications | C109G00 | Non-insulin-dependent diabetes mellitus with arthropathy | C108D00 | Insulin-dependent diabetes mellitus with nephropathy |
| **C109.13** | Type II diabetes mellitus | C108B00 | Insulin-dependent diabetes mellitus with mononeuropathy | C109611 | Type II diabetes mellitus with retinopathy |
| **C108800** | Insulin-dependent diabetes mellitus - poor control | C109C12 | Type 2 diabetes mellitus with nephropathy | C10FG00 | Type 2 diabetes mellitus with arthropathy |
| **1434** | H/O: diabetes mellitus | C10FQ00 | Type 2 diabetes mellitus with exudative maculopathy | C103y00 | Other specified diabetes mellitus with coma |
| **66A3.00** | Diabetic on diet only | C10F700 | Type 2 diabetes mellitus - poor control | C109C00 | Non-insulin-dependent diabetes mellitus with nephropathy |
| **C106.12** | Diabetes mellitus with neuropathy | C10FL00 | Type 2 diabetes mellitus with persistent proteinuria | C109111 | Type II diabetes mellitus with ophthalmic complications |
| **C109700** | Non-insulin-dependent diabetes mellitus - poor control | C108400 | Unstable insulin-dependent diabetes mellitus | C10D.11 | Maturity onset diabetes in youth type 2 |
| **66A5.00** | Diabetic on insulin | 66AV.00 | Diabetic on insulin and oral treatment | C108411 | Unstable type I diabetes mellitus |
| **66AJ.11** | Unstable diabetes | C109900 | Non-insulin-dependent diabetes mellitus without complication | C108J11 | Type I diabetes mellitus with neuropathic arthropathy |
| **C10yz00** | Diabetes mellitus NOS with other specified manifestation | C10EL00 | Type 1 diabetes mellitus with persistent microalbuminuria | C108600 | Insulin-dependent diabetes mellitus with gangrene |
| **C109A00** | Non-insulin-dependent diabetes mellitus with mononeuropathy | C108900 | Insulin-dependent diabetes maturity onset | C109F12 | Type 2 diabetes mellitus with peripheral angiopathy |

| Med code | Med term | Med code | Med term | Med code | Med term |
|---|---|---|---|---|---|
| **C102z00** | Diabetes mellitus NOS with hyperosmolar coma | C107.11 | Diabetes mellitus with gangrene | C10FL11 | Type II diabetes mellitus with persistent proteinuria |
| **C10E812** | Insulin-dependent diabetes mellitus - poor control | C107.12 | Diabetes with gangrene | C109D12 | Type 2 diabetes mellitus with hypoglycaemic coma |
| **C10E112** | Insulin-dependent diabetes mellitus with ophthalmic comps | C10FN00 | Type 2 diabetes mellitus with ketoacidosis | C108011 | Type I diabetes mellitus with renal complications |
| **C10C.12** | Maturity onset diabetes in youth type 1 | C105.00 | Diabetes mellitus with ophthalmic manifestation | C106y00 | Other specified diabetes mellitus with neurological comps |
| **C10F211** | Type II diabetes mellitus with neurological complications | C108E11 | Type I diabetes mellitus with hypoglycaemic coma | C108212 | Type 1 diabetes mellitus with neurological complications |
| **C10E512** | Insulin-dependent diabetes mellitus with ulcer | C109612 | Type 2 diabetes mellitus with retinopathy | C109511 | Type II diabetes mellitus with gangrene |
| **C10FD11** | Type II diabetes mellitus with hypoglycaemic coma | C10E200 | Type 1 diabetes mellitus with neurological complications | C109300 | Non-insulin-dependent diabetes mellitus with multiple comps |
| **C108B11** | Type I diabetes mellitus with mononeuropathy | C102100 | Diabetes mellitus, adult onset, with hyperosmolar coma | C10EM11 | Type I diabetes mellitus with ketoacidosis |
| **C10E111** | Type I diabetes mellitus with ophthalmic complications | C10F311 | Type II diabetes mellitus with multiple complications | C108H11 | Type I diabetes mellitus with arthropathy |
| **C10EE12** | Insulin-dependent diabetes mellitus with hypoglycaemic coma | C10C.00 | Diabetes mellitus autosomal dominant | C10EA11 | Type I diabetes mellitus without complication |
| **C10EA12** | Insulin-dependent diabetes without complication | C109D00 | Non-insulin-dependent diabetes mellitus with hypoglyca coma | C10FA00 | Type 2 diabetes mellitus with mononeuropathy |
| **C10y.00** | Diabetes mellitus with other specified manifestation | C10M.00 | Lipoatrophic diabetes mellitus | C108911 | Type I diabetes mellitus maturity onset |
| **C107200** | Diabetes mellitus, adult with gangrene | C10E400 | Unstable type 1 diabetes mellitus | C107100 | Diabetes mellitus, adult, + peripheral circulatory disorder |
| **C10A100** | Malnutrition-related diabetes mellitus with ketoacidosis | 66AK.00 | Diabetic - cooperative patient | C10y100 | Diabetes mellitus, adult, + other specified manifestation |
| **C10F200** | Type 2 diabetes mellitus with neurological complications | C108F00 | Insulin-dependent diabetes mellitus with diabetic cataract | C10FR00 | Type 2 diabetes mellitus with gastroparesis |
| **C105z00** | Diabetes mellitus NOS with ophthalmic manifestation | C108E00 | Insulin-dependent diabetes mellitus with hypoglycaemic coma | C10z100 | Diabetes mellitus, adult onset, + |

| Med code | Med term | Med code | Med term | Med code | Med term |
|---|---|---|---|---|---|
| | | | | | unspecified complication |
| **C109400** | Non-insulin-dependent diabetes mellitus with ulcer | C108500 | Insulin-dependent diabetes mellitus with ulcer | C10zy00 | Other specified diabetes mellitus with unspecified comps |
| **C104100** | Diabetes mellitus, adult onset, with renal manifestation | C109E12 | Type 2 diabetes mellitus with diabetic cataract | C10zz00 | Diabetes mellitus NOS with unspecified complication |
| **C104z00** | Diabetes mellitus with nephropathy NOS | C10FE00 | Type 2 diabetes mellitus with diabetic cataract | C108z00 | Unspecified diabetes mellitus with multiple complications |
| **C10E800** | Type 1 diabetes mellitus - poor control | C10E312 | Insulin-dependent diabetes mellitus with multiple complicat | C109C11 | Type II diabetes mellitus with nephropathy |
| **C10FH00** | Type 2 diabetes mellitus with neuropathic arthropathy | C109B00 | Non-insulin-dependent diabetes mellitus with polyneuropathy | C10FJ11 | Insulin-treated Type II diabetes mellitus |
| **C107.00** | Diabetes mellitus with peripheral circulatory disorder | C10z.00 | Diabetes mellitus with unspecified complication | C107z00 | Diabetes mellitus NOS with peripheral circulatory disorder |
| **C10D.00** | Diabetes mellitus autosomal dominant type 2 | C109712 | Type 2 diabetes mellitus - poor control | C103z00 | Diabetes mellitus NOS with ketoacidotic coma |
| **C109J11** | Insulin-treated non-insulin-dependent diabetes mellitus | C108812 | Type 1 diabetes mellitus - poor control | C10F300 | Type 2 diabetes mellitus with multiple complications |
| **C10FF00** | Type 2 diabetes mellitus with peripheral angiopathy | C109212 | Type 2 diabetes mellitus with neurological complications | C108H00 | Insulin-dependent diabetes mellitus with arthropathy |
| **C108711** | Type I diabetes mellitus with retinopathy | C109512 | Type 2 diabetes mellitus with gangrene | C109412 | Type 2 diabetes mellitus with ulcer |
| **C101y00** | Other specified diabetes mellitus with ketoacidosis | C108y00 | Other specified diabetes mellitus with multiple comps | C10EN11 | Type I diabetes mellitus with ketoacidotic coma |
| **C100.00** | Diabetes mellitus with no mention of complication | C10EC00 | Type 1 diabetes mellitus with polyneuropathy | C10A000 | Malnutrition-related diabetes mellitus with coma |
| **C10EE00** | Type 1 diabetes mellitus with hypoglycaemic coma | C10C.11 | Maturity onset diabetes in youth | C108D11 | Type I diabetes mellitus with nephropathy |
| **C106100** | Diabetes mellitus, adult onset, + neurological manifestation | C108811 | Type I diabetes mellitus - poor control | C109H12 | Type 2 diabetes mellitus with neuropathic arthropathy |
| **C102000** | Diabetes mellitus, juvenile type, with hyperosmolar coma | C10FD00 | Type 2 diabetes mellitus with hypoglycaemic coma | C106000 | Diabetes mellitus, juvenile, + neurological manifestation |

| Med code | Med term | Med code | Med term | Med code | Med term |
|---|---|---|---|---|---|
| **C109500** | Non-insulin-dependent diabetes mellitus with gangrene | C108000 | Insulin-dependent diabetes mellitus with renal complications | C109211 | Type II diabetes mellitus with neurological complications |
| **C10E900** | Type 1 diabetes mellitus maturity onset | C10F711 | Type II diabetes mellitus - poor control | C10EB00 | Type 1 diabetes mellitus with mononeuropathy |
| **C10EN00** | Type 1 diabetes mellitus with ketoacidotic coma | C10F100 | Type 2 diabetes mellitus with ophthalmic complications | C108512 | Type 1 diabetes mellitus with ulcer |
| **C105100** | Diabetes mellitus, adult onset, + ophthalmic manifestation | C105y00 | Other specified diabetes mellitus with ophthalmic complicatn | C10z000 | Diabetes mellitus, juvenile type, + unspecified complication |
| **Cyu2000** | [X]Other specified diabetes mellitus | C109B11 | Type II diabetes mellitus with polyneuropathy | C103100 | Diabetes mellitus, adult onset, with ketoacidotic coma |
| **C108C00** | Insulin-dependent diabetes mellitus with polyneuropathy | C10E000 | Type 1 diabetes mellitus with renal complications | C107300 | IDDM with peripheral circulatory disorder |
| **C101z00** | Diabetes mellitus NOS with ketoacidosis | C10E100 | Type 1 diabetes mellitus with ophthalmic complications | C109E00 | Non-insulin depend diabetes mellitus with diabetic cataract |
| **C103000** | Diabetes mellitus, juvenile type, with ketoacidotic coma | C10E300 | Type 1 diabetes mellitus with multiple complications | C10EA00 | Type 1 diabetes mellitus without complication |
| **Cyu2300** | [X]Unspecified diabetes mellitus with renal complications | C109H11 | Type II diabetes mellitus with neuropathic arthropathy | C105000 | Diabetes mellitus, juvenile type, + ophthalmic manifestation |
| **C10A500** | Malnutritn-relat diabetes melitus wth periph circul complctn | C10F900 | Type 2 diabetes mellitus without complication | C10E600 | Type 1 diabetes mellitus with gangrene |
| **C10EF12** | Insulin-dependent diabetes mellitus with diabetic cataract | C109E11 | Type II diabetes mellitus with diabetic cataract | C109112 | Type 2 diabetes mellitus with ophthalmic complications |
| **C10F111** | Type II diabetes mellitus with ophthalmic complications | C10F400 | Type 2 diabetes mellitus with ulcer | C107000 | Diabetes mellitus, juvenile +peripheral circulatory disorder |
| **C10EC12** | Insulin-dependent diabetes mellitus with polyneuropathy | C108211 | Type I diabetes mellitus with neurological complications | C108E12 | Type 1 diabetes mellitus with hypoglycaemic coma |
| **66As.00** | Diabetic on subcutaneous treatment | C108100 | Insulin-dependent diabetes mellitus with ophthalmic comps | C100112 | Non-insulin-dependent diabetes mellitus |
| **C108712** | Type 1 diabetes mellitus with retinopathy | C10EF00 | Type 1 diabetes mellitus with diabetic cataract | C10..00 | Diabetes mellitus |
| **C10E212** | Insulin-dependent diabetes mellitus with neurological comps | C10F611 | Type II diabetes mellitus with retinopathy | C10F.00 | Type 2 diabetes mellitus |

| Med code | Med term | Med code | Med term | Med code | Med term |
|---|---|---|---|---|---|
| **C10E611** | Type I diabetes mellitus with gangrene | C109G12 | Type 2 diabetes mellitus with arthropathy | C100011 | Insulin-dependent diabetes mellitus |
| **C10ED12** | Insulin-dependent diabetes mellitus with nephropathy | C10E411 | Unstable type I diabetes mellitus | C10FJ00 | Insulin-treated Type 2 diabetes mellitus |
| **C10FC11** | Type II diabetes mellitus with nephropathy | C109011 | Type II diabetes mellitus with renal complications | C10E.00 | Type 1 diabetes mellitus |
| **C10EL11** | Type I diabetes mellitus with persistent microalbuminuria | C109100 | Non-insulin-dependent diabetes mellitus with ophthalm comps | C108.00 | Insulin-dependent diabetes mellitus |
| **C108112** | Type 1 diabetes mellitus with ophthalmic complications | C10FB11 | Type II diabetes mellitus with polyneuropathy | C101.00 | Diabetes mellitus with ketoacidosis |
| **C10E012** | Insulin-dependent diabetes mellitus with renal complications | L180600 | Pre-existing diabetes mellitus, non-insulin-dependent | 66A4.00 | Diabetic on oral treatment |
| **C10FG11** | Type II diabetes mellitus with arthropathy | C109A11 | Type II diabetes mellitus with mononeuropathy | 66AJ.00 | Diabetic - poor control |
| **C10F511** | Type II diabetes mellitus with gangrene | L180500 | Pre-existing diabetes mellitus, insulin-dependent | 66AJ100 | Brittle diabetes |
| **C10FF11** | Type II diabetes mellitus with peripheral angiopathy | C100z00 | Diabetes mellitus NOS with no mention of complication | C109.00 | Non-insulin-dependent diabetes mellitus |
| **C10E811** | Type I diabetes mellitus - poor control | C10E.12 | Insulin-dependent diabetes mellitus | C109.11 | NIDDM - Non-insulin-dependent diabetes mellitus |
| **C109912** | Type 2 diabetes mellitus without complication | C10G.00 | Secondary pancreatic diabetes mellitus | C108700 | Insulin-dependent diabetes mellitus with retinopathy |
| **C10FP11** | Type II diabetes mellitus with ketoacidotic coma | C10FM11 | Type II diabetes mellitus with persistent microalbuminuria | C10E711 | Type I diabetes mellitus with retinopathy |
| **C10FN11** | Type II diabetes mellitus with ketoacidosis | C10F411 | Type II diabetes mellitus with ulcer | C10FA11 | Type II diabetes mellitus with mononeuropathy |
| **C109312** | Type 2 diabetes mellitus with multiple complications | C10E311 | Type I diabetes mellitus with multiple complications | C10FS00 | Maternally inherited diabetes mellitus |
| **C108311** | Type I diabetes mellitus with multiple complications | C10EC11 | Type I diabetes mellitus with polyneuropathy | C10ER00 | Latent autoimmune diabetes mellitus in adult |
| **C10EQ11** | Type I diabetes mellitus with gastroparesis | C10N100 | Cystic fibrosis related diabetes mellitus | C108A11 | Type I diabetes mellitus without complication |
| **C10E612** | Insulin-dependent diabetes mellitus with gangrene | C10EG00 | Type 1 diabetes mellitus with peripheral angiopathy | C10E911 | Type I diabetes mellitus maturity onset |
| **C109911** | Type II diabetes mellitus without complication | C10FE11 | Type II diabetes mellitus with diabetic cataract | C10G000 | Secondary pancreatic diabetes mellitus without complication |

| Med code | Med term | Med code | Med term | Med code | Med term |
|---|---|---|---|---|---|
| **L180700** | Pre-existing malnutrition-related diabetes mellitus | C10E712 | Insulin-dependent diabetes mellitus with retinopathy | C108912 | Type 1 diabetes mellitus maturity onset |
| **C10FH11** | Type II diabetes mellitus with neuropathic arthropathy | C10E511 | Type I diabetes mellitus with ulcer | C108412 | Unstable type 1 diabetes mellitus |
| **C10N000** | Secondary diabetes mellitus without complication | C104000 | Diabetes mellitus, juvenile type, with renal manifestation | | |
| **C10EP11** | Type I diabetes mellitus with exudative maculopathy | C10E912 | Insulin-dependent diabetes maturity onset | | |

## 2- Dementia codes

| Med code | Med term | Med code | Med term |
|---|---|---|---|
| **F110.00** | Alzheimer's disease | Eu10711 | [X]Alcoholic dementia NOS |
| **Eu00.00** | [X]Dementia in Alzheimer's disease | E012.11 | Alcoholic dementia NOS |
| **Eu00z11** | [X]Alzheimer's dementia unspec | E001300 | Presenile dementia with depression |
| **Eu00112** | [X]Senile dementia,Alzheimer's type | Eu02z16 | [X] Senile dementia, depressed or paranoid type |
| **F110000** | Alzheimer's disease with early onset | Eu02000 | [X]Dementia in Pick's disease |
| **Eu00011** | [X]Presenile dementia,Alzheimer's type | E001200 | Presenile dementia with paranoia |
| **Eu00z00** | [X]Dementia in Alzheimer's disease, unspecified | Eu01300 | [X]Mixed cortical and subcortical vascular dementia |
| **Eu00200** | [X]Dementia in Alzheimer's dis, atypical or mixed type | E00..00 | Senile and presenile organic psychotic conditions |
| **F110100** | Alzheimer's disease with late onset | Eu02z13 | [X] Primary degenerative dementia NOS |
| **Eu00100** | [X]Dementia in Alzheimer's disease with late onset | Eu02200 | [X]Dementia in Huntington's disease |
| **Eu00113** | [X]Primary degen dementia of Alzheimer's type, senile onset | E003.00 | Senile dementia with delirium |
| **Eu00111** | [X]Alzheimer's disease type 1 | E001z00 | Presenile dementia NOS |
| **Eu00000** | [X]Dementia in Alzheimer's disease with early onset | E002z00 | Senile dementia with depressive or paranoid features NOS |
| **Fyu3000** | [X]Other Alzheimer's disease | Eu02400 | [X]Dementia in human immunodef virus [HIV] disease |
| **Eu00012** | [X]Primary degen dementia, Alzheimer's type, presenile onset | E004z00 | Arteriosclerotic dementia NOS |
| **Eu00013** | [X]Alzheimer's disease type 2 | E001000 | Uncomplicated presenile dementia |
| **E00..12** | Senile/presenile dementia | E004000 | Uncomplicated arteriosclerotic dementia |
| **E00..11** | Senile dementia | E004300 | Arteriosclerotic dementia with depression |
| **Eu02z14** | [X] Senile dementia NOS | E002.00 | Senile dementia with depressive or paranoid features |
| **Eu02z00** | [X] Unspecified dementia | Eu01000 | [X]Vascular dementia of acute onset |
| **1461** | H/O: dementia | Eu02z11 | [X] Presenile dementia NOS |
| **Eu01.00** | [X]Vascular dementia | E001100 | Presenile dementia with delirium |
| **E000.00** | Uncomplicated senile dementia | Eu04100 | [X]Delirium superimposed on dementia |
| **E004.11** | Multi-infarct dementia | Eu02100 | [X]Dementia in Creutzfeldt-Jakob disease |
| **Eu01200** | [X]Subcortical vascular dementia | E012.00 | Other alcoholic dementia |

| Med code | Med term | Med code | Med term |
|---|---|---|---|
| **Eu02300** | [X]Dementia in Parkinson's disease | Eu01y00 | [X]Other vascular dementia |
| **Eu01.11** | [X]Arteriosclerotic dementia | E004200 | Arteriosclerotic dementia with paranoia |
| **F111.00** | Pick's disease | Eu01111 | [X]Predominantly cortical dementia |
| **Eu01100** | [X]Multi-infarct dementia | E004100 | Arteriosclerotic dementia with delirium |
| **Eu02.00** | [X]Dementia in other diseases classified elsewhere | Eu02y00 | [X]Dementia in other specified diseases classif elsewhere |
| **E001.00** | Presenile dementia | 66h..00 | Dementia monitoring |
| **E002000** | Senile dementia with paranoia | | |
| **Eu01z00** | [X]Vascular dementia, unspecified | | |
| **E004.00** | Arteriosclerotic dementia | | |
| **E002100** | Senile dementia with depression | | |
| **E041.00** | Dementia in conditions EC | | |

## 3- Antidiabetic medications codes

| Drug code | Med term |
|---|---|
| **86313998** | Human insulin 100iu/ml preloaded injection pen |
| **91274998** | Human insulin 100iu/ml preloaded injection pen |
| **97322997** | Human insulin 100iu/ml preloaded injection pen |
| **68748978** | Insulin aspart 100units/ml solution for injection 1.6ml cartridges |
| **86265998** | Insulin aspart 100units/ml solution for injection 10ml vials |
| **93570979** | Insulin aspart 100units/ml solution for injection 10ml vials |
| **99402998** | Insulin aspart 100units/ml solution for injection 10ml vials |
| **60064979** | Insulin aspart 100units/ml solution for injection 3ml cartridges |
| **68749978** | Insulin aspart 100units/ml solution for injection 3ml cartridges |
| **86264998** | Insulin aspart 100units/ml solution for injection 3ml cartridges |
| **87440979** | Insulin aspart 100units/ml solution for injection 3ml cartridges |
| **87442979** | Insulin aspart 100units/ml solution for injection 3ml cartridges |
| **98198998** | Insulin aspart 100units/ml solution for injection 3ml cartridges |
| **81164998** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86263998** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **87434979** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **87435979** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **87436979** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **87437979** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **87438979** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **91509998** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **91612998** | Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices |
| **90379998** | Insulin aspart human pyr 100 iu/ml injection 5 3ml disposable pen(s) |
| **89990998** | Insulin biphasic lispro human prb 25:75; 100 units/ml injection 5 3ml disposable pen(s) |
| **89990997** | Insulin biphasic lispro human prb 50:50; 100 units/ml injection 5 3ml disposable pen(s) |
| **96044992** | Insulin bp 100 i/u |
| **86237998** | Insulin glulisine 100units/ml solution for injection 10ml vials |
| **86551998** | Insulin glulisine 100units/ml solution for injection 10ml vials |
| **86553998** | Insulin glulisine 100units/ml solution for injection 10ml vials |

| Drug code | Med term |
|---|---|
| **85591998** | Insulin glulisine 100units/ml solution for injection 3ml cartridges |
| **86236998** | Insulin glulisine 100units/ml solution for injection 3ml cartridges |
| **86549998** | Insulin glulisine 100units/ml solution for injection 3ml cartridges |
| **47074978** | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **84421998** | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86214998** | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86215998** | Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **95158992** | INSULIN HUMAN (NEUTRAL) 40 I/U INJ |
| **64797979** | Insulin human 100units/ml solution for injection 10ml vials |
| **86319998** | Insulin human 100units/ml solution for injection 10ml vials |
| **90690998** | Insulin human 100units/ml solution for injection 10ml vials |
| **96290992** | Insulin human 100units/ml solution for injection 10ml vials |
| **96688992** | Insulin human 100units/ml solution for injection 10ml vials |
| **98474990** | Insulin human 100units/ml solution for injection 10ml vials |
| **62300979** | Insulin human 100units/ml solution for injection 3.15ml cartridges 5 cartridge |
| **86047998** | Insulin human 1mg inhalation powder blisters |
| **86046998** | Insulin human 3mg inhalation powder blisters |
| **96286992** | Insulin human velosulin 100 i/u inj 0 |
| **86168998** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **93569979** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **90012998** | Insulin lispro 100units/ml solution for injection 1.5ml cartridges |
| **90015998** | Insulin lispro 100units/ml solution for injection 1.5ml pre-filled disposable devices |
| **86253998** | Insulin lispro 100units/ml solution for injection 10ml vials |
| **86256998** | Insulin lispro 100units/ml solution for injection 10ml vials |
| **93582979** | Insulin lispro 100units/ml solution for injection 10ml vials |
| **93585979** | Insulin lispro 100units/ml solution for injection 10ml vials |
| **93586979** | Insulin lispro 100units/ml solution for injection 10ml vials |
| **93587979** | Insulin lispro 100units/ml solution for injection 10ml vials |
| **86252998** | Insulin lispro 100units/ml solution for injection 3ml cartridges |
| **86255998** | Insulin lispro 100units/ml solution for injection 3ml cartridges |
| **83403998** | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86077998** | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86249998** | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86251998** | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86254998** | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices |
| **93572979** | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices |
| **93574979** | Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices |
| **51391978** | Insulin lispro 200units/ml solution for injection 3ml pre-filled disposable devices |
| **86250998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges |
| **86029998** | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges |
| **94202992** | Insulin neusulin (neutral)(purified) 100 i/u inj |
| **96295992** | Insulin quicksol (soluble neutral) 100 i/u inj |
| **99976992** | Insulin soluble 100 i/u inj |

| Drug code | Med term |
|---|---|
| **97602992** | Insulin soluble 40 i/u inj |
| **86173998** | Insulin soluble bovine 100units/ml solution for injection 10ml vials |
| **86176998** | Insulin soluble bovine 100units/ml solution for injection 10ml vials 1 10ml vial(s) |
| **86174998** | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges |
| **86175998** | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges |
| **96050998** | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges |
| **96065998** | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges |
| **97525998** | Insulin soluble bovine 100units/ml solution for injection 3ml cartridges |
| **86312998** | Insulin soluble human 100units/ml solution for injection 10ml vials |
| **86316998** | Insulin soluble human 100units/ml solution for injection 10ml vials |
| **93589979** | Insulin soluble human 100units/ml solution for injection 10ml vials |
| **93590979** | Insulin soluble human 100units/ml solution for injection 10ml vials |
| **95162992** | Insulin soluble human 100units/ml solution for injection 10ml vials |
| **98982998** | Insulin soluble human 100units/ml solution for injection 10ml vials |
| **86314998** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **86315998** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **86317998** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **88851998** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **90202979** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **93592979** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **96787992** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **99553998** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **99557998** | Insulin soluble human 100units/ml solution for injection 3ml cartridges |
| **88003998** | Insulin soluble human crb 100iu/ml injection |
| **94292998** | Insulin soluble human emp 100unit/ml injection |
| **90689998** | Insulin soluble human prb 100unit/ml injection |
| **90691998** | Insulin soluble human pyr 100unit/ml injection |
| **93467992** | Insulin soluble inj i/u^2 |
| **96049998** | Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges |
| **98480998** | Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges |
| **94948998** | Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges 5 3ml vial(s) |
| **86183998** | Insulin soluble porcine 100units/ml solution for injection 10ml vials |
| **88413998** | Insulin soluble porcine 100units/ml solution for injection 10ml vials |
| **90207979** | Insulin soluble porcine 100units/ml solution for injection 10ml vials |
| **86185998** | Insulin soluble porcine 100units/ml solution for injection 10ml vials 1 vial |
| **86182998** | Insulin soluble porcine 100units/ml solution for injection 3ml cartridges |
| **88999998** | Insulin soluble porcine 100units/ml solution for injection 3ml cartridges |
| **86184998** | Insulin soluble porcine 100units/ml solution for injection 3ml cartridges 5 cartridge |
| **94477992** | Neutral insulin 100iu/ml injection |
| **98227998** | Neutral insulin 100iu/ml injection |
| **93594979** | Neutral insulin 100iu/ml injection cartridges |
| **97322998** | Neutral insulin 100iu/ml injection cartridges |
| **98481997** | Human isophane insulin 100iu/ml injection cartridges |

| Drug code | Med term |
|---|---|
| **91276998** | Human isophane insulin 100iu/ml preloaded injection pen |
| **86260998** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges |
| **86262998** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges |
| **87429979** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges |
| **87431979** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges |
| **87433979** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges |
| **86259998** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86261998** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87426979** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87428979** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **89554998** | Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **96062998** | Insulin biphasic 100 units/ml injection |
| **99196998** | Insulin biphasic 100 units/ml injection |
| **89555998** | Insulin biphasic aspart human pyr 30:70; 100 units/ml injection 5 3ml disposable pen(s) |
| **92376997** | Insulin biphasic isophane human crb 25:75; 100 units/ml injection |
| **90681996** | Insulin biphasic isophane human emp 25:75; 100 units/ml injection |
| **94298998** | Insulin biphasic isophane human emp 25:75; 100 units/ml injection |
| **89888998** | Insulin biphasic isophane human emp 30:70; 100 units/ml injection |
| **98226998** | Insulin biphasic isophane human emp 30:70; 100 units/ml injection |
| **98225998** | Insulin biphasic isophane human emp 50:50; 100 units/ml injection |
| **90697998** | Insulin biphasic isophane human prb 10:90; 100 units/ml injection |
| **91275998** | Insulin biphasic isophane human prb 10:90; 100 units/ml injection |
| **97052998** | Insulin biphasic isophane human prb 10:90; 100 units/ml injection |
| **90697997** | Insulin biphasic isophane human prb 20:80; 100 units/ml injection |
| **91275997** | Insulin biphasic isophane human prb 20:80; 100 units/ml injection |
| **87967998** | Insulin biphasic isophane human prb 25:75; 100 units/ml injection |
| **90682998** | Insulin biphasic isophane human prb 40:60; 100 units/ml injection |
| **91273998** | Insulin biphasic isophane human prb 40:60; 100 units/ml injection |
| **97051998** | Insulin biphasic isophane human prb 40:60; 100 units/ml injection |
| **91273997** | Insulin biphasic isophane human prb 50:50; 100 units/ml injection |
| **90684998** | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection |
| **91294998** | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection |
| **92909998** | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection |
| **94319998** | Insulin biphasic isophane human pyr 10:90; 100 units/ml injection |
| **90684997** | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection |
| **91293998** | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection |
| **92908998** | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection |
| **94328998** | Insulin biphasic isophane human pyr 20:80; 100 units/ml injection |
| **92932998** | Insulin biphasic isophane human pyr 30:70; 100 units/ml injection |
| **90683998** | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection |
| **91291998** | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection |

| Drug code | Med term |
|---|---|
| **92907998** | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection |
| **94413998** | Insulin biphasic isophane human pyr 40:60; 100 units/ml injection |
| **96076992** | Insulin bovine protamine zinc 100 i/u inj |
| **97600992** | Insulin bovine protamine zinc 40 i/u inj |
| **52071979** | Insulin degludec 100units/ml solution for injection 3ml cartridges |
| **52072979** | Insulin degludec 100units/ml solution for injection 3ml cartridges |
| **52069979** | Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices |
| **52070979** | Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices |
| **52067979** | Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices |
| **52068979** | Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices |
| **97244992** | Insulin depo s.c.s. 5 400 i/u inj |
| **86246998** | Insulin detemir 100units/ml solution for injection 3ml cartridges |
| **87472998** | Insulin detemir 100units/ml solution for injection 3ml cartridges |
| **82096979** | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices |
| **84779998** | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86245998** | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices |
| **87471998** | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices |
| **87473998** | Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86240998** | Insulin glargine 100units/ml solution for injection 10ml vials |
| **86243998** | Insulin glargine 100units/ml solution for injection 10ml vials |
| **89659979** | Insulin glargine 100units/ml solution for injection 10ml vials |
| **89661979** | Insulin glargine 100units/ml solution for injection 10ml vials |
| **46283978** | Insulin glargine 100units/ml solution for injection 3ml cartridges |
| **86238998** | Insulin glargine 100units/ml solution for injection 3ml cartridges |
| **86241998** | Insulin glargine 100units/ml solution for injection 3ml cartridges |
| **86272998** | Insulin glargine 100units/ml solution for injection 3ml cartridges |
| **89668979** | Insulin glargine 100units/ml solution for injection 3ml cartridges |
| **89673979** | Insulin glargine 100units/ml solution for injection 3ml cartridges |
| **91758998** | Insulin glargine 100units/ml solution for injection 3ml cartridges |
| **46282978** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **55553979** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **84422998** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86239998** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **86242998** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **89639979** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **89640979** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **89643979** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **92555998** | Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices |
| **46889978** | Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices |
| **46890978** | Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices |
| **96548992** | Insulin humulin m cartridge 100 i/u |
| **96284992** | Insulin humulin m4 100 i/u inj |
| **96046992** | Insulin humulin m4 cartridge 100 i/u |

| Drug code | Med term |
|---|---|
| **96285992** | Insulin hypurin protamine zinc 100 i/u inj |
| **96292992** | Insulin isophane (highly purified) 100 i/u inj |
| **93137992** | Insulin isophane (human) 100 i/u inj |
| **96283992** | Insulin isophane (nph) 100 i/u inj |
| **97598992** | Insulin isophane (nph) 40 i/u |
| **99978992** | Insulin isophane (purified) 100 i/u inj |
| **93139992** | Insulin isophane 100 i/u |
| **99977992** | Insulin isophane 50%/neutral 50% 100 i/u inj |
| **86310998** | Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges |
| **86311998** | Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges |
| **91294997** | Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **81687998** | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges |
| **86284998** | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86285998** | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **91289998** | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 5ml vials |
| **87416979** | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 1.5ml cartridges |
| **86308998** | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges |
| **86309998** | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges |
| **97052997** | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges |
| **91293997** | Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86279998** | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges |
| **86282998** | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges |
| **81790998** | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86278998** | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86281998** | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86280998** | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials |
| **86283998** | Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials |
| **87411979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 1.5ml cartridges |
| **86078998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials |
| **86300998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials |
| **86305998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials |
| **87408979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials |
| **87409979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials |
| **87410979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials |

| Drug code | Med term |
|---|---|
| **91292996** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials |
| **86301998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **86303998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **86306998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **87402979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **87403979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **87406979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **87407979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **91292998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges |
| **81963998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86298998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86304998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87401979** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90169998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90684996** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90697996** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **91275996** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **91292997** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **94337998** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **97052996** | Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86294998** | Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges |
| **86295998** | Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges |
| **91291997** | Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90683997** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges |
| **92906998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges |
| **94436998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges |
| **91290996** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials |
| **97051997** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials |
| **86169998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |

| Drug code | Med term |
|---|---|
| **86287998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **86288998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **86291998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **86318998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **87392979** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **90682997** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **91290998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **91700998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges |
| **86286998** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **91290997** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **92376996** | Insulin isophane biphasic human 50/50 100units/ml suspension for injection 5ml vials |
| **96053997** | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 1.5ml cartridges |
| **86187998** | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials |
| **86189998** | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials |
| **87390979** | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials |
| **99415998** | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials |
| **86186998** | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges |
| **86188998** | Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges |
| **88978998** | Insulin isophane biphasic Porcine 30/70 Mix 100units/ml suspension for injection 1.5ml cartridges |
| **88995998** | Insulin isophane biphasic Porcine Isophane 100units/ml suspension for injection 1.5ml cartridges |
| **96056998** | Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges |
| **98048990** | Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges |
| **86178998** | Insulin isophane bovine 100units/ml suspension for injection 10ml vials |
| **86180998** | Insulin isophane bovine 100units/ml suspension for injection 10ml vials |
| **87387979** | Insulin isophane bovine 100units/ml suspension for injection 10ml vials |
| **86177998** | Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges |
| **86179998** | Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges |
| **97526998** | Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges |
| **86081998** | Insulin isophane human 100units/ml suspension for injection 10ml vials |
| **86271998** | Insulin isophane human 100units/ml suspension for injection 10ml vials |
| **87383979** | Insulin isophane human 100units/ml suspension for injection 10ml vials |
| **87384979** | Insulin isophane human 100units/ml suspension for injection 10ml vials |
| **87385979** | Insulin isophane human 100units/ml suspension for injection 10ml vials |
| **96287992** | Insulin isophane human 100units/ml suspension for injection 10ml vials |
| **98228997** | Insulin isophane human 100units/ml suspension for injection 10ml vials |
| **86268998** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |

| Drug code | Med term |
|---|---|
| **86270998** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **86275998** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **90687998** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **90688998** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **93566979** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **93567979** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **93568979** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **94322998** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **98228996** | Insulin isophane human 100units/ml suspension for injection 3ml cartridges |
| **81426998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **81962998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86080998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86266998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86269998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86274998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90168998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90271979** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90272979** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **90686998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **91295998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **91505998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **98228998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **99554998** | Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86267998** | Insulin isophane human 100units/ml suspension for injection 5ml vials |
| **87379979** | Insulin isophane human 100units/ml suspension for injection 5ml vials |
| **97854998** | Insulin isophane human 100units/ml suspension for injection 5ml vials |
| **86276998** | Insulin isophane human vial 100unit/ml sterile suspension injection |
| **96055998** | Insulin isophane porcine 100units/ml suspension for injection 1.5ml cartridges |
| **86191998** | Insulin isophane porcine 100units/ml suspension for injection 10ml vials |
| **86194998** | Insulin isophane porcine 100units/ml suspension for injection 10ml vials |
| **87378979** | Insulin isophane porcine 100units/ml suspension for injection 10ml vials |
| **86190998** | Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges |
| **86193998** | Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges |
| **86248998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges |
| **87363979** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges |
| **87364979** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges |

| Drug code | Med term |
|---|---|
| **98895998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges |
| **83404998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **86247998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87372979** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87373979** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87376979** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **71799979** | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges |
| **86028998** | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges |
| **83405998** | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87365979** | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **87367979** | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **92323998** | Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices |
| **96289992** | Insulin novo ultratard mc 100 i/u inj |
| **96051998** | Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials |
| **97528998** | Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials |
| **96795992** | Insulin pur-in isophane 100 i/u inj |
| **96794992** | Insulin pur-in mix 15/85 100 i/u inj |
| **96792992** | Insulin pur-in mix 50/50 100 i/u inj |
| **96064992** | Insulin semitard 100 i/u inj |
| **95168992** | Insulin semitard 40 i/u inj |
| **96294992** | Insulin zinc bovine susp 100 i/u inj |
| **96057998** | Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials |
| **98268998** | Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials |
| **98817998** | Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials |
| **96689992** | Insulin zinc crystalline susp 100 i/u inj |
| **94201992** | Insulin zinc lente 100iu/ml injection |
| **95164992** | Insulin zinc lente 100iu/ml injection |
| **95846992** | Insulin zinc lente 100iu/ml injection |
| **97053998** | Insulin zinc lente 100iu/ml injection |
| **98505998** | Insulin zinc lente 100iu/ml injection |
| **99401998** | Insulin zinc lente 100iu/ml injection |
| **99480998** | Insulin zinc lente 100iu/ml injection |
| **99556998** | Insulin zinc lente 100iu/ml injection |
| **96046998** | Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials |
| **97527998** | Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials |
| **98525990** | Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials |
| **96061998** | Insulin zinc mixed bovine vial 100unit/ml sterile suspension injection |
| **90685998** | Insulin zinc mixed human 100units/ml suspension for injection 10ml vials |
| **99144998** | Insulin zinc suspension amorphous porcine 100unit/ml injection |

| Drug code | Med term |
|---|---|
| **96058998** | Insulin zinc suspension crystalline human pyr 100unit/ml long-acting injection |
| **90698998** | Insulin zinc suspension mixed bovine and porcine 100unit/ml injection |
| **96060998** | Insulin zinc suspension mixed human pyr 100unit/ml injection |
| **91160998** | Insulin zinc suspension mixed porcine 100unit/ml injection |
| **91701998** | Insuman comb 25 100iu/ml Injection |
| **95163992** | Isophane insulin 100iu/ml injection |
| **96045998** | Isophane insulin 100iu/ml injection |
| **96282992** | Isophane insulin 100iu/ml injection |
| **96291992** | Isophane insulin 100iu/ml injection |
| **97323998** | Isophane insulin 100iu/ml injection |
| **97599992** | Isophane insulin 100iu/ml injection |
| **98481998** | Isophane insulin 100iu/ml injection |
| **99359998** | Isophane insulin 100iu/ml injection |
| **99532998** | Isophane insulin 100iu/ml injection |
| **99533998** | Isophane insulin 100iu/ml injection |
| **90821994** | Hypodermic insulin injection pen reusable for 1.5ml cartridge 1 unit dial up / range 1-16 units |
| **90820994** | Hypodermic insulin injection pen reusable for 1.5ml cartridge 2 unit dial up / range 2-32 units |
| **67235994** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units |
| **67236994** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units |
| **51014978** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units |
| **51015978** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units |
| **51016978** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units |
| **80085994** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units |
| **89081994** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units |
| **89082994** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units |
| **90508994** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units |
| **87306979** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units |
| **87319994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units |
| **88211994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units |
| **88973994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units |
| **90098994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units |
| **51053978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **51054978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |

| Drug code | Med term |
|---|---|
| **67757994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **67758994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **76725994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **78813994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **78814994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **82463994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **82464994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **82465994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **83993994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **84255978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **84256978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **84257978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **84258978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **84259978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **84260978** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **87008994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **87415994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **87416994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **91641994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **89662994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-70 units |
| **89663994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-70 units |
| **72423994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units |
| **72430994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units |
| **81423994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units |
| **81468994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units |
| **90828994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units |
| **90829994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units |
| **90830994** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units |

| Drug code | Med term |
|---|---|
| **87317994** | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units |
| **88210994** | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units |
| **88974994** | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units |
| **90819994** | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units |
| **96047998** | Insulin neutral human 100unit/ml injection |
| **96048998** | Insulin neutral human 100unit/ml injection |
| **63546979** | Insulin human 500units/ml solution for injection 20ml vials |
| **63547979** | Insulin human 500units/ml solution for injection 20ml vials |
| **81688998** | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges |
| **82457998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials |
| **82458998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials |
| **82916998** | Metformin 1g oral powder sachets sugar free |
| **82918998** | Metformin 1g oral powder sachets sugar free |
| **82919998** | Metformin 500mg oral powder sachets sugar free |
| **82917998** | Metformin hydrochloride 500mg sachets |
| **88528998** | Troglitazone 200mg tablet |
| **88523998** | Troglitazone 200mg tablets |
| **88528996** | Troglitazone 400mg tablet |
| **88523996** | Troglitazone 400mg tablets |
| **96981998** | Acetohexamide 500mg tablets |
| **99754998** | Acetohexamide 500mg tablets |
| **95870992** | Butamide cap |
| **96755998** | Chlorpropamide 100mg tablets |
| **99246990** | Chlorpropamide 100mg tablets |
| **99764998** | Chlorpropamide 100mg tablets |
| **96687998** | Chlorpropamide 250mg tablets |
| **96755997** | Chlorpropamide 250mg tablets |
| **98188989** | Chlorpropamide 250mg tablets |
| **99247989** | Chlorpropamide 250mg tablets |
| **99764997** | Chlorpropamide 250mg tablets |
| **97133992** | Chlorpropamide 500 mg tab |
| **97236992** | Daonil 10 mg tab |
| **97057997** | Glibenclamide 2.5mg tablets |
| **97127998** | Glibenclamide 2.5mg tablets |
| **97537998** | Glibenclamide 2.5mg tablets |
| **97552990** | Glibenclamide 2.5mg tablets |
| **97583998** | Glibenclamide 2.5mg tablets |
| **98664989** | Glibenclamide 2.5mg tablets |
| **99145998** | Glibenclamide 2.5mg tablets |
| **99580989** | Glibenclamide 2.5mg tablets |
| **99582989** | Glibenclamide 2.5mg tablets |

| Drug code | Med term |
|---|---|
| **99668998** | Glibenclamide 2.5mg tablets |
| **93556979** | Glibenclamide 5mg tablets |
| **96220990** | Glibenclamide 5mg tablets |
| **97057998** | Glibenclamide 5mg tablets |
| **97097997** | Glibenclamide 5mg tablets |
| **97127997** | Glibenclamide 5mg tablets |
| **97537997** | Glibenclamide 5mg tablets |
| **97583997** | Glibenclamide 5mg tablets |
| **98664990** | Glibenclamide 5mg tablets |
| **99580990** | Glibenclamide 5mg tablets |
| **99582990** | Glibenclamide 5mg tablets |
| **99668997** | Glibenclamide 5mg tablets |
| **99787998** | Glibenclamide 5mg tablets |
| **85901998** | Glibenclamide 5mg/5ml oral suspension |
| **91559998** | Glibornuride 25mg tablet |
| **99588998** | Glibornuride 25mg tablets |
| **68690978** | Gliclazide 30mg modified-release tablets |
| **82304998** | Gliclazide 30mg modified-release tablets |
| **82989998** | Gliclazide 30mg modified-release tablets |
| **83916998** | Gliclazide 30mg modified-release tablets |
| **83949998** | Gliclazide 30mg modified-release tablets |
| **91407998** | Gliclazide 30mg modified-release tablets |
| **92831990** | Gliclazide 30mg modified-release tablets |
| **96283997** | Gliclazide 30mg modified-release tablets |
| **62836979** | Gliclazide 40mg tablets |
| **82136998** | Gliclazide 40mg tablets |
| **82137998** | Gliclazide 40mg tablets |
| **86018998** | Gliclazide 40mg/5ml oral suspension |
| **55225978** | Gliclazide 60mg modified-release tablets |
| **84493978** | Gliclazide 60mg modified-release tablets |
| **84494978** | Gliclazide 60mg modified-release tablets |
| **88135998** | Gliclazide 80mg tablets |
| **93545979** | Gliclazide 80mg tablets |
| **93546979** | Gliclazide 80mg tablets |
| **95025990** | Gliclazide 80mg tablets |
| **95898990** | Gliclazide 80mg tablets |
| **96283998** | Gliclazide 80mg tablets |
| **96427990** | Gliclazide 80mg tablets |
| **96495990** | Gliclazide 80mg tablets |
| **97026990** | Gliclazide 80mg tablets |
| **97032990** | Gliclazide 80mg tablets |
| **97154990** | Gliclazide 80mg tablets |
| **97166990** | Gliclazide 80mg tablets |

| Drug code | Med term |
|---|---|
| **97303998** | Gliclazide 80mg tablets |
| **97538990** | Gliclazide 80mg tablets |
| **97590990** | Gliclazide 80mg tablets |
| **97889990** | Gliclazide 80mg tablets |
| **97938990** | Gliclazide 80mg tablets |
| **98133990** | Gliclazide 80mg tablets |
| **88447997** | Glimepiride 1mg tablets |
| **88449997** | Glimepiride 1mg tablets |
| **93564990** | Glimepiride 1mg tablets |
| **88447998** | Glimepiride 2mg tablets |
| **88449998** | Glimepiride 2mg tablets |
| **93528979** | Glimepiride 2mg tablets |
| **88447996** | Glimepiride 3mg tablets |
| **88449996** | Glimepiride 3mg tablets |
| **88334998** | Glimepiride 4mg tablets |
| **88355998** | Glimepiride 4mg tablets |
| **93483979** | Glimepiride 4mg tablets |
| **96281998** | Glipizide 2.5mg tablets |
| **96282998** | Glipizide 2.5mg tablets |
| **96282997** | Glipizide 5mg tablets |
| **96893990** | Glipizide 5mg tablets |
| **97146990** | Glipizide 5mg tablets |
| **97202990** | Glipizide 5mg tablets |
| **97834990** | Glipizide 5mg tablets |
| **99419998** | Glipizide 5mg tablets |
| **99591998** | Glipizide 5mg tablets |
| **96280998** | Gliquidone 30mg tablets |
| **99589998** | Gliquidone 30mg tablets |
| **95150998** | Tolazamide 100mg tablet |
| **95149998** | Tolazamide 100mg tablets |
| **95150997** | Tolazamide 250mg tablet |
| **95149997** | Tolazamide 250mg tablets |
| **95672992** | Tolbutamide 1 gm tab |
| **94371992** | Tolbutamide 100 mg tab |
| **95674992** | Tolbutamide 250 mg tab |
| **97089998** | Tolbutamide 500mg tablets |
| **97109998** | Tolbutamide 500mg tablets |
| **98053990** | Tolbutamide 500mg tablets |
| **99195998** | Tolbutamide 500mg tablets |
| **99347990** | Tolbutamide 500mg tablets |
| **99349990** | Tolbutamide 500mg tablets |
| **54496979** | Metformin 1g modified-release tablets |
| **74441978** | Metformin 1g modified-release tablets |

| Drug code | Med term |
|---|---|
| **76199978** | Metformin 1g modified-release tablets |
| **81344998** | Metformin 1g modified-release tablets |
| **83031998** | Metformin 1g modified-release tablets |
| **83032998** | Metformin 1g modified-release tablets |
| **89128979** | Metformin 1g modified-release tablets |
| **89129979** | Metformin 1g modified-release tablets |
| **95272992** | Metformin 250 mg tab |
| **54786979** | Metformin 500mg modified-release tablets |
| **58558979** | Metformin 500mg modified-release tablets |
| **74453978** | Metformin 500mg modified-release tablets |
| **74454978** | Metformin 500mg modified-release tablets |
| **81158998** | Metformin 500mg modified-release tablets |
| **81701998** | Metformin 500mg modified-release tablets |
| **83619998** | Metformin 500mg modified-release tablets |
| **87053998** | Metformin 500mg modified-release tablets |
| **87054998** | Metformin 500mg modified-release tablets |
| **87883998** | Metformin 500mg modified-release tablets |
| **89868979** | Metformin 500mg modified-release tablets |
| **89870979** | Metformin 500mg modified-release tablets |
| **95880998** | Metformin 500mg modified-release tablets |
| **93469979** | Metformin 500mg tablets |
| **94235992** | Metformin 500mg tablets |
| **94248990** | Metformin 500mg tablets |
| **95600990** | Metformin 500mg tablets |
| **96111990** | Metformin 500mg tablets |
| **96270990** | Metformin 500mg tablets |
| **96850990** | Metformin 500mg tablets |
| **97087998** | Metformin 500mg tablets |
| **97110990** | Metformin 500mg tablets |
| **98125990** | Metformin 500mg tablets |
| **98493989** | Metformin 500mg tablets |
| **98654989** | Metformin 500mg tablets |
| **99149990** | Metformin 500mg tablets |
| **99513990** | Metformin 500mg tablets |
| **99514990** | Metformin 500mg tablets |
| **99590998** | Metformin 500mg tablets |
| **71281979** | Metformin 500mg/5ml oral solution sugar free |
| **79512979** | Metformin 500mg/5ml oral solution sugar free |
| **85673998** | Metformin 500mg/5ml oral solution sugar free |
| **85674998** | Metformin 500mg/5ml oral solution sugar free |
| **87536998** | Metformin 500mg/5ml oral solution sugar free |
| **89188979** | Metformin 500mg/5ml oral solution sugar free |
| **91686990** | Metformin 500mg/5ml oral solution sugar free |

| Drug code | Med term |
|---|---|
| **92983990** | Metformin 500mg/5ml oral solution sugar free |
| **93167990** | Metformin 500mg/5ml oral solution sugar free |
| **83732998** | Metformin 750mg modified-release tablets |
| **83733998** | Metformin 750mg modified-release tablets |
| **95270992** | Metformin 800 mg tab |
| **93459979** | Metformin 850mg tablets |
| **95271992** | Metformin 850mg tablets |
| **97087997** | Metformin 850mg tablets |
| **97110989** | Metformin 850mg tablets |
| **98125989** | Metformin 850mg tablets |
| **98493990** | Metformin 850mg tablets |
| **98654990** | Metformin 850mg tablets |
| **99513989** | Metformin 850mg tablets |
| **99514989** | Metformin 850mg tablets |
| **99590997** | Metformin 850mg tablets |
| **91221998** | Metformin hydrochloride 500mg tablets |
| **91221997** | Metformin hydrochloride 850mg tablets |
| **98475997** | Acarbose 100mg tablets |
| **98915997** | Acarbose 100mg tablets |
| **98475998** | Acarbose 50mg tablets |
| **98915998** | Acarbose 50mg tablets |
| **39144978** | Albiglutide 30mg powder and solvent for solution for injection pre-filled disposable devices |
| **78729978** | Alogliptin 12.5mg / Metformin 1g tablets |
| **78730978** | Alogliptin 12.5mg / Metformin 1g tablets |
| **78727978** | Alogliptin 12.5mg tablets |
| **78728978** | Alogliptin 12.5mg tablets |
| **78725978** | Alogliptin 25mg tablets |
| **78726978** | Alogliptin 25mg tablets |
| **78723978** | Alogliptin 6.25mg tablets |
| **78724978** | Alogliptin 6.25mg tablets |
| **76401978** | Canagliflozin 100mg tablets |
| **76402978** | Canagliflozin 100mg tablets |
| **76980978** | Canagliflozin 100mg tablets |
| **76981978** | Canagliflozin 100mg tablets |
| **76399978** | Canagliflozin 300mg tablets |
| **76400978** | Canagliflozin 300mg tablets |
| **56931978** | Canagliflozin 50mg / Metformin 1g tablets |
| **56932978** | Canagliflozin 50mg / Metformin 1g tablets |
| **56930978** | Canagliflozin 50mg / Metformin 850mg tablets |
| **53327979** | Dapagliflozin 10mg tablets |
| **53328979** | Dapagliflozin 10mg tablets |
| **76992978** | Dapagliflozin 5mg / Metformin 1g tablets |
| **76993978** | Dapagliflozin 5mg / Metformin 1g tablets |

| Drug code | Med term |
|---|---|
| **76990978** | Dapagliflozin 5mg / Metformin 850mg tablets |
| **76991978** | Dapagliflozin 5mg / Metformin 850mg tablets |
| **53325979** | Dapagliflozin 5mg tablets |
| **53326979** | Dapagliflozin 5mg tablets |
| **53433978** | Dulaglutide 0.75mg/0.5ml solution for injection pre-filled disposable devices |
| **53434978** | Dulaglutide 0.75mg/0.5ml solution for injection pre-filled disposable devices |
| **53431978** | Dulaglutide 1.5mg/0.5ml solution for injection pre-filled disposable devices |
| **53432978** | Dulaglutide 1.5mg/0.5ml solution for injection pre-filled disposable devices |
| **70447978** | Empagliflozin 10mg tablets |
| **70448978** | Empagliflozin 10mg tablets |
| **45827978** | Empagliflozin 12.5mg / Metformin 1g tablets |
| **45828978** | Empagliflozin 12.5mg / Metformin 1g tablets |
| **45826978** | Empagliflozin 12.5mg / Metformin 850mg tablets |
| **70445978** | Empagliflozin 25mg tablets |
| **70446978** | Empagliflozin 25mg tablets |
| **45823978** | Empagliflozin 5mg / Metformin 1g tablets |
| **45824978** | Empagliflozin 5mg / Metformin 1g tablets |
| **45822978** | Empagliflozin 5mg / Metformin 850mg tablets |
| **84693998** | Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices |
| **84696998** | Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices |
| **55150978** | Exenatide 2mg powder and solvent for prolonged-release suspension for injection pre-filled disposable devices |
| **55151978** | Exenatide 2mg powder and solvent for prolonged-release suspension for injection pre-filled disposable devices |
| **81305998** | Exenatide 2mg powder and solvent for prolonged-release suspension for injection vials |
| **81307998** | Exenatide 2mg powder and solvent for prolonged-release suspension for injection vials |
| **84694998** | Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices |
| **84697998** | Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices |
| **94470992** | Glymidine 500mg tablets |
| **96264998** | Glymidine sodium 500mg tablet |
| **96253997** | Guar gum 5g granules sachets sugar free |
| **96051992** | Guar gum 5g/sachet |
| **93448979** | Guar gum 5g/sachet granules |
| **96252998** | Guar gum 5g/sachet granules |
| **98803998** | Guar gum 5g/sachet granules |
| **96253996** | Guar gum 90% granules |
| **96253998** | Guar gum mini tablets |
| **55818978** | Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices |
| **55819978** | Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices |
| **54906979** | Linagliptin 2.5mg / Metformin 1g tablets |
| **54907979** | Linagliptin 2.5mg / Metformin 1g tablets |

| Drug code | Med term |
|---|---|
| **54904979** | Linagliptin 2.5mg / Metformin 850mg tablets |
| **54905979** | Linagliptin 2.5mg / Metformin 850mg tablets |
| **81159998** | Linagliptin 5mg tablets |
| **81160998** | Linagliptin 5mg tablets |
| **55842978** | Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices |
| **82793998** | Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices |
| **82794998** | Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices |
| **52041979** | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices |
| **52043979** | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices |
| **52044979** | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices |
| **52042979** | Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices and Lixisenatide 20micrograms/0 |
| **52039979** | Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices |
| **52040979** | Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices |
| **87180998** | Metformin & rosiglitazone 1g+2mg tablets |
| **87179998** | Metformin & rosiglitazone 1g+4mg tablets |
| **87771998** | Metformin & rosiglitazone 500mg+1mg tablets |
| **87770998** | Metformin & rosiglitazone 500mg+2mg tablets |
| **82068998** | Metformin 1g / Sitagliptin 50mg tablets |
| **83401998** | Metformin 1g / Sitagliptin 50mg tablets |
| **87166998** | Metformin with rosiglitazone 1000mg + 2mg tablet |
| **87165998** | Metformin with rosiglitazone 1000mg + 4mg tablet |
| **87774998** | Metformin with rosiglitazone 500mg + 1mg tablet |
| **87772998** | Metformin with rosiglitazone 500mg + 2mg tablet |
| **88131997** | Nateglinide 120mg tablets |
| **88132997** | Nateglinide 120mg tablets |
| **88131996** | Nateglinide 180mg tablets |
| **88132996** | Nateglinide 180mg tablets |
| **88131998** | Nateglinide 60mg tablets |
| **88132998** | Nateglinide 60mg tablets |
| **85622998** | Pioglitazone 15mg / Metformin 850mg tablets |
| **85624998** | Pioglitazone 15mg / Metformin 850mg tablets |
| **85625998** | Pioglitazone 15mg / Metformin 850mg tablets |
| **91880990** | Pioglitazone 15mg tablets |
| **92237998** | Pioglitazone 15mg tablets |
| **92238998** | Pioglitazone 15mg tablets |
| **47709978** | Pioglitazone 30mg tablets |
| **82196978** | Pioglitazone 30mg tablets |
| **92237997** | Pioglitazone 30mg tablets |
| **92238997** | Pioglitazone 30mg tablets |
| **87884998** | Pioglitazone 45mg tablets |

| Drug code | Med term |
|---|---|
| **87885998** | Pioglitazone 45mg tablets |
| **85267998** | Repaglinide 1mg tablets |
| **91923997** | Repaglinide 1mg tablets |
| **91924997** | Repaglinide 1mg tablets |
| **92996979** | Repaglinide 1mg tablets |
| **85266998** | Repaglinide 2mg tablets |
| **91923996** | Repaglinide 2mg tablets |
| **91924996** | Repaglinide 2mg tablets |
| **85268998** | Repaglinide 500microgram tablets |
| **91908990** | Repaglinide 500microgram tablets |
| **91923998** | Repaglinide 500microgram tablets |
| **91924998** | Repaglinide 500microgram tablets |
| **93009979** | Repaglinide 500microgram tablets |
| **87775998** | Rosiglitazone 1mg / metformin 500mg tablets |
| **87182998** | Rosiglitazone 2mg / metformin 1g tablets |
| **87773998** | Rosiglitazone 2mg / metformin 500mg tablets |
| **89763998** | Rosiglitazone 2mg tablet |
| **90048998** | Rosiglitazone 2mg tablet |
| **87181998** | Rosiglitazone 4mg / metformin 1g tablets |
| **89763997** | Rosiglitazone 4mg tablets |
| **90048997** | Rosiglitazone 4mg tablets |
| **89763996** | Rosiglitazone 8mg tablets |
| **90048996** | Rosiglitazone 8mg tablets |
| **53006979** | Saxagliptin 2.5mg / Metformin 1g tablets |
| **53007979** | Saxagliptin 2.5mg / Metformin 1g tablets |
| **53004979** | Saxagliptin 2.5mg / Metformin 850mg tablets |
| **53005979** | Saxagliptin 2.5mg / Metformin 850mg tablets |
| **81513998** | Saxagliptin 2.5mg tablets |
| **81514998** | Saxagliptin 2.5mg tablets |
| **82573998** | Saxagliptin 5mg tablets |
| **82575998** | Saxagliptin 5mg tablets |
| **84639998** | Sitagliptin 100mg tablets |
| **84640998** | Sitagliptin 100mg tablets |
| **59373979** | Sitagliptin 25mg tablets |
| **59374979** | Sitagliptin 25mg tablets |
| **59371979** | Sitagliptin 50mg tablets |
| **59372979** | Sitagliptin 50mg tablets |
| **84008998** | Vildagliptin 50mg / Metformin 1g tablets |
| **84010998** | Vildagliptin 50mg / Metformin 1g tablets |
| **84009998** | Vildagliptin 50mg / Metformin 850mg tablets |
| **84011998** | Vildagliptin 50mg / Metformin 850mg tablets |
| **84338998** | Vildagliptin 50mg tablets |
| **84341998** | Vildagliptin 50mg tablets |

| Drug code | Med term |
|---|---|
| **60326979** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units |
| **66897979** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units |
| **87307979** | Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units |
| **86523979** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units |
| **70706979** | Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units |
| **87303979** | Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units |
| **54995979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/29gauge |
| **60752979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/30gauge |
| **29482978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge |
| **60750979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge |
| **82276978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32.5gauge |
| **72620994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge |
| **73402978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/33gauge |
| **61938979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/29gauge |
| **60323979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/30gauge |
| **29581978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge |
| **31584978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge |
| **37574978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge |
| **29580978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge |
| **32286978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32.5gauge |
| **53032979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32gauge |
| **62402979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/29gauge |
| **37573978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge |
| **82274978** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32.5gauge |
| **53030979** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32gauge |
| **61587979** | Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 4.5mm/31gauge |
| **77055978** | Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 4mm/32gauge |
| **87233979** | Hypodermic needle sterile single use 0.5mm/25gauge 16mm |
| **87232979** | Hypodermic needle sterile single use 0.5mm/25gauge 25mm |

| Drug code | Med term |
|---|---|
| **84568978** | Hypodermic u100 insulin syringe sterile single use / single patient use 0.3ml with 8mm safety needle 0.3mm/30gauge |
| **84565978** | Hypodermic u100 insulin syringe sterile single use / single patient use 0.5ml with 12mm safety needle 0.33mm/29gauge |
| **84606978** | Hypodermic u100 insulin syringe sterile single use / single patient use 1ml with 12mm safety needle 0.33mm/29gauge |
| **63546979** | Insulin human 500units/ml solution for injection 20ml vials |
| **63547979** | Insulin human 500units/ml solution for injection 20ml vials |
| **81688998** | Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges |
| **82457998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials |
| **82458998** | Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials |
| **30899978** | Needle free insulin delivery system |
| **30900978** | Needle free insulin delivery system |
| **30901978** | Needle free insulin delivery system |
| **84168979** | Needle free insulin delivery system |
| **87885994** | Hypodermic u100 insulin syringe sterile single use / single patient use 0.3ml with 12mm needle 0.33mm/29gauge |
| **88474994** | Hypodermic u100 insulin syringe sterile single use / single patient use 0.3ml with 8mm needle 0.3mm/30gauge |
| **95243994** | Generic sabre single use hypodermic single use needle 0.4mm 27g 12mm (sabre international) |
| **83563994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12.7mm/29gauge |
| **83558994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/28gauge |
| **83560994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge |
| **83565994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge |
| **83562994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge |
| **83559994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/30gauge |
| **83564994** | Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge |
| **83102994** | Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 10mm/29gauge |
| **83101994** | Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 12mm/29gauge |
| **83104994** | Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 6mm/31gauge |
| **83103994** | Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 8mm/31gauge |
| **46249978** | Metformin 1g modified-release tablets |
| **84268978** | Metformin 1g modified-release tablets |
| **28977978** | Metformin 1g/5ml oral solution sugar free |
| **79510979** | Metformin 850mg/5ml oral solution |
| **28975978** | Metformin 850mg/5ml oral solution sugar free |
| **79508979** | Metformin 850mg/5ml oral suspension |
| **85554998** | Metformin 850mg capsules |
| **85555998** | Metformin oral solution |

| Drug code | Med term |
|---|---|
| **69061979** | Gliclazide 120mg/5ml oral suspension |
| **81260998** | Gliclazide 80mg/5ml oral suspension |
| **92999979** | Repaglinide 500microgram tablets |
| **31126978** | Sitagliptin 50mg/5ml oral solution |

## 4- Hypoglycaemia codes

| Med code | Med term |
|---|---|
| **66Ad.00** | Hypoglycaemic attack requiring 3rd party assistance |
| **C108E00** | Insulin-dependent diabetes mellitus with hypoglycaemic coma |
| **C108E11** | Type I diabetes mellitus with hypoglycaemic coma |
| **C108E12** | Type 1 diabetes mellitus with hypoglycaemic coma |
| **C109D00** | Non-insulin-dependent diabetes mellitus with hypoglyca coma |
| **C109D11** | Type II diabetes mellitus with hypoglycaemic coma |
| **C109D12** | Type 2 diabetes mellitus with hypoglycaemic coma |
| **C10EE00** | Type 1 diabetes mellitus with hypoglycaemic coma |
| **C10EE11** | Type I diabetes mellitus with hypoglycaemic coma |
| **C10EE12** | Insulin-dependent diabetes mellitus with hypoglycaemic coma |
| **C10FD00** | Type 2 diabetes mellitus with hypoglycaemic coma |
| **C10FD11** | Type II diabetes mellitus with hypoglycaemic coma |
| **C110.00** | Hypoglycaemic coma |
| **C110z00** | Hypoglycaemic coma NOS |
| **C112.00** | Hypoglycaemia unspecified |
| **C112000** | Reactive hypoglycaemia NOS |
| **C112100** | Spontaneous hypoglycaemia NOS |
| **C112z00** | Hypoglycaemia unspecified NOS |
| **C116.00** | Other hypoglycaemia |
| **C116000** | Post-prandial hypoglycaemia |
| **C11y100** | Drug-induced hypoglycaemia without coma |
| **Cyu3000** | [X]Other hypoglycaemia |
| **F374500** | Polyneuropathy in hypoglycaemia |

## 5- Smoking status codes

| Med code | Med term |
|---|---|
| **137..00** | Tobacco consumption |
| **137..11** | Smoker - amount smoked |
| **1371** | Never smoked tobacco |
| **1371.11** | Non-smoker |
| **1372** | Trivial smoker - < 1 cig/day |
| **1372.11** | Occasional smoker |
| **1373** | Light smoker - 1-9 cigs/day |
| **1374** | Moderate smoker - 10-19 cigs/d |
| **1375** | Heavy smoker - 20-39 cigs/day |

| Med code | Med term |
|---|---|
| **1376** | Very heavy smoker - 40+cigs/d |
| **1377** | Ex-trivial smoker (<1/day) |
| **1378** | Ex-light smoker (1-9/day) |
| **1379** | Ex-moderate smoker (10-19/day) |
| **137A.00** | Ex-heavy smoker (20-39/day) |
| **137B.00** | Ex-very heavy smoker (40+/day) |
| **137C.00** | Keeps trying to stop smoking |
| **137E.00** | Tobacco consumption unknown |
| **137F.00** | Ex-smoker - amount unknown |
| **137G.00** | Trying to give up smoking |
| **137H.00** | Pipe smoker |
| **137J.00** | Cigar smoker |
| **137K.00** | Stopped smoking |
| **137K000** | Recently stopped smoking |
| **137L.00** | Current non-smoker |
| **137M.00** | Rolls own cigarettes |
| **137N.00** | Ex pipe smoker |
| **137O.00** | Ex cigar smoker |
| **137P.00** | Cigarette smoker |
| **137P.11** | Smoker |
| **137Q.00** | Smoking started |
| **137Q.11** | Smoking restarted |
| **137R.00** | Current smoker |
| **137S.00** | Ex-smoker |
| **137T.00** | Date ceased smoking |
| **137V.00** | Smoking reduced |
| **137X.00** | Cigarette consumption |
| **137Y.00** | Cigar consumption |
| **137Z.00** | Tobacco consumption NOS |
| **137a.00** | Pipe tobacco consumption |
| **137b.00** | Ready to stop smoking |
| **137c.00** | Thinking about stopping smoking |
| **137d.00** | Not interested in stopping smoking |
| **137e.00** | Smoking restarted |
| **137f.00** | Reason for restarting smoking |
| **137g.00** | Cigarette pack-years |
| **137h.00** | Minutes from waking to first tobacco consumption |
| **137j.00** | Ex-cigarette smoker |
| **137l.00** | Ex roll-up cigarette smoker |
| **137m.00** | Failed attempt to stop smoking |
| **13WK.00** | No smokers in the household |
| **13p..00** | Smoking cessation milestones |
| **13p0.00** | Negotiated date for cessation of smoking |
| **13p4.00** | Smoking free weeks |
| **13p5.00** | Smoking cessation programme start date |

| Med code | Med term |
|---|---|
| **13p5000** | Practice based smoking cessation programme start date |
| **13p8.00** | Lost to smoking cessation follow-up |
| **388B.00** | Pack-years |
| **63C5.00** | Maternal tobacco abuse |
| **6791** | Health ed. - smoking |
| **67A3.00** | Pregnancy smoking advice |
| **67H1.00** | Lifestyle advice regarding smoking |
| **67H6.00** | Brief intervention for smoking cessation |
| **745H.00** | Smoking cessation therapy |
| **745H000** | Nicotine replacement therapy using nicotine patches |
| **745H100** | Nicotine replacement therapy using nicotine gum |
| **745H200** | Nicotine replacement therapy using nicotine inhalator |
| **745H300** | Nicotine replacement therapy using nicotine lozenges |
| **745H400** | Smoking cessation drug therapy |
| **745Hy00** | Other specified smoking cessation therapy |
| **745Hz00** | Smoking cessation therapy NOS |
| **8B2B.00** | Nicotine replacement therapy |
| **8B3Y.00** | Over-the-counter nicotine replacement therapy |
| **8B3f.00** | Nicotine replacement therapy provided free |
| **8BP3.00** | Nicotine replacement therapy provided by community pharmacis |
| **8CAL.00** | Smoking cessation advice |
| **8CAg.00** | Smoking cessation advice provided by community pharmacist |
| **8CdB.00** | Stop smoking service opportunity signposted |
| **8H7i.00** | Referral to smoking cessation advisor |
| **8HBM.00** | Stop smoking face to face follow-up |
| **8HBP.00** | Smoking cessation 12 week follow-up |
| **8HTK.00** | Referral to stop smoking clinic |
| **8HkQ.00** | Referral to NHS stop smoking service |
| **8I2I.00** | Nicotine replacement therapy contraindicated |
| **8I2J.00** | Bupropion contraindicated |
| **8I39.00** | Nicotine replacement therapy refused |
| **8I3M.00** | Bupropion refused |
| **8IAj.00** | Smoking cessation advice declined |
| **8IEK.00** | Smoking cessation programme declined |
| **8IEM.00** | Smoking cessation drug therapy declined |
| **8IEo.00** | Referral to smoking cessation service declined |
| **8T08.00** | Referral to smoking cessation service |
| **9N2k.00** | Seen by smoking cessation advisor |
| **9N4M.00** | DNA - Did not attend smoking cessation clinic |
| **9NS0200** | Referral for smoking cessation service offered |
| **9NdV.00** | Consent given follow-up after smoking cessation intervention |
| **9NdW.00** | Consent given for smoking cessation data sharing |
| **9NdY.00** | Declin cons follow-up evaluation after smoking cess interven |
| **9NdZ.00** | Declined consent for smoking cessation data sharing |
| **9Ndf.00** | Consent given for follow-up by smoking cessation team |

| Med code | Med term |
|---|---|
| **9Ndg.00** | Declined consent for follow-up by smoking cessation team |
| **9OO..00** | Anti-smoking monitoring admin. |
| **9OO..11** | Stop smoking clinic admin. |
| **9OO1.00** | Attends stop smoking monitor. |
| **9OO2.00** | Refuses stop smoking monitor |
| **9OO3.00** | Stop smoking monitor default |
| **9OO4.00** | Stop smoking monitor 1st lettr |
| **9OO5.00** | Stop smoking monitor 2nd lettr |
| **9OO6.00** | Stop smoking monitor 3rd lettr |
| **9OO7.00** | Stop smoking monitor verb.inv. |
| **9OO8.00** | Stop smoking monitor phone inv |
| **9OO9.00** | Stop smoking monitoring delete |
| **9OOA.00** | Stop smoking monitor.chck done |
| **9OOB.00** | Stop smoking invitation short message service text message |
| **9OOB000** | Stop smoking invitation first SMS text message |
| **9OOB100** | Stop smoking invitation second SMS text message |
| **9OOB200** | Stop smoking invitation third SMS text message |
| **9OOZ.00** | Stop smoking monitor admin.NOS |
| **9kc..00** | Smoking cessation - enhanced services administration |
| **9kc0.00** | Smoking cessatn monitor template complet - enhanc serv admin |
| **9km..00** | Ex-smoker annual review - enhanced services administration |
| **9km..11** | Ex-smoker annual review |
| **9kn..00** | Non-smoker annual review - enhanced services administration |
| **9kn..11** | Non-smoker annual review |
| **9ko..00** | Current smoker annual review - enhanced services admin |
| **9ko..11** | Current smoker annual review |
| **E023.00** | Nicotine withdrawal |
| **E251.00** | Tobacco dependence |
| **E251000** | Tobacco dependence, unspecified |
| **E251100** | Tobacco dependence, continuous |
| **E251300** | Tobacco dependence in remission |
| **E251z00** | Tobacco dependence NOS |
| **Eu17.00** | [X]Mental and behavioural disorder due to use of tobacco |
| **Eu17100** | [X]Mental and behav dis due to use of tobacco: harmful use |
| **Eu17200** | [X]Mental and behav dis due to use tobacco: dependence syndr |
| **H310100** | Smokers' cough |
| **SMC..00** | Toxic effect of tobacco and nicotine |
| **TD14A00** | Smoke NOS from conflagration in store |
| **U609900** | [X]Bupropion causing adverse effects in therapeutic use |
| **ZG23300** | Advice on smoking |
| **ZRBm200** | Fagerstrom test for nicotine dependence |
| **ZRBm211** | FTND - Fagerstrom test for nicotine dependence |
| **ZRaM.00** | Motives for smoking scale |
| **ZRao.00** | Occasions for smoking scale |
| **ZRb3.00** | Pack-years |

| Med code | Med term |
|---|---|
| **ZRh4.00** | Reasons for smoking scale |
| **ZRh4.11** | RFS - Reasons for smoking scale |
| **ZV11600** | [V]Personal history of tobacco abuse |
| **ZV4K000** | [V]Tobacco use |
| **ZV6D800** | [V]Tobacco abuse counselling |

## 6- Alcohol consumption codes

| Med code | Med term |
|---|---|
| **1282** | FH: Alcoholism |
| **1282.11** | Alcoholic in the family |
| **1282.12** | Alcoholic offspring |
| **12X0.00** | Family history of alcohol misuse |
| **136..00** | Alcohol consumption |
| **1361.11** | Non-drinker alcohol |
| **1361.12** | Non-drinker alcohol |
| **1367** | Stopped drinking alcohol |
| **1368** | Alcohol consumption unknown |
| **1369** | Suspect alcohol abuse - denied |
| **136K.00** | Alcohol intake above recommended sensible limits |
| **136L.00** | Alcohol intake within recommended sensible limits |
| **136S.00** | Hazardous alcohol use |
| **136T.00** | Harmful alcohol use |
| **136V.00** | Alcohol units per week |
| **136W.00** | Alcohol misuse |
| **136X.00** | Alcohol units consumed on heaviest drinking day |
| **136Z.00** | Alcohol consumption NOS |
| **13Ho000** | Witness to adult alcohol misuse |
| **13L3.11** | Alcoholic spouse |
| **13L3.13** | Husband alcoholic |
| **13Wf.00** | Alcohol misuser in household |
| **13Y8.00** | Alcoholics anonymous |
| **13ZY.00** | Disqualified from driving due to excess alcohol |
| **1462** | H/O: alcoholism |
| **1B1c.00** | Alcohol-induced hallucinations |
| **1D19.00** | Pain in lymph nodes after alcohol consumption |
| **2126C00** | Alcohol dependence resolved |
| **2577** | O/E - breath - alcohol smell |
| **2577.11** | O/E - alcoholic breath |
| **388u.00** | Fast alcohol screening test |
| **38D2.00** | Single alcohol screening questionnaire |
| **38D3.00** | Alcohol use disorders identification test |
| **38P0300** | HoNOSCA item 4 - alcohol, substance/solvent misuse |
| **4I91.11** | Breath alcohol level |
| **63C7.00** | Maternal alcohol abuse |

| Med code | Med term |
|---|---|
| **63CM.00** | Paternal alcohol abuse |
| **66e..00** | Alcohol disorder monitoring |
| **66e0.00** | Alcohol abuse monitoring |
| **6892** | Alcohol consumption screen |
| **68S..00** | Alcohol consumption screen |
| **7P22100** | Delivery of rehabilitation for alcohol addiction |
| **8BA8.00** | Alcohol detoxification |
| **8BAs.00** | Alcohol relapse prevention |
| **8BAu.00** | Alcohol harm reduction programme |
| **8BAw.00** | Alcohol twelve step programme |
| **8CAM.00** | Patient advised about alcohol |
| **8CAM000** | Advised to abstain from alcohol consumption |
| **8CdK.00** | Specialist alcohol treatment service signposted |
| **8G32.00** | Aversion therapy - alcoholism |
| **8H35.00** | Admitted to alcohol detoxification centre |
| **8H7p.00** | Referral to community alcohol team |
| **8HHe.00** | Referral to community drug and alcohol team |
| **8HkG.00** | Referral to specialist alcohol treatment service |
| **9EQ..11** | Police:venesect-alcohol |
| **9EQ..12** | Police:venesect-alcohol |
| **9k11.00** | Alcohol consumption counselling |
| **9k12.00** | Alcohol misuse - enhanced service completed |
| **9NJz.00** | In-house alcohol detoxification |
| **9NN2.00** | Under care of community alcohol team |
| **C150500** | Alcohol-induced pseudo-Cushing's syndrome |
| **E01..00** | Alcoholic psychoses |
| **E010.00** | Alcohol withdrawal delirium |
| **E011.00** | Alcohol amnestic syndrome |
| **E011000** | Korsakov's alcoholic psychosis |
| **E011100** | Korsakov's alcoholic psychosis with peripheral neuritis |
| **E011z00** | Alcohol amnestic syndrome NOS |
| **E012.00** | Other alcoholic dementia |
| **E012.11** | Alcoholic dementia NOS |
| **E012000** | Chronic alcoholic brain syndrome |
| **E013.00** | Alcohol withdrawal hallucinosis |
| **E014.00** | Pathological alcohol intoxication |
| **E015.00** | Alcoholic paranoia |
| **E01y.00** | Other alcoholic psychosis |
| **E01y000** | Alcohol withdrawal syndrome |
| **E01yz00** | Other alcoholic psychosis NOS |
| **E01z.00** | Alcoholic psychosis NOS |
| **E23..00** | Alcohol dependence syndrome |
| **E23..11** | Alcoholism |
| **E23..12** | Alcohol problem drinking |
| **E230.00** | Acute alcoholic intoxication in alcoholism |

| Med code | Med term |
|---|---|
| **E230.11** | Alcohol dependence with acute alcoholic intoxication |
| **E230000** | Acute alcoholic intoxication, unspecified, in alcoholism |
| **E230100** | Continuous acute alcoholic intoxication in alcoholism |
| **E230200** | Episodic acute alcoholic intoxication in alcoholism |
| **E230300** | Acute alcoholic intoxication in remission, in alcoholism |
| **E230z00** | Acute alcoholic intoxication in alcoholism NOS |
| **E231.00** | Chronic alcoholism |
| **E231000** | Unspecified chronic alcoholism |
| **E231100** | Continuous chronic alcoholism |
| **E231200** | Episodic chronic alcoholism |
| **E231300** | Chronic alcoholism in remission |
| **E231z00** | Chronic alcoholism NOS |
| **E23z.00** | Alcohol dependence syndrome NOS |
| **E250.00** | Nondependent alcohol abuse |
| **E250.12** | Hangover (alcohol) |
| **E250.14** | Intoxication - alcohol |
| **E250000** | Nondependent alcohol abuse, unspecified |
| **E250100** | Nondependent alcohol abuse, continuous |
| **E250200** | Nondependent alcohol abuse, episodic |
| **E250300** | Nondependent alcohol abuse in remission |
| **E250z00** | Nondependent alcohol abuse NOS |
| **Eu10.00** | [X]Mental and behavioural disorders due to use of alcohol |
| **Eu10011** | [X]Acute alcoholic drunkenness |
| **Eu10211** | [X]Alcohol addiction |
| **Eu10212** | [X]Chronic alcoholism |
| **Eu10411** | [X]Delirium tremens, alcohol-induced |
| **Eu10511** | [X]Alcoholic hallucinosis |
| **Eu10512** | [X]Alcoholic jealousy |
| **Eu10513** | [X]Alcoholic paranoia |
| **Eu10514** | [X]Alcoholic psychosis NOS |
| **Eu10611** | [X]Korsakov's psychosis, alcohol-induced |
| **Eu10711** | [X]Alcoholic dementia NOS |
| **Eu10712** | [X]Chronic alcoholic brain syndrome |
| **Eu10800** | [X]Alcohol withdrawal-induced seizure |
| **F11x000** | Cerebral degeneration due to alcoholism |
| **F11x011** | Alcoholic encephalopathy |
| **F144000** | Cerebellar ataxia due to alcoholism |
| **F25B.00** | Alcohol-induced epilepsy |
| **F375.00** | Alcoholic polyneuropathy |
| **F394100** | Alcoholic myopathy |
| **G555.00** | Alcoholic cardiomyopathy |
| **G852300** | Oesophageal varices in alcoholic cirrhosis of the liver |
| **J153.00** | Alcoholic gastritis |
| **J610.00** | Alcoholic fatty liver |
| **J611.00** | Acute alcoholic hepatitis |

| Med code | Med term |
|---|---|
| **J612.00** | Alcoholic cirrhosis of liver |
| **J612000** | Alcoholic fibrosis and sclerosis of liver |
| **J613.00** | Alcoholic liver damage unspecified |
| **J613000** | Alcoholic hepatic failure |
| **J617.00** | Alcoholic hepatitis |
| **J617000** | Chronic alcoholic hepatitis |
| **J670800** | Alcohol-induced acute pancreatitis |
| **J671000** | Alcohol-induced chronic pancreatitis |
| **L254.11** | Suspect fetal damage from maternal alcohol |
| **L255300** | Maternal care for (suspected) damage to fetus from alcohol |
| **PK80.00** | Fetal alcohol syndrome |
| **PK83.00** | Fetus and newborn affected by maternal use of alcohol |
| **Q007100** | Fetus/neonate affected by placental/breast transfer alcohol |
| **Q007111** | Fetal alcohol syndrome |
| **R103.00** | [D]Alcohol blood level excessive |
| **SLH3.00** | Alcohol deterrent poisoning |
| **SM0..00** | Alcohol causing toxic effect |
| **SM00.00** | Ethyl alcohol causing toxic effect |
| **SM00100** | Denatured alcohol causing toxic effect |
| **SM00200** | Grain alcohol causing toxic effect |
| **SM00z00** | Ethyl alcohol causing toxic effect NOS |
| **SM01.00** | Methyl alcohol causing toxic effect |
| **SM01100** | Wood alcohol causing toxic effect |
| **SM01z00** | Methyl alcohol causing toxic effect NOS |
| **SM02.00** | Isopropyl alcohol causing toxic effect |
| **SM02200** | Rubbing alcohol causing toxic effect |
| **SM02z00** | Isopropyl alcohol causing toxic effect NOS |
| **SM03000** | Amyl alcohol causing toxic effect |
| **SM03100** | Butyl alcohol causing toxic effect |
| **SM03200** | Propyl alcohol causing toxic effect |
| **SM0y.00** | Other alcohol causing toxic effect |
| **SM0z.00** | Alcohol causing toxic effect NOS |
| **SyuG000** | [X]Toxic effect of other alcohols |
| **T90..00** | Accidental poisoning by alcohol, NEC |
| **T900.00** | Accidental poisoning by alcoholic beverages |
| **T901.00** | Accidental poisoning by other ethyl alcohol and its products |
| **T901000** | Accidental poisoning by denatured alcohol |
| **T901200** | Accidental poisoning by grain alcohol NOS |
| **T901z00** | Accidental poisoning by ethyl alcohol NOS |
| **T902.00** | Accidental poisoning by methyl alcohol |
| **T902100** | Accidental poisoning by wood alcohol |
| **T902z00** | Accidental poisoning by methyl alcohol NOS |
| **T903.00** | Accidental poisoning by isopropyl alcohol |
| **T903200** | Accidental poisoning by rubbing alcohol substitute |
| **T903300** | Accidental poisoning by secondary propyl alcohol |

| Med code | Med term |
|---|---|
| **T903z00** | Accidental poisoning by isopropyl alcohol NOS |
| **T90y.00** | Accidental poisoning by other alcohols |
| **T90z.00** | Accidental poisoning by alcohol NOS |
| **TJH3.00** | Adverse reaction to alcohol deterrents |
| **U1A9.00** | [X]Accident poisoning/exposure to alcohol |
| **U1A9000** | [X]Accident poison/exposure to alcohol at home |
| **U1A9100** | [X]Accid poison/expos to alcohol at res institut |
| **U1A9200** | [X]Acc poison/expos alcohol school/pub admin area |
| **U1A9300** | [X]Accid pois/expos alcohol in sport/athletic area |
| **U1A9400** | [X]Accid poison/expos alcohol in street/highway |
| **U1A9500** | [X]Accid poison/expos alcohol trade/service area |
| **U1A9600** | [X]Acc pois/expos alcohol indust/construct area |
| **U1A9700** | [X]Accident poison/exposure to alcohol on farm |
| **U1A9y00** | [X]Accid pois/expos to alcohol other spec place |
| **U1A9z00** | [X]Accid poison/expos to alcohol unspecif place |
| **U209.00** | [X]Intent self poison/exposure to alcohol |
| **U209000** | [X]Int self poison/exposure to alcohol at home |
| **U209100** | [X]Intent self poison alcohol at res institut |
| **U209200** | [X]Int self poison alcohol school/pub admin area |
| **U209300** | [X]Int self poison alcohol in sport/athletic area |
| **U209400** | [X]Intent self pois alcohol in street/highway |
| **U209500** | [X]Intent self pois alcohol trade/service area |
| **U209600** | [X]Int self pois alcohol indust/construct area |
| **U209700** | [X]Int self poison/exposure to alcohol on farm |
| **U209y00** | [X]Int self poison alcohol other spec place |
| **U209z00** | [X]Intent self poison alcohol unspecif place |
| **U409.00** | [X]Poisoning/exposure, ? intent, to alcohol |
| **U409000** | [X]Poison/exposure ?intent, to alcohol at home |
| **U409100** | [X]Pois/expos ?intent to alcohol at res institut |
| **U409200** | [X]Pois/exp ?intent alcohol school/pub admin area |
| **U409300** | [X]Pois/exp ?intent alcohol in sport/athletic area |
| **U409400** | [X]Pois/expos ?intent alcohol in street/highway |
| **U409500** | [X]Pois/expos ?intent alcohol trade/service area |
| **U409600** | [X]Poison/exposure, ?intent, alcohol indust/construct area |
| **U409700** | [X]Poison/exposure ?intent, to alcohol on farm |
| **U409y00** | [X]Pois/exp ?intent to alcohol other spec place |
| **U409z00** | [X]Pois/expos ?intent to alcohol unspecif place |
| **U60H300** | [X]Alcohol deterrents caus adverse effects in therapeut use |
| **U60H311** | [X] Adverse reaction to alcohol deterrents |
| **U81..00** | [X]Evid of alcohol involv determind by level of intoxication |
| **Z191.00** | Alcohol detoxification |
| **Z191100** | Alcohol withdrawal regime |
| **Z191200** | Planned reduction of alcohol consumption |
| **Z191211** | Alcohol reduction programme |
| **Z191400** | Self-monitoring of alcohol intake |

| Med code | Med term |
|---|---|
| **Z4B1.00** | Alcoholism counselling |
| **Z9KF400** | Removal of alcohol |
| **Z9KF600** | Removing alcohol from home |
| **ZC22200** | Advice to change alcoholic drink intake |
| **ZC2H.00** | Advice to change alcohol intake |
| **ZG23100** | Advice on alcohol consumption |
| **ZR1E.00** | Alcohol dependence scale |
| **ZV11300** | [V]Personal history of alcoholism |
| **ZV11311** | [V]Problems related to lifestyle alcohol use |
| **ZV1A000** | [V]Family history of alcohol abuse |
| **ZV4KC00** | [V] Alcohol use |
| **ZV57A00** | [V]Alcohol rehabilitation |
| **ZV61511** | [V]Alcoholism in family |
| **1362.11** | Drinks rarely |
| **1362.12** | Drinks occasionally |
| **136a.00** | Increasing risk drinking |
| **136A.00** | Ex-trivial drinker (<1u/day) |
| **136b.00** | Feels should cut down drinking |
| **136B.00** | Ex-light drinker - (1-2u/day) |
| **136c.00** | Higher risk drinking |
| **136C.00** | Ex-moderate drinker - (3-6u/d) |
| **136d.00** | Lower risk drinking |
| **136D.00** | Ex-heavy drinker - (7-9u/day) |
| **136E.00** | Ex-very heavy drinker-(>9u/d) |
| **136F.00** | Spirit drinker |
| **136G.00** | Beer drinker |
| **136H.00** | Drinks beer and spirits |
| **136I.00** | Drinks wine |
| **136J.00** | Social drinker |
| **136M.00** | Current non-drinker |
| **136N.00** | Light drinker |
| **136O.00** | Moderate drinker |
| **136P.00** | Heavy drinker |
| **136Q.00** | Very heavy drinker |
| **136R.00** | Binge drinker |
| **136Y.00** | Drinks in morning to get rid of hangover |
| **Eu10500** | [X]Mental & behav dis due to use alcohol: psychotic disorder |
| **E011200** | Wernicke-Korsakov syndrome |
| **Eu10300** | [X]Mental and behav dis due to use alcohol: withdrawal state |
| **Eu10100** | [X]Mental and behav dis due to use of alcohol: harmful use |
| **Eu10200** | [X]Mental and behav dis due to use alcohol: dependence syndr |
| **Eu10600** | [X]Mental and behav dis due to use alcohol: amnesic syndrome |
| **Eu10000** | [X]Mental & behav dis due to use alcohol: acute intoxication |
| **Eu10y00** | [X]Men & behav dis due to use alcohol: oth men & behav dis |
| **Eu10700** | [X]Men & behav dis due alcoh: resid & late-onset psychot dis |

| Med code | Med term |
|---|---|
| **Eu10400** | [X]Men & behav dis due alcohl: withdrawl state with delirium |
| **Eu10z00** | [X]Ment & behav dis due use alcohol: unsp ment & behav dis |
| **E250.11** | Drunkenness NOS Current Drinker |
| **1361** | Teetotaller Non-drinker |
| **E250.13** | Inebriety NOS Current Drinker |
| **Z786200** | Drinking practice Non-specified drinker |
| **9k19.00** | Alcohol assesment declined - enhanced services admin Non-specified drinker |
| **9k19.11** | Alcohol assessment declined Non-specified drinker |

## 7- BMI codes

| Med code | Med term |
|---|---|
| **22KA.00** | Target body mass index |
| **22KB.00** | Baseline body mass index |
| **22KC.00** | Obese class I (body mass index 30.0 - 34.9) |
| **22KD.00** | Obese class II (body mass index 35.0 - 39.9) |
| **22KE.00** | Obese class III (BMI equal to or greater than 40.0) |
| **22K..00** | Body Mass Index |
| **22K1.00** | Body Mass Index normal K/M2 |
| **22K2.00** | Body Mass Index high K/M2 |
| **22K3.00** | Body Mass Index low K/M2 |
| **22K4.00** | Body mass index 25-29 - overweight |
| **22K5.00** | Body mass index 30+ - obesity |
| **22K6.00** | Body mass index less than 20 |
| **22K7.00** | Body mass index 40+ - severely obese |
| **22K8.00** | Body mass index 20-24 - normal |
| **22K9.00** | Body mass index centile |
| **22K9000** | Baseline body mass index centile |
| **22Z..00** | Height and Weight |
| **229Z.00** | O/E - height NOS |
| **229..00** | O/E - height |
| **22A..00** | O/E - weight |
| **22A7.00** | Baseline weight |
| **22AZ.00** | O/E - weight NOS |
| **66C..11** | Weight monitoring |
| **6878.11** | Weight screen |

## 8- HbA1c codes

| Med code | Med term |
|---|---|
| **42W..00** | Hb. A1C - diabetic control |
| **42W..11** | Glycosylated Hb |
| **42W..12** | Glycated haemoglobin |
| **42W1.00** | Hb. A1C < 7% - good control |

| | |
|---|---|
| **42W2.00** | Hb. A1C 7-10% - borderline |
| **42W3.00** | Hb. A1C > 10% - bad control |
| **42W4.00** | HbA1c level (DCCT aligned) |
| **42W5.00** | HbA1c levl - IFCC standardised |
| **42W5000** | HbA1c(diagnos ref rnge)IFCC st |
| **42W5100** | HbA1c(monitoring rnges)IFCC st |
| **42WZ.00** | Hb. A1C - diabetic control NOS |
| **66Ae.00** | HBA1c target |
| **66Ae000** | HbA1c target level - IFCC standardised |
| **44TL.00** | Total glycosylated haemoglobin level |
| **44TB.00** | Haemoglobin A1c level |
| **44TB000** | Haemoglobin A1c (diagnostic reference range) |
| **44TB100** | Haemoglobin A1c (monitoring ranges) |
| **44TC.00** | Haemoglobin A1 level |

## 9- Comorbidities codes

| **Depression codes** | | **Heart Failure codes** | | **Cerebrovascular disease codes** | |
|---|---|---|---|---|---|
| **Med code** | **Med term** | **Med code** | **Med term** | **Med code** | **Med term** |
| **2257.00** | O/E - depressed | 1O1..00 | Heart failure confirmed | G615.00 | Bulbar haemorrhage |
| **1B17.00** | Depressed | 8B29.00 | Cardiac failure therapy | G616.00 | External capsule haemorrhage |
| **1B17.11** | C/O - feeling depressed | G58..00 | Heart failure | G617.00 | Intracerebral haemorrhage, intraventricular |
| **1B17.12** | C/O - feeling unhappy | G58..11 | Cardiac failure | G618.00 | Intracerebral haemorrhage, multiple localised |
| **1B1N.00** | Poor self esteem | G580.00 | Congestive heart failure | G619.00 | Lobar cerebral haemorrhage |
| **1BJ..00** | Loss of confidence | G580.11 | Congestive cardiac failure | G61X.00 | Intracerebral haemorrhage in hemisphere, unspecified |
| **1BP..00** | Loss of interest | G580.12 | Right heart failure | G61X000 | Left sided intracerebral haemorrhage, unspecified |
| **1BP0.00** | Loss of interest in previously enjoyable activity | G580.13 | Right ventricular failure | G61X100 | Right sided intracerebral haemorrhage, unspecified |
| **1BQ..00** | Loss of capacity for enjoyment | G580.14 | Biventricular failure | G61z.00 | Intracerebral haemorrhage NOS |
| **1BT..00** | Depressed mood | G580000 | Acute congestive heart failure | G62..00 | Other and unspecified intracranial haemorrhage |
| **1BT..11** | Low mood | G580100 | Chronic congestive heart failure | G620.00 | Extradural haemorrhage - non-traumatic |

| Depression codes | | Heart Failure codes | | Cerebrovascular disease codes | |
|---|---|---|---|---|---|
| **1BT..12** | Sad mood | G580200 | Decompensated cardiac failure | G621.00 | Subdural haemorrhage - non-traumatic |
| **1BU..00** | Loss of hope for the future | G580300 | Compensated cardiac failure | G622.00 | Subdural haematoma - non-traumatic |
| **E118.00** | Seasonal affective disorder | G580400 | Congestive heart failure due to valvular disease | G623.00 | Subdural haemorrhage NOS |
| **E11y200** | Atypical depressive disorder | G581.00 | Left ventricular failure | G62z.00 | Intracranial haemorrhage NOS |
| **E11z200** | Masked depression | G581.11 | Asthma - cardiac | G63..11 | Infarction - precerebral |
| **E130.00** | Reactive depressive psychosis | G581.12 | Pulmonary oedema - acute | G63y000 | Cerebral infarct due to thrombosis of precerebral arteries |
| **E130.11** | Psychotic reactive depression | G581.13 | Impaired left ventricular function | G63y100 | Cerebral infarction due to embolism of precerebral arteries |
| **E135.00** | Agitated depression | G581000 | Acute left ventricular failure | G64..12 | Infarction - cerebral |
| **E200300** | Anxiety with depression | G582.00 | Acute heart failure | G640000 | Cerebral infarction due to thrombosis of cerebral arteries |
| **E204.00** | Neurotic depression reactive type | G583.00 | Heart failure with normal ejection fraction | G641000 | Cerebral infarction due to embolism of cerebral arteries |
| **E204.11** | Postnatal depression | G583.11 | HFNEF - heart failure with normal ejection fraction | G64z.00 | Cerebral infarction NOS |
| **E211200** | Depressive personality disorder | G583.12 | Heart failure with preserved ejection fraction | G64z.11 | Brainstem infarction NOS |
| **E290.00** | Brief depressive reaction | G584.00 | Right ventricular failure | G64z.12 | Cerebellar infarction |
| **E290z00** | Brief depressive reaction NOS | G58z.00 | Heart failure NOS | G64z000 | Brainstem infarction |
| **E291.00** | Prolonged depressive reaction | G58z.11 | Weak heart | G64z200 | Left sided cerebral infarction |
| **E2B0.00** | Postviral depression | G58z.12 | Cardiac failure NOS | G64z300 | Right sided cerebral infarction |
| **E2B1.00** | Chronic depression | 14A6.00 | | G64z400 | Infarction of basal ganglia |
| **Eu32.00** | [X]Depressive episode | 14AM.00 | | G665.00 | Pure motor lacunar syndrome |
| **Eu33y00** | [X]Other recurrent depressive disorders | 1736.00 | | 7017000 | Evacuation of subdural haematoma |
| **Eu33z00** | [X]Recurrent depressive disorder, unspecified | 1J60.00 | | 7032000 | Evacuation of extradural haematoma |
| **Eu33z11** | [X]Monopolar depression NOS | 388D.00 | | 1JA1000 | Suspected cerebrovascular accident |
| **Eu34100** | [X]Dysthymia | 585f.00 | | 1JA1011 | Suspected stroke |
| **Eu34111** | [X]Depressive neurosis | 585g.00 | | 8Hd6.00 | Admission to stroke unit |
| **Eu34112** | [X]Depressive personality disorder | 661M500 | | A94y600 | Rupture of syphilitic cerebral aneurysm |

| Depression codes | | Heart Failure codes | | Cerebrovascular disease codes | |
|---|---|---|---|---|---|
| **Eu34113** | [X]Neurotic depression | 662f.00 | | C154211 | Adrenocortical haemorrhage |
| **Eu34114** | [X]Persistant anxiety depression | 662g.00 | | Fyu5700 | [X]Other vascular syndroms/brain in cerebrovasculr diseases |
| **Eu3y111** | [X]Recurrent brief depressive episodes | 662h.00 | | G676000 | Cereb infarct due cerebral venous thrombosis, nonpyogenic |
| **Eu41200** | [X]Mixed anxiety and depressive disorder | 662i.00 | | G6W..00 | Cereb infarct due unsp occlus/stenos precerebr arteries |
| **Eu41211** | [X]Mild anxiety depression | 662p.00 | | G6X..00 | Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs |
| **Eu53011** | [X]Postnatal depression NOS | 662T.00 | | Gyu6000 | [X]Subarachnoid haemorrhage from other intracranial arteries |
| **Eu53012** | [X]Postpartum depression NOS | 662W.00 | | Gyu6200 | [X]Other intracerebral haemorrhage |
| **R007z13** | [D]Postoperative depression | 679W100 | | Gyu6300 | [X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs |
| **1B1U.00** | Symptoms of depression | 679X.00 | | Gyu6400 | [X]Other cerebral infarction |
| **1B1U.11** | Depressive symptoms | 67D4.00 | | Gyu6E00 | [X]Subarachnoid haemorrh from intracranial artery, unspecif |
| **62T1.00** | Puerperal depression | 8CeC.00 | | Gyu6F00 | [X]Intracerebral haemorrhage in hemisphere, unspecified |
| **8BK0.00** | Depression management programme | 8CL3.00 | | Gyu6G00 | [X]Cereb infarct due unsp occlus/stenos precerebr arteries |
| **9H90.00** | Depression annual review | 8CMK.00 | | S62..00 | Cerebral haemorrhage following injury |
| **9H91.00** | Depression medication review | 8CMW800 | | S62..11 | Extradural haemorrhage following injury |
| **9H92.00** | Depression interim review | 8H2S.00 | | S62..13 | Subdural haemorrhage following injury |
| **E112.00** | Single major depressive episode | 8HBE.00 | | S62..14 | Traumatic cerebral haemorrhage |
| **E112.11** | Agitated depression | 8Hg8.00 | | S622.00 | Closed traumatic subdural haemorrhage |
| **E112.12** | Endogenous depression first episode | 8HgD.00 | | S623.00 | Open traumatic subdural haemorrhage |
| **E112.13** | Endogenous depression first episode | 8HHb.00 | | S624.00 | Closed traumatic extradural haemorrhage |

| Depression codes | | Heart Failure codes | | Cerebrovascular disease codes | |
|---|---|---|---|---|---|
| **E112.14** | Endogenous depression | 8HHz.00 | | S624.11 | Epidural haematoma following injury |
| **E112000** | Single major depressive episode, unspecified | 8Hk0.00 | | S625.00 | Open traumatic extradural haemorrhage |
| **E112100** | Single major depressive episode, mild | 8HTL.00 | | S626.00 | Epidural haemorrhage |
| **E112200** | Single major depressive episode, moderate | 8HTL000 | | S628.00 | Traumatic subdural haemorrhage |
| **E112300** | Single major depressive episode, severe, without psychosis | 8IE0.00 | | S629.00 | Traumatic subdural haematoma |
| **E112400** | Single major depressive episode, severe, with psychosis | 8IE1.00 | | S629000 | Traumatic subdural haematoma without open intracranial wound |
| **E112z00** | Single major depressive episode NOS | 9h1..00 | | S629100 | Traumatic subdural haematoma with open intracranial wound |
| **E113.00** | Recurrent major depressive episode | 9h11.00 | | S62A.00 | Traumatic extradural haematoma |
| **E113.11** | Endogenous depression - recurrent | 9h12.00 | | S62A100 | Traumatic extradural haematoma with open intracranial wound |
| **E113000** | Recurrent major depressive episodes, unspecified | 9hH..00 | | S62z.00 | Cerebral haemorrhage following injury NOS |
| **E113100** | Recurrent major depressive episodes, mild | 9hH0.00 | | S63..00 | Other cerebral haemorrhage following injury |
| **E113200** | Recurrent major depressive episodes, moderate | 9hH1.00 | | S63z.00 | Other cerebral haemorrhage following injury NOS |
| **E113300** | Recurrent major depressive episodes, severe, no psychosis | 9N0k.00 | | G66..11 | CVA unspecified |
| **E113400** | Recurrent major depressive episodes, severe, with psychosis | 9N2p.00 | | G66..00 | Stroke and cerebrovascular accident unspecified |
| **E113700** | Recurrent depression | 9N4s.00 | | G64..11 | CVA - cerebral artery occlusion |
| **E113z00** | Recurrent major depressive episode NOS | 9N4w.00 | | 14A7.12 | H/O: stroke |
| **E2B..00** | Depressive disorder NEC | 9N6T.00 | | G66..13 | CVA - Cerebrovascular accident unspecified |
| **Eu32000** | [X]Mild depressive episode | 9On..00 | | G64..13 | Stroke due to cerebral arterial occlusion |
| **Eu32100** | [X]Moderate depressive episode | 9On0.00 | | G66..12 | Stroke unspecified |

| Depression codes | | Heart Failure codes | | Cerebrovascular disease codes | |
|---|---|---|---|---|---|
| **Eu32200** | [X]Severe depressive episode without psychotic symptoms | 9On1.00 | | 14A7.11 | H/O: CVA |
| **Eu32211** | [X]Single episode agitated depressn w'out psychotic symptoms | 9On2.00 | | G61..11 | CVA - cerebrovascular accid due to intracerebral haemorrhage |
| **Eu32212** | [X]Single episode major depression w'out psychotic symptoms | 9On3.00 | | ZV12512 | [V]Personal history of cerebrovascular accident (CVA) |
| **Eu32213** | [X]Single episode vital depression w'out psychotic symptoms | 9On4.00 | | G667.00 | Left sided CVA |
| **Eu32300** | [X]Severe depressive episode with psychotic symptoms | 9Or..00 | | G663.00 | Brain stem stroke syndrome |
| **Eu32311** | [X]Single episode of major depression and psychotic symptoms | 9Or0.00 | | 662M.00 | Stroke monitoring |
| **Eu32313** | [X]Single episode of psychotic depression | 9Or1.00 | | 9h2..00 | Exception reporting: stroke quality indicators |
| **Eu32314** | [X]Single episode of reactive depressive psychosis | 9Or2.00 | | 9h21.00 | Excepted from stroke quality indicators: Patient unsuitable |
| **Eu32400** | [X]Mild depression | 9Or3.00 | | 9h22.00 | Excepted from stroke quality indicators: Informed dissent |
| **Eu32y00** | [X]Other depressive episodes | 9Or4.00 | | G668.00 | Right sided CVA |
| **Eu32y11** | [X]Atypical depression | 9Or5.00 | | 14AB.00 | H/O: TIA |
| **Eu32y12** | [X]Single episode of masked depression NOS | G1yz100 | | 8HBJ.00 | Stroke / transient ischaemic attack referral |
| **Eu32z00** | [X]Depressive episode, unspecified | G210.00 | | G664.00 | Cerebellar stroke syndrome |
| **Eu32z11** | [X]Depression NOS | G210100 | | 662e.00 | Stroke/CVA annual review |
| **Eu32z12** | [X]Depressive disorder NOS | G211100 | | 9N4X.00 | DNA - Did not attend stroke clinic |
| **Eu32z13** | [X]Prolonged single episode of reactive depression | G21z100 | | 8HTQ.00 | Referral to stroke clinic |
| **Eu32z14** | [X] Reactive depression NOS | G230.00 | | ZV12511 | [V]Personal history of stroke |
| **Eu33.00** | [X]Recurrent depressive disorder | G232.00 | | 388I.00 | Stroke risk |
| **Eu33.11** | [X]Recurrent episodes of depressive reaction | G234.00 | | 6F...00 | Stroke prevention |
| **Eu33.12** | [X]Recurrent episodes of psychogenic depression | G400.00 | | 9Om0.00 | Stroke/transient ischaemic attack monitoring first letter |
| **Eu33.13** | [X]Recurrent episodes of reactive depression | G41z.11 | | 662o.00 | Haemorrhagic stroke monitoring |
| **Eu33.14** | [X]Seasonal depressive disorder | G554000 | | 6F...11 | CVA prevention |

| Depression codes | | Heart Failure codes | | Cerebrovascular disease codes | |
|---|---|---|---|---|---|
| **Eu33.15** | [X]SAD - Seasonal affective disorder | G554011 | | 9Om..00 | Stroke/transient ischaemic attack monitoring administration |
| **Eu33000** | [X]Recurrent depressive disorder, current episode mild | G557100 | | 9N0p.00 | Seen in stroke clinic |
| **Eu33100** | [X]Recurrent depressive disorder, current episode moderate | G5y4z00 | | 14A7.00 | H/O: CVA/stroke |
| **Eu33200** | [X]Recurr depress disorder cur epi severe without psyc sympt | G5yy900 | | 9Om1.00 | Stroke/transient ischaemic attack monitoring second letter |
| **Eu33211** | [X]Endogenous depression without psychotic symptoms | G5yyA00 | | 9Om2.00 | Stroke/transient ischaemic attack monitoring third letter |
| **Eu33212** | [X]Major depression, recurrent without psychotic symptoms | G5yyB00 | | ZLEP.00 | Discharge from stroke serv |
| **Eu33214** | [X]Vital depression, recurrent without psychotic symptoms | Q48y100 | | L440.11 | CVA - cerebrovascular accident in the puerperium |
| **Eu33300** | [X]Recurrent depress disorder cur epi severe with psyc symp | R2y1000 | | 9Om3.00 | Stroke/transient ischaemic attack monitoring verbal invitati |
| **Eu33311** | [X]Endogenous depression with psychotic symptoms | SP11111 | | 13YA.00 | Stroke group member |
| **Eu33313** | [X]Recurr severe episodes/major depression+psychotic symptom | ZRad.00 | | 7P24200 | Delivery of rehabilitation for stroke |
| **Eu33314** | [X]Recurr severe episodes/psychogenic depressive psychosis | | | L440.12 | Stroke in the puerperium |
| **Eu33315** | [X]Recurrent severe episodes of psychotic depression | | | 8HHM.00 | Ref to multidisciplinary stroke function improvement service |
| **Eu33y00** | [X]Other recurrent depressive disorders | | | C315100 | Mitochond encephalopathy, lact acidosis & strokelike episode |
| **Eu33z00** | [X]Recurrent depressive disorder, unspecified | | | 14AK.00 | H/O: Stroke in last year |
| **Eu33z11** | [X]Monopolar depression NOS | | | 9Om4.00 | Stroke/transient ischaemic attack monitoring telephone invte |
| **Eu3y111** | [X]Recurrent brief depressive episodes | | | G6...00 | Cerebrovascular disease |
| **1465.00** | H/O: depression | | | G60..00 | Subarachnoid haemorrhage |

| Depression codes | | Heart Failure codes | | Cerebrovascular disease codes | |
|---|---|---|---|---|---|
| **E113500** | Recurrent major depressive episodes,partial/unspec remission | | | G600.00 | Ruptured berry aneurysm |
| **E113600** | Recurrent major depressive episodes, in full remission | | | G601.00 | Subarachnoid haemorrhage from carotid siphon and bifurcation |
| **Eu32312** | [X]Single episode of psychogenic depressive psychosis | | | G602.00 | Subarachnoid haemorrhage from middle cerebral artery |
| **Eu32500** | [X]Major depression, mild | | | G603.00 | Subarachnoid haemorrhage from anterior communicating artery |
| **Eu32600** | [X]Major depression, moderately severe | | | G604.00 | Subarachnoid haemorrhage from posterior communicating artery |
| **Eu32700** | [X]Major depression, severe without psychotic symptoms | | | G605.00 | Subarachnoid haemorrhage from basilar artery |
| **Eu32800** | [X]Major depression, severe with psychotic symptoms | | | G606.00 | Subarachnoid haemorrhage from vertebral artery |
| **Eu32900** | [X]Single major depr ep, severe with psych, psych in remiss | | | G60X.00 | Subarachnoid haemorrh from intracranial artery, unspecif |
| **Eu32A00** | [X]Recurr major depr ep, severe with psych, psych in remiss | | | G60z.00 | Subarachnoid haemorrhage NOS |
| **Eu33213** | [X]Manic-depress psychosis,depressd,no psychotic symptoms | | | G61..00 | Intracerebral haemorrhage |
| **Eu33312** | [X]Manic-depress psychosis,depressed type+psychotic symptoms | | | G61..12 | Stroke due to intracerebral haemorrhage |
| **Eu33316** | [X]Recurrent severe episodes/reactive depressive psychosis | | | G610.00 | Cortical haemorrhage |
| **Eu33400** | [X]Recurrent depressive disorder, currently in remission | | | G611.00 | Internal capsule haemorrhage |
| | | | | G612.00 | Basal nucleus haemorrhage |
| | | | | G613.00 | Cerebellar haemorrhage |
| | | | | G614.00 | Pontine haemorrhage |

| Hypertension codes | | Cerebrovascular accident codes | | Myocardial infarction codes | |
|---|---|---|---|---|---|
| **Med code** | **Med term** | **Med code** | **Med term** | **Med code** | **Med term** |
| **6627.00** | Good hypertension control | G66..11 | CVA unspecified | 1J61.00 | Suspected ischaemic heart disease |

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|---|---|---|---|---|---|
| **6628.00** | Poor hypertension control | G66..00 | Stroke and cerebrovascular accident unspecified | 3222.00 | ECG:shows myocardial ischaemia |
| **6629.00** | Hypertension:follow-up default | G64..11 | CVA - cerebral artery occlusion | 3232.00 | ECG: old myocardial infarction |
| **2126100** | Hypertension resolved | 14A7.12 | H/O: stroke | 3233.00 | ECG: antero-septal infarct. |
| **14A2.00** | H/O: hypertension | G66..13 | CVA - Cerebrovascular accident unspecified | 3234.00 | ECG:posterior/inferior infarct |
| **1JD..00** | Suspected hypertension | G64..13 | Stroke due to cerebral arterial occlusion | 3235.00 | ECG: subendocardial infarct |
| **212K.00** | Hypertension resolved | G66..12 | Stroke unspecified | 3236.00 | ECG: lateral infarction |
| **246M.00** | White coat hypertension | 14A7.11 | H/O: CVA | 5533.00 | Angiocardiography abnormal |
| **662..12** | Hypertension monitoring | **Obesity codes** | | | 5543.00 |
| **662b.00** | Moderate hypertension control | **Med code** | **Med term** | 7920.00 | Saphenous vein graft replacement of coronary artery |
| **662c.00** | Hypertension six-month review | 1444 | H/O: obesity | 7920.11 | Saphenous vein graft bypass of coronary artery |
| **662d.00** | Hypertension annual review | 222A.00 | O/E - obese | 7921.00 | Other autograft replacement of coronary artery |
| **662F.00** | Hypertension treatm. started | 22A5.11 | O/E - obese | 7921.11 | Other autograft bypass of coronary artery |
| **662H.00** | Hypertension treatm.stopped | 22K5.00 | Body mass index 30+ - obesity | 7922.00 | Allograft replacement of coronary artery |
| **662O.00** | On treatment for hypertension | 22K7.00 | Body mass index 40+ - severely obese | 7922.11 | Allograft bypass of coronary artery |
| **662P.00** | Hypertension monitoring | 22KC.00 | Obese class I (body mass index 30.0 - 34.9) | 7923.00 | Prosthetic replacement of coronary artery |
| **7Q01.00** | High cost hypertension drugs | 22KD.00 | Obese class II (body mass index 35.0 - 39.9) | 7923.11 | Prosthetic bypass of coronary artery |
| **8CR4.00** | Hypertension clinical management plan | 22KE.00 | Obese class III (BMI equal to or greater than 40.0) | 7924.00 | Revision of bypass for coronary artery |
| **8HT5.00** | Referral to hypertension clinic | 66C..00 | Obesity monitoring | 7925.00 | Connection of mammary artery to coronary artery |
| **8I3N.00** | Hypertension treatment refused | 66C1.00 | Initial obesity assessment | 7925.11 | Creation of bypass from mammary artery to coronary artery |
| **9h3..00** | Exception reporting: hypertension quality indicators | 66C2.00 | Follow-up obesity assessment | 7926.00 | Connection of other thoracic artery to coronary artery |
| **9h31.00** | Excepted from hypertension qual indicators: Patient unsuit | 66C4.00 | Has seen dietician - obesity | 7928.00 | Transluminal balloon angioplasty of coronary artery |

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|---|---|---|---|---|---|
| **9h32.00** | Excepted from hypertension qual indicators: Informed dissent | 66C6.00 | Treatment of obesity started | 7928.11 | Percutaneous balloon coronary angioplasty |
| **9N03.00** | Seen in hypertension clinic | 66CE.00 | Reason for obesity therapy - occupational | 3213111 | Positive exercise ECG test |
| **9N1y200** | Seen in hypertension clinic | 66Ce.00 | Telehealth obesity monitoring | 7920000 | Saphenous vein graft replacement of one coronary artery |
| **9N4L.00** | DNA - Did not attend hypertension clinic | 66CM.00 | Risk health associ overweight and obesity, at increased risk | 7920100 | Saphenous vein graft replacement of two coronary arteries |
| **9OI..00** | Hypertension monitoring admin. | 66CN.00 | Risk health associated overweight and obesity, at high risk | 7920200 | Saphenous vein graft replacement of three coronary arteries |
| **9OI..11** | Hypertension clinic admin. | 66CP.00 | Risk health associ overweight and obesity, at very high risk | 7920300 | Saphenous vein graft replacement of four+ coronary arteries |
| **9OI1.00** | Attends hypertension monitor. | 66CS.00 | Inter-risk hlth overwght obesity adv diet phys act cons drug | 7921000 | Autograft replacement of one coronary artery NEC |
| **9OI2.00** | Refuses hypertension monitor. | 66CX.00 | Obesity multidisciplinary case review | 7921100 | Autograft replacement of two coronary arteries NEC |
| **9OIA.00** | Hypertension monitor.chck done | 66CZ.00 | Obesity monitoring NOS | 7921200 | Autograft replacement of three coronary arteries NEC |
| **9OIA.11** | Hypertension monitored | 8CV7.00 | Anti-obesity drug therapy commenced | 7921300 | Autograft replacement of four of more coronary arteries NEC |
| **G20..00** | Essential hypertension | 8T11.00 | Referral to multidisciplinary obesity clinic | 7922000 | Allograft replacement of one coronary artery |
| **G200.00** | Malignant essential hypertension | 9OK..00 | Obesity monitoring admin. | 7922100 | Allograft replacement of two coronary arteries |
| **G201.00** | Benign essential hypertension | 9OK..11 | Obesity clinic administration | 7922200 | Allograft replacement of three coronary arteries |
| **G202.00** | Systolic hypertension | 9OK1.00 | Attends obesity monitoring | 7922300 | Allograft replacement of four or more coronary arteries |
| **G203.00** | Diastolic hypertension | 9OK2.00 | Refuses obesity monitoring | 7923000 | Prosthetic replacement of one coronary artery |
| **G20z.00** | Essential hypertension NOS | 9OK3.00 | Obesity monitoring default | 7923100 | Prosthetic replacement of two coronary arteries |
| **G20z.11** | Hypertension NOS | 9OK4.00 | Obesity monitoring 1st letter | 7923200 | Prosthetic replacement of three coronary arteries |
| **G241.00** | Secondary benign hypertension | 9OK5.00 | Obesity monitoring 2nd letter | 7923300 | Prosthetic replacement of four or more coronary arteries |
| **G241000** | Secondary benign renovascular hypertension | 9OK6.00 | Obesity monitoring 3rd letter | 7924000 | Revision of bypass for one coronary artery |

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| **G241z00** | Secondary benign hypertension NOS | 9OK7.00 | Obesity monitoring verbal inv. | 7924100 | Revision of bypass for two coronary arteries |
| **G24z100** | Hypertension secondary to drug | 9OK8.00 | Obesity monitor phone invite | 7924200 | Revision of bypass for three coronary arteries |
| **L122.00** | Other pre-existing hypertension in preg/childbirth/puerp | 9OKA.00 | Obesity monitoring check done | 7925000 | Double anastomosis of mammary arteries to coronary arteries |
| **L122000** | Other pre-existing hypertension in preg/childb/puerp unspec | 9OKZ.00 | Obesity monitoring admin.NOS | 7925100 | Double implant of mammary arteries into coronary arteries |
| **L122100** | Other pre-existing hypertension in preg/childb/puerp - deliv | C38..00 | Obesity and other hyperalimentation | 7925300 | Single anastomosis of mammary artery to coronary artery NEC |
| **L122300** | Other pre-exist hypertension in preg/childb/puerp-not deliv | C380.00 | Obesity | 7925311 | LIMA single anastomosis |
| **L122z00** | Other pre-existing hypertension in preg/childb/puerp NOS | C380000 | Obesity due to excess calories | 7925312 | RIMA single anastomosis |
| **L127.00** | Pre-eclampsia or eclampsia with pre-existing hypertension | C380100 | Drug-induced obesity | 7925400 | Single implantation of mammary artery into coronary artery |
| **L127z00** | Pre-eclampsia or eclampsia + pre-existing hypertension NOS | C380200 | Extreme obesity with alveolar hypoventilation | 7926000 | Double anastom thoracic arteries to coronary arteries NEC |
| **L128.00** | Pre-exist hypertension compl preg childbirth and puerperium | C380300 | Morbid obesity | 7926200 | Single anastomosis of thoracic artery to coronary artery NEC |
| **6146200** | Hypertension induced by oral contraceptive pill | C380400 | Central obesity | 7926300 | Single implantation thoracic artery into coronary artery NEC |
| **G24zz00** | secondary hypertension nos | C380500 | Generalised obesity | 7927500 | Open angioplasty of coronary artery |
| **G25..00** | stage 1 hypertension (nice - nat ins for hth clin ex | C380600 | Adult onset obesity | 7928000 | Percut transluminal balloon angioplasty one coronary artery |
| **G25..11** | stage 1 hypertension | C380700 | Lifelong obesity | 7928100 | Percut translum balloon angioplasty mult coronary arteries |
| **G26..00** | severe hypertension (nat inst for health clinical ex | C38y011 | Obesity hypoventilation syndrome | 7928200 | Percut translum balloon angioplasty bypass graft coronary a |
| **G26..11** | severe hypertension | C38z.00 | Obesity and other hyperalimentation NOS | 7928300 | Percut translum cutting balloon angioplasty coronary artery |
| **G27..00** | hypertension resistant to drug therapy | C38z000 | Simple obesity NOS | 7929000 | Percutaneous transluminal laser coronary angioplasty |

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|---|---|---|---|---|---|
| **G28..00** | stage 2 hypertension (nice - nat ins for hth clin ex | Cyu7.00 | [X]Obesity and other hyperalimentation | 7929300 | Rotary blade coronary angioplasty |
| **G2y..00** | other specified hypertensive disease | Cyu7000 | [X]Other obesity | 7929400 | Insertion of coronary artery stent |
| **G2z..00** | hypertensive disease nos | ZC2CM00 | Dietary advice for obesity | 7929500 | Insertion of drug-eluting coronary artery stent |
| **G672.00** | hypertensive encephalopathy | ZV65319 | [V]Dietary counselling in obesity | 7929600 | Percutaneous transluminal atherectomy of coronary artery |
| **G672.11** | hypertensive crisis | 66C5.00 | Treatment of obesity changed | 14A3.00 | H/O: myocardial infarct <60 |
| **Gyu2.00** | [x]hypertensive diseases | **Dyslipidaemia codes** | | | 14A4.00 |
| **Gyu2000** | [x]other secondary hypertension | **Med code** | **Med term** | 14A5.00 | H/O: angina pectoris |
| **Gyu2100** | [x]hypertension secondary to other renal disorders | 13B3.00 | Low cholesterol diet | 14AA.00 | H/O: heart disease NOS |
| **6624.00** | borderline hyperten:yearly obs | 1W2..00 | Probable familial hypercholesterolaemia | 14AH.00 | H/O: Myocardial infarction in last year |
| **662G.00** | hypertensive treatm.changed | 44P3.00 | Serum cholesterol raised | 14AJ.00 | H/O: Angina in last year |
| **7Q01y00** | other specified high cost hypertension drugs | 44P4.00 | Serum cholesterol very high | 14AL.00 | H/O: Treatment for ischaemic heart disease |
| **8B26.00** | antihypertensive therapy | 8CA4700 | Patient advised re low cholesterol diet | 14AT.00 | Chest pain on exertion |
| **8BL0.00** | patient on maximal tolerated antihypertensive therap | C320.00 | Pure hypercholesterolaemia | 14AW.00 | H/O acute coronary syndrome |
| **F404200** | blind hypertensive eye | C320.11 | Familial hypercholesterolaemia | 182A.00 | Chest pain on exertion |
| **F421300** | hypertensive retinopathy | C320000 | Familial hypercholesterolaemia | 187..00 | Frequency of angina |
| **G2...00** | hypertensive disease | C320y00 | Other specified pure hypercholesterolaemia | 1J61.00 | Suspected ischaemic heart disease |
| **G2...11** | bp - hypertensive disease | C320z00 | Pure hypercholesterolaemia NOS | 322..00 | ECG: myocardial ischaemia |
| **G20..11** | high blood pressure | C329.00 | Hypercholesterolaemia | 322Z.00 | ECG: myocardial ischaemia NOS |
| **G20..12** | primary hypertension | **Chronic kidney disease** | | | 323..00 |
| **G21..00** | hypertensive heart disease | **Med code** | **Med term** | 323Z.00 | ECG: myocardial infarct NOS |
| **G210.00** | malignant hypertensive heart disease | 451F.00 | Glomerular filtration rate | 32B..00 | ECG: Q-wave |

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| **G210000** | malignant hypertensive heart disease without ccf | 451E.00 | GFR calculated abbreviated MDRD | 32B2.00 | ECG: Q-wave abnormal |
| **G210100** | malignant hypertensive heart disease with ccf | 451G.00 | GFR calculated abbreviated MDRD adj for African Americ orign | 32B3.00 | ECG: Q-wave pathological |
| **G210z00** | malignant hypertensive heart disease nos | K05..00 | Chronic renal failure | 32BZ.00 | ECG: Q-wave NOS |
| **G211.00** | benign hypertensive heart disease | K050.00 | End-stage renal failure | 32E4.00 | ECG: S-T depression |
| **G211000** | benign hypertensive heart disease without ccf | K0D..00 | End-stage renal disease | 44H3.00 | Cardiac enzymes abnormal |
| **G211100** | benign hypertensive heart disease with ccf | 1Z13.00 | Chronic kidney disease stage 4 | 44H3000 | Cardiac enzymes abnormal - first set |
| **G211z00** | benign hypertensive heart disease nos | 1Z12.00 | Chronic kidney disease stage 3 | 44HJ.00 | Plasma creatinine phosphokinase MB isoenzyme level |
| **G21z.00** | hypertensive heart disease nos | 1Z14.00 | Chronic kidney disease stage 5 | 44MH.00 | Plasma troponin T level |
| **G21z000** | hypertensive heart disease nos without ccf | 66i..00 | Chronic kidney disease monitoring | 44p2.00 | Cardiac troponin positive |
| **G21z011** | cardiomegaly - hypertensive | K05..12 | End-stage renal failure | 5C11.00 | Radionuclide heart study abnormal |
| **G21z100** | hypertensive heart disease nos with ccf | 1Z1B.00 | Chronic kidney disease stage 3 with proteinuria | 661M000 | Angina self-management plan agreed |
| **G21zz00** | hypertensive heart disease nos | 1Z15.00 | Chronic kidney disease stage 3A | 662..00 | Cardiac disease monitoring |
| **G22..00** | hypertensive renal disease | 1Z1H.00 | Chronic kidney disease stage 4 with proteinuria | 662..11 | Heart disease monitoring |
| **G22..11** | nephrosclerosis | 1Z1C.00 | Chronic kidney disease stage 3 without proteinuria | 662K.00 | Angina control |
| **G220.00** | malignant hypertensive renal disease | 1Z1E.00 | Chronic kidney disease stage 3A without proteinuria | 662K000 | Angina control - good |
| **G221.00** | benign hypertensive renal disease | 1Z1G.00 | Chronic kidney disease stage 3B without proteinuria | 662K100 | Angina control - poor |
| **G222.00** | hypertensive renal disease with renal failure | 1Z1F.00 | Chronic kidney disease stage 3B with proteinuria | 662K200 | Angina control - improving |
| **G22z.00** | hypertensive renal disease nos | 1Z16.00 | Chronic kidney disease stage 3B | 662K300 | Angina control - worsening |
| **G22z.11** | renal hypertension | 1Z1L.00 | Chronic kidney disease stage 5 without proteinuria | 662Kz00 | Angina control NOS |
| **G23..00** | hypertensive heart and renal disease | 1Z1J.00 | Chronic kidney disease stage 4 without proteinuria | 662N.00 | CHD monitoring |

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| **G230.00** | malignant hypertensive heart and renal disease | 1Z1D.00 | Chronic kidney disease stage 3A with proteinuria | 662Z.00 | Cardiac disease monitoring NOS |
| **G231.00** | benign hypertensive heart and renal disease | 1Z1K.00 | Chronic kidney disease stage 5 with proteinuria | 66f..00 | Cardiovascular disease monitoring |
| **G232.00** | hypertensive heart&renal dis wth (congestive) heart | **Myocardial infarction codes** | | 66f1.00 | Cardiovascular disease interim monitoring |
| **G233.00** | hypertensive heart and renal disease with renal fail | **Med code** | **Med term** | 6A2..00 | Coronary heart disease annual review |
| **G234.00** | hyperten heart&renal dis+both(congestv) heart and ren | 7924y00 | Other specified revision of bypass for coronary artery | 6A4..00 | Coronary heart disease review |
| **G23z.00** | hypertensive heart and renal disease nos | 7924z00 | Revision of bypass for coronary artery NOS | 792..11 | Coronary artery bypass graft operations |
| **G24..00** | secondary hypertension | 7925y00 | Connection of mammary artery to coronary artery OS | 7920y00 | Saphenous vein graft replacement of coronary artery OS |
| **G240.00** | secondary malignant hypertension | 7925z00 | Connection of mammary artery to coronary artery NOS | 7920z00 | Saphenous vein graft replacement coronary artery NOS |
| **G240000** | secondary malignant renovascular hypertension | 7926z00 | Connection of other thoracic artery to coronary artery NOS | 7A56000 | Percutaneous transluminal arterial thrombolysis reconstruct |
| **G240z00** | secondary malignant hypertension nos | 7928y00 | Transluminal balloon angioplasty of coronary artery OS | 7A56400 | Percutaneous transluminal balloon angioplasty of artery |
| **G244.00** | hypertension secondary to endocrine disorders | 7928z00 | Transluminal balloon angioplasty of coronary artery NOS | 7A6G100 | Peroperative angioplasty |
| **G24z.00** | secondary hypertension nos | 792B000 | Endarterectomy of coronary artery NEC | 7A6H300 | Prosthetic graft patch angioplasty |
| **G24z000** | secondary renovascular hypertension nos | 792C.00 | Other replacement of coronary artery | 7A6H400 | Percutaneous transluminal angioplasty of vascular graft |
| **Arrhythmias codes** | | 792C000 | Replacement of coronary arteries using multiple methods | 889A.00 | Diab mellit insulin-glucose infus acute myocardial infarct |
| **Med code** | **Med term** | 792Cy00 | Other specified replacement of coronary artery | 8B27.00 | Antianginal therapy |
| **G57..00** | Cardiac dysrhythmias | 792Cz00 | Replacement of coronary artery NOS | 8B3k.00 | Coronary heart disease medication review |
| **G57..11** | Cardiac arrhythmias | 792D.00 | Other bypass of coronary artery | 8BGC.00 | Long-term dual antiplatelet drug therapy indicated |

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| **G570.00** | Paroxysmal supraventricular tachycardia | 792Dy00 | Other specified other bypass of coronary artery | 8CMP.00 | Coronary heart disease care plan |
| **G570000** | Paroxysmal atrial tachycardia | 792Dz00 | Other bypass of coronary artery NOS | 8F9..00 | Cardiac rehabilitation |
| **G570100** | Paroxysmal atrioventricular tachycardia | 793G.00 | Perc translumin balloon angioplasty stenting coronary artery | 8F90.00 | Cardiac rehabilitation - phase 1 |
| **G570200** | Paroxysmal junctional tachycardia | 793G000 | Perc translum ball angio insert 1-2 drug elut stents cor art | 8F91.00 | Cardiac rehabilitation - phase 2 |
| **G570300** | Paroxysmal nodal tachycardia | 793G100 | Perc tran ball angio ins 3 or more drug elut stents cor art | 8F92.00 | Cardiac rehabilitation - phase 3 |
| **G570z00** | Paroxysmal supraventricular tachycardia NOS | 793G200 | Perc translum balloon angioplasty insert 1-2 stents cor art | 8IEY.00 | Chronic obstructive pulmon dis wr self managem plan declined |
| **G571.00** | Paroxysmal ventricular tachycardia | 793G300 | Percutaneous cor balloon angiop 3 more stents cor art NEC | 8L40.00 | Coronary artery bypass graft operation planned |
| **G571.11** | Ventricular tachycardia | G5yz.00 | Other heart disease NOS | 8L41.00 | Coronary angioplasty planned |
| **G572.00** | Paroxysmal tachycardia unspecified | G5z..00 | Heart disease NOS | 8LF..00 | Coronary angiography planned |
| **G572000** | Essential paroxysmal tachycardia | Gyu3.00 | [X]Ischaemic heart diseases | 8T04.00 | Referral to Angina Plan self-management programme |
| **G572z00** | Paroxysmal tachycardia NOS | Gyu3000 | [X]Other forms of angina pectoris | 9Ob..00 | Coronary heart disease monitoring administration |
| **G573.00** | Atrial fibrillation and flutter | Gyu3200 | [X]Other forms of acute ischaemic heart disease | 9Ob0.00 | Attends coronary heart disease monitoring |
| **G573000** | Atrial fibrillation | Gyu3300 | [X]Other forms of chronic ischaemic heart disease | 9Ob1.00 | Refuses coronary heart disease monitoring |
| **G573100** | Atrial flutter | Z677.00 | [X]Subsequent myocardial infarction of unspecified site | 9Ob2.00 | Coronary heart disease monitoring default |
| **G573200** | Paroxysmal atrial fibrillation | ZL22200 | [X]Other forms of heart disease | 9Ob3.00 | Coronary heart disease monitoring 1st letter |
| **G573300** | Non-rheumatic atrial fibrillation | ZV45700 | [X]Atherosclerosis of other arteries | 9Ob4.00 | Coronary heart disease monitoring 2nd letter |
| **G573400** | Permanent atrial fibrillation | ZV45800 | Mechanical complication of coronary bypass | 9Ob5.00 | Coronary heart disease monitoring 3rd letter |
| **G573500** | Persistent atrial fibrillation | ZV45K11 | Cardiac rehabilitation class | 9Ob6.00 | Coronary heart disease monitoring verbal invitation |
| **G573600** | Paroxysmal atrial flutter | ZV45L00 | Under care of cardiac rehabilitation nurse | 9Ob8.00 | Coronary heart disease monitoring check done |

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| **G573700** | Chronic atrial fibrillation | ZV45700 | [V]Presence of aortocoronary bypass graft | 9Ob9.00 | Coronary heart disease monitoring telephone invite |
| **G573800** | Typical atrial flutter | ZV45800 | [V]Presence of coronary angioplasty implant and graft | G....12 | Cardiac diseases |
| **G573900** | Atypical atrial flutter | ZV45K00 | [V]Presence of coronary artery bypass graft | G....13 | Heart diseases |
| **G573z00** | Atrial fibrillation and flutter NOS | ZV45K11 | [V]Presence of coronary artery bypass graft - CABG | G5...00 | Other forms of heart disease |
| **G574.00** | Ventricular fibrillation and flutter | ZV45L00 | [V]Status following coronary angioplasty NOS | G501.00 | Post infarction pericarditis |
| **G574000** | Ventricular fibrillation | ZV57900 | [V]Cardiac rehabilitation | G574000 | Ventricular fibrillation |
| **G574011** | Cardiac arrest-ventricular fibrillation | 7929100 | Percut transluminal coronary thrombolysis with streptokinase | G5y..00 | Other specified heart disease |
| **G574100** | Ventricular flutter | 7929111 | Percut translum coronary thrombolytic therapy-streptokinase | G5yyz00 | Other ill-defined heart disease NOS |
| **G574z00** | Ventricular fibrillation and flutter NOS | 7A54700 | Percutaneous transluminal thrombolysis of artery | 8IEY.00 | Chronic obstructive pulmon dis wr self managem plan declined |
| **G575.00** | Cardiac arrest | 7A6S300 | Percutaneous transluminal venous thrombolysis NEC | 8L40.00 | Coronary artery bypass graft operation planned |
| **G575.11** | Cardio-respiratory arrest | G3...00 | Ischaemic heart disease | 8L41.00 | Coronary angioplasty planned |
| **G575.12** | Asystole | G3...11 | Arteriosclerotic heart disease | 8LF..00 | Coronary angiography planned |
| **G575000** | Cardiac arrest with successful resuscitation | G3...12 | Atherosclerotic heart disease | 8H7v.00 | Referral to cardiac rehabilitation nurse |
| **G575100** | Sudden cardiac death, so described | G3...13 | IHD - Ischaemic heart disease | 8I37.00 | Coronary heart disease monitoring refused |
| **G575200** | Electromechanical dissociation with successful resuscitation | G30..00 | Acute myocardial infarction | 8I3a.00 | Cardiac rehabilitation declined |
| **G575300** | Electromechanical dissociation | G30..11 | Attack - heart | 8H2V.00 | Admit ischaemic heart disease emergency |
| **G575z00** | Cardiac arrest, unspecified | G30..12 | Coronary thrombosis | G30..14 | Heart attack |
| **G576.00** | Ectopic beats | G30..13 | Cardiac rupture following myocardial infarction (MI) | G30..15 | MI - acute myocardial infarction |

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| **G576.11** | Premature beats | G305.00 | Lateral myocardial infarction NOS | G30..16 | Thrombosis - coronary |
| **G576000** | Ectopic beats unspecified | G306.00 | True posterior myocardial infarction | G30..17 | Silent myocardial infarction |
| **G576011** | Extrasystoles | G307.00 | Acute subendocardial infarction | G300.00 | Acute anterolateral infarction |
| **G576100** | Supraventricular ectopic beats | G307000 | Acute non-Q-wave infarction | G301.00 | Other specified anterior myocardial infarction |
| **G576200** | Ventricular ectopic beats | G307100 | Acute non-ST segment elevation myocardial infarction | G301000 | Acute anteroapical infarction |
| **G576300** | Atrial premature depolarization | G308.00 | Inferior myocardial infarction NOS | G301100 | Acute anteroseptal infarction |
| **G576400** | Junctional premature depolarization | G309.00 | Acute Q-wave infarct | G301z00 | Anterior myocardial infarction NOS |
| **G576500** | Ventricular premature depolarization | G30A.00 | Mural thrombosis | G302.00 | Acute inferolateral infarction |
| **G576z00** | Ectopic beats NOS | G30B.00 | Acute posterolateral myocardial infarction | G303.00 | Acute inferoposterior infarction |
| **G577.00** | Sinus arrhythmia | G30X.00 | Acute transmural myocardial infarction of unspecif site | G304.00 | Posterior myocardial infarction NOS |
| **G578.00** | Atrial standstill | G30X000 | Acute ST segment elevation myocardial infarction | G311100 | Unstable angina |
| **G57y.00** | Other cardiac dysrhythmias | G30y.00 | Other acute myocardial infarction | G311200 | Angina at rest |
| **G57y.11** | Pulsus alternans | G30y000 | Acute atrial infarction | G311300 | Refractory angina |
| **G57y.12** | Pulse missed beats | G30y100 | Acute papillary muscle infarction | G311400 | Worsening angina |
| **G57y.13** | Skipped beat | G310.00 | Postmyocardial infarction syndrome | G311500 | Acute coronary syndrome |
| **G57y.14** | Heart beats irregular | G310.11 | Dressler's syndrome | G311z00 | Preinfarction syndrome NOS |
| **G57y000** | Persistent sinus bradycardia | G311.00 | Preinfarction syndrome | G312.00 | Coronary thrombosis not resulting in myocardial infarction |
| **G57y100** | Severe sinus bradycardia | G311.11 | Crescendo angina | G31y.00 | Other acute and subacute ischaemic heart disease |
| **G57y200** | Brugada syndrome | G311.12 | Impending infarction | G31y000 | Acute coronary insufficiency |
| **G57y300** | Sick sinus syndrome | G311.13 | Unstable angina | G31y100 | Microinfarction of heart |
| **G57y400** | Sinoatrial node dysfunction NOS | G331.11 | Variant angina pectoris | G31y200 | Subendocardial ischaemia |
| **G57y500** | Wandering atrial pacemaker | G332.00 | Coronary artery spasm | G31y300 | Transient myocardial ischaemia |

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| **G57y600** | Nodal rhythm disorder | G33z.00 | Angina pectoris NOS | G31yz00 | Other acute and subacute ischaemic heart disease NOS |
| **G57y700** | Sinus tachycardia | G33z000 | Status anginosus | G32..00 | Old myocardial infarction |
| **G57y800** | Bigeminal pulse | G33z100 | Stenocardia | G32..11 | Healed myocardial infarction |
| **G57y900** | Supraventricular tachycardia NOS | G33z200 | Syncope anginosa | G32..12 | Personal history of myocardial infarction |
| **G57yA00** | Re-entry ventricular arrhythmia | G33z300 | Angina on effort | G33..00 | Angina pectoris |
| **G57yz00** | Other cardiac dysrhythmia NOS | G33z400 | Ischaemic chest pain | G330.00 | Angina decubitus |
| **G57z.00** | Cardiac dysrhythmia NOS | G311.14 | Angina at rest | G330000 | Nocturnal angina |
| **COPD codes** | | G311000 | Myocardial infarction aborted | G330z00 | Angina decubitus NOS |
| **Med code** | **Med term** | G30y200 | Acute septal infarction | G331.11 | Variant angina pectoris |
| **14OX.00** | At risk of COPD exacerbation | G30yz00 | Other acute myocardial infarction NOS | G332.00 | Coronary artery spasm |
| **661M300** | COPD self-management plan agreed | G30z.00 | Acute myocardial infarction NOS | G33z.00 | Angina pectoris NOS |
| **661N300** | COPD self-management plan review | G33z500 | Post infarct angina | G33z000 | Status anginosus |
| **66Yd.00** | COPD accident and emergency attendance since last visit | G33z600 | New onset angina | | |
| **66Ye.00** | Emergency COPD admission since last appointment | G33z700 | Stable angina | | |
| **66Yf.00** | Number of COPD exacerbations in past year | G33zz00 | Angina pectoris NOS | | |
| **66Yl.00** | COPD self-management plan given | G34..00 | Other chronic ischaemic heart disease | | |
| **66Yi.00** | Multiple COPD emergency hospital admissions | G340.00 | Coronary atherosclerosis | | |
| **66YL.11** | COPD follow-up | G340.11 | Triple vessel disease of the heart | | |
| **8CeD.00** | Preferred place of care for next exacerbation of COPD | G340.12 | Coronary artery disease | | |
| **8H2R.00** | Admit COPD emergency | G340000 | Single coronary vessel disease | | |
| **8Hkw.00** | Referral to COPD community nursing team | G340100 | Double coronary vessel disease | | |
| **9e03.00** | GP OOH service notified of COPD care plan | G341.00 | Aneurysm of heart | | |

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| **9h5..00** | Exception reporting: COPD quality indicators | G341.11 | Cardiac aneurysm | | |
| **9h51.00** | Excepted from COPD quality indicators: Patient unsuitable | G341000 | Ventricular cardiac aneurysm | | |
| **9h52.00** | Excepted from COPD quality indicators: Informed dissent | G341100 | Other cardiac wall aneurysm | | |
| **9kf..00** | COPD - enhanced services administration | G341z00 | Aneurysm of heart NOS | | |
| **9kf0.00** | COPD patient unsuitable for pulmonary rehab - enh serv admin | G342.00 | Atherosclerotic cardiovascular disease | | |
| **9kf0.11** | COPD patient unsuitable for pulmonary rehabilitation | G343.00 | Ischaemic cardiomyopathy | | |
| **9NgP.11** | On COPD (chr obstruc pulmonary disease) supportv cre pathway | G344.00 | Silent myocardial ischaemia | | |
| **14B3.12** | History of chronic obstructive pulmonary disease | G31..00 | Other acute and subacute ischaemic heart disease | | |
| **14OJ.00** | At risk of chronic obstructive pulmonary disease | 793Gy00 | OS perc translumina balloon angioplast stenting coronary art | | |
| **1J71.00** | Suspected chronic obstructive pulmonary disease | 793Gz00 | Perc translum balloon angioplasty stenting coronary art NOS | | |
| **38Dg.00** | Chronic obstructive pulmonary disease assessment test | 7A4B800 | Percut translum thrombolysis femoral graft streptokinase | | |
| **66YB.00** | Chronic obstructive pulmonary disease monitoring | 7A54000 | Percutaneous transluminal angioplasty of artery NEC | | |
| **66YB000** | Chronic obstructive pulmonary disease 3 monthly review | 7A54500 | Rotary blade angioplasty | | |
| **66YB100** | Chronic obstructive pulmonary disease 6 monthly review | 7A54800 | Percutaneous transluminal atherectomy | | |
| **66YB200** | Telehealth chronic obstructive pulmonary disease monitoring | G34y.00 | Other specified chronic ischaemic heart disease | | |
| **66YD.00** | Chronic obstructive | G34y000 | Chronic coronary insufficiency | | |

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| | pulmonary disease monitoring due | | | | |
| **66Yg.00** | Chronic obstructive pulmonary disease disturbs sleep | G34y100 | Chronic myocardial ischaemia | | |
| **66Yh.00** | Chronic obstructive pulmonary disease does not disturb sleep | G34yz00 | Other specified chronic ischaemic heart disease NOS | | |
| **66YL.00** | Chronic obstructive pulmonary disease follow-up | G34z.00 | Other chronic ischaemic heart disease NOS | | |
| **66YM.00** | Chronic obstructive pulmonary disease annual review | G34z000 | Asymptomatic coronary heart disease | | |
| **66YS.00** | Chronic obstructive pulmonary disease monitoring by nurse | G35..00 | Subsequent myocardial infarction | | |
| **66YT.00** | Chronic obstructive pulmonary disease monitoring by doctor | G350.00 | Subsequent myocardial infarction of anterior wall | | |
| **66Yz200** | Shared care chronic obstructive pulmonary disease monitoring | G351.00 | Subsequent myocardial infarction of inferior wall | | |
| **679V.00** | Health education - chronic obstructive pulmonary disease | G353.00 | Subsequent myocardial infarction of other sites | | |
| **8BMW.00** | Issue of chronic obstructive pulmonary disease rescue pack | G35X.00 | Subsequent myocardial infarction of unspecified site | | |
| **8CE6.00** | Chronic obstructive pulmonary disease leaflet given | G33z100 | Stenocardia | | |
| **8CMV.00** | Has chronic obstructive pulmonary disease care plan | G33z200 | Syncope anginosa | | |
| **8CMW500** | Chronic obstructive pulmonary disease care pathway | 8F93.00 | Cardiac rehabilitation - phase 4 | | |
| **8CR1.00** | Chronic obstructive pulmonary disease clini management plan | 7921y00 | Other autograft replacement of coronary artery OS | | |

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| **8IEZ.00** | Chronic obstructive pulmonary disease rescue pack declined | 7921z00 | Other autograft replacement of coronary artery NOS | | |
| **9NgP.00** | On chronic obstructive pulmonary disease supprtv cre pathway | 7922y00 | Other specified allograft replacement of coronary artery | | |
| **9Nk7000** | Seen in chronic obstructive pulmonary disease clinic | 7922z00 | Allograft replacement of coronary artery NOS | | |
| **9Oi..00** | Chronic obstructive pulmonary disease monitoring admin | 7923z00 | Prosthetic replacement of coronary artery NOS | | |
| **9Oi0.00** | Chronic obstructive pulmonary disease monitoring 1st letter | G381.00 | Postoperative transmural myocardial infarction inferior wall | | |
| **9Oi1.00** | Chronic obstructive pulmonary disease monitoring 2nd letter | G382.00 | Postoperative transmural myocardial infarction other sites | | |
| **9Oi2.00** | Chronic obstructive pulmonary disease monitoring 3rd letter | G383.00 | Postoperative transmural myocardial infarction unspec site | | |
| **9Oi3.00** | Chronic obstructive pulmonary disease monitoring verb invite | G384.00 | Postoperative subendocardial myocardial infarction | | |
| **9Oi4.00** | Chronic obstructive pulmonary disease monitor phone invite | G38z.00 | Postoperative myocardial infarction, unspecified | | |
| **H3...00** | Chronic obstructive pulmonary disease | G39..00 | Coronary microvascular disease | | |
| **H36..00** | Mild chronic obstructive pulmonary disease | G3y..00 | Other specified ischaemic heart disease | | |
| **H37..00** | Moderate chronic obstructive pulmonary disease | G3z..00 | Ischaemic heart disease NOS | | |
| **H38..00** | Severe chronic obstructive pulmonary disease | Gyu3400 | [X]Acute transmural myocardial infarction of unspecif site | | |
| **H39..00** | Very severe chronic obstructive pulmonary disease | SP07600 | Coronary artery bypass graft occlusion | | |

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| **H3B..00** | Asthma-chronic obstructive pulmonary disease overlap syndrom | G366.00 | Thrombosis atrium,auric append&vent/curr comp foll acute MI | | |
| **H3y..11** | Other specified chronic obstructive pulmonary disease | G38..00 | Postoperative myocardial infarction | | |
| **H3z..11** | Chronic obstructive pulmonary disease NOS | G380.00 | Postoperative transmural myocardial infarction anterior wall | | |
| **Hyu3100** | [X]Other specified chronic obstructive pulmonary disease | G33z100 | Stenocardia | | |

## 10- Diabetes microvascular complications

| Neuropathy codes | | Diabetic foot codes | | Retinopathy codes | |
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| **Med code** | **Med term** | **Med code** | **Med term** | **Med code** | **Med term** |
| **F372.12** | Diabetic neuropathy | M037200 | Cellulitis in diabetic foot | F420.00 | Diabetic retinopathy |
| **F372.11** | Diabetic polyneuropathy | 9NND.00 | Under care of diabetic foot screener | F420200 | Preproliferative diabetic retinopathy |
| **66Ac.00** | Diabetic peripheral neuropathy screening | 8H7r.00 | Refer to diabetic foot screener | F420100 | Proliferative diabetic retinopathy |
| **M271100** | Neuropathic diabetic ulcer - foot | 8I6G.00 | Diabetic foot examination not indicated | F420000 | Background diabetic retinopathy |
| **F171100** | Autonomic neuropathy due to diabetes | 2G5A.00 | O/E - Right diabetic foot at risk | F420600 | Non-proliferative diabetic retinopathy |
| **F372200** | Asymptomatic diabetic neuropathy | 66Ab.00 | Diabetic foot examination | 8HBG.00 | Diabetic retinopathy 12 month review |
| **F372.00** | Polyneuropathy in diabetes | M271000 | Ischaemic ulcer diabetic foot | 2BBQ.00 | O/E - left eye background diabetic retinopathy |
| **F372100** | Chronic painful diabetic neuropathy | 2G5B.00 | O/E - Left diabetic foot at risk | 2BBP.00 | O/E - right eye background diabetic retinopathy |
| **F3y0.00** | Diabetic mononeuropathy | 2G5E.00 | O/E - Right diabetic foot at low risk | F420z00 | Diabetic retinopathy NOS |
| **F372000** | Acute painful diabetic neuropathy | 2G5I.00 | O/E - Left diabetic foot at low risk | 8I3X.00 | Diabetic retinopathy screening refused |
| **C10FA11** | Type II diabetes mellitus with mononeuropathy | R054300 | [D]Widespread diabetic foot gangrene | 2BBT.00 | O/E - right eye proliferative diabetic retinopathy |
| **C10F211** | Type II diabetes mellitus with neurological complications | 2G5J.00 | O/E - Left diabetic foot at moderate risk | 2BBR.00 | O/E - right eye preproliferative diabetic retinopathy |
| **C108B11** | Type I diabetes mellitus with mononeuropathy | 2G5F.00 | O/E - Right diabetic foot at moderate risk | 2BBJ.00 | O/E - no right diabetic retinopathy |

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| **C106.12** | Diabetes mellitus with neuropathy | 2G5G.00 | O/E - Right diabetic foot at high risk | 2BBV.00 | O/E - left eye proliferative diabetic retinopathy |
| **C106.00** | Diabetes mellitus with neurological manifestation | 2G5K.00 | O/E - Left diabetic foot at high risk | 2BBS.00 | O/E - left eye preproliferative diabetic retinopathy |
| **C106.13** | Diabetes mellitus with polyneuropathy | 2G5L.00 | O/E - Left diabetic foot - ulcerated | 2BBK.00 | O/E - no left diabetic retinopathy |
| **C108J12** | Type 1 diabetes mellitus with neuropathic arthropathy | 2G5H.00 | O/E - Right diabetic foot - ulcerated | 68A7.00 | Diabetic retinopathy screening |
| **C10FB00** | Type 2 diabetes mellitus with polyneuropathy | 2G5W.00 | O/E - left chronic diabetic foot ulcer | 8HBH.00 | Diabetic retinopathy 6 month review |
| **C106z00** | Diabetes mellitus NOS with neurological manifestation | 66AW.00 | Diabetic foot risk assessment | 68A9.00 | Diabetic retinopathy screening offered |
| **C108B00** | Insulin-dependent diabetes mellitus with mononeuropathy | 2G5V.00 | O/E - right chronic diabetic foot ulcer | F420700 | High risk proliferative diabetic retinopathy |
| **C10F200** | Type 2 diabetes mellitus with neurological complications | 66Aq.00 | Diabetic foot screen | 2BBk.00 | O/E - right eye stable treated prolif diabetic retinopathy |
| **C10FH00** | Type 2 diabetes mellitus with neuropathic arthropathy | **Nephropathy codes** | | 2BBo.00 | O/E - sight threatening diabetic retinopathy |
| **C106100** | Diabetes mellitus, adult onset, + neurological manifestation | **Med code** | **Med term** | 68AB.00 | Diabetic digital retinopathy screening offered |
| **C108J00** | Insulin-dependent diab mell with neuropathic arthropathy | K01x100 | Nephrotic syndrome in diabetes mellitus | 8HI1.00 | Referral for diabetic retinopathy screening |
| **C109H00** | Non-insulin-dependent d m with neuropathic arthropathy | C108D11 | Type I diabetes mellitus with nephropathy | F420800 | High risk non-proliferative diabetic retinopathy |
| **C108C00** | Insulin-dependent diabetes mellitus with polyneuropathy | C108D11 | Type I diabetes mellitus with nephropathy | C10E711 | Type I diabetes mellitus with retinopathy |
| **C10E200** | Type 1 diabetes mellitus with neurological complications | C10ED12 | Insulin-dependent diabetes mellitus with nephropathy | C10E711 | Type I diabetes mellitus with retinopathy |
| **C109B00** | Non-insulin-dependent diabetes mellitus with polyneuropathy | C10FC11 | Type II diabetes mellitus with nephropathy | C108700 | Insulin-dependent diabetes mellitus with retinopathy |
| **C109212** | Type 2 diabetes mellitus with neurological complications | C104.11 | Diabetic nephropathy | C109600 | Non-insulin-dependent diabetes mellitus with retinopathy |

| | | | | | |
|---|---|---|---|---|---|
| **C10EC00** | Type 1 diabetes mellitus with polyneuropathy | C10ED00 | Type 1 diabetes mellitus with nephropathy | C10E700 | Type 1 diabetes mellitus with retinopathy |
| **C109B11** | Type II diabetes mellitus with polyneuropathy | C10FC00 | Type 2 diabetes mellitus with nephropathy | C10F600 | Type 2 diabetes mellitus with retinopathy |
| **C109H11** | Type II diabetes mellitus with neuropathic arthropathy | C109C12 | Type 2 diabetes mellitus with nephropathy | C108711 | Type I diabetes mellitus with retinopathy |
| **C108211** | Type I diabetes mellitus with neurological complications | C104z00 | Diabetes mellitus with nephropathy NOS | C108712 | Type 1 diabetes mellitus with retinopathy |
| **C10FB11** | Type II diabetes mellitus with polyneuropathy | C108D00 | Insulin-dependent diabetes mellitus with nephropathy | C109612 | Type 2 diabetes mellitus with retinopathy |
| **C109A11** | Type II diabetes mellitus with mononeuropathy | C109C00 | Non-insulin-dependent diabetes mellitus with nephropathy | C10F611 | Type II diabetes mellitus with retinopathy |
| **C108200** | Insulin-dependent diabetes mellitus with neurological comps | C109C11 | Type II diabetes mellitus with nephropathy | 2BBl.00 | O/E - left eye stable treated prolif diabetic retinopathy |
| **C10EJ00** | Type 1 diabetes mellitus with neuropathic arthropathy | | | C109611 | Type II diabetes mellitus with retinopathy |
| **C109200** | Non-insulin-dependent diabetes mellitus with neuro comps | | | C10E712 | Insulin-dependent diabetes mellitus with retinopathy |
| **C108J11** | Type I diabetes mellitus with neuropathic arthropathy | | | | |
| **C106y00** | Other specified diabetes mellitus with neurological comps | | | | |
| **C108212** | Type 1 diabetes mellitus with neurological complications | | | | |
| **C10FA00** | Type 2 diabetes mellitus with mononeuropathy | | | | |
| **C109H12** | Type 2 diabetes mellitus with neuropathic arthropathy | | | | |
| **C106000** | Diabetes mellitus, juvenile, + neurological manifestation | | | | |
| **C109211** | Type II diabetes mellitus with neurological complications | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **C10EB00** | Type 1 diabetes mellitus with mononeuropathy | | | | |
| **C109A00** | Non-insulin-dependent diabetes mellitus with mononeuropathy | | | | |
| **C10EC11** | Type I diabetes mellitus with polyneuropathy | | | | |

## Appendix 11 Ethical Approvals for studies included in the PhD research

### SRC Feedback

**Researcher Name:** UCL School of Pharmacy
**Organisation:** Alaa Alsharif
**SRC Reference Number:** 18THIN054
**Date:** 4th July 2018
**Study title:** The Association between Dementia and The Risk of Hypoglycaemia Events among Patients with diabetes

**Committee opinion:** Approved

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**The following feedback has been supplied by the SRC.**

*Notes from the Chair:*

| **Advice**<br>(General advice for the researchers as information only) |
|---|
| A) Hypoglycaemic events are poorly documented. You may wish to state as hypoglycaemic event resulting in primary care consultation. |
| B) The researchers might want to consider matching their control group to the dementia group on age and sex as the dementia group will be much older. And/or to consider a minimum age criteria for the control group (?50 years). We feel it is critical to have minimum age at entry (example of 50 or above) when comparing the hypo event between the exposed and control group.<br><br>Another option to counter immortal time bias would be to perform a matched cohort study with assigning the same index date to the control patients as that of the corresponding exposed patient. |
| C) The researchers might want to consider using negative binomial regression for objective 3 as the poisson assumption of equal mean and variance of the event rate may not hold.<br><br>How will patients with multiple events be treated? |

Approved documents:

| Approved document | Version | Date |
|---|---|---|
| SRC_Protocol_18THIN054_v1_10-05-2018 | 1 | 10/05/2018 |
| | | |

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We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words "The Health Improvement Network (THIN)" within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

[redacted]

**Page 1**

SRC
Scientific Review Committee

Mustafa Dungarwalla

## SRC Feedback

**Researcher Name:** Alaa Alsharif
**Organisation:** UCL School of Pharmacy
**SRC Reference Number:** 18THIN011
**Date:** 23rd March 2018
**Study title:** Trends of anti-diabetic medications utilisation in people with diabetes mellitus and dementia: A population based study in the United Kingdom.

**Committee opinion:** Approved

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**The following feedback has been supplied by the SRC.**

*Notes from the Chair:*

*Approved*

Approved documents:

| Approved document | Version | Date |
|---|---|---|
| SRC_Protocol_18THIN011_v2_13-03-2018 | 2 | 13/03/2018 |
| SRC_Researcher_responses_18THIN011 | | |

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We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

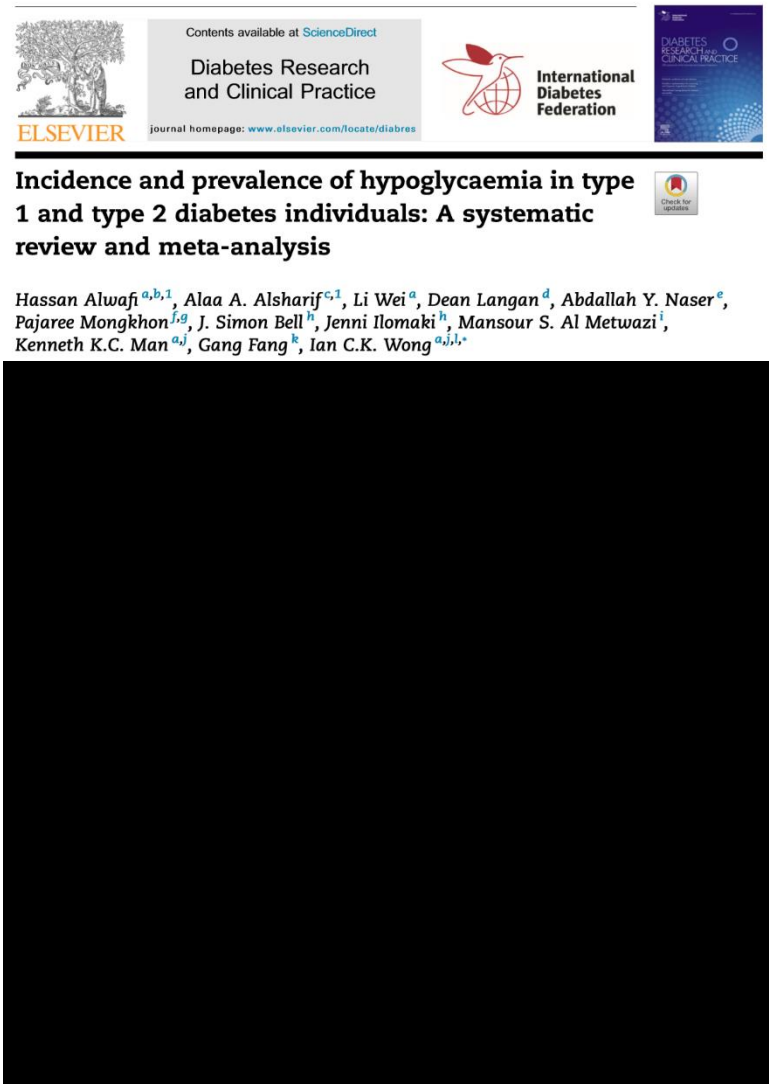
References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words "The Health Improvement Network (THIN)" within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

[redacted]

Mustafa Dungarwalla
**Consultant**

## Appendix 12 Publications



Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

ELSEVIER

International Diabetes Federation

# Incidence and prevalence of hypoglycaemia in type 1 and type 2 diabetes individuals: A systematic review and meta-analysis

Hassan Alwafi [a,b,1], Alaa A. Alsharif [c,1], Li Wei [a], Dean Langan [d], Abdallah Y. Naser [e], Pajaree Mongkhon [f,g], J. Simon Bell [h], Jenni Ilomaki [h], Mansour S. Al Metwazi [i], Kenneth K.C. Man [a,j], Gang Fang [k], Ian C.K. Wong [a,j,l,*]

Journal of Alzheimer's Disease 75 (2020) 607–615
DOI 10.3233/JAD-191115
IOS Press



# Prevalence and Incidence of Dementia in People with Diabetes Mellitus