Hypoglycaemia in type 2 Diabetes: Impact, burden and management

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Abstract

The overall aim of the programme of work was to contribute to the current body of knowledge around the impact and burden of hypoglycaemia in people with type 2 diabetes. An additional aim was to consider how hypoglycaemia in type 2 diabetes is currently managed from the patient's perspective.

A systematic review and meta-analysis was carried out to estimate the prevalence and incidence of hypoglycaemia within population based studies of type 2 diabetes.

A qualitative study was also carried out to explore the views and experiences of people with type 2 diabetes who have experienced hypoglycaemia

Key findings:

- Hypoglycaemia is prevalent within the type 2 diabetes population. The prevalence of hypoglycaemia is 45% for mild/moderate and 6% for severe, and on average an individual with type 2 diabetes experiences 19 mild/moderate episodes and 0.8 severe episodes per year.
- Hypoglycaemia is particularly prevalent amongst those on insulin (mild/moderate: prevalence = 52%; severe: prevalence = 21%, yet still fairly common for treatment regimens that include sulphonylureas (mild/moderate: prevalence = 33%; severe: prevalence = 5%. Severe hypoglycaemia prevalence was the same 5% for those on treatment regimens that did or did not include sulphonylureas.
- Hypoglycaemic episodes often interrupt daily life and activities, with symptoms, causes and overall experience varying between individuals and ethnicity.
- Management of hypoglycaemia is influenced by an individual's degree of empowerment and engagement with their healthcare practitioner

Based on the findings from this programme of work, recommendations are provided for clinical practice and future research to improve management of hypoglycaemia in type 2 diabetes.

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List of abbreviations

Abbreviations are written in full the first time that they are used in each chapter.

ADA = American Diabetes Association

BG = Blood glucose

CDA = Canadian Diabetes Association

CGMS = Continuous glucose monitoring systems

CI = Confidence interval

EE model = Empowerment and engagement model

EMEA = European Agency for Evaluation of Medicinal Products

GLP-1 ra = Glucagon-like peptide receptor agonists

DPP-4i = Dipeptidyl peptidase 4 Inhibitors

HCP = Healthcare practitioner

HbA1c = Glycosylated Hemoglobin A1C

NHS = National Health Service

NICE = National Institute for Health and Care Excellence

SA = South Asian

SGLT2i = Sodium-glucose co-transporter-2 inhibitor

SMBG = Self-monitoring blood glucose

T2DM = Type 2 diabetes mellitus

WE = White European

Chapter 1: Introduction to thesis

1.1 Rationale for researching hypoglycaemia in T2DM

Hypoglycaemia in patients with diabetes can be defined as "abnormally low plasma glucose concentration that exposes the individual to potential harm"(1). Hypoglycaemia research has historically focused on type 1 diabetes, with some consideration of its relationship with insulin treated type 2 diabetes mellitus (T2DM). However, with the prevalence of T2DM being higher than in type 1 diabetes and growing (2), new treatments are being increasingly introduced and with the risk factors for hypoglycaemia being common within the T2DM population, there is a need for future research in this area (2).

Hypoglycaemia is both a burden to the individual and the economy. Unpleasant symptoms are usually experienced during episodes (3), along with the risk of serious consequences such as coma, major vascular events or adverse effects on cognitive function (4-6). Episodes can also impact on individual's daily lives in terms of work, driving, social activities and overall quality of life (7-11). Hypoglycaemia is also a burden to the economy in terms of resources and cost. Direct health costs include costs of diagnosis, lifestyle interventions, ongoing treatment and management, and complications. In addition to this there are indirect costs from mortality, sickness, reduced work productivity and informal care (12).

Research into hypoglycaemia within T2DM real world population based studies is limited, particularly for prevalence. Data is needed to better understand the scale of the problem, its impact on the individual and how it is currently managed. This will enable the individualisation of care and give insight to help improve collaborative management of hypoglycaemia between clinicians and patients. It will also enable the design of educational programmes for successful self-management of hypoglycaemia, as well as highlighting those most at risk of an episode and the serious consequences.

1.2 Aims and objectives

Therefore, the overall aims of the programme of work in this thesis were to:

- Contribute to the current body of knowledge around the impact and burden of hypoglycaemia in T2DM.
- Consider how hypoglycaemia in T2DM is currently managed from the patient's perspective.

The specific objectives were to:

- Collate and evaluate the current literature reporting the prevalence and the incidence of hypoglycaemia in real world T2DM populations and compare by treatment regimen.
- Identify levels of knowledge and understanding of hypoglycaemia in people with T2DM.
- Explore attitudes, experiences and symptoms of hypoglycaemic episodes.
- Explore people's behaviours which aim to prevent or self-treat future hypoglycaemic episodes and associated feelings.
- Understand attitudes and experiences about disclosure of hypoglycaemia.

1.3 Overview of work undertaken

Organisation of this thesis:

Chapter 2 provides an overview of hypoglycaemia in people with T2DM as background for the thesis.

Chapter 3 presents a systematic review and meta-analysis of the prevalence and incidence of hypoglycaemia within population based studies of T2DM.

Chapter 4 presents the results of a qualitative study exploring the views and experiences of people with T2DM who have experienced hypoglycaemia.

Chapter 5 considers the implications for clinical practice and recommendations for future research for the overall programme of work.

The references and appendices associated with this programme of work are included at the end of this thesis.

Chapter 2 Hypoglycaemia: An overview

2.1 Chapter overview

This chapter provides an overview of hypoglycaemia in people with T2DM as background for the thesis. What the term hypoglycaemia means and the symptoms associated with hypoglycaemia are reviewed (section 2.2), followed by the burden of hypoglycaemic episodes to both the individual and the economy. Prevalence (2.4) and risk factors (2.5) are then presented, with current clinical recommendations outlined (2.6), before lastly presenting an overview of practitioner and patient role in diabetes management (2.7).

2.2 What is hypoglycaemia

2.2.1 Symptoms of hypoglycaemia

Hypoglycaemia in patients with diabetes can be defined as "abnormally low plasma glucose concentration that exposes the individual to potential harm"[1]. Unless a patient has hypoglycaemia unawareness, symptoms are a key indicator of the onset of an episode. The blood glucose level at which individuals experience hypoglycaemic symptoms varies, largely explained by their overall diabetes control. For example, if a patient has poorly controlled diabetes and/or infrequent hypoglycaemia they may experience symptoms at a higher blood glucose threshold than an individual who has tight overall glycaemic control [13, 14]. Additionally, symptoms are subjective and can vary substantially between individuals. Symptoms can alert an individual that their blood glucose is declining, prompting action to treat and prevent this deteriorating further [15]. Common symptoms can be classified as: neuroglycopenic (confusion, drowsiness, odd behaviour, speech difficulty, decreased coordination, headache) and autonomic (sweating, palpitations, hunger, shaking, nausea)[15]. These 11 symptoms form the validated Edinburgh Hypoglycaemia Scale (3) which is commonly used by researchers in the assessment of hypoglycaemia symptoms.

2.2.2 Classifications of hypoglycaemia

The blood glucose cut off value which can be deemed "low" clinically has been an area for research and debate. However, current clinical classifications of the severity of hypoglycaemic episodes are generally now in agreement, shown in table 2.1. The American Diabetes Association (ADA) (1), Canadian Diabetes Association (CDA) (16) and European Agency for Evaluation of Medicinal Products (EMEA) (17) definitions, all propose progressive stage definitions. The initial mild/moderate stages differ slightly across definitions. The ADA and EMEA both describe mild/moderate hypoglycaemia as not requiring assistance, typical hypoglycaemia symptoms either present (documented) or not present (asymptomatic) and a blood glucose value of ≤3.9 mmol/L. The CDA propose the initial stages of hypoglycaemia are characterised by autonomic and/or neuroglycopenic symptoms, ability to self-treat and a blood glucose value of < 4.0mmol/L. However, they all are in agreement with the definition of severe hypoglycaemia being that the individual needs assistance for recovery.

The use of an appropriate hypoglycaemia classification is important. This is due to the potential impact on research in terms of incidence and prevalence for population studies and the recommendations for newer therapies in clinical trials. Classifications for hypoglycaemic episodes can also be open to subjectivity and individual circumstances. Factors such as age (18), varying degree and presence of symptoms, and the disruption an episode may have on a person's life can all affect how an episode is classified (19).

Table 2. 1 Definitions and classifications of hypoglycaemia

Source	Definition
Canadian Diabetes Association (CDA) (16)	**Mild** - Autonomic symptoms only - Ability to self-treat – BG^a < 4.0mmol/L **Moderate** - Autonomic and Neuroglycopenic symptoms, Ability to self-treat **Severe** - Individual requires assistance, Unconsciousness may occur, BG^a <2.8 mmol/L
European Agency for Evaluation of Medicinal Products (EMEA) (17)	**Asymptomatic hypoglycaemia** - Not accompanied by typical symptoms of hypoglycaemia, BG^a ≤ 3.9 mmol/L **Documented symptomatic hypoglycaemia** - Typical symptoms of hypoglycaemia, BG^a ≤ 3.9 mmol/L **Severe hypoglycaemia** - Requiring assistance, Possible induced seizure or coma, BG^a may not be available, Neurological recovery attributable to the restoration of BG^a to normal
American Diabetes Association (ADA) (1)	**Probable symptomatic hypoglycaemia** - Symptoms of hypoglycaemia, Not accompanied by BG ≤3.9 mmol/L **Documented hypoglycaemia** - Symptoms of hypoglycaemia, BG ≤3.9 mmol/L **Asymptomatic hypoglycaemia** - Not accompanied by symptoms of hypoglycaemia, BG ≤3.9 mmol/L **Severe hypoglycaemia** - Requiring assistance, Possible induced seizure or coma, BG^a may not be available, Neurological recovery attributable to the restoration of BG^a to normal

^{a} plasma glucose

2.3 Burden of episodes

2.3.1 Burden of episodes to the individual

Hypoglycaemia can be a great burden to the individual and impact on everyday life. It can often take up to four hours to mentally recover from an episode (20) and over 30 minutes for energy levels to be restored (21). This has implications for the impact hypoglycaemia could have on interrupting and hindering the individual at work, social situations and daily activities (7). Non-severe hypoglycaemia has been shown to cause loss to working hours in 10%-20% of those experiencing an episode, with overall productivity whilst still at work being lower. It appears nocturnal episodes have the most impact on work, with more people being late for work or missing a full day compared to daytime episodes (8, 9).

Additionally the literature has shown links with depressive symptoms, heightened anxiety, lower psychological wellbeing, higher diabetes related distress and overall quality of life (10, 22-24).

Currently if an individual has had more than one episode of severe hypoglycaemia in the last 12 months then their driving licence could be revoked (25). This can have major implications for the individual, causing a loss of independence, identity and increase in depressive symptoms (11, 26).

In addition to the direct effects of hypoglycaemia, there may be substantial indirect impacts to an individual, including poor medication adherence, reduced physical activity; hyperglycaemia and subsequently long-term serious health consequences. This might be caused by fear of hypoglycaemia and compensatory behaviours such as increasing food consumption, to avoid hypoglycaemic episodes (20).

2.3.2 Economy and resources

In regards to the economic burden hypoglycaemia poses in T2DM, the cost is substantial. It is estimated that the cost of moderate hypoglycaemic events to the National Health Service (NHS) in the UK for one year is around £23 million, and for severe hypoglycaemia around £16 million (12). Furthermore if the prevalence of T2DM continues to rise and current care regimens are maintained, by 2035 the cost could rise to an estimated £40 million for moderate hypoglycaemia and around £21 million for severe hypoglycaemia (12).

2.4 Prevalence

A review of the literature concluded that the average individual with type 1 diabetes experiences approximately two episodes of mild hypoglycaemia per week, and an annual incidence of between one to two episodes per year for severe episodes (27).

The frequency of hypoglycaemia in T2DM has been explored less, although studies suggest that the incidence of hypoglycaemic events is lower in T2DM than in type 1 (28) The prevalence of hypoglycaemia in T2DM will be explored in detail throughout chapter 3. Despite the lower frequency of hypoglycaemia, the estimated cost of hypoglycaemia is around £6 million higher in the UK for T2DM than type 1 diabetes mellitus (12). This is due to a much higher prevalence rate of T2DM (2).

It is important to consider the frequency of hypoglycaemia in T2DM separately to type 1 diabetes as there are significant variations that exist between the two populations. There are established differences in the underlying biological processes between the two conditions (29), as well as population characteristics. In terms of ethnicity, age and body mass index, the type 1 diabetes population is similar to the national population profile. This is not the case in the T2DM population. Prevalence of T2DM considerably higher for

people of Asian ethnicities (13%), the elderly aged 70-84 years (15%) and for obese individuals (51%) (2).

2.5 Risk factors

In order to avoid long-term complications of T2DM, emphasis is placed on improving blood glucose control through pharmacological treatment (30-32). To help achieve tight glycaemic control, people with T2DM are frequently placed on intensive treatment regimens, including earlier initiation of insulin and multiple therapies. A recent meta-analysis revealed that intensive glycaemic control in people with T2DM can result in a 17% reduction in non-fatal myocardial infarction and a 15% reduction in coronary heart disease events (33). However, the topic of glycaemic management and pharmacological treatments is becoming more complex, as tight blood glucose control can be a difficult task to accomplish without increasing the incidence of hypoglycaemic events (34-37). It is now recognised that blood glucose targets and treatment need to be individualised. Newer therapies and more treatment combinations, are increasingly becoming available, with the aim of maximising glucose control without the increased risk of hypoglycaemia (30, 38).

In addition to treatment regimens there are a number of other currently identified causes and risk factors which increase the risk of hypoglycaemia in T2DM. Hypoglycaemia unawareness is a major risk factor for severe hypoglycaemic events. The subjective sensations that are interpreted as symptoms are not exclusive to hypoglycaemia (3) and vary immensely in terms of intensity and patterns between individuals. In order to help avoid hypoglycaemia unawareness each individual needs to become familiar with their own particular symptomatic profile (39, 40).

However, it is not just symptom interpretation that is a cause of hypoglycaemia unawareness. In the T2DM elderly population, evidence suggests that symptoms of hypoglycaemia decline with age (41). The elderly population have also been shown to have a higher prevalence of hypoglycaemic episodes. A study of around 4000 patients in primary care showed older people (≥70 years)

reported significantly more episodes than younger (<60 years) people (42). Overall, 12.8% of older people reported experiencing hypoglycaemic episodes compared with 9.0% of younger people. Significant differences were also seen for symptomatic episodes without a need for help (9.2% vs. 5.6%) and symptomatic episodes with a need for medical assistance (0.7% vs. 0.1%), in older and younger people respectively. The elderly are also particularly susceptible to the effects of hypoglycaemia with an increased risk of brain injury (6) or major vascular events such as stroke, myocardial infarction, acute cardiac failure, and ventricular arrhythmias (43, 44).

The presence of co-morbidities as a potential risk factor is also relevant to the T2DM population, as many people also suffer with issues such as microvascular and macrovascular disease (45, 46). Increasing physical activity and weight loss is recommended in the management of T2DM to help improve glycaemic control, promote weight loss and also target issues such as high blood pressure and lipids. However, due to the resulting improvements in insulin resistance for up to 16 hours following activity (47), the individual may be exposed to an increased risk of hypoglycaemia.

2.5.1 Progression from mild to severe episodes

Certain risk factors within the T2DM population increase the risk of a hypoglycaemic event progressing from requiring self-treatment (mild) to requiring aid from others or hospitalisation (severe). Fluctuations in blood glucose concentrations can influence the glycaemic threshold at which symptoms are initiated (48). Therefore the onset of symptoms may be followed by severe cognitive dysfunction and the ability to self-treat in a very short space of time. This may be more of a problem in the elderly (40) and older age is a prominent characteristic of the T2DM population (2).

Patients who have knowledge of hypoglycaemia, especially of predisposing symptoms and appropriate self-treatment methods are more likely to prevent an episode from increasing in severity. However, knowledge of hypoglycaemia within the T2DM population has previously been shown to be relatively low (15,

49-52). Furthermore, even with the appropriate knowledge of how to self-treat hypoglycaemia, people do not necessarily adhere to clinically recommended guidelines for treatment. The symptoms of hypoglycaemia such as disorientation and hunger sensations, reversion to habituated behaviour and worry about under-treatment can all impact on ingesting fixed recommended quantities of fast-acting carbohydrate (53).

Impaired awareness of hypoglycaemia has also been shown to be a prominent risk factor for severe hypoglycaemia(54). It reduces the glycaemic threshold for the onset of symptoms and therefore hinders the individual's opportunity to self-treat an episode (39, 55).

2.6 Current recommendations

2.6.1 Treatment regimens for T2DM

At present National Institute for Health and Care Excellence (NICE) recommend stepwise treatment following a monotherapy, dual therapy, triple therapy or insulin therapy route, see figure 2.1 (56). This is based on an algorithm considering the following factors: the effectiveness of the drug treatment in terms of metabolic response; safety and tolerability of the drug treatment; the person's individual clinical circumstances, for example, comorbidities and risks from polypharmacy; the person's individual preferences and needs; licensed indications or combinations available; and cost (if two drugs in the same class are appropriate, the option with the lowest acquisition cost should be chosen). The generic treatment triage recommendation starts with metformin alone. This is followed by adding dipeptidyl peptidase 4 (DPP-4) inhibitor, pioglitazone, sulfonylurea or in some cases a sodium-glucose co-transporter-2 (SGLT2) inhibitor. If glycaemic control is still not optimal, intensification of therapy by adding a further oral-antidiabetic drug would be considered. Lastly, insulin would be recommended along with metformin. If metformin is not tolerated then a DPP-4 inhibitor, pioglitazone, sulfonylurea, SGLT2 inhibitor or a glucagon-like peptide (GLP-1) receptor agonist would be used with insulin (figure 2.1). When

choosing the type of insulin and regimen, there is a strong consideration recommended for symptomatic/problematic hypoglycaemia (Table 2.2). If this is a persistent problem then type of insulin should be switched. Along with the initiation of insulin a structured programme employing active dose titration that encompasses management of hypoglycaemia is also recommended.
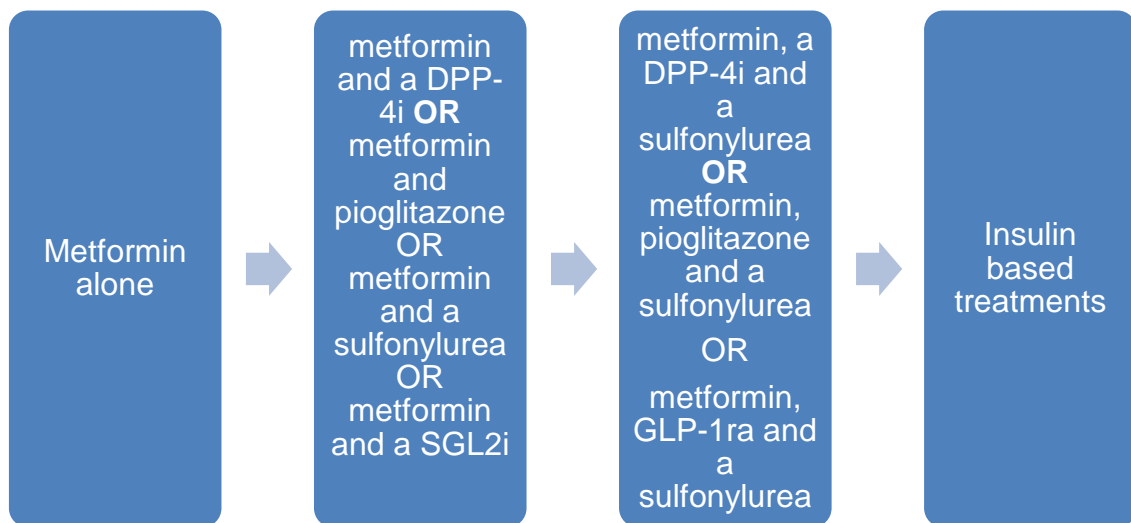
| Metformin alone | → | metformin and a DPP-4i **OR** metformin and pioglitazone OR metformin and a sulfonylurea OR metformin and a SGL2i | → | metformin, a DPP-4i and a sulfonylurea **OR** metformin, pioglitazone and a sulfonylurea OR metformin, GLP-1ra and a sulfonylurea | → | Insulin based treatments |

Abbreviations: DPP-4i = Dipeptidyl peptidase 4 Inhibitor, GLP-1 ra = Glucagon-like peptide receptor inhibitor, SGLT2i = sodium-glucose co-transporter-2 inhibitor

Figure 2. 1 Generic NICE treatment pathway for T2DM

Table 2. 2 Key references to hypoglycaemia in NICE 2015 guidelines

NICE recommendations 2015

Insulin based treatments

- When starting insulin therapy in adults with T2DM, use a structured programme employing active insulin dose titration that encompasses management of hypoglycaemia.
- Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or hypoglycaemia is a problem.
- Consider switching to insulin detemir or insulin glargine from NPH insulin if target HbA1c is not reached because of significant hypoglycaemia or patients who experience significant hypoglycaemia.

HbA1c measurement and targets

- Encourage patients to achieve blood glucose target and maintain it unless any resulting adverse effects (including hypoglycaemia).
- For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%).
- Consider relaxing the target HbA1c level for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycaemia, and people who drive or operate machinery as part of their job.
- If adults with T2DM achieve an HbA1c level that is lower than their target and they are not experiencing hypoglycaemia, encourage them to maintain it.

Self-monitoring of blood glucose

- Do not routinely offer SMBG levels for adults with T2DM unless: there is evidence of hypoglycaemic episodes or the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery.
- Consider short-term SMBG levels to confirm suspected hypoglycaemia.

2.6.2 Blood glucose management

2.6.2.1 HbA1c (Glycosylated Hemoglobin A1C) measurement and targets

Current recommendations from NICE (56) have a focus on individualisation of HbA1c targets. A key focus is to achieve the HbA1c target set unless there are any resulting adverse effects such as hypoglycaemia. If a patient's diabetes treatment regimen is associated with risk of hypoglycaemia, then their HbA1c target should be elevated to 53 mmol/mol (7.0%), as opposed to 48 mmol/mol (6.5%) for those on treatment not associated with hypoglycaemia. The guidelines also emphasise the need to relax in the elderly, who are at high risk of the consequences of hypoglycaemia. They also recommend relaxation of targets for people who may be at risk of falling, have impaired awareness of hypoglycaemia, or drive or operate machinery as part of their job.

2.6.2.2 Self-monitoring of blood glucose (SMBG)

Blood glucose monitoring can be a vital component in preventing and managing hypoglycaemia (57, 58). However, due to cost implications (56, 57) it is currently not feasible for all patients with T2DM to be prescribed blood glucose monitoring equipment. NICE (56) recommend that all patients with T2DM using insulin, and those on oral medication which may cause hypoglycaemia, are encouraged to use blood glucose monitoring equipment. However, for people who are non-insulin dependent, recommendations and research findings are slightly more complex. Research has shown that SMBG can heighten patient awareness of lifestyle choices and behaviours on blood glucose values (59).Though the effect on psychological wellbeing can be a burden (60), patients can feel a sense of success if values are within target but a sense of failure if they are high (59). NICE guidelines (56) recommend for those people with T2DM not treated with insulin, SMBG "should be used only when individuals with diabetes (and/or their care-givers) and/or their healthcare practitioner (HCP) have the knowledge, skills and willingness to incorporate SMBG monitoring and therapy adjustment into their diabetes care plan in order to attain agreed treatment goals". They state that it can be offered in the

following instances where the patient: experiences symptomatic hypoglycaemia, is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant, or is planning to become pregnant. Short-term use of SMBG can also be considered to confirm suspected hypoglycaemia. The guidance for SMBG use in people not treated with insulin emphasizes the importance of using SMBG as a tool to aid the patients understanding of diabetes and activeness in managing their condition, whilst also helping in the optimization of treatment titration and lifestyle modifications, particularly in the early days of diagnosis (56).

2.7 Practitioner and patient role in diabetes management

2.7.1 The traditional medical model

The traditional medical model (61) places responsibility with HCPs in prescribing appropriate treatment and ensuring this is carried out or fulfilled. Consultations focus on questioning and assessing clinical issues, whilst also monitoring treatment adherence, eye, foot and blood checks. Referral decisions (to dieticians, nurses and the education team) are made by HCPs without always considering individual patient needs and preferences. Treatment goals and plans are often set and guided by the HCP, clinical measures taking precedence over the emotional and cognitive aspects of being diagnosed and living with diabetes, subsequently impacting on motivation to adopt self-care behaviours and glycaemic control (62). This can lead to a patient and HCP seeing each other as opponents, with conflicting views and the patient feeling punished, for example being overweight or having a high HbA1c (63). However present care has become more collaborative, incorporating self-care management education for the patient, with concepts such as empowerment and engagement becoming increasingly accepted and part of the care process (61).

2.7.2 Engagement with HCP

A patients engagement with their HCP is considered an important element of healthcare delivery and chronic illness management (64). Connected relationships with strong communication have been shown to be beneficial for disease management in a number of ways. Good communication can increase patients sense of well-being and security within the relationship, leading to more confidence and motivation in managing their illness (65). A review of nurse communication styles and the impact on patient outcomes also found it positively improved patient satisfaction and overall health (66). The review along with other studies also highlighted the importance of the relationship in treatment adherence. An engaged relationship can enable a partnership with mutually acceptable treatment plans and goals (64). Communication is key for information exchange between the patient and HCP; how information is delivered and provided by the HCP has been shown to be one of the most important care pathways (67). A collaborative continuous relationship between a HCP and a patient is also encouraged is a fundamental part of the success of another important concept for care, "patient empowerment" (68).

2.7.3 Empowerment

The concept of patient empowerment centres on healthcare being something which is done "with" the patient and not "to" the patient. It aims to facilitate self-directed behaviour change and is viewed as a continuum where the level of empowerment can change over time (69).

Patient empowerment has been shown to be beneficial in many areas of diabetes, and is generally accepted as an integral part of routine diabetes care. Successful management of T2DM often involves making changes to routine behaviours and lifestyle choices, which are embedded in daily life and are the patient's preference. Empowered patients will generally choose meaningful, informed and realistic goals related to weight loss, nutrition, physical activity and overall lifestyle (69). Empowerment-based interventions within T2DM focus on diabetes self-management and coping, taking place in primary, secondary and

community care settings, The nationally used DESMOND programme for people with newly diagnosed T2DM centre around supporting patients to discover and work out knowledge, and to allow this to inform the goals and plans they make for themselves (70). A recent structured self-management programme based on DESMOND was shown to reduce the incidence of hypoglycaemia, despite improving glycaemic control (71).

There have also been other successful interventions involving traditional teaching formats and also peer or professional support. Positive results have been shown from just a few sessions, but with many studies the programmes last up to six months. Data is limited on hypoglycaemia outcomes specifically, though other outcomes of interest which have been shown to improve after an empowerment programme include clinical factors such as: HbA1c (72-74), systolic and diastolic blood pressure (73, 74), physical stress, BMI (73), retinopathy and nephropathy (75). Overall diabetes knowledge can increase (74) along with confidence of knowledge (76), improved illness attitudes (72), perceived treatment effectiveness (72) and depressive symptoms (74). Positive lifestyle and behaviour changes have also been shown to improve including: physical activity (74), healthy diet (73, 74), foot care (74), SMBG (73, 74), and medication adherence (74).

2.7.4 The patient activation model

A widely used model which incorporates concepts from both empowerment and engagement with HCPs, emphasising the vital part patients can play in successful care is "The patient activation model" (77). Patient activation is a behavioural non-disease specific concept, being defined as 'an individual's knowledge, skill and confidence for managing their health and health care'. Understanding their role in the care process whilst feeling confident and capable of fulfilling their role, are characteristics of those with high activation. These highly activated patients with long term health conditions are more likely to engage in positive health behaviours and be more successful in managing their conditions. However, it has been suggested that between 25 and 40 per cent of the population have low levels of activation (78).

The model considers issues which may affect a patient's capability to manage their illness. When a patient is newly diagnosed with diabetes they are often advised to change multiple aspects of their lifestyle, including the introduction of new medication, dietary changes and increasing physical activity. If the patient is low in confidence and feels they lack the skills or knowledge to carry out these changes it is likely they will feel overwhelmed. The model proposes that the patient may try to make the changes, but when they cannot make all of them, they are likely to make none. It is therefore important that the HCP understands how low activation may hinder patients in self-managing their health.

Patient activation is usually measured by a self-completion questionnaire called the Patient Activation Measure" (77). The measure provides a score between 0 and 100 is often used to determine an individual's progress. However for the use of interventions, a four tier level of activation is used, table 4.1.

Table 4.1 Levels of Patient Activation

The four levels of Patient Activation
Level 1 Individuals tend to be passive and feel overwhelmed by managing their own health. They may not understand their role in the care process
Level 2 Individuals may lack the knowledge and confidence to manage their health.
Level 3 Individuals appear to be taking action but may still lack the confidence and skill to support their behaviours.
Level 4 Individuals have adopted many of the behaviours needed to support their health but may not be able to maintain them in the face of life stressors.

2.7.5 Primary care

Generally in the UK patients who have complications due to their diabetes such as reoccurring hypoglycaemia are referred to specialist care for temporary guidance or ongoing care (79). All other patients with T2DM receive an annual review (56) in a primary care centre by a diabetes specialist nurse, a practice

nurse who has undertaken specialist training or their GP. However, as a recent review (80) highlighted management in primary care is not without its problems. The review found that physicians were very aware of the limited time and resources available to them, unhappy with the compromises they consequently had to make to meet evolving targets. Confidence in guideline knowledge and skills, particularly when facilitating lifestyle changes and insulin initiation were also notably lacking. Physicians were found to be frustrated with lack of patient adherence and anxious regarding treatment intensification, with uncertainty about where clinical responsibility lies. Quality of care and range of services has also been shown to vary substantially across practices (81, 82). A report by the national nursing research unit found that larger practices are more likely to have experienced nurses with post-graduate qualifications in diabetes (83). The same report found people that with diabetes are on average are receiving fewer consultations per year than in the past, despite the ratio of consultations to doctors or nurses within primary care being higher.

2.8 Concluding remarks

This chapter has provided background on hypoglycaemia in T2DM for the work presented in the following chapters. Hypoglycaemia can be defined as abnormally low blood glucose with symptoms such as shaking and nausea. Episodes can be of great burden to both the economy and individual, with particular characteristics of the type 2 diabetes population making them particularly at risk of an episode and potentially serious consequences. Blood glucose management in type 2 diabetes to a degree focuses on the avoidance of hypoglycaemia, with newer therapies being introduced and patient empowerment and involvement increasingly being considered.

The next chapter (Chapter 3) describes a systematic review and meta-analysis which collates and evaluates the current literature reporting the prevalence and incidence of hypoglycaemia in population based studies of T2DM.

Chapter 3: Prevalence and Incidence of hypoglycaemia in 532,542 people with Type 2 diabetes mellitus (T2DM) on oral therapies and insulin: a systematic review and meta-analysis of population based studies

3.1 Introduction

3.1.1 Chapter Overview

This chapter presents a systematic review and meta-analyses, conducted to review the existing evidence of the prevalence and incidence of hypoglycaemia in Type 2 diabetes mellitus (T2DM). The introduction outlines the rational and aims of the review, with the methods then described in section 3.2. The synthesised data and results of the meta-analyses are then presented (section 3.3), followed by the strengths and limitations of the review and relationship to other literature (section 3.4). Contributions for the work in this chapter are presented in Appendix 1.

3.1.2 Background and rational

The considerable cost and burden hypoglycaemia in T2DM is associated with to the individual and economy is covered in chapter 2. Identified potential risk factors for hypoglycaemia in T2DM are also covered in the previous chapter.

Hypoglycaemia prevalence in real world T2DM settings has been considered to a degree (84, 85). Reviews conclude that hypoglycaemia is a common and potentially dangerous side effect of some medications used for type 2 diabetes but prevalence varies widely between population based studies 1% to 17%). However, there has not been a systematic review and meta-analyses of the literature. Previously published systematic reviews that have considered hypoglycaemic episodes in T2DM have tended to focus on clinical trials of the safety and efficacy of a particular drug (37, 86-91). Clinical trials usually exclude participants at higher risk of hypoglycaemia, attract more motivated and

selective participants, have a treat to target design and place participants on treatment regimens specifically for the study. Consequently, generalisability of findings to real world settings may be limited and hypoglycaemia prevalence and incidence in clinical trials may be lower than in clinical practice. Knowing the incidence of hypoglycaemia is important to provide insight into its impact both clinically and from a patient level. It enables the planning of resources, exploration of risk factors and design of interventions for prevention of hypoglycaemia. Additionally, the frequency and severity of hypoglycaemia is often used as a rationale for the use of newer treatments and as a clinical indicator for the choice of treatment patients are placed on.

3.1.3 Aim

This systematic review aimed to collate and evaluate the current literature reporting the prevalence (proportion of people) and the incidence (rate of episodes) of hypoglycaemia in a real world T2DM population.

3.2 Methods

3.2.1 Search Strategy and Study Selection

Electronic bibliographic databases Ovid Medline (including in-process and other non-indexed citations) and Embase from 1998 to February 2014 and Cochrane (issue 2, 2014) were searched, using a combination of keywords and MeSH terms with English and American spellings. The search terms used covered T2DM, hypoglycaemia prevalence and hypoglycaemia incidence. An example search strategy tailored for Ovid medline can be found seen in Appendix 2.

The primary aim of this systematic review was to explore the prevalence and incidence of hypoglycaemia in people with T2DM within a general population-based setting. Included observational studies where: 1) the study population were a defined general population sampled from either a defined geographical location, attendees at a primary, secondary or other healthcare centre, or people registered on a health service or health insurance database; 2) the study

population (or sub-population) all had T2DM and were aged ≥ 18 years old; 3) they were published in English language; and 4) they were published as full papers. Studies were additionally required to report the number of T2DM participants who had experienced ≥ 1 hypoglycaemic episode, the incidence of hypoglycaemic episodes experienced, or data to allow the calculation of one of these measures. No restrictions were applied relating to the classification, definition or measurement of how hypoglycaemia was utilised by studies. Studies were excluded if: 1) they were pharmacological trials or the study methods involved any alteration to a participant's treatment or care, either pharmacological or behavioural; 2) the majority of participants were pregnant, fasting, on a restrictive diet, or were selected on the basis of having a specific acute or chronic illness; 3) participants were selected on the basis of their hypoglycaemia history or recent initiation of treatment regime; 4) participants were sampled via an established survey/consumer panel or a consumer database; or 5) hypoglycaemia rates were solely reported over less than one week.

Following removal of duplicate publications, titles and abstracts were reviewed independently by myself and another team member to identify studies that met the inclusion criteria. Where it was unclear from the abstract whether the inclusion criteria were met, the full article was retrieved and reviewed. In instances where there were disagreements between reviewers, a third reviewer was consulted.

3.2.2 Data extraction

I developed and pilot tested a data extraction form, with adaptations made accordingly, Appendix 3. Myself and another team member extracted data independently from included studies.

Where data were available, the following were extracted for each study: 1) study details (including study design, year published and country); 2) population details (including sample source, mean age, ethnicity, mean HbA1c (Glycosylated Haemoglobin A1C), sex, treatment regimens, and previous

cardiovascular disease or events); 3) methods used to measure hypoglycaemia (self-report questionnaires, prospective diaries, emergency department admission records, claims databases); 4) the time period hypoglycaemia was measured over; and 5) severity measured (definition given by the study). Outcome data were extracted for the proportion of T2DM participants only who had experienced at least one hypoglycaemic episode (prevalence) and the incidence rate of episodes experienced (or data to calculate).

3.2.3 Quality assessment

I conducted a search for an appropriate tool to assess the quality of the studies included. However, quality assessment tools designed for cross-sectional, prevalence and observational studies are limited (92). I therefore decided to create an assessment of quality based on elements from the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (93), the Cochrane Collaboration Risk of Bias Tool (94) and the quality assessment tool for systematic reviews of Observational Studies (QATSO) (95). The quality assessment tool (appendix 4) was created specifically for studies reporting the prevalence of hypoglycaemic episodes in non-interventional population studies. The tool allowed for assessment of important study quality variables, including the data source and measurement prevalence was based upon. Two reviewers (myself and another team member), independently assessed all studies for methodological quality. Each criterion was given a score of ++, + or -, and an overall quality grade was assigned for each of the following: sample bias (sample source representative and described well, sampling method, eligibility criteria applied and described, sufficient sample response), data collection bias (data collection tool well described, measurement reliability), and confounding and explanatory factors considered.

3.2.4 Data synthesis

For analytic and descriptive purposes, hypoglycaemia was categorised and defined by severity of the episode measured within the study. Where possible, based on the description given in the paper, studies were categorised as either

mild/moderate or severe. Mild/moderate hypoglycaemia was referred to by studies when no third party assistance was needed during a hypoglycaemic episode. Severe hypoglycaemia was used by studies when third party assistance was required. However, some studies did not specify a severity when gathering some or all of the hypoglycaemia data; these data were classified as "unspecified" hypoglycaemia. It was assumed that the "unspecified" data covered both severe and mild/moderate hypoglycaemia. Where a study reported data separately for more than one of the classifications (severe, mild/moderate and unclassified), I extracted and analysed the data separately. If a study reported zero hypoglycaemic events, I entered 0.001 into the meta-analysis to avoid the study being excluded (94). Where two prevalence or incidence means were reported in a paper for different populations, the pooled mean was calculated (94). Population treatment categories relating to hypoglycaemia prevalence and incidence were based on the available data. Where possible, data were grouped into: insulin, with or without oral glucose-lowering therapies; sulphonylureas, non-insulin but with or without other oral glucose-lowering therapies; non-sulphonylureas, non-insulin and non sulphonylurea oral glucose-lowering therapies; or mixed oral glucose-lowering therapies, non-insulin but no further description given relating to type of oral glucose-lowering therapies. For studies where treatment categories were not mutually exclusive, if the whole population were pharmacologically controlled, data for insulin were subtracted from the overall data, where possible, and the remaining data were grouped in the mixed oral glucose-lowering therapy category.

For the primary outcome of interest (the proportion of people who had experienced hypoglycaemia), I conducted meta-analyses for mild/moderate episodes, severe episodes and unspecified episodes. Sub-analyses within these categories were then carried out by treatment regime of the population. I also carried out a sub-analysis for severe hypoglycaemia which specifically required emergency or medical assistance. Meta-regression was used to assess the following potential explanatory variables at the study-level: mean

age, percentage of male participants, mean HbA1c level, and the time over which hypoglycaemia was measured.

I carried out further meta-analyses for the rate of hypoglycaemic episodes per person year, for the three categories of, mild/moderate, severe and unspecified. Again, analyses were stratified by therapy option.

When calculating confidence intervals for meta-analyses, negative values can be found. All confidence intervals were therefore capped at 0.00, due to it not being plausible to have a negative confidence interval for prevalence or incidence.

The I^2 statistic(96) was used to calculate the proportion of total variation in study estimates due to heterogeneity. Due to high levels of heterogeneity found, random-effects models(97) were used to represent the inter-study variation when calculating pooled effect sizes. Publication bias(98) was also assessed, as it has been previously shown that studies with statistically significant results are more likely to be published than those finding a null result. Funnel plots(99) were one of the methods used to assess if publication bias was present within the studies. The plots displayed effect sizes against a measure of study size. The Egger test(100) was then used to measure funnel plot asymmetry and further indicate if bias was present.

This was carried out separately for studies reporting, mild/moderate, severe and unspecified events and separately for prevalence and incidence. Significance was set at P<0.05, all p-values are two-sided and 95% confidence intervals are quoted throughout. I performed all analyses in Stata version 13 (StataCorp, College Station, TX), codes for your meta and meta-regression analyses can be found in Appendix 5.

3.3 Results

3.3.1 Identification of studies

Results relating to the identification process for eligible studies are summarised in Figure 3.1. Searches yielded 3348 citations, and 3063 unique titles and abstracts were screened for eligibility. Following full text retrieval of 285 potentially relevant papers, 239 were subsequently excluded, leaving 46 papers eligible for inclusion in the analyses.

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┌─────────────────────────────┐
│  Records identified through  │
│     database searching       │
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│        (n = 3348)            │
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│ Articles screened on basis   │          │                      │
│    of title and abstract     │ ───────▶ │  Excluded (n =2778)  │
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│ Full text articles assessed  │          │ Excluded (n = 239)                    │
│   for eligibility (n = 285)  │          │                                       │
└─────────────────────────────┘          │ Reasons                               │
               │          ──────────────▶ │                                       │
               │                          │ Newly initiated on and/or changes     │
               │                          │ made to treatment/care (n= 130); Data │
               │                          │ relating to primary/secondary aim not │
               ▼                          │ available (n = 21); Alteration to     │
┌─────────────────────────────┐          │ diabetes care by study (n = 16);      │
│ Studies meeting inclusion    │          │ Hypoglycaemia rates measured < 1 week │
│  criteria & included in      │          │ (n = 5); Study population selected on │
│    systematic review         │          │ the basis of hypoglycaemia history    │
│                              │          │ (n = 13); Participants sampled via    │
│        (n = 46)              │          │ survey/consumer panel/database (n =   │
└─────────────────────────────┘          │ 10); Participants on a restrictive    │
               │                          │ diet (n  1); Publication type (e.g.   │
               │                          │ review, letter, conference abstract)  │
               │                          │ (n = 33); Further duplicates (n = 10) │
               ▼                          └───────────────────────────────────────┘
┌─────────────────────────────┐
│ Studies included in          │
│ quantitative synthesis       │
│     (meta-analysis)          │
│                              │
│      (n = 46 studies)        │
└─────────────────────────────┘
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Figure 3. 1 Flowchart of selection of studies from search to final inclusion

3.3.2 Summary of included studies

Descriptive characteristics including the definitions and descriptions of hypoglycaemia used by the 46 studies included in the systematic review are summarised in Table 3.1 and 3.2. All studies were observational, with 27 being cross-sectional, 11 prospective, six retrospective and two used a mixed methods design cross-sectional/prospective (n=1) or cross-sectional/retrospective (n=1). Papers included were published from 1998 to 2013 inclusive. The number of participants within each study ranged from 41 to 361,210. Studies were conducted in Europe (n=25), North America (n=14), Australia (n=2), and Eastern/South East Asia (n=5). Ethnicity was poorly reported; of the nine (19.6%) studies that reported ethnicity, the proportion of non-white participants ranged from 17% to 100%. Population samples were obtained from either health clinic attendees (n=21), diabetes registries/databases (n=8), health insurance databases (n=7), emergency department records (n=4), community populations (n=3) or pharmacy records (n=2).

Table 3. 1 Characteristics of studies included in the systematic review (A)

First author (year)	Country	Sample size	Male %	Mean Hba1c% mmol/mol	CVD events Hypo : No hypo	Non-white %	Mean Age (years)	Length of therapy (years)
Akram 2006(101)	Denmark	401	58	8.3 (67.2) (median)		NR	66 (median)	7 (median) (insulin)
Allen 2004(102)	UK	41	63.4	NR		NR	NR	1.4 (mean) (insulin)
Andel 2008(103)	Central/ Eastern Europe	8,231	47.3	7.7 (60.7)		NR	62.2	NR
Aung 2011(104)	UK	10,66	51	7.3 (56.3)	Myocardial infaraction 24%:13% Angina 44%:26% Stroke 10%:5% Transient ischaemic attack 5%:24%	NR	67.9	NR
Bourdelmarc-hasson 2007	France	2,832	60.6	7.1 (54.1)		NR	63.8	NR
Chan 2010	Asia	2,257	49.4	7.5 (58.5)		NR	NR	NR
Davis 2005	UK	590	58	NR		NR	NR	Not reported for the study cohort included for hypo analysis
Davis 2010	Australia	616	52.3	NR		NR	67	NR
Donnelly 2004	UK	173	53	8.9 (73.8)		NR	65	NR
Green 2012	USA	3,000	40.4	NR	Heart Disease 31%:22%	NR	NR	NR
Gurlek 1999	Turkey	114	44.7	NR		NR	58.9	NR
Henderson 2003	UK	215	NR	8.6 (70.5)		NR	NR	NR
Holstein 2003	Germany	9,000	NR	NR		NR	NR	NR
Honkasalo 2011	Finland	1,065	NR	NR		NR	NR	NR
Jaap 1998	UK	132	NR	NR		NR	NR	NR

Johnston 2012(105)	USA	361,210	51.6	NR	Iscaemic heart disease 26%:19% Congestive heart failure 12%:6% Myocardial infaraction 2%:1% Angina 2%:1% Transient ischaemic attack 7%:5%	NR	NR	NR
Katon 2013(106)	USA	4,117	51.9	NR		19.9	63.4	NR
Krnacova 2012(107)	Czeh Republic	37,459	NR	NR		NR	NR	NR
Lecomte 2008(108)	France	3,324	53.8	NR		NR	NR	NR
Leese 2003(109)	UK	7,678	52	NR		NR	65.8	NR
Leiter 2005(110)	Canada	133	NR	7.52 (58.5)		NR	59.9	10.2 (mean) (insulin)
Lin 2013(111)	Taiwan	15,404	45.1	NR	Iscaemic heart disease 27%:15% Cardiovascular disease 83%:63%	100	64.2	NR
Lipska 2013(112)	USA	9,094	50	7.5 (58.5)	Congestive heart failure 14%:6% Cerebrovascular disease 9%:4% Myocardial infaraction 9%:6%	74.3	59.5	NR
Lundkvist 2005(113)	Sweden	309	60	NR	Macro (mean complications) 0.24:0.25	NR	65	NR
Maggi 2013(114)	Italy	1,342	52.5	7.2 (55.2)		NR	73.3	NR
McCoy 2012(115)	USA	797	NR	NR		NR	NR	NR
McCoy 2013(116)	USA	326	53.1	7.6 (59.6)		NR	67.1	
Miller 2001(117)	USA	1,055	28.2	7.6 (59.6)		93.8	60.9	NR
Murata 2004(118)	USA	344	NR	NR		NR	NR	8.1 (insulin) (mean)
Neil 2007(119)	USA	5,965	NR	NR		NR	NR	NR
Ooi 2011(120)	Malaysia	170	41.2	8.02 (64.2)		100	NR	NR

Parsaik 2013(121)	USA	5,534	NR	NR		NR	NR	NR
Pettersson 2011(19)	Sweden	430	61	6.3 (45.4)	Macrovascular events 33%:32%	NR	69	NR
Rombopoulos 2013(122)	Greece	6,631	55	NR		NR	NR	NR
Samann 2013(123)	Germany	4,481	56	NR		NR	66	NR
Sarkar 2010(124)	USA	14,357	51	7.6 (59.6)		78	58	NR
Schopman 2010(54)	UK	110	51.6	NR		NR	NR	6.5 (median) (insulin)
Skinner 2014(125)	Australia	1,926	NR	NR		NR	NR	NR
Stahl 1999(126)	Switzerland	2,529	NR	NR		NR	NR	NR
Stargardt 2009(127)	Germany	392	57.4	7.2 (55.2)		NR	62.7	NR
Vexiau 2008(128)	France	400	53.6	7.2 (55.2)	Macrovascular events 26%:17%	NR	62.1	NR
Whitmer 2009(129)	USA	16,667	54.6	NR	Heart disease 84%:62% Stroke 44%:29%	37.2	64.9	6.6 (mean) (insulin
Williams 2012(10)	USA	813	58	NR		17	57	NR
Yun 2013(130)	Korea	878	38	8.8 (72.7)		NR	55.3	NR
The UK Hypoglycaemia study group 2007(131)	UK	274	70.1	7.5 (58.5)		NR	61	not reported for the study cohort included for hypo analysis
Zhang 2013(132)	China	586	59.2	7.5 (58.5)		100	55.1	NR

Abbreviations; HbA1c - glycated haemoglobin, NR - not reported, CVD – Cardiovascular disease, Hypo - hypoglycaemia

Table 3. 2: Characteristics of studies included in the systematic review (B)

First author (year)	Data Source (Hypo info)	Sampling method	Sample source	Design	Time hypo measured over	Hypo definition	Analysis[d]
Akram 2006	Questionnaire/ Recall	Consecutive	Health clinic attendees (outpatients diabetes clinic, single centre)	Cross-sectional	1 Year	Need for assistance	Severe[b]
Allen 2004	Prospective Diary	Consecutive	Health clinic/centre (outpatients, single centre)	Prospective	3 Months	Required glucose/glucogen. If tested BG <3.5mmol/L	Mild[a], Severe[b]
Andel 2008	Questionnaire/ Recall/Diary	Consecutive	Health clinic attendees (secondary care outpatient diabetes centres, multicentre)	Cross-sectional	1 Year	Local clinical standards + guidelines	Severe[b]
Aung 2011	Questionnaire/ Recall	Random	Diabetes registry/database (1 geographical location)	Cross-sectional	1 Year	Need for assistance	Severe[b]
Bourdelmarc-hasson 2007	Questionnaire/ Recall	Random	Health insurance database (national)	Cross-sectional	1 Year	Need for assistance	Severe[b]
Chan 2010	Questionnaire/ Recall	Consecutive	Health clinic attendees (outpatients, multicentre)	Cross-sectional	6 Months	Level of assistance/interruption to activities	Unspecified[c], Mild[a], Severe[b]
Davis 2005	Questionnaire/ Recall	Stratified	Health clinic records or from previous study	Cross-sectional	3 Months	Level of Symptoms, behvaiour, assistance	Unspecified[c], Mild[a], Severe[b]
Davis 2010	Questionnaire/ Recall	Non-random	Community population (particular geographical location)	Prospective	6.4 months (Mean)	Diagnosed by health service	Severe[b]
Donnelly 2004	Prospective Diary	Random	Diabetes registry/database (1 geographical location)	Prospective	1 Month	Need for assistance	Unspecified[c], Mild[a], Severe[b]
Green 2012	Questionnaire/ Recall	Stratified random	Community population (postcode defined)	Cross-sectional	1 Year	Low BG	Unspecified[c]

Gurlek 1999	Questionnaire/ Recall	Unclear	Health clinic attendees (outpatients, single centre)	Retrospective	3.33 years (mean)	Help needed due to neuroglycopenia/requi red parenteral glucose	Severe[b]
Henderson 2003	Questionnaire/ Recall	Random	Health clinic attendees (outpatients, diabetes clinic, single centre)	Cross-sectional	1 Year	Required glucose/glucagon, level of assitance	Unspecified[c], Mild[a], Severe[b]
Holstein 2003	Emergency records	All patients included that met inclusion criteria	Emergency records from one geographical location	Prospective	4 Years	Required intravenous glucose/glucagon. Confirmed BG.	Severe[b]
Honkasalo 2011	Questionnaire/ Recall/ Emergency dep records	All participants eligible invited	Health insurance database (2 geographical locations)	Cross-sectional/ Retrospective	1 Year	Need for assistance	Severe[b]
Jaap 1998	Questionnaire/ Recall	Consecutive	Health clinic attendees (outpatients, diabetes clinic, multicentre)	Cross-sectional	2 Months	Symptoms resolved with glucose/glucagon	Unspecified[c]
Johnston 2012	Claims database	All patients included that met inclusion criteria	Health insurance database	Retrospective	1 Year	Need for assistance	Severe[b]
Katon 2013	Emeregncy dep records/Health insurer	All participants eligible invited	Diabetes registry/database (primary care centres)	Prospective	5 years	Emergency visit or hospitalisation	Severe[b]
Krnacova 2012	Emergency records	All patients included that met inclusion criteria	Emergency records from one geographical location	Prospective	1 Year	Assistance of emergency services	Severe[b]
Lecomte 2008	Questionnaire/ Recall	Random	Health insurance database (national)	Cross-sectional	2 Year	Need for assistance	Severe[b]
Leese 2003	Emergency records	All patients included that met inclusion criteria	Diabetes registry/database (1 geographical location)	Prospective	3 Year	BG <3.5 mmol/L- glucose/glucagon needed	Severe[b]
Leiter 2005	Questionnaire/ Recall	Convenience	Health clinic attendees (multicentre)	Cross-sectional	1 month/1 year	BG <4.0mmol/L or <2.8 with assistance	Mild[a], Severe[b]
Lin 2012	Claims database/ Health insurer	Random	Health insurance database (national)	Retrospective	2 Years	Medical assistance required	Severe[b]

Lipska 2013	Questionnaire/ Recall	Stratified random	Diabetes registry/database (1 geographical location)	Cross-sectional	1 Year	Need for assistance	Severe[b]
Lundkvist 2005	Questionnaire/ Recall	Convenience	Health clinic attendees (7 centres)	Cross-sectional	2 Year	Level of assistance or BG <3.3 mmol/L	Unspecified[c], Severe[b]
Maggi 2013	Questionnaire/ Recall	Consecutive	Health clinic attendees (57 diabetes centres)	Cross-sectional	3 Months	Requiring hospitalisation	Unspecified[c], Severe[b]
McCoy 2012	Questionnaire/ Recall	Convenience	Health clinic attendees (diabetes clinic, single centre)	Cross-sectional	6 Months	Level of symptoms, assistance	Severe[b]
McCoy 2013	Questionnaire/ Recall	All patients included that met inclusion criteria	Diabetes registry/database (1 geographical location)	Cross-sectional	6 Months	Level of symptoms, assistance	Severe[b]
Miller 2001	Questionnaire/ Recall	All patients who met inclusion criteria and had sufficient data included	Health clinic attendees (diabetes clinic, single centre)	Cross-sectional	3.17 Months (mean)	Symptoms, behaviour, need for assistance or glucose <3.3mmol/L	Unspecified[c], Severe[b]
Murata 2004	Prospective Diary	Random	Pharmacy records (3 centres)	Prospective	11 Months (mean)	BG<3.3mmol/L	Unspecified[c]
Neil 2007	Questionnaire/ Recall	All participants eligible invited	Pharmacy records (5 centres)	Cross-sectional	6 Months	Need for assistance	Unspecified[c], Severe[b]
Ooi 2011	Questionnaire/ Recall	Consecutive	Health clinic attendees (primary care, 7 centres)	Cross-sectional	1 Year	Symptoms	Unspecified[c]
Parsaik 2013	Emergency records	All patients included that met inclusion criteria	Emergency records from one geographical location	Retrospective	6 years	Assistance of emergency services	Severe[b]
Pettersson 2010	Questionnaire/ Recall	Consecutive	Health clinic attendees (primary care, multicentre)	Cross-sectional	6 Months	Level of assistance/interruption to activities	Unspecified[c], Severe[b]
Rombopoulos 2013	Questionnaire/ Recall	Random	Community population (defined geographical locations distributed)	Cross-sectional	3 Months	Laboratory-confirmed clinical symptomatic	Unspecified[c], Severe[b]
Samann	Questionnaire/ Recall/	All participants	Health insurance	Retrospective	1 Year	Coma or	Severe[b]

2012	Emergency dep records	eligible invited	database			glucose/glucagon required	
Sarkar 2010	Questionnaire/ Recall	Stratified random	Health insurance database	Cross-sectional	1Year	Passing out or need for assistance	Severe[b]
Schopman 2009	Questionnaire/ Recall/ Prospective diary	Random	Health clinic attendees (secondary care, diabetes clinic, single centre)	Cross-sectional/ Prospective	1 month/1 year	Need for assistance or BG <3.3 mmol/L	Severe[b]
Skinner 2013	Questionnaire/ Recall	Random	Diabetes registry/database (national)	Cross-sectional	1 week	Low BG	Unspecified[c]
Stahl 1999	Emergency records	All patients included that met inclusion criteria	Emergency records from one geographical location	Retrospective	1 Year	Hospital Admission	Severe[b]
Stargardt 2009	Questionnaire/ Recall	Convenience	Health clinic attendees (92 centres)	Cross-sectional	6 Months	According to level of assistance/interruption to activities	Unspecified[c], Severe[b]
Vexiau 2008	Questionnaire/ Recall	Non-random	Health clinic attendees (primary care, 98 centres)	Cross-sectional	7 Months	According to level of assistance/interruption to activities	Unspecified[c], Mild[a], Severe[b]
Whitmer 2009	Emergency records	All participants eligible invited	Diabetes registry/database	Prospective	22 years	Emergency department diagnosis	Severe[b]
Williams 2012	Questionnaire/ Claims database	Random	Health insurance database	Cross-sectional	1 Year	Symptoms or BG <70mg/dL	Unspecified[c], Severe[b]
Yun 2013	Questionnaire/ Recall/ Emergency dep records	Consecutive	Health clinic attendees (outpatients, single centre)	Prospective	10.42 years (median)	Assistance needed to actively administer carbohydrate	Severe[b]
The UK Hypoglycaemia study group 2007	Prospective diary	Stratified	Health clinic attendees (secondary diabetes, 6 centres)	Prospective	10.50 months (median)	Symptoms or glucose BG <3.0 mmol/L + according to level of assistance	Mild[a], Severe[b]
Zhang 2013	Questionnaire/ Recall	Consecutive	Health clinic attendees (secondary care, outpatients, single centre)	Cross-sectional	3 Months	NR	Unspecified[c]

Abbreviations; HbA1c - glycated haemoglobin, NR - not reported, BG - blood sugar, Hypo – hypoglycaemia, [a]Mild/moderate hypoglycaemia - no third party assistance was needed, [b]Severe hypoglycaemia - third party assistance was required,.[c]Unspecified hypoglycaemia- severity not specified when gathering some or all of the hypoglycaemia data, [d]Category for meta-analysis

Over half of the studies reported only severe hypoglycaemia (n=24), while three studies reported severe and mild/moderate. There were six studies which reported data on unspecified hypoglycaemia, eight which reported data on unspecified hypoglycaemia along with severe, and five which reported data on unspecified, mild/moderate and severe. For studies reporting the prevalence of hypoglycaemia, the time period used for recall of previous hypoglycaemic episodes ranged from one month to 22 years. The majority of studies (n = 17) measured episodes over a period of 12 months. The measurement period for studies reporting the incidence of hypoglycaemia, ranged from one week to 22 years. The most frequently used was 12 months (9/21). A variety of methods/sources, either alone or in combination, were utilised to obtain relevant data. These included questionnaires (n = 25), emergency department records (n = 7), prospective diaries (n = 4), and claims databases (n = 3).

3.3.3 Study quality

A breakdown of study quality is shown in Table 3.3 Most studies received a high quality grading for the consideration of data collection bias (42/46, 91.3%) and confounding and explanatory factors (43/46, 93.5%). However, under half of studies scored well for sample bias (15/46, 32.6%).

Table 3. 3 Quality assessment of included studies

Author, Year	Sample Bias					Data Collection			Confounding factors
	Sample source representative and described well	Sampling method	Eligibility criteria applied and described	Sufficient sample response	Sample Bias overall	Data collection tool well described	Measurement reliability	Data Collection overall	Consideration of confounding explanatory factors
Akram, 2006	+	-	++	+	+	++	+	++	++
Allen, 2004	+	-	++	-	-	++	++	++	++
Andel, 2008	++	-	++	-	-	++	+	++	-
Aung, 2011	++	+	++	-	+	++	+	++	++
Bourdelmarch-asson, 2007	++	+	++	-	+	++	+	++	++
Chan, 2010	++	-	++	-	-	++	+	++	++
Davis, 2005	++	++	++	-	+	++	+	++	++
Davis, 2010	++	-	++	+	+	++	++	++	++
Donnelly, 2004	++	+	++	-	+	++	++	++	++
Green, 2012	++	++	++	+	++	++	+	++	++
Gurlek, 1999	+	-	++	-	-	+	+	+	++
Henderson, 2003	+	+	++	-	+	++	+	++	++
Holstein, 2003	++	++	++	++	++	++	++	++	++
Honkasalo, 2011	++	++	++	+	++	++	+	++	++
Jaap, 1998	++	-	++	-	-	++	+	++	++

Johnston, 2012	++	++	++	++	++	++	++	+	++
Katon, 2013	++	++	++	+	++	++	++	++	++
Krnacova, 2012	++	++	+	++	++	++	++	++	++
Lecomte, 2008	++	+	++	-	+	++	+	++	++
Leese, 2008	++	++	++	++	++	++	++	++	++
Leiter, 2005	++	-	++	++	+	++	+	++	++
Lin, 2012	++	+	++	++	++	++	++	++	++
Lipska, 2013	++	++	++	+	++	++	+	++	++
Lundkvist, 2005	++	-	++	-	-	++	+	++	++
Maggi, 2013	++	-	++	-	-	+	+	+	++
McCoy, 2012	+	-	++	-	-	++	+	++	++
McCoy, 2013	++	++	++	-	+	++	+	++	++
Miller, 2001	+	++	++	++	++	++	+	++	++
Murata, 2004	++	+	++	-	+	++	++	++	++
Neil, 2007	++	++	++	-	++	++	+	++	++
Ooi, 2011	++	-	++	-	-	+	+	+	-
Parsaik, 2013	++	++	++	++	++	++	++	++	++
Pettersson, 2010	++	-	++	-	-	++	+	++	++
Rombopoulos, 2013	++	+	+	-	+	++	+	++	++

Samann, 2012	++	++	++	-	+	++	++	++	++
Sarkar, 2010	++	++	++	+	++	++	+	++	++
Schopman, 2009	+	+	++	-	+	++	+	++	++
Skinner, 2013	+	++	++	-	+	++	+	++	++
Stahl, 1999	++	++	++	++	++	++	++	++	++
Stargardt, 2009	++	-	++	-	-	++	+	++	-
Vexiau, 2008	++	-	++	-	-	++	+	++	++
Whitmer, 2009	++	++	++	++	++	++	++	++	++
Williams, 2012	++	+	++	-	+	+	+	+	++
Yun, 2013	+	-	++	+	+	++	+	++	++
The hypoglycaemia study group, 2007	++	++	++	++	++	++	++	++	++
Zhang, 2013	+	-	++	-	-	+	+	+	++

*Criteria were marked on a scale of "++", "+" or "-"

3.3.4 Prevalence of people who have experienced hypoglycaemia

Overall 46 studies involving 532,542 participants were included for the meta-analyses examining the prevalence (proportion of people who had experienced hypoglycaemia). Eight papers involving 4,083 participants, measuring over a period of one month to 10.5 months, reported mild/moderate hypoglycaemia. The pooled prevalence of people who had experienced hypoglycaemia was 0.45 (95% CI 0.33 to 0.56; Figure 3.2). In relation to those on insulin as a diabetes treatment regime, the prevalence was 0.52 (95% CI 0.37 to 0.67) compared with 0.33 (95% CI 0.24 to 0.42) for sulphonylureas, Table 3.4. Data were not available to calculate any further treatment categories.

Study ID	ES (95% CI)	% Weight
Henderson 2003	0.64 (0.57, 0.70)	12.55
Donnelly 2004	0.42 (0.35, 0.50)	12.40
Allen 2004	0.20 (0.07, 0.32)	11.40
Leiter 2005	0.73 (0.65, 0.80)	12.36
Davis 2005	0.52 (0.48, 0.56)	12.85
The UK Hypoglycaemia study group 2007	0.50 (0.44, 0.56)	12.62
Vexiau 2008	0.29 (0.25, 0.34)	12.81
Chan 2010	0.29 (0.27, 0.31)	13.01
Overall (I-squared = 97.8%, p = 0.000)	0.45 (0.33, 0.56)	100.00

NOTE: Weights are from random effects analysis

Figure 3.2 Forest plot showing the proportion of people experiencing mild/moderate hypoglycaemia in each study and the overall pooled estimate

The meta-analysis for the prevalence of severe hypoglycaemia included 40 papers involving 528,310 participants, measuring over a period of one month to 22 years, with a pooled prevalence of 0.06 (95% CI 0.05 to 0.07; Figure 3.3). For people on insulin as a treatment regime, the prevalence was relatively

higher (0.21 [95% CI 0.16 to 0.25]) when compared with regimens involving sulphonylurea (0.05 [95% CI 0.02 to 0.07]), non sulphonylurea therapies (0.05 [95% CI 0.03 to 0.07] and mixed oral glucose- lowering therapies (0.05 [95% CI 0.02 to 0.07]); Table 3.4). In 14 studies involving 473,481 participants, severe hypoglycaemic episodes were restricted to only those requiring medical assistance (not any third party assistance), the overall pooled prevalence was 0.05 (95% CI 0.03 to 0.06). When these studies were excluded the overall pooled prevalence for severe hypoglycaemia was 0.08 (95% CI 0.06 to 0.10), see Table 3.4.

Study ID	ES (95% CI)	% Weight
Gurlek 1999	0.18 (0.11, 0.26)	1.08
Stahl 1999	0.01 (0.01, 0.02)	2.77
Miller 2001	0.00 (0.00, 0.01)	2.77
Leese 2003	0.01 (0.01, 0.01)	2.78
Henderson 2003	0.15 (0.10, 0.20)	1.64
Holstein 2003	0.01 (0.01, 0.02)	2.78
Donnelly 2004	0.03 (0.00, 0.05)	2.33
Allen 2004	0.00 (-0.00, 0.00)	2.78
Leiter 2005	0.14 (0.08, 0.20)	1.33
Davis 2005	0.04 (0.02, 0.06)	2.58
Lundkvist 2005	0.02 (0.01, 0.04)	2.56
Akram 2006	0.16 (0.13, 0.20)	1.98
Bourdelmarchasson 2007	0.08 (0.07, 0.09)	2.70
Neil 2007	0.09 (0.08, 0.10)	2.74
The UK Hypoglycaemia study group 2007	0.12 (0.08, 0.16)	1.91
Lecomte 2008	0.10 (0.09, 0.11)	2.69
Andel 2008	0.02 (0.02, 0.02)	2.77
Vexiau 2008	0.04 (0.02, 0.06)	2.50
Schopman 2009	0.03 (-0.00, 0.06)	2.16
Stargardt 2009	0.04 (0.02, 0.06)	2.50
Whitmer 2009	0.09 (0.08, 0.09)	2.77
Sarkar 2010	0.11 (0.10, 0.12)	2.76
Davis 2010	0.08 (0.06, 0.11)	2.42
Chan 2010	0.07 (0.06, 0.08)	2.69
Pettersson 2010	0.02 (0.01, 0.03)	2.63
Honkasalo 2011	0.07 (0.06, 0.09)	2.59
Aung 2011	0.08 (0.06, 0.10)	2.57
Johnston 2012	0.05 (0.05, 0.05)	2.78
Krnacova 2012	0.00 (0.00, 0.00)	2.78
Lin 2012	0.02 (0.02, 0.02)	2.78
McCoy 2012	0.03 (0.02, 0.04)	2.66
Samann 2012	0.00 (0.00, 0.01)	2.78
Williams 2012	0.08 (0.07, 0.10)	2.50
Yun 2013	0.13 (0.10, 0.15)	2.42
Katon 2013	0.07 (0.06, 0.08)	2.73
Rombopoulos 2013	0.12 (0.11, 0.12)	2.73
Parsaik 2013	0.09 (0.08, 0.10)	2.73
McCoy 2013	0.17 (0.13, 0.21)	1.84
Maggi 2013	0.02 (0.01, 0.03)	2.73
Lipska 2013	0.11 (0.10, 0.11)	2.75
Overall (I-squared = 99.7%, p = 0.000)	0.06 (0.05, 0.07)	100.00

NOTE: Weights are from random effects analysis

-.255   0   .255
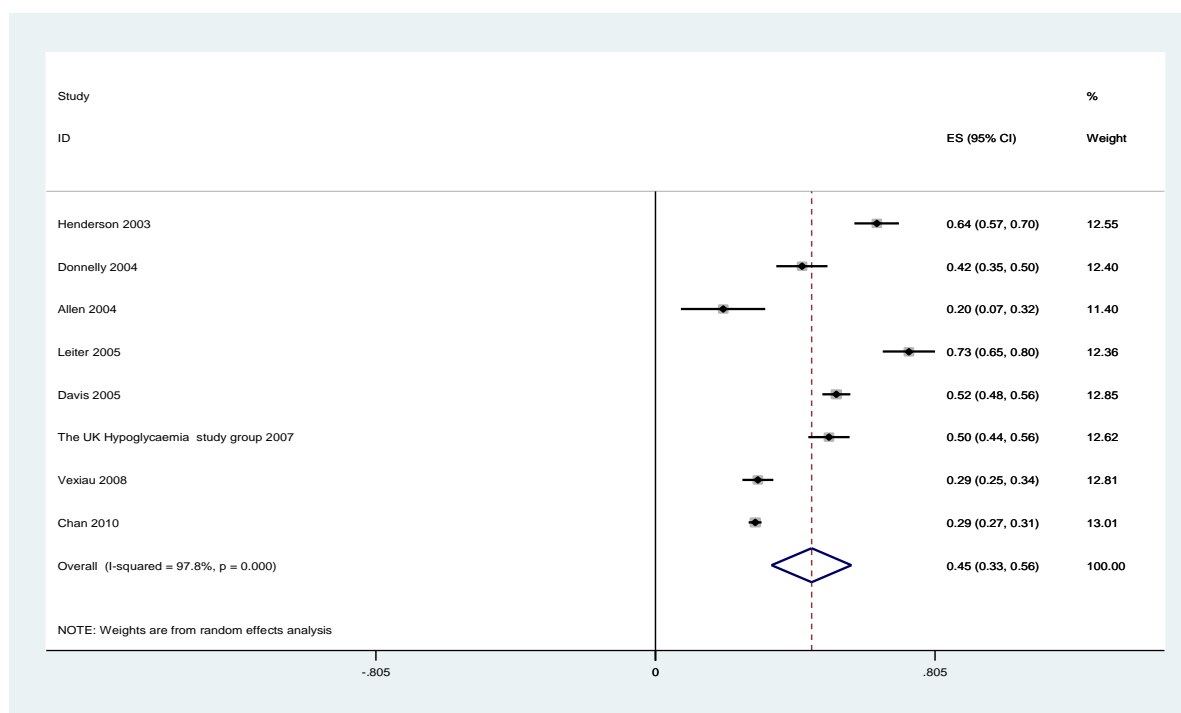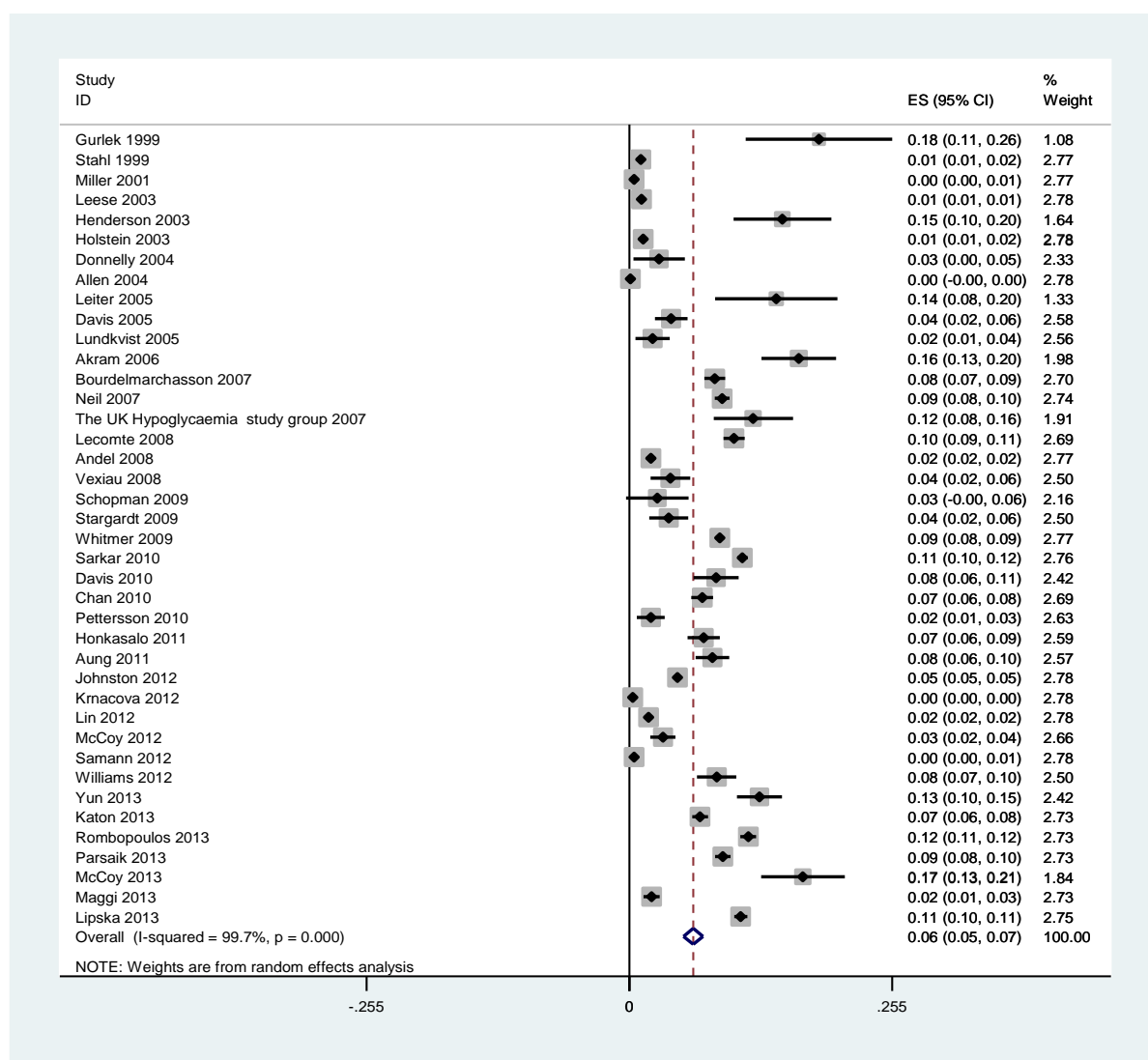
Figure 3. 3 Forest plot showing the proportion of people experiencing severe hypoglycaemia in each study and the overall pooled estimate

Table 3. 4 Prevalence and incidence of people experiencing hypoglycaemia by severity and treatment regime

	Unspecified		Mild/Moderate		Severe	
	Prevalence	*Incidence (person year)*	*Prevalence*	*Incidence (person year*	*Prevalence*	*Incidence (person year)*
Insulin[a]						
N studies (subjects)	8 (2539)	3 (649)	5 (728)	3 (513)	20 (17881)	11 (6851)
Pooled estimate (95% CI)	0.57 (0.42 to 0.71)	9.25 (1.38 to 17.13)	0.52 (0.37 to 0.67)	23.31 (0.00 to 58.98)	0.21 (0.16 to 0.25)	1.05 (0.00 to 3.69)
I^2	98.4%	99.7%	94.5%	100.0%	99.7%	92.8%
Sulphonylureas[b]						
N studies (subjects)	6 (8390)	0 (0)	2 (508)	1 (108)	8 (12872)	3 (3538)
Pooled estimate (95% CI)	0.26 (0.02 to 0.50)	Insufficient data	0.33 (0.24 to 0.42)	1.92 (0.51 to 3.33)	0.05 (0.02 to 0.07)	0.01 (0.00 to 0.55)
I^2	98.4%		69.1%	N/A	98.5%	0.0%
Non-sulphonylureas[c]						
N studies (subjects)	4 (2135)	0 (0)	0 (0)	0 (0)	2 (646)	0 (0)
Pooled estimate (95% CI)	0.26 (0.02, to 0.50)	Insufficient data	Insufficient data	Insufficient data	0.05 (0.03 to 0.07)	Insufficient data
I^2	99.6%				0.0%	
Mixed oral glucose-lowering therapies [d]						
N studies (subjects)	2 (568)	0 (0)	0 (0)	0 (0)	7 (35041)	2 (1861)
Pooled estimate (95% CI)	0.40 (0.30 to 0.51)	Insufficient data	Insufficient data	Insufficient data	0.05 (0.02 to 0.07)	0.01 (0.00 to 5.16)
I^2	0.0%				99.5%	0.0%
Proportion overall[e]						
N studies (subjects)	18 (24804)	5 (5575)	8 (4083)	4 (621)	40 (528310)	19 (76254)
Pooled estimate (95% CI)	0.43 (0.36 to 0.50)	27.78 (0.00 to 58.20)	0.45 (0.34 to 0.57)	19.03 (0.00 to 51.08)	0.06(0.05 to 0.07)	0.80 (0.00 to 2.15)
I^2	99.4%	100.0%	97.8%	100.0%	99.7%	87.0%

Abbreviations: CI, Confidence Interval

[a]Insulin (with or without oral glucose-lowering therapies)

[b]Sulphonylureas (non-insulin but with or without other oral glucose-lowering therapies)

[c]Non-sulphonylureas (non-insulin and non-sulphonylurea oral glucose-lowering therapies)

[d]Mixed oral glucose-lowering therapies (non-insulin but no further description given relating to type of oral glucose-lowering therapies).

[e]All studies combined regardless of treatment

Eighteen papers involving 24,804 participants, measuring over one month to one year, reported data for the prevalence of unspecified type of hypoglycaemia (severity of hypoglycaemia experienced was not specified when data collecting, assumed to cover both mild/moderate and severe episodes), with a pooled prevalence of 0.43 (95% confidence interval (CI) 0.36 to 0.50), Table 3.4.

There was high heterogeneity shown between studies reporting mild/moderate (I^2 = 98.0%), severe (I^2 = 99.7%) unspecified (I^2 = 99.4%) hypoglycaemia prevalence. A possible explanatory variable for this was the different time period hypoglycaemia was measured over between studies. This along with other explanatory variables: year of publication, mean HbA1c, mean age, and percentage of male participants were carried out in a meta-regression on the prevalence of, mild/moderate, severe and unspecified hypoglycaemia. No variables were shown to be statistically significant, see Table 3.5.

Table 3. 5 Meta-regression results showing the effect of study-level variables on the proportion of people experiencing each severity of hypoglycaemia

Explanatory variable	N studies	Effect (95% CI)	P-value
Unspecified Hypoglycaemia			
Mean age, years	14	0.00 (0.00, 0 .00)	0.52
% Male participants	9	0.00 (0.00, 0.00)	0.31
Mean HbA1c, %	10	0.15 (0.00, 0.31)	0.06
Time, years	16	0.11 (0.00, 0.44)	0.46
Year of publication	18	0.00 (0.00, 0.00)	0.06
Mild/Moderate Hypoglycaemia			
Mean age, years	6	0.00 (0.00, 0.00)	0.81
% Male participants	4	0.00 (0.00, 0.01)	0.75
Mean HbA1c, %	6	0.07 (0.00, 0.41)	0.63
Time, years	7	0.00 (0.00, 0.56)	0.28
Year of publication	8	0.00 (0.00, 0.04)	0.28
Severe Hypoglycaemia			
Mean age, years	31	0.00 (0.00, 0.00)	0.98
% Male participants	25	0.00 (0.00, 0.00)	0.18
Mean HbA1c, %	18	0.03 (0.00, 0.07)	0.12
Time, years	39	0.00 (0.00, 0.01)	0.41
Year of publication	40	0.00 (0.00, 0.01)	0.41

Abbreviations: CI, Confidence Interval; HbA1c, glycated haemoglobin

3.3.5 Incidence of hypoglycaemic episodes per person-year

The pooled incidence of hypoglycaemic episodes per person-year for mild/moderate and severe hypoglycaemia was 19.03 (95% CI 0.00 to 51.08) and 0.80 (95% CI 0.00 to 2.15, Table 3.4, Figure 3.4), respectively. Unspecified hypoglycaemia episodes showed a pooled incidence of 27.78 (95% CI 0.00 to 58.20; per person–year). Those on insulin experienced 23.31 (95% CI 0.00 to 58.98) mild/moderate and 1.05 (95% CI 0.00 to 3.69) severe episodes per person-year. Data were not available to calculate any further treatment categories for mild/moderate, but a further incidence of 0.01 (95% CI 0.00 to 0.55) for those on sulphoylureas experiencing severe episodes was estimated.
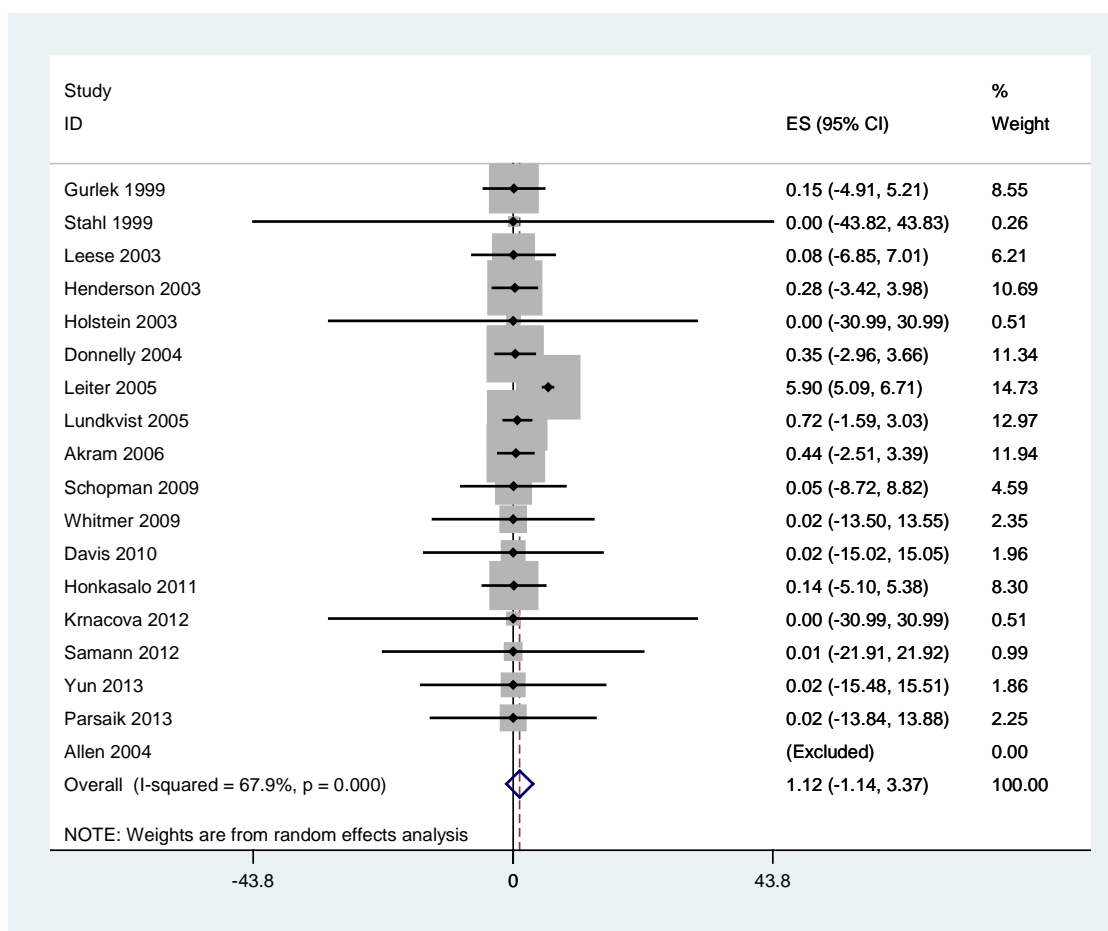
Study ID	ES (95% CI)	% Weight
Gurlek 1999	0.15 (-4.91, 5.21)	8.55
Stahl 1999	0.00 (-43.82, 43.83)	0.26
Leese 2003	0.08 (-6.85, 7.01)	6.21
Henderson 2003	0.28 (-3.42, 3.98)	10.69
Holstein 2003	0.00 (-30.99, 30.99)	0.51
Donnelly 2004	0.35 (-2.96, 3.66)	11.34
Leiter 2005	5.90 (5.09, 6.71)	14.73
Lundkvist 2005	0.72 (-1.59, 3.03)	12.97
Akram 2006	0.44 (-2.51, 3.39)	11.94
Schopman 2009	0.05 (-8.72, 8.82)	4.59
Whitmer 2009	0.02 (-13.50, 13.55)	2.35
Davis 2010	0.02 (-15.02, 15.05)	1.96
Honkasalo 2011	0.14 (-5.10, 5.38)	8.30
Krnacova 2012	0.00 (-30.99, 30.99)	0.51
Samann 2012	0.01 (-21.91, 21.92)	0.99
Yun 2013	0.02 (-15.48, 15.51)	1.86
Parsaik 2013	0.02 (-13.84, 13.88)	2.25
Allen 2004	(Excluded)	0.00
Overall (I-squared = 67.9%, p = 0.000)	1.12 (-1.14, 3.37)	100.00

NOTE: Weights are from random effects analysis

Figure 3. 4 Forest plot showing the incidence of severe hypoglycaemia in each study and the overall pooled estimate

There was high heterogeneity shown between studies reporting mild/moderate (I^2 = 100.0%), severe (I^2 = 67.9%) unspecified (I^2 = 100.0%) hypoglycaemia prevalence. A possible explanatory variable for this was the different time period hypoglycaemia was measured over between studies. This along with other explanatory variables: year of publication, mean HbA1c, mean age, and percentage of male participants were carried out in a meta-regression on the incidence of, mild/moderate, severe and unspecified hypoglycaemia. No variables were shown to be statistically significant, except for mean HbA1c for severe events and mean age for mild events, see Table 3.6.

Table 3. 6 Meta-regression results showing the effect of study-level variables on the incidence of hypoglycaemia

Explanatory variable	N studies	Effect (95% CI)	P-value
Unspecified Hypoglycaemia			
Mean age, years	6	0.11 (-1.25, 1.48)	0.83
% Male participants	2	Insufficient observations	
Mean HbA1c, %	6	-2.46 (-11.15, 6.22)	0.48
Time, years	4	38.94 (-139.98, 217.856)	0.45
Year of publication	6	3.59 (-1.44, 8.63)	0.12
Mild/Moderate Hypoglycaemia			
Mean age, years	3	-0.97 (-1.34, -0.59)	0.02
% Male participants	2	Insufficient observations	
Mean HbA1c, %	3	3.67 (-70.03, 77.36)	0.64
Time, years	3	-221.79 (-3511.29, 3067.69)	0.55
Year of publication	3	55.95 (-76.90, 188.80)	0.12
Severe Hypoglycaemia			
Mean age, years	11	-0.03 (-0.22, 0.16)	0.71
% Male participants	10	-0.57 (-1.28, 0.13)	0.10
Mean HbA1c, %	5	-4.90 (-7.94, -1.87)	0.01
Time, years	17	-0.04 (-0.69, 0.62)	0.91
Year of publication	17	-0.04 (-0.67, 0.60)	0.90

Abbreviations: CI, Confidence Interval; HbA1c, glycated haemoglobin

3.3.6 Publication bias

There appeared to be publication bias for studies reporting prevalence of severe hypoglycaemia (p=0.04), with studies reporting lower prevalence appearing to be missing from published literature, figure 3.4. However, when analysis was carried out separating the study results relating to medical assistance only, from any third party assistance, there was no evidence of

publication bias (p=0.41 and; p=0.36 respectively). No other significant publication bias was shown for prevalence (mild/moderate p=0.09, unspecified p=0.37) or for incidence (mild/moderate p=0.06, severe p=0.91, unspecified p=0.06).
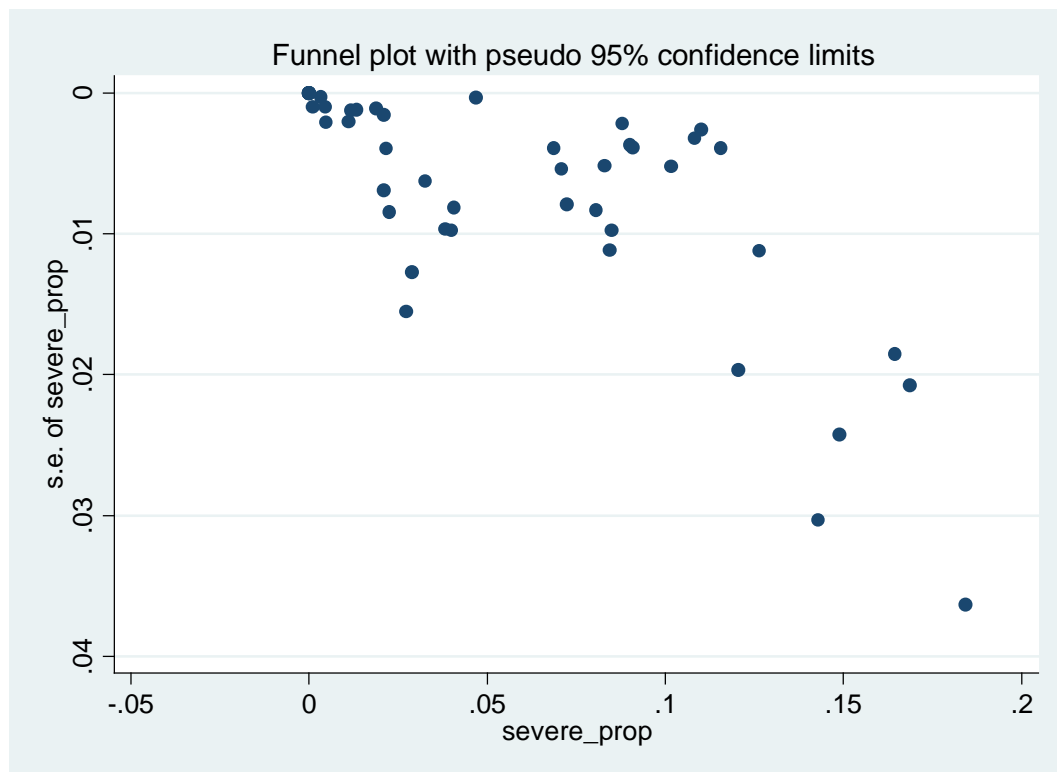

Figure 3.5 Funnel plot of population based studies reporting severe hypoglycaemia

3.4 Discussion

3.4.1 Summary of findings

This review of 46 studies (n=532,542) estimates that the prevalence (proportion of people) of hypoglycaemia is 45% for mild/moderate and 6% for severe in population-based studies of T2DM, and that on average an individual with T2DM experiences 19 mild/moderate episodes and 0.8 severe episodes per year. Hypoglycaemia is particularly prevalent amongst those on insulin (mild/moderate: prevalence = 52%, incidence = 23 events/ year; severe: prevalence = 21%, incidence = 1 event/year, yet still fairly common for treatment regimens that include sulphonylureas (mild/moderate: prevalence = 33%, incidence = 1.92 events/year; severe: prevalence = 5, incidence = 0.01 events/year. Severe hypoglycaemia prevalence was the same 5% for those on treatment regimens that did or did not include sulphonylureas.

3.4.2 Relationship to other literature

Previous literature focusing on hypoglycaemia in T2DM in a real-world setting is limited. One report of severe hypoglycaemia prevalence in clinical trials also considered severe hypoglycaemia prevalence in population based studies, but did not examine mild/moderate episodes nor provide pooled estimates (84). Various systematic reviews have considered hypoglycaemia prevalence within randomised controlled trials involving people with T2DM (86-89). These tend to focus on individuals using insulin and their results indicate that severe hypoglycaemia prevalence is below 1%, which is substantially lower than our pooled estimate of 6% from population-based studies. Mild/moderate hypoglycaemia is reported less in clinical trials, though recent meta-analyses of clinical trials showed pooled prevalences of 10% (range 0.7% - 22%) for those on sulphonylureas (133), and 20% to 52% for those on insulin (134-136). Our estimate for sulphonylureas was higher at 33% (range 30% - 39%), but for insulin was similar, albeit at the higher end of the scale, at 52% (range 20% - 72%). Mild/moderate hypoglycaemia prevalence was fairly consistent across

trials, as was the case in the population-based studies in this review. Randomised controlled trials often do not reflect real life situations as treatment regimens are more aggressively titrated than in standard clinical practice, and participants are often highly selected and generally do not include those at higher risk of hypoglycaemia. Therefore, the generalizability of results from trials is limited.

3.4.3 Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis published which focuses on population-based studies of hypoglycaemia in people with T2DM. The review adhered to the Cochrane (94) and PRISMA (137) recommended standards for systematic reviews. It involved robust methodology such as duplicate reviewing, and only included population-based studies which reported prevalence and/or incidence rates specifically for a T2DM population, making the results applicable to the T2DM general population. The results follow the American Diabetes Association (ADA) Workgroups recommendations that both the proportion of patients experiencing hypoglycaemia and event rates for each severity are reported (138).

There was high heterogeneity between studies, which was not explained by any of the study level covariates considered. Therefore, the high heterogeneity is likely to be due to the very narrow confidence intervals associated with the proportion estimates, or to other study characteristics which were not measured, reported or extracted. Publication bias appeared to be a possibility for the published studies on severe hypoglycaemia. However, this appeared to be due to the different definitions of severe hypoglycaemia, since no such bias was present when studies that defined severe as requiring medical assistance were separated from those using the standard definition (requiring any third party assistance).

A strict consensus definition was not found across studies (table 3.2). Due to the nature of a large proportion of the studies (questionnaire/interview/medical records), a biochemical definition was rarely used. It must be acknowledged

that this does create some difficulty when collating and combining results across studies. For some studies this may have caused under or over reporting. Subsequently, the only way to define and analyse hypoglycaemia was by severity and whether or not third party assistance was required during an episode. Other factors which must be considered when discussing the limitations of the work relate to not all hypoglycaemic episodes reported in the studies being necessarily confirmed and consequently over or under estimating the prevalence. Also, in some cases hypoglycaemic events can be asymptomatic and may have been missed and not reported. These issues are common in population based studies, where study design often includes questionnaires and costs of implementing CGMS for a long period of time are unachievable.

The way in which studies categorised different glucose lowering therapies also varied considerably, if indeed they reported hypoglycaemia by treatment categories at all. Therefore, it was only possible to use broader treatment categories in these analyses. It is important to note here also, that the event rate calculated for severe hypoglycaemia in those using sulphonylureas may appear particularly low. This is likely to be due to two of the three studies used to calculate this result only measuring "very severe" hypoglycaemia, those that specifically needed emergency treatment.

Additionally, studies varied considerably in length of time hypoglycaemia prevalence was related to; as a result a specific time period for prevalence could not be established. This was particularly the case for severe hypoglycaemia. However, a meta-regression was carried out for time hypoglycaemia was measured over on prevalence and it was not found to significantly affect the prevalence reported between studies.

Data from some studies could not be grouped by the severity of hypoglycaemia (mild/moderate or severe). These data were therefore labelled as "unspecified" and assumed to include any type of hypoglycaemic episodes. Nocturnal hypoglycaemia was not analysed due to the lack of reporting within studies.

3.5 Concluding remarks

This chapter presented a systematic review and meta-analyses of the prevalence and incidence of hypoglycaemia in T2DM within real world population based studies. The review showed that hypoglycaemia is considerably prevalent amongst people with T2DM. The implications for practice and research will be discussed in chapter 5. The review has been published in PLOS One and I also presented the work at Diabetes UK 2015.

Chapter 4: Views, experiences and knowledge of hypoglycaemia in Type 2 diabetes mellitus (T2DM)

4.1 Introduction

The systematic review presented in chapter 3 provided prevalence and incidence rates for hypoglycaemic episodes showed that they are considerably prevalent amongst people with T2DM. Further exploration and descriptive in-depth data are needed to explain and understand them further from patient perspectives and the potential implications.

4.1.1 Chapter overview

This chapter presents a qualitative study carried out to explore and understand the views and experiences of people with T2DM who have experienced hypoglycaemia. The introduction (section 4.1) highlights issues relating to hypoglycaemia that have been found from previous studies, and require further exploration through qualitative research. The rationale and aims of this study are also described in this section. Following this, section 4.2 describes the methods, section 4.3 and 4.4 shows the descriptive results by key themes and differences by ethnic origin, whilst 4.5 proposes an analytical framework which has arisen from the findings. The relationship to previous literature and strengths and weaknesses of the study are then discussed (section 4.6). Contributions for the work in this chapter are described in Appendix 1.

4.1.2 Background and rationale

The impact of hypoglycaemia in T2DM and the importance of research into this area are covered in chapter 2. However, in brief, hypoglycaemia in T2DM is a burden to the National health service (NHS), financially and in terms of resources such as facilities, staffing and time (12). Hypoglycaemic episodes also have a risk of serious long and short term health consequences for

individuals. They can impact on many other issues also such as driving, social relationships and quality of life (10, 20, 139).

Optimum management of diabetes is vital in helping to prevent hypoglycaemic episodes. Careful management of diabetes through education, treatment, physical activity and food all play a role in prevention (140). The patient is central in their management, with concepts such as engagement with healthcare practitioner (HCP) (64, 65) and empowerment (69) discussed in section 2.7 often incorporated into care.

Much of the published research evidence on hypoglycaemia is derived from quantitative studies focusing on rates (chapter 3), quality of life (23), fear of hypoglycaemia (20) and driving (26). There is a lack of in-depth data around hypoglycaemia within T2DM. Previous qualitative studies have tended to focus on type 1 diabetes (53, 141, 142) or were conducted in non UK populations. One study conducted in Ukraine within a T2DM population explored the impact of hypoglycaemia and briefly considered the patient-physician relationship (143). Another explored how Singapore Chinese adults viewed hypoglycaemia and its impact, though the study only considered views of six participants (144).

An exploration of people's experiences through qualitative research can provide an insight of their understanding and knowledge of hypoglycaemia and behaviours associated with the prevention and management of hypoglycaemic episodes. These insights have the potential to help understand further the preventative methods patients take and the negative impact hypoglycaemia can potentially have on physical and mental health. It is also important to explore further the circumstances in which hypoglycaemia is disclosed to HCPs and possible reasons behind the lack of disclosure. This will help to provide information on potential facilitators to encourage disclosure, which in turn could enable HCPs to offer appropriate education or treatment modification advice in order to prevent future episodes.

4.1.3 Aim and Objectives

The overall aim of the research was to explore and understand the views and experiences of people with T2DM who have experienced hypoglycaemia. The specific objectives were:

- To identify levels of knowledge and understanding of hypoglycaemia
- To explore attitudes, experiences and symptoms of hypoglycaemic episodes
- To explore people's behaviour which aim to prevent or self-treat future hypoglycaemic episodes and associated feelings
- To understand attitudes and experiences about disclosure of hypoglycaemia
- To compare and contrast findings in relation to ethnicity and age

4.2 Methods

Ethics and governance approvals (appendix 6) were obtained from: NRES Committee East Midlands; NHS Leicester City CCG; NHS West Leicestershire CCG; NHS East Leicestershire & Rutland CCG; and University Hospitals of Leicester NHS Trust.

4.2.1 Design

A qualitative study using principles underlying grounded theory and semi-structured interviews was conducted. The principles of grounded theory used included (145):

- Theory is grounded in the data with an inductive methodology
- Open flexible approach with simultaneous involvement with data analysis and data collection
- Guiding interests used for starting points as opposed to limiting your data analysis – analytical categories developed from the data rather than preconceived concepts or hypotheses

- Data analysis is inductive - generating theory rather than starting with a theoretical framework
- Data analysis starts early on in data collection with emerging analysis shaping future data collection – subsequently collecting more data around emerging themes

4.2.2 Topic guide

Initially a brief topic guide to help with guiding the interviews was drafted, the content of which was informed by existing literature (covered in section 4.1.2). This helped with determining some initial areas of exploration and questions for the interviews. An invitation was then sent out to the T2DM patient participation group at Leicester General Hospital to attend a focus group, with a view to obtaining their advice about the wording of some questions and feedback on what they felt some of the likely responses to questions would be. Eight members in total participated in the focus group meeting and were from diverse ethnic backgrounds. Their contributions helped to refine and add several new lines of enquiry and were used to prepare a further draft of the topic guide.

Areas the focus group provided feedback on included:

- Knowledge and understanding of hypoglycaemia
- Source of knowledge regarding hypoglycaemia
- Hypoglycaemia symptom experience
- Self-treatment methods for hypoglycaemia
- Utilisation of third party support during an episode of hypoglycaemia (including friends, family, work colleagues and HCPS)
- Treatment or lifestyle modifications following an episode of hypoglycaemia
- Attitudes and experiences about disclosure of hypoglycaemia (including HCPs, work colleagues and family)

The guide was intended to be a flexible instrument allowing scope for additional lines of enquiry to emerge during the interviews and was therefore revised as

any new issues emerged during data collection. Questions were often open ended, with additional probes for the interviewer to use if needed. A final version of the topic guide can be seen in appendix 7.

4.2.3 Recruitment

It was anticipated that up to 20 interviews would be required to enable an exploration of participant accounts and address the study's aims and objectives, within the limited timeframe available for recruitment, data collection and analysis.

A quota sampling frame (appendix 8) was developed to help guide the recruitment process, to ensure a purposive sample of participants were recruited, and enable the capture a of diverse range of views and experiences based on the following factors:

- Different treatment regimens, including insulin and/or oral glucose-lowering therapies
- Differing hypoglycaemia severity experience (mild, severe or both),
- Age, gender and ethnicity.

The recruitment process involved contacting participants who had previously participated in another hypoglycaemia related study (HYPO study - ethics number 11/EM//0228) and had given their consent to be contacted about other studies. These previous participants were sent a letter of invitation to participate in this study by the Principal Investigator of the HYPO study (appendix 9). Invitation letters were sent out in batches of 50 until the required response was reached. To enable purposive sampling, potential participants were asked to return a reply slip with completed information relating to: age, ethnicity, diabetes treatment regimen and type of hypoglycaemia previously experienced. Once a reply slip was returned selected participants were contacted and an interview was arranged. Those participants who were not included were contacted, thanked and advised they would not be needed for this study. In instances where a reply slip was returned reporting no hypoglycaemia (making the

respondent ineligible), confirmation was sought from their questionnaire for the HYPO study.

Inclusion and exclusion criteria

Participants for this study were required to be:

- Adults aged 18 years or over with T2DM
- Have previously experienced at least one hypoglycaemic episode

Recruitment and data collection were guided by emerging themes and the recruitment process discontinued when the quota was achieved as theoretical saturation was reached.

4.2.4 Data Collection and Recording

Interviews took place at either a specialist outpatients department or a primary care health centre in Leicester. Full written informed consent was obtained from participants (and any family member present in the interview) immediately before the interview commenced. An example consent form can be found in appendix 10. The interviews were conducted by the author in English language, audio-recorded and transcribed verbatim by an independent professional transcribing company. A reflexive diary for all interviews was kept to record observations and reflections on the process and content of the interviewing. Entries included rapport with volunteer, contextual issues that may have influenced the quality and content of the interview and additional issues identified for inclusion in subsequent interviews.

4.2.5 Data analysis

Preliminary analysis was undertaken during the data collection to respond to emergent themes of relevance to the aims and objectives of the study. Upon completion of the recruitment detailed analysis of the data involved taking an inductive approach, to ensure findings were grounded in the data.

The detailed analysis commenced with a process of open coding themes. This was followed by grouping of these themes to progressively and systematically develop an initial provisional coding frame. This process utilised the constant comparison approach to data analysis (145). The provisional coding frame consisted of descriptive and conceptual categories. Progressive and systematic recoding of data using constant comparison continued until a final coding frame was reached. NVivo software was used throughout the process to aid with open and progressive coding. Framework charts were also used once the final coding framework had been developed/formed to help with data management and organisation, and to facilitate an informed insight of relationships and links between themes.

4.3 Descriptive results

The following section describes the characteristics of the final sample of participants

4.3.1 Final sample

150 invitations were sent out, with 53 respondents. 22 volunteers were subsequently invited to be interviewed, two of which did not attend, leaving a final sample of 20. In four of the interviews the participants spouse or a close relation were also present and took part in the interview. The interviews were conducted with 10 participants on only oral glucose-lowering therapy and 10 on insulin (+/- oral glucose lowering therapy), which is in line with our quota sampling frame. Of those on insulin four, were or South Asian Origin and six were White European. Detailed sample characteristic can be seen in Table 4.2.

Table 4. 2 Characteristics of participants interviewed

	N (%)
Sex	
Male (M)	13 (65)
Female (F)	7 (35)
Age (years)	
44 – 54	4 (20)
55 – 64	9 (45)
65 – 77	7 (35)
Ethnicity	
White European (WE)	9 (45)
South Asian (SA)	9 (45)
Other (O)	2 (10)
Medication	
OAD'S, n=10 (50%) Metformin	
Metformin alone	2 (20)
Metformin + Pioglitazone	1 (20)
Metformin + Repaglinide	1 (10)
Metformin + Sulphonylurea	3 (30)
Metformin + Sulphonylurea + DPP-4i	2 (20)
DPP-4i alone	1 (10)
Insulin, n=10 (50%)	
Insulin alone	1 (10)
Insulin + Metformin	8 (80)
Insulin + GLP-1ra	1 (10)
Diabetes Duration (years)	
3 – 5	2 (10)
6 – 10	9 (45)
11 – 20	9 (45)

Abbreviations: DPP-4i = Dipeptidyl peptidase 4 Inhibitor, GLP-1 ra= Glucagon-like peptide receptor inhibitor

4.3.2 Themes identified from the interviews

The following section provides an overall descriptive summary of participant experiences relating to hypoglycaemia. This is followed by the presentation of the analytical framework developed inductively from the data.

4.3.2.1 Severity and frequency of hypoglycaemia

Participant experiences relating to severity and frequency of hypoglycaemic episodes were varied. Hypoglycaemia for some participants was a weekly occurrence, whilst for others it occurred yearly. Nearly half of the participants had experienced both mild and severe hypoglycaemia (n=8), whilst the other half had experienced only mild (n=9) and for one only severe.

4.3.2.2 Where did they happen?

Participants described experiencing hypoglycaemic episodes at work, or whilst undertaking activities such as walking or shopping. One of these participants discussed his experience of a hypoglycaemic episode whilst out going for a long walk and eventually finding someone to assist him:

"…..I was suffering from pain so I just keep walking you know, like holding the fence, this and that, so walking on the path and pavement, then I reach end of going near the…. Avenue, so which is near….. That was six, seven miles from my house so I sit down there, then I saw somebody passing by, then I was in the sense so I ask him "Can I use your phone?" ……so I asked somebody to help me to dial the number. So they done it and I spoke to my wife. She said "Where you been?" you know "You've been out for nearly six hours, seven hours" so I had the money in my pocket but I couldn't see anything". (M, 55-64, SA, Insulin + Metformin)

4.3.2.3 Symptoms

People experienced a variety of symptoms with the most common being shaking and sweating. Additional symptoms reported by around half of the participants included: confusion, not being able to think clearly, feeling light headed and giddy, being weak, drained or tired. Less common symptoms included hunger, panic and anxiety, nausea, pain and blurred vision.

".....sweating like a pig and feel like I've got spiders crawling on me, it's the sweat dribbling". (F, 44-54, SA, Metformin + Repaglinide)

4.3.2.4 Causes

Overall (regardless of treatment), patients attributed a range of factors that they perceived to cause their hypoglycaemia. For example, they mentioned their busy lifestyle and pace of life leading them to neglect taking a break to eat food.

"I've been so busy doing other things. I've been out and about and I've forgotten to eat" (Male, 44-54, WE, Metformin + Sulphonylurea + DPP-4i)

One person felt that travelling to another country led to changes to his physical activity routines, environment and the consumption of foods from another culture.

"Well it's lower when I'm in India because I can eat and sweat a lot as well and I walk a lot as well" (M, 64-77, SA, Metformin + Sulphonylurea)

Additionally, a few people also talked of stress, anxiety and alcohol as causes.

"I always think that if I'm being quite anxious, nervous, worried, then that affects me" (F, 55-64, WE, Insulin + Metformin)

For those participants specifically on insulin, medication was a commonly suggested cause. Participants miscalculated insulin dosages in relation to food, exercise, timing and adjustment of doses as illustrated by the following participant:

"Yeah, if I'd taken more than I needed to take for example with Rapid then that could bring a hypo" (F, 55-64, WE, Insulin + Metformin)

4.3.2.5 Awareness of impending hypoglycaemia and treatment approaches

Overall, participants appeared to take a very pragmatic approach to a hypoglycaemic episode, most claiming to know as soon as an episode was commencing and prioritising prompt treatment.

Treatment strategies included being prepared and carrying dextrose tablets

"What I do is I carry supplies of those glucose tablets. Lucozade ones" (M, 44-54, SA, Metformin + Sulphonylurea)

In contrast, a minority of participants relied on buying sugary drinks from a shop to treat a hypoglycaemic episode as and when they happened

"If I'm out and about I'd probably get a sugary drink" (M, 55-64, WE, Metformin + Pioglitazone)

4.3.2.6 Experience of hypoglycaemia

Participants varied in their thoughts and feelings in the midst of an episode. It was described by some like being in a different world, alternate reality or a change in perception of the present moment.

"A very thin gossamer veil between me and reality, sort of dangling down, there's nothing I can see, nothing I can feel. But come on, wake up, get a grip, you know, bring yourself out of whatever it is and you're not quite with it. It's so difficult to describe." (M, 64-77, WE, Insulin + Metformin)

The symptoms of weakness and fatigue were also embodied during the episodes by some and illustrated by the following participant:

".....feeling like nothing – a piece of paper or a wasted band". (M, 44-54, WE, Metformin + Sulphonylurea + DPP-4i)

Others felt anger at themselves for feeling this way or getting to this stage and anger at others who tried to communicate with them. Fear and panic were also

felt from those wondering what was happening to them, possibilities such as a heart attack being considered.

'I've done it again. I've worn myself down, and I know I shouldn't.' (M, 44-54, SA, Metformin + Sulphonylurea)

4.3.2.7 Nocturnal

Some participants specifically talked about their experiences of nocturnal episodes which gave little or no warning signs of their commencement and led to one participant describing how she woke up in the middle of an episode.

"So you can actually be further down the hypo trail by the time you actually get up and react to it. But you can't but wake up, but sort of you can doze again, while it's happening, and that happens sometimes" (M, 44-54, WE, Insulin + Metformin)

A few participants also emphasised how tired and dozy they felt during a nocturnal episode and making it difficult to be completely awake. Participant's nocturnal episodes were particularly worrying, resulting in fears about not being able to wake up:

"I found it quite worrying, the fact that what would have happened if I hadn't have woken up. That was the bit that worried me and would, [my husband], be aware if I wasn't moving or, you know, hadn't noticed that I wasn't with it." (F, 55-64, WE, Insulin + Metformin)

In regards to treatment specifically for nocturnal episodes, it was common for people to store this by their bedside. A few participants talked of over eating when treating their nocturnal hypoglycaemia, as they were worried that it would occur again.

"I think I have in the night, do tend to overeat to compensate for the low blood sugar and in the morning it probably is higher than I would like it to be. But I think if you're going to go to sleep again I'd rather it be higher than it needs to

be, rather than if you're awake then I wouldn't probably take as much to eat to compensate" (F, 55-64, WE, Insulin + Metformin)

4.3.2.8 Blood sugar monitoring and level

Some people tested their blood sugar very regularly, whilst others tested once a week, when they didn't feel very well, or very rarely. The level participants aimed to keep their blood sugar at varied from 4 mmol/L to 10 mmol/L. Around half of the people had a lower target of between 4 mmol/L and 7 mmol/L whilst the other half varied between 7 mmol/L, and 10 mmol/L. The level people determined whether they were having a hypoglycaemic episode also varied, mostly <4 mmol/L or <5 mmol/L was used, though a few used a lower value of <3 mmol/L.

4.4 Ethnic differences in the reporting of episodes

There were notable differences in some areas of the interviews between South Asian and White European participants.

South Asian participants appeared to be more aware and conscious of others during an episode, whilst White European participants rarely acknowledged others when discussing their experience in middle of an episode.

"And the last thing I want to do is – I don't want to be a bit of a fussing from anybody. You know, they think, "Oh, what's wrong? Why is he sweating?" You know "Why is it you're not…?" Things like that. No, I don't want to – it's not nice" (M, 44-54, SA, Metformin + Sulphonylurea)

"Whatever, I don't feel like to take anything, then to say "look take this" or either "give me a chocolate drink" or "give me a coffee with 2 sugars in it" (M, 55-64, SA, Insulin + Metformin)

South Asian participants were also more likely to report discussing their diabetes with others.

"….friends of mine, both have, all have got diabetes. First husband started then the wife got it. The same thing with me. My husband started and I got it. We all have diabetes. We all get together and talk about it" (F, 64-77, SA, Insulin + Metformin)

"I wanted to know if it (hypoglycaemia) was normal" (F, 44-54 SA, Metformin + Repaglinide)

Experiences during the episodes appeared to be generally similar between ethnic groups, except for some of the symptoms reported. Those of South Asian origin were the only participants to report experiencing hunger as a symptom of hypoglycaemia. Whilst white European participants were more likely to refer to sensations in particular areas of the body, for example ears, hands or legs.

The majority of participants who reported issues and barriers to attending clinic appointments or receiving regular healthcare for their diabetes were also South Asian.

4.5 The analytical model

The empowerment and engagement (EE) model:

The analysis of the conceptual themes indicated that it was possible to categorise how engaged and empowered participants were with the prevention and management of their hypoglycaemia, and the impact their relationship with their HCP had on this process.

The categorisation informed the development of a model of engagement and empowerment in the form of a continuum, which facilitates an identification and understanding of how participants move up and down over time and may have stronger engagement than empowerment, or vice versa. The model is displayed on a continuum (fig 4.1).

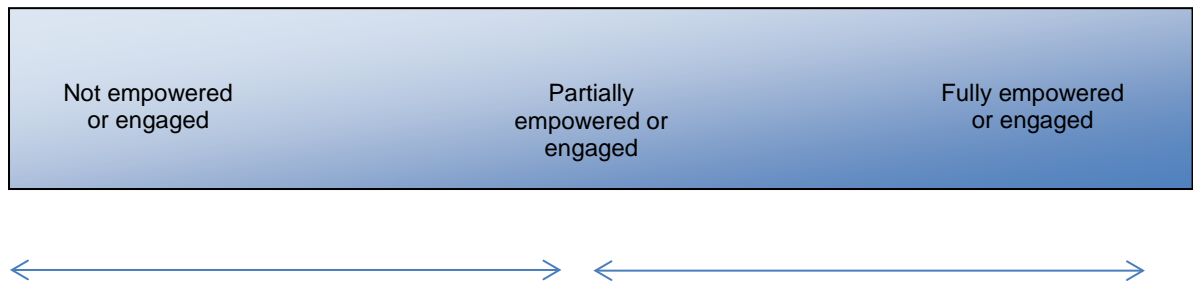| Not empowered or engaged	Partially empowered or engaged	Fully empowered or engaged

Figure 4.1 The empowerment and engagement (EE) model

Data from the model are also presented descriptively below, organised in three sections according to the continuum: not empowered or engaged, partially empowered or engaged, and fully empowered or engaged. Within each of these sections the key factors that placed participants within these categories are discussed in addition to how these influenced a move along the continuum. For those in the partially engaged and empowered category, they were engaged or empowered in certain areas but not in others; hence, this diversity is illustrated by horizontal arrows. At the end of the continuum it was possible to delineate absolute experiences of engagement and empowerment.

4.5.1 Not empowered or engaged (2 participants)

There were several inter-related factors that resulted in two of the participants being disengaged and disempowered with their management of hypoglycaemia. These key factors are discussed in turn below.

4.5.1.2 Attitudes to managing their diabetes and hypoglycaemia

These participants were disengaged and disempowered with their management of diabetes and subsequently hypoglycaemia. This was illustrated by their lack of interest and understanding, with one participant stating that they are on *"mild things"* (participant *M, 70, SA, Metformin + Sulphonylurea + DPP-4i*) and another *"not bothering much"* (*M, 59, WE, Metformin + Pioglitazone*). This was particularly evident for one of these participants who seemed to take a passive

approach to taking his medication, handing over responsibility to his wife to determine what medication to take and when.

"Frankly speaking, my medication is all put in a box by my wife for me" (M, 64-77, SA, Metformin + Sulphonylurea + DPP-4i)

The disengagement and disempowerment with diabetes was also evident in their discussions about their experiences of hypoglycaemia. Their responses suggested that their approach to hypoglycaemia could be characterised as dismissiveness and nonchalance, even though one of the participants had required third party assistance with treating an episode.

"I don't really give it much thought" "I just plod along, whatever" (M, 55-64, WE, Metformin + Pioglitazone)

Unsurprisingly, participants were not currently very motivated to prevent hypoglycaemia, with one participant saying he was *"tired of trying to prevent".* (M, 64-77, SA, Metformin + Sulphonylurea + DPP-4i)

The other participant made no effort to prevent hypoglycaemia, mentioning barriers such as work shift patterns.

"Because obviously I don't eat properly – working shifts" (M, 55-64, WE, Metformin + Pioglitazone)

Consequently, this lack of engagement with their hypoglycaemia resulted in both the participants not carrying treatment for hypoglycaemia with them.

Interviewer: *"…so do you ever carry anything around with you or is it always a go into a shop?"*

Participant: *"(laughing) No nip into a shop." (M, 55-64, WE, Metformin + Pioglitazone)"*

4.5.1.3 HCP relationship

Beliefs about HCP relationship and disclosure

Participants in the group believed in only going to see their HCP if they were ill, not for routine check-ups.

"I don't believe in going unless you're really bad, you know…….because like I've said I don't like going to the doctors." (M, 55-64, WE, Metformin + Pioglitazone)

"As long as you're going normally, all right.   Just let it go' (M, 64-77, SA, Metformin + Sulphonylurea + DPP-4i)

One participant in particular viewed interaction within consultations as where he was *"just moaned at".* (M, 55-64, WE, Metformin + Pioglitazone)

This view of HCP relations was reflected when participants discussed their decisions not to disclose their hypoglycaemic episodes to their HCP. Both participants perceived that the HCP had never discussed hypoglycaemia or enquired about, it and they did not feel it was important to bring up themselves.

"I didn't think it was important" (M, 64-77, SA, Metformin + Sulphonylurea + DPP-4i)

Interviewer: *"So when you had for example the episodes where you passed out, did you feel like you wanted to tell the doctor or nurse?"*

Respondent: "*No"*

Interviewer: "*No?"*

Respondent:" *I just carry on"* (M, 55-64, WE, Metformin + Pioglitazone)

One participant particularly felt this was due to a focus on controlling high blood sugar during consultations with the HCP.

"Well they just go on about it being high" (M, 55-64, WE, Metformin + Pioglitazone)

4.5.1.4 Role of others (non-professionals)

In contrast to the minimal role of the HCP in this group, participant's spouses and work colleagues played a prominent role, from providing help during episodes to prompting the participant to see their HCP.

"It's happened twice at work…but luckily there's people about, you know" (M, 55-64, WE, Metformin + Pioglitazone)

"She (wife) is my first doctor, actually" (M, 64-77, SA, Metformin + Sulphonylurea + DPP-4i)

For one of the participants they themselves had to play a prominent role in helping another during a hypo in the past. However, these experiences had not seemed to motivate or impacted on this participant's own management of hypoglycaemia.

"It would drop or go right up or whatever; it's frightening. And once I had to give this injection to her tummy because she was sparko. And I left her once and she passed out, and they reckon she was on the living floor for thirty hours and they said a bit longer she could have died." (M, 55-64, WE, Metformin + Pioglitazone)

4.5.1.5 Knowledge sources and interest in learning

Participants in this group had not been on formal education courses for diabetes and knowledge sourced from their HCP was very limited.

"No one's actually spoken to me about what to do if it's dropped" (M, 55-64, WE, Metformin + Pioglitazone)

Instead, knowledge tended to be gained experientially or gathered over the years. The first time one participant learnt about hypoglycaemia was when he

actually experienced an episode. He did not know the early signs and the episode consequently resulted in needing third party assistance.

4.5.2 Partially empowered and engaged (11 participants)

These participants were more empowered and engaged than those discussed above. However, there were various different factors within the group that prevented and hindered them being fully empowered and engaged. These factors are discussed below.

4.5.2.1 Hypoglycaemia view

Around half the participants in this group saw themselves at moderate risk of hypoglycaemia. They viewed it as a potentially serious event but without excessive worry.

"..you know I am on my own a lot. If anything happens to me in the day time nobody is there to look after me." (F, 64-77, SA, Insulin + Metformin)

One participant saw episodes as their own fault, whilst another saw low blood sugar worse than high.

"*Well high blood sugar you can cope, right? …..So when it's low sugar you feel weak and shivering, you get tired"* (M, 55-64, SA, Insulin + Metformin)

Another became confused and worried in the middle of an episode as to whether there was a problem with his heart or sugar.

"….see I'm suffering from my heart disease as well, sometimes I get confused" (M, 55-64, SA, Insulin + Metformin)

The other half of participants had relatively low risk perception of episodes occurring, with one participant perceiving he would be more at risk if he was on insulin.

"You see I don't think about it. Maybe if I was on insulin I would" (F, 55-64, B, Metformin)

Episodes in this group of participants were seen as something they just had to deal with and move on from. One participant described hypoglycaemia as something that was not "immediately terminal". (M, 64-77, WE, Insulin + Metformin)

4.5.2.2 Prevention, medication and knowledge

The majority of participants were fairly engaged with preventing hypoglycaemia and were therefore proactive with preventative methods, such as adjusting their dietary intake in response to medication and meal regularity. Such preventative measures were based on experiential learning and knowledge gained from HCP.

"….if I know I'm not going to be eating for a little while yet, for an hour or so, maybe longer, then I don't take…….I have it before my meal so I don't take it till I'm ready to have that meal sort of thing" (M, 44-54, WE, Metformin + Sulphonylurea + DPP-4i)

This engagement also resulted in them taking preventative measures such as carrying sweets and chocolate.

However, not all the participants in this group felt empowered, as illustrated by two participants, one of whom due to a lack of blood testing strips felt she was unable to identify a safe level of blood sugar and consequently 'over ate' to avoid hypoglycaemia.

"I prefer to overeat because then I can curl up and sleep it off." "I always used to-two hours after eating, that's when I used to test, but now I don't do that now you see because they don't give me the strips to do it so I don't know what's going to happen" (F, 55-64, O, Metformin)

For another participant, hypoglycaemia prevented her from fasting for Ramadan. The fear of hypoglycaemia as she lived on her own and lack of confidence in adjusting insulin were both factors in this.

"I got scared. I stopped fasting. And about that, now that fasting is so long I will be dead twice. I can hardly manage it if I fast from morning to, about four, five…. the house is blessed in that way that you're fasting and you get a closeness, you're close up to the god that you are doing it for him. So these things are – I don't want to lose them." (F, 64-77, SA, Insulin + Metformin)

In other cases there were misconceptions regarding insulin, resulting from limited knowledge. One participant was adamant that insulin was given to relieve a hypoglycaemic episode, another did not carry glucose tablets with them as they felt this was only needed if on insulin and others perceived insulin to be attributed to diabetes complications more than diabetes itself.

This limited knowledge also resulted in reliance on the HCP to help adjust medication to help prevent hypoglycaemia.

4.5.2.3 HCP Relationship

System barriers

For a few of the participants there appeared to be system barriers preventing them from getting to a discussion at all with their HCP about their diabetes and hypoglycaemia. Two of the participants had previously been under specialist care for their diabetes and were transferred to primary care management. However, both patients were now lacking any substantial HCP input for their diabetes and hypoglycaemia, with little contact in 6 months for one, and several years for another.

Interviewer: "If you've got any questions about your insulin, you've got any questions about food, who would you go to?"

Respondent: "Really nobody. I don't go to anybody". (F, 55-64, WE, Insulin + Metformin)"

View of HCP healthcare system and disclosure to HCP

Those that did not disclose

Amongst those participants in this group who did not disclose their hypoglycaemia to a HCP, there were a variety of issues relating to participant's views of their HCP and the healthcare system. Participants discussed the lack of interest and time they felt the HCP had, and the scope of what the HCP could do being limited to changing or explaining medication.

"Well they haven't got time. If you've got serious problem you can talk to them and they explain you or they change your diabetes or diet or they can change your tablet, that's all they can do." (M, 55-64, SA, Insulin + Metformin)

"Doctors don't want to know, 'cause you go in there; you've got five minutes to tell them about your problems. And it's not long enough." (M, 44-54, WE, Metformin + Sulphonylurea + DPP-4i)

Some viewed going to an appointment at a healthcare clinic as only needed if the problem was very serious (in the participants opinion), or terminal. The general practices were viewed as too busy, with no available appointments and a scarce resource for one that should be used as infrequently as possible.

"When you ask for appointment… all fully booked for one and a half month" (F, 64-77, SA, Insulin + Metformin)

"I mean, they're so busy, you know, and I don't mean that as a pass off, I mean, you very, very rarely, if you wanted, you know, to see the doctor, you ain't going to do it because you can't get in and that's no.1, so you wouldn't go for something as simple as going low sugar" (M, 64-77, WE, Insulin + Metformin)

Hypoglycaemia in these cases was often viewed to be expected and normal part of diabetes, manageable, not that important and not terminal. Participants in some cases did not feel that the HCP input was needed, or they did not want to keep raising issues with the HCP and be a burden.

"No, no I've not mentioned that (hypoglycaemia). I thought it was par for the course, to be honest" (F, 64-77, WE, Metformin + Sulphonylurea)

One of these participants determined his hypoglycaemia at 4mmol/L. He wrote all his sugars down in a chart and these were reviewed by the physician at his appointments. However hypoglycaemia was never discussed, with neither the HCP nor patient ever raising the topic. The participant disclosed his sugars but did not volunteer the information that he had deemed himself to have experienced hypoglycaemia. This showed lack of communication between the HCP and patient.

Those that did disclose

The majority of participants in this group did, however, disclose to their HCP. Participants said they felt their HCP was someone who they needed to keep informed and it was important to let them know about hypoglycaemia. They saw HCP's as knowledgeable, someone they could learn from and gain advice and guidance.

"Well I could get some advice you know so they're helpful" (M, 60, SA, Insulin + Metformin)

A few participants also wanted to be reassured that what they were experiencing was normal.

"Um, well I think they ought to know and, you know, how do I know how many I should be having, you know, what is a lot of little hypos" (F, 55-64, WE, Insulin + Metformin)

Most participants experienced a positive outcome of disclosing by having an explorative discussion after with their HCP.

"I want to learn something what they're going to tell me and they did tell me….. after breakfast every 2 hours you must check your blood sugar and if you think you feel like really low you must take either tea with a biscuit or anything, don't wait til one o'clock!" (M, 55-64, SA, Insulin + Metformin)

However for a few participants there were communication issues. Future plans were dictated by the HCP rather than discussed. In one instance miscommunication led the participant to leave with the incorrect assumption that his diabetes medication had been increased due to hypoglycaemia.

"Um… no, I was more or less told to, you know, sort yourself out. You're not eating right, this is what you should be doing. Um… but not in any depth" (M, 55-64 WE, Insulin + GLP-1ra)

Interviewer: *"Did you tell the doctor about those episodes?"*

Respondent: *"Yeah"*

Interviewer: "*You did?"*

Respondent:*"...they gave me tablets. That's it."*

Interviewer: "*OK, so you told them you'd had an episode of low blood sugar and they gave you tablets?"*

Respondent: *"Yeah, that's It"* (M, 44-54, WE, Metformin + Sulphonylurea + DPP-4i)

4.5.2.4 Role of others (non-professionals)

The role of spouses, family and friends generally within this group demonstrated a lack of independence and autonomy. A number of participants often used the term "we" when talking about either day to day management of hypoglycaemia, leaning about hypoglycaemia or when disclosing to the HCP about an episode.

"It wasn't actually me that rang… it was my wife that rang up" (M, 55-64, WE, Insulin + GLP-1 ra)

Some of the participants in this group had also required the help of a third party during an episode, again emphasizing reliance on others in their management.

"We had to have an ambulance out. My husband was, you know, he didn't know what was going on, I sort of said I think it's something to do with my diabetes but I was not really with it, he couldn't make sense out of me" (F, 55-64, WE, Insulin + Metformin)

Participants in this group did all disclose their potential risk of hypoglycaemia to family friends or co-workers, though, motivation of doing so varied.

One reason was safety, particularly at work, with participants wanting to ensure they could receive help and support if needed during an episode. This reflected the participants view of hypoglycaemia as an important issue.

"As a safety issue really……..Go down to the boiler house or anything like that, I used to say to them 'if I'm not up in half an hour come and find me', you know." (M, 55-64 WE, Insulin + GLP-1 ra)

However, for other participants disclosure was not that important and only undertaken when it came up in conversation.

"I don't feel it that important to go and tell people" (F, 65-77, WE, Metformin + Sulphonylurea)

On the other hand a few participants only disclosed their experiences of hypoglycaemia to warn others of the risk they might be themselves of experiencing hypoglycaemia. This was regardless of if others had diabetes or not.

"…just to inform them so that like even though they're not diabetic, sometimes, and if they start feeling funny it might be because their sugar levels are low" (M, 44-54, WE, Metformin + Sulphonylurea + DPP-4i)

4.5.2.5 Knowledge sources and interest in learning

Under half of the participants in this group recalled ever being formally told about hypoglycaemia by their HCP and, in those that were informed, there were mixed views about the information and advice they had received.

Generally participants felt it had been rushed, lacking depth and did not motivate them to prevent or take control of hypoglycaemia management.

"They've mentioned it but they haven't really talked and gone into any depth with it" (M, 55-64 WE, Insulin + GLP-1 ra)

"Your blood sugar and all this…goes two ways. Sometimes it can go high; sometimes it can go low "(M, 44-54, WE, Metformin + Sulphonylurea + DPP-4i)

There were other sources of knowledge for a few participants, such as pharmacists and paramedics. One participant gained information from the paramedics who were called when she had a hypoglycaemic episode. The participant explained this was the first time they had heard of hypoglycaemia.

Within this group participants generally had low interest and motivation to learn through literature (i.e. leaflets, books), lacking activeness in sourcing information themselves.

Some participants felt bombarded and confused by being given information on hypoglycaemia in this way. Others discussed that their interest and absorption diminished shortly after starting to read.

"you read item no.1 and it is up to item no.10 and you say oh forget it I'll read it later on" (M, 55-64, SA, Insulin + Metformin)

 The majority of participants in this group had not been on any formal education courses for their diabetes. For those that had attended, there were mixed responses.

A few participants described the experience as extremely helpful in understanding hypoglycaemia in the context of their overall diabetes management. However, another participant felt that she/he had been bombarded with information and this led to feelings of confusion.

It was evident from some participants within this group that learning from their own experience of hypoglycaemia was both common and a favoured way of

learning. They felt it helped to really understand hypoglycaemia, using their own instinct and body as a teacher to learn what worked for them and how they responded.

"…down a few years now, I know exactly when it's going to happen and I've got really good initial signs so I know, but back then I didn't." (F, 55-64, WE, Insulin + Metformin)

4.5.3 Fully empowered and engaged (7 participants)

These participants demonstrated empowerment and engagement across a number of inter-related factors. These are discussed below.

4.5.3.1 Hypoglycaemia view

Participants in this group tended to be very aware of their risk of hypoglycaemia and the potential consequences of an episode. They were confident and felt in control dealing with an episode.

"I'm aware of what it can lead to. So if I feel one coming on, I will try and stop it there and then before it gets too low" (F, 55-64, WE, Insulin + Metformin)

"….as long as you know what to do when it happens, that's the solution isn't it? And knowing that you'll come round pretty quickly after a glass of orange is also, you know, you know that you are going to come out of it" (M, 44-54, WE, Insulin + Metformin)

Within this group of participants, there was also an element of worry about hypoglycaemia, often resulting in preventative action being taken.

"If I travel anywhere, or doing anything which I know I'm not going to have access to food or drink, or anything like that, I deliberately raise my sugar levels" (M, 44-54, SA, Metformin + Sulphonylurea)

4.5.3.2 Prevention and medication"

Active planning and forward thinking was evident in this group. Some participants deliberately raised blood sugar levels (slightly) for situations where they anticipated food would not be convenient to consume or activity levels would be raised.

"So what I'll do is I've got the kit at home, so I'll test myself. I'm usually seven and eight, which I think is OK for me..... what I'll do is I'll just take one more (dextrose), and it'll just go to nine; then I find that that will keep me going for a couple of hours." (M, 51, SA, Metformin + Sulphonylurea)

Most participants mentioned carrying treatment with them wherever they went and were conscious to eat regularly.

"I always have sugar in my pocket. Always." (M, 44-54, WE, Insulin + Metformin)

 Participants in this group exhibited a very good understanding of their diabetes medication, enabling them to be able to use it as a preventative method for avoiding hypoglycaemia. They appeared to demonstrate independence when the the doses and timing needed adjusting, whilst still maintaining discussions and input with their HCP.

"I had a certain amount of carbs and I put in effort that is equal to that then I'm going to negate the carbs that are there. So, anymore, that, that is going to take my sugar low. So, if I'm having insulin to balance the carbs that I'm having and I'm doing exercise, like say unbeknown it comes along. These things happen, I do more running about, or whatever, then that can lead to a hypo earlier, or my blood sugar being at the point where I need to do something about it a lot earlier than if I just had the insulin" (M, 44-54, WE, Insulin + Metformin)

4.5.3.3 HCP relationship

Unlike the participants in other groups, individuals did not tend to discuss system barriers (such as time) and had a generally positive view of their HCP, with all participants experiencing continuity of care.

Participants discussed the link between continuity and feeling that the HCP knows their history and their story, and that from prior interaction they knew the HCP would help them. The participants talked of how they required more than a HCP reading their history from a computer screen. Continuity ensured personal details that could not be written down or read were evident. Participants also tended to feel that consultations were more personalised, making them feel more at ease.

"I think it's more of a personal care because you're seeing the same person. They get to know you and if you've got anything you want to ask they probably might be able to know……I think at the old practice because I'd seen the nurse quite a few times, I felt quite confident with her, with what she knew about me and I think she was quite happy to let me do what I was doing cos it seemed to be working OK. Whereas with the new, I've only seen her twice, so I don't really know, I don't feel as at ease as I did before" (F, 55-64, WE, Insulin + Metformin)

It was evident that these factors were fundamental in participants disclosing hypoglycaemia, and overall having overall collaborative successful management of their diabetes and subsequently hypoglycaemia.

"I think it's just you know where people hide the problems then it's a bit difficult, but I think when you're more closer with your diabetic nurse as well in that sense, like a friend, it helps a lot." (M, 55-64, SA, Insulin)

Participants tended to have positive outcomes from disclosure, with explorative discussion and precautions actively taken.

"My diabetic nurse will ask me, 'Have you suffered any hypos recently…. and if so, when? And what did I eat before that? What was I doing?" (M, 44-54, SA, Metformin + Sulphonylurea)

Participants disclosed for a number of reasons. They felt at ease with their HCP, feeling it as important to inform them of hypoglycaemia, and viewing them as knowledgeable and able to help.

"I want her to know everything that is relevant, in order to put her in a position of looking after me as best she can. I know she wants to look after me as best she can, and I don't want to do anything to get in the way of that." (M, 65-77, WE, Insulin + Metformin)

4.5.3.4 Role of others (non-professionals)

In contrast to the other groups, the physical assistance of "others" was never required during an episode for any of these participants. This emphasises a level of independence in their hypoglycaemia management.

Some participants in this group were aware and conscious, however, of the impact their episodes had on others and the help that might be needed if they did not manage to rectify an episode themselves.

"That's potentially life-threatening, not only for myself but for any other motorists. I become a risk then". (M, 44-54, SA, Metformin + Sulphonylurea)

All participants in this group disclosed to friends, family, co-workers or anyone else they felt needed to know, with no evidence of any barriers. They disclosed so that people around them would know and understand what was happening and what to do. Participants were not ashamed of their diabetes and commented on the positive responses they had received from disclosing.

"I think it's important that you let people know because if you do go into a hypo and you can't get into anything and they don't know what's wrong with you, you know, and you'd go too far into one and they don't know, they won't know how to treat you" (F, 55-64, WE, Insulin + Metformin)

4.5.3.5 Knowledge

Participants in this group did not tend to be restricted to one type of learning source for hypoglycaemia information, showing evidence instead of using an array of sources. Self-learning was popular, again emphasising their level of independence and motivation with hypoglycaemia management. Reading was very popular, with participants commenting they were able to re-read and reflect on the information, and use as a reminder. They felt it was their choice to read, showing proactiveness, enjoyment and choosing any wider reading they felt was needed.

"I went and looked through the detailed working of the metformin." (M, 65-77, SA, Metformin)

Additionally, another source of self-learning favoured was the television, with a few participants feeling it was a very effective way for them to learn.

Learning directly from their HCP was another popular source of knowledge, which is likely linked to the good relationship between participant and HCP in this group (as discussed previously). Participants described the information gained this way as being delivered clearly, personalised detailed, with ongoing information available from the HCP.

"She's a very good communicator…. Gave me a lot of confidence" (M, 65-77, WE, Insulin + Metformin)

Additionally, a few participants also indirectly learnt through their own professional training as a HCP or through a close family members diagnosis and education.

All the participants in this group had been to some type of formal education covering hypoglycaemia. The participants all found the education they received informative and helpful. A few participants however, did highlight the differing levels of prior knowledge levels within the group receiving education, feeling they knew more than a lot of people there and therefore some information

appeared repetitive. This reflects the proactiveness and interest within this group to absorb and learn information on hypoglycaemia even before they had attended a formal education course.

Most of the participants learnt from their own experience, what works for them and their individual reactions to hypoglycaemia. Experience increased confidence and also helped them to become aware of the risk of hypoglycaemia.

"It's just come on over time, when you learn how you know your condition is yourself, what can lead to a hypo, how you feel when you have a hypo and how you treat it." (F, 55-64, WE, Insulin + Metformin)

4.5.3 Summary table

Table 4. 3 Summary of the main characteristic for EE model groups

	Not empowered	Semi empowered	
Attitudes to managing their diabetes and hypoglycaemia	Disengaged and disempowered with their management of diabetes and subsequently hypoglycaemia. They lack interest, understanding and motivation regarding hypoglycaemia management.	Low risk perception within this group stems from lack of knowledge. If knowledge is sufficient, this group generally see hypoglycaemia as a potentially serious event that requires attention for prevention and management. Participants tend to be fairly engaged and motivated with management. Lack of engagement with management relates to lack of knowledge, resulting in low confidence, misconceptions and an over reliance on the HCP. They appear to learn largely from experiential learning and HCP interaction.	Participants in this group tended to be very aware of their risk of hypoglycaemia and the potential consequences of an episode. This results in them often taking preventative action and forward planning. They are confident and feel in control dealing with an episode People in this group exhibit confidence, understanding and a balance between independence and working together with their HCP.
Beliefs about HCP relationship and disclosure, system barriers	They generally feel that there is no need to see a HCP for routine check-ups and it is only necessary to go if you are feeling unwell. Disclosure of hypoglycaemia in this group is an issue as unless the HCP heavily probes, it is not seen as important enough to make the HCP aware.	This group of people are more likely to have issues surrounding their diabetes check-up appointments. In some instances there are issues around not receiving any care at all, for others it is their perception of the HCP and GP surgery or the necessity and importance of a check-up. These factors along with view of hypoglycaemia, are all factors playing a part in how productive diabetes appointments are and if the patient discloses or discusses their experience of hypoglycaemia.	These people have generally positive views of their HCP, with all participants experiencing continuity of care. They have collaborative successful management. Their relationship and interaction with the HCP is fundamental in the high disclose rate within this group. Participants tended to have positive outcomes from disclosure, with explorative discussion and precautions actively taken.

Role of others (non-professionals)	Spouses and work colleagues play a prominent role, from providing help during episodes to prompting visits to see the HCP.	This group tend to display a lack of complete independence and autonomy in either their day to day management of hypoglycaemia, leaning about hypoglycaemia or when disclosing to the HCP about an episode. They are more likely to have needed the help of a third party during an episode.	In contrast to the other groups, the physical assistance of "others" was never required during an episode for any of these participants. They are more likely to be aware and conscious of the impact their episodes could have on others and the help that might be needed if they did not manage to rectify an episode themselves.
Knowledge sources and interest in learning	Participants in this group have not been on formal education courses for diabetes and knowledge sourced from their HCP is very limited. Motivation to learn is very low, with what knowledge there is gained experientially or gathered over the years.	Knowledge is not always successfully or at all sourced from their HCP due to miscommunication, view and method of delivery from the HCP. Learning through literature is also not generally successful, either due to motivation or confusion when trying to understand the information. Formal education is also not overly common in this group and when attended can have a mixed response. Some find it very useful whilst others risk leaving feeing confused and overwhelmed without asking further questions for clarification. It is experiential learning that appears to be the most common and generally favoured within this group.	This group of people tend to be interested, motivated and interactive with their learning and sourcing of knowledge on hypoglycaemia. They utilise a variety of methods including self-learning through reading or watching television. They also learn well through their HCP. All the participants in this group have been to some type of formal education covering hypoglycaemia. However, group education tended to highlight the differing levels of prior knowledge this group had to others. Most of the participants also learnt from their own experience, what works for them and their individual reactions to hypoglycaemia.

4.6 Discussion

4.6.1 Key findings

Hypoglycaemic episodes often interrupt daily life and activities, with common symptoms experienced being shaking and sweating. The blood glucose level at which these symptoms occurred varied between participants. Pace of life, changes in routine and physical activity were all commonly cited causes, with those on insulin also experiencing hypoglycaemia due to miscalculation of food or timing issues. The majority of participants acted promptly to treat hypoglycaemia and carried treatment with them. However, participants reported a very different experience of nocturnal episodes, emphasising the lack of warning compared to daytime episodes and the difficulty they felt waking up to treat.

Nearly all the participants tested their blood sugar at least occasionally, with targets for optimal control and self- diagnosis of hypoglycaemia varying considerably between them. In-depth descriptions were given by participants as to how it felt to experience an episode. Feelings of being in an alternate reality along with fear, panic and anger were all described in the midst of an episode.

There were notable differences in some areas of interviewee accounts between South Asian participants and White European. One area of difference was in relation to others (non-professionals). South Asian participants appeared to be more aware and conscious of others during an episode and reported discussing hypoglycaemia more. There were also differences in symptoms of hypoglycaemia, with only those of South Asian origin experiencing hunger and White European participants being more likely to refer to sensations in particular areas of the body. The majority of participants who reported issues and barriers to attending clinic appointments or receiving regular healthcare for their diabetes were also South Asian.

During analysis of the data there appeared to be clear differences between participants in their level of empowerment (independence, confidence, proactiveness and knowledge) and engagement with their own management and HCP. This led to the development of the EE model, where participants were placed along a continuum depending on their level of empowerment and engagement. Participants position on the continuum was reflected in their hypoglycaemia management, views and experiences.

4.6.2 Previous literature

As stated previously, there is limited qualitative research focusing on hypoglycaemia in T2DM. One study conducted in Ukraine within a T2DM population explored the impact of hypoglycaemia and briefly considered the patient- physician relationship (143). Similarly to the data I collected, in this study it was noted that some participants lacked any information at all on hypoglycaemia when they experienced their first episodes, resulting in them being dangerously unaware of what they were experiencing. Participants also had similar worries in this study compared to my findings of their Inability to foresee hypoglycaemic events and events occurring in particular circumstances such as work or in public.

Another study explored how a small number (6) of Singapore Chinese adults experienced hypoglycaemia (144). In contrast to my findings, the participants from this study underestimated the impact of hypoglycaemia. However, this was likely due to these patients only experiencing mild and infrequent episodes, compared with the range and type of episodes experienced by participants in the data I collected. The study also found that participants viewed HCPs as just information providers, characterised by being detached and impersonal. This is varied from the patterns which emerged from my data, where HCP-patient relationships varied with degree of engagement.

My findings also expand on previous results from quantitative studies. It has been reported through quantitative evidence that disclosure of hypoglycaemic episodes to HCPs is low, with 15% disclosing mild hypoglycaemia events(146).

The data provided here showed that this could be due to a number of factors including: view of hypoglycaemia, patient-physician communication, system barriers, view of the HCP and expectations of disclosure.

Previous quantitative literature has also linked data to the impact hypoglycaemia has on people and their lives (7, 10, 22). My findings expand on this describing in detail recollections of how people felt in the middle of an episode, such as being in a different world or alternate reality, some feeling worried, others feeling angry or just tired and fatigued. It was found that hypoglycaemia had a substantial impact on some participant's lives in terms of planning to avoid an episode, with some deliberately raising their blood glucose values. It was also a source of worry for some, with most finding it an inconvenience at least to their lives.

Overall it was shown from the interviews that alterations to treatment following an episode were not common. This is reflected in previous quantitative literature, where only 50% were shown to make alterations(146).

In regards to the EE model proposed from this work, the widely recognised patient activation model (discussed in chapter 2) has similar properties and concepts(77). The model's premise is patient "activation", which is the level of knowledge, skills and confidence a person has in managing their own health and health care. It is not disease specific but has been applied to T2DM and is has been shown those less "activated" are more likely to attend hospital for hypoglycaemia (147).

The model proposes that people who have low levels of "activation" are less likely to play an active role in their heath and independently managing it. They are poorer at seeking help or following HCP advice, often preferring not to think about their health at all. The EE model follows similar ideas and concepts, with the levels of "activation" focusing around the confidence, knowledge and motivation people have in managing their own health. The EE model also expands on the impact and role of the HCP- patient relationship and how this all relates specifically to the management of hypoglycaemia.

4.6.3 Strengths and limitations

The study addresses a gap in the literature needed to expand on previous quantitative data, providing in-depth data on hypoglycaemia within the T2DM population. An insight is provided into the experience of episodes regarding the context, emotional and physical feelings, consequences, management and the role of differences between individuals. It also enabled the development of the EE model which has implications for everyday clinical practice, education and management of episodes.

The study used sound methodology, including principles of grounded theory and an iterative approach to data collection and analysis. This allowed for refinement of the topic guide throughout, adapting to the interviews and also consequently exploring some issues in more detail, for example the impact of continuity of care and the experience of learning through formal education and leaflets. An example of how this was put into effect can be seen in appendix 7, where the first and final versions of the adapted topic guide are shown.

The use of a purposive sampling frame allowed for a diverse sample in terms of hypoglycaemia frequency and severity, gender, diabetes treatment and ethnicity. This aided in development of the topic guide, and provided in-depth data derived from views and experiences of a varied population.

The data collection strategy of conducting 20 interviews was successful in identifying key themes and interviews were terminated at the point when no new themes were emergent.

Although the study included both White European and South Asian participants, due to resources available non-english speaking participants could not be interviewed. It is acknowledged that this may have had some influence on differences found.

It is also recognised that the insight provided for the HCP and patient relationship is only based on data from the patients perspective. The HCP

perspective is needed to provide a complete picture of the issues, concerns and facilitators raised from this data.

One of the study aims was to also make comparisons between participants in terms of age. We hoped to achieve this by including age in our sampling framework. However, due to the responses we received we could not include anyone under the age of 44 of over the age of 77. This may have influenced our findings that there were no notable differences between individuals in terms of age in the interview data.

The sample was drawn from those whose diabetes was managed in primary care. Issues may be different for patients managed mainly in specialist care, however, the majority of people with T2DM are managed in primary care.

Unfortunately, there were only two participants who were classified into the less engaged and empowered group. This meant that there were less data available to analyse and describe for the group. Based on the conclusions drawn, one explanation could be that individuals with lower empowerment or engagement levels are less likely to volunteer to participate and engage in a research studies.

4.7 Concluding remarks

This chapter presented a qualitative study exploring the views and experiences of people with T2DM who have experienced hypoglycaemia. The results show how hypoglycaemia affects people's everyday lives and the factors which may influence this impact. An analytical model was also developed from the findings, focused around an individual's level of empowerment and engagement with their HCP. The next chapter will summarise the main findings from the thesis and discuss recommendations for clinical practice and future research along with strengths and weaknesses of the work carried out.

Chapter 5: Overall discussion: summary, implications and recommendations

5.1 Chapter overview

This chapter presents a summary of the main aims and findings from the thesis (5.2), followed by the recommendations for clinical practice and future research (5.3). The strengths and weaknesses of the overall programme of work are then reviewed (5.4), with concluding remarks for the thesis presented lastly.

5.2 Summary of Programme of work

Chapter 1 presented the rationale and aims, whilst chapter 2 gave background on hypoglycaemia in people with Type 2 diabetes mellitus (T2DM). The overall aim of the programme of work in the thesis was to contribute to the current body of knowledge around the impact and burden of hypoglycaemia in T2DM. The work additionally aimed to consider how hypoglycaemia in T2DM is currently managed from the patient's perspective.

Chapter 3 presented a systematic review and meta-analyses which aimed to collate and evaluate the current literature reporting the prevalence (proportion of people) and the incidence (rate of episodes) of hypoglycaemia in real world population-based studies of T2DM. The review included 46 studies (n=532,542). The findings estimated that the prevalence of hypoglycaemia is 45% for mild/moderate and 6% for severe and that on average an individual with T2DM experiences 19 mild/moderate episodes and 0.8 severe episodes per year. Hypoglycaemia was shown to be particularly prevalent amongst those on insulin, yet still fairly common for treatment regimens of oral glucose-lowering therapies only.

The qualitative study described in chapter 4 explored the views and experiences of people with T2DM who have a history of hypoglycaemia.

The findings showed that hypoglycaemic episodes often interrupt daily life and activities, with common symptoms experienced being shaking and sweating. Pace of life, changes in routine and physical activity were all commonly cited causes, with those on insulin also experiencing hypoglycaemia due to miscalculation of food or timing issues. The majority of participants acted promptly to treat hypoglycaemia and carried treatment with them. Participants reported a different experience of nocturnal episodes, emphasising the lack of warning compared to daytime episodes and the difficulty they experienced waking up to treat.

Nearly all the participants tested their blood glucose at least occasionally, with targets for optimal control and self- diagnosis of hypoglycaemia varying considerably between them. In-depth descriptions were given by participants as to how it felt to experience an episode. Feelings of being in an alternate reality along with fear, panic and anger were all described in the midst of an episode. There were notable differences in some areas of the interviews between South Asian and White European participants, particularly in symptoms experienced and the experience of system barriers for clinic appointments. During analysis of the data there appeared to be clear differences between participants in terms of level empowerment (independence, confidence, proactiveness and knowledge) and engagement with their healthcare practitioner (HCP) (including disclosure of hypoglycaemia, communication and view of the HCP). This led to the development of the empowerment and engagement (EE) model.

5.3 Recommendations

5.3.1 Implications for clinical practice

5.3.1.1 Systematic review and meta-analyses

The review presented in chapter 3 shows that hypoglycaemia is prevalent amongst people with T2DM. The results highlight an urgent need for raising awareness within everyday clinical practice, particularly as prior evidence has suggested underreporting within this setting (110).

An important rationale used for newer therapies is that they have a lower incidence of hypoglycaemia than traditional therapies. (148). My results therefore provide support for the introduction of newer therapies, which focus on lowering the risk of hypoglycaemia.

From the available data I was unable to provide a pooled hypoglycaemia prevalence for newer therapies. As anticipated, prevalence of hypoglycaemia was high amongst those on insulin. This supports the focus on educating insulin users on hypoglycaemia, making them aware of risks and preventative methods. However, analysis of other treatment regimens (involving sulphonylureas and/or non-sulphonylureas), suggested that hypoglycaemia does still occur in those on alternative treatment regimens. Therefore, when considering treatment options, hypoglycaemia risk consideration should be incorporated through the individualisation of treatment regimens prescribed (30). Blood glucose targets should also be individualised and in some cases a higher target may be optimal for the patient (149).

Based on the pooled estimate from this review, an individual with T2DM experiences on average approximately one severe episode of hypoglycaemia per year. Severe episodes are a burden on both the individual and healthcare utilisation, due to their cost and the significant dangers that can result from an episode (12, 84). Severe episodes can have consequences for driving, with increasingly stricter guidelines in the UK stating currently if an individual has more than one episode of severe hypoglycaemia in the last twelve months it could be considered to revoke their driving licence (25). This can have major implications for the individual, causing loss of independence, identity and increase in depressive symptoms (11, 26).

The pooled results that show an individual with T2DM experiences 19 mild/moderate episodes on average per year is also important to highlight. There has been previous work considering the impact of mild/moderate hypoglycaemia within T2DM but data are lacking regarding the prevalence. It is important to consider the patient level costs and burdens associated with mild hypoglycaemia and not solely healthcare level issues relating to severe

episodes. The quantity of mild/moderate episodes could substantially impact on work, social situations and daily activities (7). The episodes may unfortunately become a common occurrence in an individual's life, subsequently decreasing general quality of life. Furthermore, with each mild/moderate episode, there is a risk they could progress to a severe episode if not treated appropriately. Knowing the incidence and risk factors of mild hypoglycaemia aids the design of successful interventions to prevent hypoglycaemia progressing from mild/moderate to severe. This could be done by educating patients on preventing episodes or noticing the signs early on in a mild episode and treating it accordingly to prevent progression.

The results showing that hypoglycaemia is considerably prevalent in T2DM also highlight the importance of successful educational programmes incorporating hypoglycaemia. Programmes should be focused on successfully increasing knowledge of hypoglycaemia in relation to appropriate self-treatment methods, risk factors and predisposing symptoms (71), as knowledge has previously been shown to be low in the T2DM population (150, 151).

5.3.1.2 Qualitative study

The results from the qualitative study presented in chapter 4 emphasize the importance of addressing hypoglycaemia in everyday clinical practice. The in-depth accounts given, illustrate how traumatic and disruptive even mild episodes can be for the individual experiencing them. The accounts given by those completely unaware of what hypoglycaemia was when they first experienced an episode, highlight how vital it is for all patients to be educated on at least the basics of what hypoglycaemia is, the symptoms and how to effectively treat.

It is also evident from the results that nocturnal hypoglycaemia should be highlighted and to a degree discussed separately from daytime hypoglycaemia. The data demonstrated it to be a different experience, with treatment often being more urgent as the individual is usually at a lower blood glucose level by the time they have awoken. Nocturnal episodes can also be harder to act upon

as the individual can misinterpret the symptom of drowsiness as feeling tired. Recommendations should also be focused on appropriate treatment for these episodes, as the data showed individuals were more likely to eat too much through fear of the episode reoccurring during the same night.

The study also highlights individual differences between patients and the impact this may have on approaches and management of hypoglycaemia. The data support that it is not just the treatment regimen which needs considering in evaluating the risk and impact of an episode but also patient lifestyle and demographics (such as ethnicity).

Participants did prioritise hypoglycaemia and treatment when it was actually occurring, but not so much before it occurred and in their everyday lives. It should be noted the difficulty some people have in fitting the consideration of hypoglycaemia into their busy lives. People from this study did not tend to prioritise eating, taking a break or generally slowing down sometimes to avoid hypoglycaemia, with most people showing a lack of planning and some feeling uncomfortable taking breaks in social situations or work. However, when encouraging the daily consideration and planning to avoid hypoglycaemia, caution should be taken of the detrimental effect too much planning and worry could have on the individual. This was shown in a small proportion of patients who feared and worried about hypoglycaemia on a daily basis. A balance between healthy consideration of the risk of hypoglycaemia and being able to maintain a low level of worry in everyday life would be the optimal achievement for a patient with diabetes.

The findings also highlight individual differences in terms of varying glucose values used by individuals to self-diagnose hypoglycaemia. Participants reported the value they used to determine hypoglycaemia, with a variation from 5mmol/L to 3mmol/L. This along with the different blood glucose value symptoms and interruption to daily activities were experienced should be considered by HCPs when discussing hypoglycaemia.

A key case within the interviews was the participant who had their blood glucose strips discontinued by their HCP. This had led the participant to worry immensely when they could have a hypoglycaemic episode, with no method of checking their glucose for reassurance. The patient in turn started to overeat, preferring to experience high blood sugar and avoid low. Blood glucose monitoring is costly to the NHS (National health service) and it is therefore understandable that caution needs to be taken when prescribing test strips. However, if the patient is at risk of hypoglycaemia, then the question arises of the benefits to the individual and potential cost of hypoglycaemia consequences outweighing the initial cost of prescribing blood glucose monitoring equipment. The key issue here, which was a common issue throughout some of the interviews, was HCP-patient communication. The HCP was not aware the patient was experiencing hypoglycaemia, which would have made it difficult to assess their hypoglycaemia risk. The patient was on metformin alone, however had a busy lifestyle.

The data strongly supports optimization of the HCP-patient relationship for successful hypoglycaemia management. Miscommunication or lack of productive communication could greatly hinder effective management. Simply "telling someone" to make a difficult behaviour change is usually not enough, especially if they are embedding lifestyle changes or treatment changes (which may be daunting for the patient). If HCPs purely tell patients how to manage their diabetes, they do not have the control or opportunity to ensure it is being carried out. On the other hand, if the patient is engaged with their management and the relationship, the HCP is in a better position to ensure the patient has the tools to implement changes and successfully manage their hypoglycaemia. This ideally would go beyond a one-off consultation, with ongoing discussions, updates and adaptions.

The EE model has implications for everyday clinical practice and self-management education programmes. How a patient's level of empowerment and engagement may help determine their needs for managing hypoglycaemia. Regarding those that are on the low end of the scale for empowerment and/or engagement, increasing motivation and interest should be key. Once the patient

is more engaged with their own health and HCP, facilitating confidence, independence and knowledge should be less challenging. Once a patient has the fundamental interest and motivation in their own heath, focus should be on increasing knowledge and optimizing the HCP-patient relationship. With knowledge, skills and confidence to manage their hypoglycaemia evident, focus should be on ensuring the patient and their HCP maintain communication and that management of hypoglycaemia is successfully maintained, with revision where necessary of coping and preventative methods. However, unsuccessful application of empowerment has often been due to HCP misconceptions of meaning and implementation. Therefore, clarity and understanding is vital when implementing models such as this. Additionally, the relationship needs to be continuous and self-involving on both sides for empowerment to be successful (16).

5.3.2 Implications for future research

5.3.2.1 Systematic review and meta-analyses

A limited number of studies within the review provided prevalence and incidence rates separately for mild/moderate episodes of hypoglycaemia in a T2DM population (8/46, 17.4%). This review highlights the need for research specifically into the occurrence of mild/moderate episodes, and their risk factors. The majority of studies reporting mild episodes were also only in people using insulin, so further consideration of other treatment regimens was difficult. Research into mild episodes is however more challenging than severe in terms of reliability and access to data, with data collection methods limited to continuous glucose monitoring systems (CGMS), prospective diary recording, and retrospective recall. CGMS is the most reliable but can be costly and so generally involve small populations and short data collection periods (152, 153). Prospective diary recording is another option, though again studies tend to have smaller numbers and reliability has been questioned (154). Retrospective recall is convenient and the least costly, though potentially less reliable in terms of time limit for recall. However, it has been shown that by asking the frequency of episodes rather than absolute numbers reliability can be improved. (116) Data

from retrospective recall using a large population could be used to complement a smaller study using either prospective diaries or CGMS.

Nearly all the studies included in the review considered severe episodes (40/46, 87%). Severe episodes can be collected from a variety of sources, including emergency department records and claims databases, as well as methods used for mild types of hypoglycaemia. The results suggest however that by using only emergency treated hypoglycaemia data, prevalence appears to comprise just half of all those experiencing severe events. Using complementary methods of recall and emergency department records appear to be the best for reliability and capturing all episodes. Questionnaires also enable the exploration of important factors associated with hypoglycaemia such as the impact to the individual.

Some studies (6/46, 13%) did not specify the severity of hypoglycaemia experienced by participants when data collecting. These fell into the "unspecified" category and can be used to ascertain the overall impact of hypoglycaemia, laying the foundations to then explore specific severities of episodes. However, they only give an inclination of how many mild/moderate or severe episodes have been experienced. Further research should be aware by using only unspecified hypoglycaemia within studies, participants could potentially interpret what is meant by hypoglycaemia in different ways, with some for example only reporting severe.

The use of an appropriate and standardised hypoglycaemia definition is important, particularly when collecting or reviewing prevalence or incidence data. There was a consensus across studies when defining hypoglycaemia by severity, using the level of help required from a third party as a determinant. However, a biochemical or recognised standardised definition was rarely and inconsistently4 used. This was likely due to the nature of some of the studies data collection methods, for example questionnaires. Future prevalence studies should be aware of the importance of using an appropriate definition and its potential impact on their finding which can impact on important issues such as recommendations for newer therapies, driving restrictions and overall care

received by patients. It is important that a standardised definition such as the widely used American Diabetes Association workgroup's (138) is utilised across studies of hypoglycaemia.

Data collection methods also varied across studies in terms of the time period hypoglycaemia was measured over. Interestingly though, this did not significantly increase the proportion of people experiencing hypoglycaemia within a study. The proportion did increase slightly, but not significantly. This has implications for the design of future studies, in terms of measuring over a time period long enough to capture a realistic picture of hypoglycaemia while avoiding potentially unnecessary cost of a longer term study.

More research is needed in relation to the potential risks associated with particular glucose lowering therapies. Population based studies are inconsistent in how they group and report treatment regimens, making it difficult to collate data across studies. There is a lack of published population based literature comparing sulphonylurea and non-sulphonylurea treatment regimens. There is also a need for real world prevalence figures for newer glucose lowering agents compared with traditional therapy regimens. Another risk factor which is not frequently considered in the literature is ethnicity. This is a factor which may impact on hypoglycaemia rates due to the higher prevalence of diabetes in some ethnic sub populations. Risk factors and causes for hypoglycaemia need to be established so that targeted education interventions can be designed and clinicians are aware of who is most at risk of hypoglycaemia.

5.3.2.2 Qualitative study

The study findings highlight a range of issues surrounding hypoglycaemia but further qualitative and quantitative data are still needed to support and elaborate the findings.

The findings suggest that nocturnal and daytime hypoglycaemic episodes are experienced and managed differently. Distinguishing between the two types of episodes should be considered in future research of prevalence and management of episodes. Educational interventions should aim to equip

patients with information on how to deal with both these types of episodes, ensuring they know what to expect and how is best to treat. The first of two key issues identified from the data related to the lack of warning before the onset of a nocturnal episode. Participants described waking from sleep to the episode having progressed considerably and action being needed immediately, with trouble thinking clearly. The second issue was around peoples tendency to overeat during night time hypoglycaemia. This was due to fear of hypoglycaemia reoccurring, therefore appropriate treatment and reassurance should be addressed in future educational interventions.

Following on from the recommendations based on findings from the review, ways to individualise care and treatment should be explored further. It is apparent from the descriptive results that people experience hypoglycaemia differently. The causes and their experience during and management following an event differ substantially. The EE model helps to understand these variations, categorising people by their empowerment and engagement with their HCP and subsequent impact on their management of hypoglycaemia. Further research would be beneficial in looking at the effect of educational programmes based upon a patient's place along the EE model continuum. For example, if a patient was low in engagement and empowerment then interventions should firstly focus on increasing their overall engagement with managing hypoglycaemia, as opposed to trying to increase knowledge. A patient needs to be willing, interested and motivated to listen and learn before the knowledge is presented to them.

The qualitative findings suggest that people of south Asian origin experience different symptoms to those of White European ethnicity. This would benefit from further exploration via quantitative study data to ascertain the strength of this association. Secondly, data indicating that South Asian participants were more likely to report issues and barriers to attending clinic appointments or receiving regular healthcare for their diabetes needs further attention. Quantitative data from a larger sample, perhaps in the form of an audit or questionnaire would be beneficial in addressing the size and significance of this problem.

The study provides insightful data into patient experiences and perspectives on the management of hypoglycaemia within the primary care setting. There is a particular consideration of communication between the HCP and patient, with issues relating to disclosure. Future research should focus on these issues from a HCP perspective, enabling a full picture to be presented considering both viewpoints. HCP input should be sought through further qualitative work on the issues raised by the patients, along with any additional concerns the HCPs may have. The facilitators and positive aspects of what enables a good relationship, successful management and full disclosure of episodes between patient and HCP should also be explored further from a HCP point of view.

5.4 Strengths and limitations of the overall programme of work

This programme of work involved varied and robust methodology and data analysis techniques. The review adhered to the Cochrane (94) and PRISMA (137) recommended standards for systematic reviews. The analysis involved descriptive data synthesis along with meta-analyses. The qualitative study presented in the thesis used sound methodology, including principles of grounded theory and an iterative approach to data collection and analysis.

This programme of work also made a unique contribution to the body of knowledge on hypoglycaemia in T2DM. This is the first systematic review and meta-analyses to consolidate the evidence on hypoglycaemia in population based studies of T2DM.

The qualitative study presents novel data from a multi-ethnic population, with very few qualitative studies within T2DM previously published. It presents data which is both descriptive and analytical and can be applied to everyday clinical practice and informs future research.

Studies were inconsistent in the reporting of certain factors, leading to limitations for the findings of the review. Firstly, a biochemical definition of hypoglycaemia was rarely used, therefore, hypoglycaemia was analysed by severity and whether or not third party assistance was required during an

episode. The way in which studies categorised different glucose lowering therapies also varied considerably. Therefore, it was only possible to use broader treatment categories in these analyses. Additionally, studies varied considerably in length of time hypoglycaemia prevalence was related to; as a result a specific time period for prevalence could not be established.

The qualitative study did achieve a diverse sample in terms of ethnicity. However, experiences reported in the interviews, particularly when referring to those within the healthcare system were based upon experience within one geographical location (Leicestershire) and only English speaking individuals. It is also acknowledged that the HCP perspective is needed to provide a complete picture of the issues, concerns and facilitators raised from the findings. Another potential limitation of the study is the age range of the participants. Due to the responses we received we could not include anyone under the age of 44 or over the age of 77. This may have influenced our findings that there were no notable differences between individuals in terms of age in the interview data.

5.5 Concluding remarks

The work presented in this thesis contributes to the current body of knowledge around the impact, burden and management of hypoglycaemia in T2DM.

The data shows that hypoglycaemia (mild and severe) in T2DM is prevalent and can have a substantial impact on the individual. Management of hypoglycaemia is complex, with individual empowerment, lifestyle, demographics and patient-physician relationship all play an important role.

Appendices

Appendix 1: Contribution to the work carried out

1) *Systematic review and meta-analysis*

The systematic review, including the extraction and collation of all data and meta-analyses were conducted by the author of this thesis. However, in order to ensure that guidelines for best practice (94) were followed there was some collaborative work involved. The review of papers for inclusion was carried out in duplicate by myself and another team member. Data extraction and quality assessment for papers included in the review were carried out independently by the author and another team member. Meta-analyses were carried out by the author, with guidance from an expert statistician.

2) *Qualitative study*

All elements of the study, except for transcription of the interviews were carried out by the author. This included applying for ethical approval, interviewing the participants and data analysis. Advice was also sought from two additional researchers with experience in qualitative research during data analysis, particularly the development of the empowerment and engagement (EE) model.

Appendix 2: Search strategy for Ovid MEDLINE

1. Diabetes Mellitus, Type 2/

2. (type adj "2" adj diabet$).ti,ab.

3. (diabet$ adj type adj (type adj "2" adj diabet$)).ti,ab.

4. (diabet$ adj6 (type adj3 (type adj "2" adj diabet$))).ti,ab.

5. (type adj3 (type adj "2" adj diabet$) adj6 diabetes).ti,ab.

6. 1 or 2 or 3 or 4 or 5

7. Hypoglycemia/

8. Incidence/

9. Prevalence/

10. 8 or 9

11. 7 and 10

12. (hypoglyc$ adj4 prevalence).ti,ab.

13. (hypoglyc$ adj4 incidence).ti,ab.

14. (hypoglyc$ adj4 rate$).ti,ab.

15. (hypoglyc$ adj4 occurrence$).ti,ab.

16. (hypoglyc adj4 frequen$).ti,ab.

17. (hypoglyc$ adj4 event$).ti,ab.

18. (hypoglyc$ adj4 episode$).ti,ab.

19. (hypoglyc$ adj4 risk$).ti,ab.

20. (hypoglyc$ adj4 frequen$).ti,ab.

21. 11 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20

22. 21 and 6

23. animal/ not (animal/ and human/)

24. 22 not 23

25. limit 24 to english language

26. "review"/

27. 25 not 26

Appendix 3: Data extraction form

Data extraction form

Eligibility checklist			
	Yes	No	Notes
Study population or subgroup - Type 2 Diabetes = 100%			If no, exclude
Adults aged 18 or over from when the study started			If no, exclude
Study sample is primarily people who are pregnant, fasting or have acute chronic illnesses			If yes, exclude
The paper is either a review article or RCT study comparing drug trials or treatment regimen			If yes, exclude
Frequency of hypoglycaemia is reported in the results			If no, exclude

Study Details	
First author	
Publication date	
Title of paper	
Journal	
Country of first author	
Type of study	
Number of arms	

Follow-up time	
Notes	

Population			
	Overall	Hypo's reported	No Hypo's reported
Population size (type 2 diabetes)			
Mean age			
N (%) Male N (%) Female			
Ethnicity White Black or black British Asian or Asian British Chinese Mixed			
Country of habitat			
HbA1c Mean Range			

SD			
BMI			
Mean			
Range			
SD			
Notes			

Diabetes medical history of population			
	Overall	No Hypo's	Hypo's
Co-morbidities (%)			
Time since diagnosis			
Mean			
Range			
SD			

diabetes treatment regimes			
Diet only			
Metformin only			
Sulphonylurea only			
Insulin only			
Incretin/glp-1			
Dpp-4 inhibitor			
Mixed (insulin + oral/s)			
Mixed (oral)			
Mixed (insulin)			
Diet Only			
One oral			
More than one oral			
Insulin only			
Mixed (insulin + oral/s)			
Mixed (oral)			
Mixed (insulin)			
Notes			

,

Definition of hypoglycaemia used	
Blood glucose level used to define	

Definition used	
Recognised definition	Yes ☐　　　No ☐
Differentiation between type of hypoglycaemic episode	Only one classification of hypoglycaemia used ie. ONLY severe. If so state which ☐ Two-tiered (severe and mild) ☐ Three-tiered (severe, mild and moderate) ☐ Nocturnal ☐

Notes	

Measure of Hypoglycaemia	
Blood test	Constant Glucose monitoring: ☐ Self-monitoring: ☐ Taken by healthcare professional: ☐
Data obtained	Prospectively ☐ Retrospectively ☐ Validated Questionnaire/Question ☐ If so please specify: Non-validated question/questionnaire ☐ Diary ☐ Medical Records GP: ☐ Ambulance: ☐ Hospital: ☐ Other: ☐ If other please specify:
Notes	

Frequency of hypoglycaemic episodes	
Prevalence/Incidence	<u>Prevalence reported and over what time</u> <u>Incidence reported per patient years</u>

	<u>If Prevalence and incidence not reported record:</u> *N population (type 2 diabetes)* *N of regular hypoglycemic events* *And* *N of hypoglycemic events and over what time period* *Total person years*
Notes	

Appendix 4: Codes for your meta and meta-regression analyses

metan any_prop any_se, random label(namevar=author, year=year)

metan any_noninsulindrughypo_prop any_noninsulindrughypo_se, random label(namevar=author, year=year)

metan any_insulinhypo_prop any_insulinhypo_se, random label(namevar=author, year=year)

metan severe_prop severe_se, random label(namevar=author, year=year)

metan severe_noninsulindrughypo_prop severe_noninsulindrughypo_se, random label(namevar=author, year=year)

```
metan severe_insulinhypo_prop severe_insulinhypo_se, random label(namevar=author, year=year)

metan severe_prop severe_se if severedefinition== "general external assitance" , random

metan severe_prop severe_se if severedefinition== "Emergency  treatment" , random

metan mild_prop mild_se, random label(namevar=author, year=year)

metan mild_noninsulindrughypo_prop mild_noninsulindrughypo_se, random label(namevar=author, year=year)

metan mild_insulinhypo_prop mild_insulinhypo_se, random label(namevar=author, year=year)

metan event_any event_any_se, random label(namevar=author, year=year)

metan event_mild event_mild_se, random label(namevar=author, year=year)

metan event_severe event_severe_se, random label(namevar=author, year=year)

metareg any_prop hba1c, wsse(any_se) graph

metareg any_prop male, wsse(any_se) graph

metareg any_prop age, wsse(any_se) graph

metareg severe_prop male, wsse(severe_se) graph

metareg severe_prop severe_time12, wsse(severe_se) graph

metan severe_propma severe_sema, random label(namevar=author, year=year)

metareg severe_prop age, wsse(severe_se) graph

metareg mild_prop mild_time12, wsse(mild_se) graph

metareg event_any hba1c, wsse(event_any_se) graph

metareg event_any male, wsse(event_any_se) graph

metareg event_any age, wsse(event_any_se) graph

metareg event_severe male, wsse(event_severe_se) graph

metareg event_severe hba1c, wsse(event_severe_se) graph

metareg event_severe severe_time12, wsse(event_severe_se) graph

metan severe_propma severe_sema, random label(namevar=author, year=year)

metareg event_severe age, wsse(event_severe_se) graph

metareg event_mild mild_time12, wsse(event_mild_se) graph

metareg event_mild hba1c, wsse(event_mild_se) graph

metareg event_mild male, wsse(event_mild_se) graph
```

metareg event_mild age, wsse(event_mild_se) graph

metabias any_prop any_se

metafunnel any_prop any_se

metabias event_any event_any_se

metafunnel event_any event_any_se

metabias mild_prop mild_se

metafunnel mild_prop mild_se

metabias event_mild event_mild_se

metafunnel event_mild event_mild_se

metabias severe_prop severe_se

metafunnel severe_prop severe_se

metabias severe_propga severe_sega, egger graph

metabias severe_propma severe_sema, egger graph

Appendix 5: Quality assessment form

<u>Selection bias</u>

Was the sample source representative of the population intended to the study and well described? (e.g.)

Very (++) (e.g emergency department records, health clinic multi centre)

Somewhat (+) (e.g health clinic, single centre)

Not very (-) (e.g consumer database/panel)

Was the sampling method appropriate to reduce bias?

Very (++) (e.g all of the population included, stratified random)

Somewhat (+) (e.g random)

Not very (-) (e.g convenience, consecutive)

Was there a suitable eligibility criteria applied and described?

Yes and described (++)

Yes but not described (+)

No (-)

What percentage of selected individuals agreed to participate?

80% - 100% (++)

Not applicable due to all patients from the source used (++)

60%-79% (+)

Less than 60% (-)

Can't tell (-)

<u>Data collection method</u>

Was the data collection tool for the number of hypoglycaemic episodes well described?

Very (++)

Somewhat (+)

Not very (-)

Was the measurement of hypoglycaemia reliable?

Measurement of hypoglycaemia not clearly defined (-)

Self – reported retrospectively (eg. Questionnaire) (+)

Recorded in emergency department records and/or blood glucose reading (++)

<u>Appropriate analysis</u>

Did the investigators report that they controlled for confounding factors (e.g stratification, matching, restriction, adjustment)?

Yes (++)

No (-)

Notes – tool used to assess the methodological quality and to assess the extent the analysis matched the study objectives – consideration of confounding factors not necessarily to do with hypoglycaemia rates – but related to primary/secondary outcomes of study

Quality score	
External validity: • Selection Bias scores combined	
Internal validity: • Data collection method and Appropriate analysis scores combined	

Appendix 6: Ethics and governance approvals

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 2
Royal Standard Place
Nottingham
NG1 6FS
Telephone: 0115 8839390

22 July 2014
Dr Alison Dunkley
Research Associate in Nursing
University of Leicester
University of Leicester, Diabetes Research Centre
Leicester General Hospital
Leicester
LE5 4PW

Dear Dr Dunkley **Study title:**   **Views, experiences and knowledge of hypoglycaemia in Type 2 Diabetes**
REC reference: **14/EM/0225**
IRAS project ID: **147905**

 The Proportionate Review Sub-committee of the NRES Committee East Midlands - Nottingham 2 reviewed the above application on 19 May 2014.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager Ms Liza Selway.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study. **You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.**

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were: *Document*	*Version*	*Date*
Covering letter on headed paper	Chloe Redshaw	12 May 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)	University of Leicester - Sue Banbury	03 April 2014
Interview schedules or topic guides for participants	1	01 December 2013
Letters of invitation to participant	1	01 December 2013
Other [Patient Reply Slip] Other [Post Interview slip]	1	01 December 2013
Participant consent form [Patient Consent]	1	01 December 2013
Participant consent form [Relative/Friend Consent]	1	01 December 2013
Participant information sheet (PIS)	1	01 December 2013
REC Application Form	147905/608102/1/34	10 April 2014
Referee's report or other scientific critique report	Ms Naina Patel	
Referee's report or other scientific critique report	Jo Byrne	
Referee's report or other scientific critique report	Jo Byrne (signed)	
Research protocol or project	1	01 December 2013

proposal

Summary CV for Chief Investigator (CI)	Dr Alison Dunkley	27 March 2014
Summary CV	Kamlesh Khunti	26 March 2014
Summary CV	Chloe Louise Redshaw	10 March 2014

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

14/EM/0225   **Please quote this number on all correspondence**

Yours sincerely

Dr Martin Hewitt
Chair

Enclosures: *List of names and professions of members*
                                           who took part in the review
                                           "After ethical review – guidance for
                                           researchers"

Copy to: Wendy Gamble,
                                           Roz Sorrie, Comprehensive Local
                                           Research Network (CLRN)

NRES Committee East Midlands - Nottingham 2
Attendance at PRS Sub-Committee of the REC meeting on 19 May 2014

Committee Members: *Name*	*Profession*	*Present*	*Notes*
Mr Simon Deery	Junior Doctor	Yes	
Dr Martin Hewitt	Consultant Paediatric Oncologist	Yes	
Dr Simon Roe	Consultant Nephrologist	Yes	

Also in attendance: *Name*   *Position (or reason for attending)*
Mrs Carolyn Halliwell   REC Assistant

DIRECTORATE OF RESEARCH & DEVELOPMENT
Director: Professor Nigel Brunskill
Assistant Director: Dr David Hetmanski
Head of Research Operations: Carolyn Maloney

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226
21/10/2014

Professor Kamlesh Khunti
University of Leicester
Professor of Primary Care Diabetes & Vascular Med
Department of Health Sciences
College of Medicine, Biological Scientist and Psychology
22-28 Princess Road West
Leicester
LE1 6TP

Dear Professor Kamlesh Khunti

Ref: UHL 11354
Title: Views, experiences and knowledge of hypoglycaemia in
Type 2 Diabetes
Project Status: Project Approved
End Date: 19/12/2014
Date of Valid Application: 16/10/2014
Days remaining to recruit first patient: 65 Days

I am pleased to confirm that with effect from the date of this letter, the above study has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust. The research must be conducted in line with the Protocol and fulfil any contractual obligations agreed between UHL & the Sponsor. If you identify any issues during the course of your research that are likely to affect these obligations you must contact the R&D Office.

In order for the UHL Trust to comply with targets set by the Department of Health through the 'Plan for Growth', there is an expectation that the first patient will be recruited within 70 days of receipt of a Valid Application. The date that a Valid application was received is detailed above, along with the days remaining to recruit your first patient. **It is essential that you notify the UHL Data Management Team as soon as you have recruited your first patient to the study either by email to RDData@uhl-tr.nhs.uk or by phone 0116 258 4573.**

If we have not heard from you within the specified time period we will contact you
not only to collect the data, but also to record any issues that may have arisen to

prevent you from achieving this target. It is essential that you get in touch with us
if there is likely to be a problem in achieving this target so that we can discuss potential solutions. The Trust is contractually obliged to meet the 70 day target and if an adequate reason acceptable to the NIHR has not been submitted to explain the issues preventing the recruitment of your first participant, the Trust will be financially penalised.

In addition, we are required to publish the Title, REC Reference number, local target recruitment and actual recruitment as well as 70 days data for this study on a quarterly basis on the UHL public accessed website.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Description Version
Interview schedules or topic guides for
Participants V1
Dated: 01 December 2013
Letters of invitation to participant V1 Dated: 01 December 2013
Other [Patient Reply Slip] V1
Dated: 01 December 2013

Participant consent form [Patient
Consent]
V1 Dated: 01 December 2013

Participant consent form
[Relative/Friend Consent]
V1 Dated: 01 December 2013

Participant information sheet (PIS) V1
Dated: 01 December 2013

Research protocol or project proposal
V1 Dated: 01 December 2013

**Staff Approved to work on this study
at University Hospitals of Leicester**
Prof Kamlesh Khunti
CV and GCP received

Dr Alison Dunkley
CV and GCP received – Consent assessment N/A
Miss Chloe Redshaw
CV, GCP and Consent assessment all received
Letter of Access also received valid from 24.03.2014 until 31.04.2014

Please note: This approval only covers for The University Hospitals of Leicester- Approval for Primary care Trust will need to be sought separately
Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

Undertaking research in the NHS comes with a range of regulatory responsibilities. Please ensure that you and your research team are familiar with, and understand the roles and responsibilities both collectively and

individually.

Documents listing the roles and responsibilities for all individuals involved in research can be found on the R&D pages of the Public Website. It is important that you familiarise yourself with the Standard Operating Procedures, Policies and all other relevant documents which can be located by visiting www.leicestershospitals.nhs.uk/aboutus/education-and-research

The R&D Office is keen to support and facilitate research where ever possible. If

you have any questions regarding this or other research you wish to undertake in

the Trust, please contact this office. Our contact details are provided on the attached sheet.

We wish you every success with your research.

Yours sincerely
Carolyn Maloney

Head of Research Operations

Encs: .R&D Office Contact Information

NHS
Leicester City
Clinical Commissioning Group
City Headquarters
St John's House
30 East Street
Leicester
LE1 6NB
Tel: 0116 295 1478
www.leicestercityccg.nhs.uk

NHS
West Leicestershire
Clinical Commissioning Group

NHS
East Leicestershire and Rutland
Clinical Commissioning Group

25-07-2014

Professor Kamlesh Khunti
Leicester Diabetes Research Centre
Diabetes Research Centre, Leicester Diabetes Centre
Leicester General Hospital
Leicester
LE5 4PW

Ref: LCR290514
REC Ref: 14/EM/0225
End Date: 19/12/2014
Project Status: Assured

Dear Professor Kamlesh Khunti,

Re: Views, experiences and knowledge of hypoglycaemia in Type 2 Diabetes

I am pleased to confirm that **Leicester City Clinical Commissioning Group** which provides the Primary Care R&D Service across Leicester, Leicestershire and Rutland, has received a review of this research study via the Coordinated System for gaining NHS Permission (CSP) from the Clinical Research Network: East Midlands. This review confirms that the appropriate study-wide and local research governance checks have been undertaken and that this study complies with the requirements of the Research Governance Framework and national legislation. In conjunction with the local discussions the Clinical Research Network: East Midlands have had with you regarding participating as a site for this study, I am now happy to formally provide assurance for this study to proceed within **Leicester City CCG, East Leicestershire & Rutland CCG**

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and West Leicestershire CCG. Your research has been entered onto our primary care research database.

This assurance is provided with the following conditions: that no additional costs are incurred at the site (s) as a result of this study being undertaken and unmet service support costs will be provided by the Clinical Research Network: East Midlands.

Please reply to this letter confirming the expected start date and duration of the study. As part of the Research Governance Framework it is important that the Leicester City CCG R&D office is notified as to the outcome of your research. As such the Clinical Research Network: East Midlands will request feedback once the research has finished along with details of dissemination of your findings. We may also request brief updates of your progress from time to time, dependent on duration of the study.

Similarly, if at anytime details relating to the research project or research team change, the Leicester City CCG R&D office must be informed.

The documents reviewed for assurance are as follows:

Document Title	Version	Date	REC Approval
REC favourable opinion letter	N/A	20-05-2014	N/A
Interview schedules or topic guides for participants	1	01-12-2013	20-05-2014
Letters of invitation to participant	1	01-12-2013	20-05-2014
Other [Patient Reply Slip]	1	01-12-2013	20-05-2014
Participant consent form [Patient Consent]	1	01-12-2013	20-05-2014
Participant consent form [Relative/Friend Consent]	1	01-12-2013	20-05-2014
Participant information sheet (PIS)	1	01-12-2013	20-05-2014
Research protocol or project proposal	1	01-12-2013	20-05-2014

If you have any further questions regarding this or other primary care research you may wish to undertake in the Leicester, Leicestershire and Rutland area, please feel free to contact me again, or the Clinical Research Network: East Midlands Primary Care research office. I wish you every success with the research.

Yours sincerely

Deb Wall
R&D Manager

Leicester City CCG
Tel: 0116 295 1520

Email: debbie.wall@leicestercityccg.nhs.uk
CC:

Janice Strand, Locality Manager, Division 5 (Primary Care), Clinical Research Network

Appendix 7: Topic guide

> **The Hypoglycaemia Interview Study**

Note: Topic guide designed to be a flexible tool which is open to revision as new areas of interest arise during the process of data collection.

1. Diagnosis of diabetes and source of knowledge and understanding about hypoglycaemia

A. Can you tell me a bit about how you were diagnosed with diabetes?
Probe:

- symptoms
- How did you feel

B. Prior to being diagnosed with diabetes had you heard about hypos or not? Probe:

- When?
- Who from?
- What had they heard?

C. Did your doctor or nurse talk about hypos with you at any point during the treatment of your diabetes or not?
If yes:

Probe:

- Can you recall what they said?
- What can healthcare professionals do to help you remember information? What was it about that interaction that helped you remember?
- At point did they talk about hypos? Prompt: before or after experienced a hypo?
- How did what they said help you to understand about hypos? Probe
  - understand their causes
    or symptoms

  - how to prevent them?
- How did the conversation make you feel??

If no:

Probe:

- Whether the participant discussed hypos with the doctor or nurse and why?

Do you see the same doctor/nurse regarding your diabetes?

How do you feel about this?

- Do you think this has any effect on whether you discuss hypo's with them? Why? What is it about the relationship?

- How do you feel the level of confidence is balanced across the relationship? You in them? Them in you?
- To what level do you feel they are a professional or friend?
- If does not discus hypo's – do they discuss other aspects of diabetes openly – why not hypo's?

D. Have u been on any education programmes/read any leaflets for hypoglycaemia

If yes

Probe:

- What did you find helpful/good about it?
- What do you feel could be improved

E. In an ideal world how could you be informed about hypo's?
Probe: education programmes, general talking in clinic, leaflets, telephone support, internet, group meetings

2. <u>**Participant understanding and knowledge of hypoglycaemia**</u>

A. Ok, based on what you have heard and experienced can you tell me what you understand about hypos?

Probe:

- Source of knowledge? Prompt: self-education, family and friends, doctor/nurse, attended education sessions?

- *Symptoms or blood sugar used to define?*

B. *Is the term hypoglycaemia commonly used to you ie. By healthcare professionals? Or is low blood sugar used?*
- *Probe: What do you understand is mean by <u>hyper</u>glycaemia and <u>hypo</u>glycaemia? Some people can confuse the meanings of these terms do you feel this way ever?*

C. *What do you think causes hypos?*
Probe:
- *Do you think there is a relationship between hypo's and physical activity (not just strenuous exercise perhaps waking around town. Probe how interact?*
- *Do you think there is a relationship between alcohol and hypo's. Probe how interact?*

D. *What do you understand about your medication?*
Probe:
- *Hypo's?*
- *What else would you like to know?*
- *If does not understand medication – how does this make you feel?*

3. <u>Experience and frequency of hypoglycaemia</u>

A. Can you tell me about your experience/s of having a hypo/s?
Probe:
- Symptoms
- Frequency
- Causes
- Severity

- Daytime/nocturnal
- How you feel after an episode? Prompt: emotionally and physically. Probe: how long for?

Self-treatment methods for hypoglycaemia

How do you usually treat your hypoglycaemia?
Probe:
- Type of food/substance and amount
- Treatment based on advice (if yes, who from) or trial and error
- Why do you think this treatment is good?

Does this differ at all?
Probe:
- according to symptoms or blood sugar level or convenience
- Nocturnal?

Do you carry around with you things to treat your hypos?
Probe methods of treatment?

Is it easy or difficult to get the right balance of blood sugar after a hypo?
Probe:
- what is the right/correct level for you
- Sometimes blood sugar can go too high because it's difficult to get the right balance, is this something that you have experienced or not? If yes: How often

Utilisation of third party support during an episode of hypoglycaemia (including friends, family, work colleagues and healthcare professionals)

Do you ever require the help of someone else when having a hypo?

Probe: friends, family, work colleagues, health professionals
If yes: Emotionally, mentally not just physical?
What role did they play?
How often?
Nocturnal?

Treatment or lifestyle modifications following an episode of hypoglycaemia
Do you make any alterations to your medication following an episode or not?
Probe: medication dose/type, blood sugar testing, purposefully keeping blood sugar high to avoid future episodes, eating more to prevent

Changes to your lifestyle
Probe: Exercise, diet, education, socially

Do you discuss these changes with health care professionals/friends/family?
Probe: Before or after changes made

Can you talk about the ways in which you prevent hypo's from happening?
Probe: medication, diet, exercise, blood sugar level target

Do you self-monitor your blood sugar on a regular basis? How regular? Do you feel it is important to self-monitor? Why?
- *If yes:* How do you feel about self-monitoring your blood glucose?
- If no: Why not?
- What are your personal barriers to self-monitoring?
- What could be done to help you monitor more often?

- Do you feel you think your feelings towards self-monitoring of blood glucose has any effect on your experience of hypoglycaemia?

Attitudes and experiences about disclosure of hypoglycaemia (including healthcare professionals, work colleagues and family)

Is it easy or difficult to talk about hypoglycaemia with:

- Family
- Friends
- Colleagues

Probe:
- what can make it difficult
- what can make it easier to talk about?

Do you feel obliged to/or feel it's something you have to do? it is necessary?
If still in work or have been in past: Was there anything particularly good or bad about work regarding your diabetes? Barriers? Support?

Sometimes people can disclose that they have had hypos and it's resulted in them having positive support and reactions and for others it's been the opposite. What's been your experience?

Is it easy or difficult to talk about hypoglycaemia with your doctor/nurse?

Probe:
- what can make it difficult
- what can make it easier to talk about?

Do you feel it is important to talk to your doctors/nurse about your hypoglycaemia experiences?
Probe:
- Why/why not

If disclose to doctor/nurse
For some people disclosing their hypoglycaemia to doctors/nurses results in them having positive support and reactions and for others it's been the opposite. What's been your experience?

Confidence and feeling of control
Has your level of confidence in dealing with hypo's changed over time?
Probe:
- Since diabetes diagnosis
- Since having hypo's
How? Why? What has changed?

To what degree do you feel in control of hypo's?
Probe:
- is this the same for other areas of your diabetes ie. Treatment medications, high blood sugar?
- What effect do you think the level of control you have has?
- What could help you feel more in control? What could healthcare professionals do?

Summarise interview back to interviewee

Ok so we are coming towards the end of the interview is there anything else you would like to add about your experiences or feeling regarding hypo's? anything at all?

Appendix 8: Sampling frame

Characteristics	No required	No Interviewed
Male	8-12	1111111111111
Female	8-12	1111111
Insulin	8-12	1111111111
Non-insulin	8-12	1111111111
White	7-9	111111111
Asian	7-9	111111111
Other	2-6	11
Severe	8-12	1
Mild +/- severe	8-12	11111111
Mild		111111111
30-45	6-9	1
46-59	6-9	111111111
60+	6-9	111111111
70+		1

Appendix 9: Invitation letter

PCDS
Primary Care Diabetes Society

University of Leicester

hypostudy interview

< Address >

University of Leicester
Diabetes Research Centre
Leicester Diabetes Centre
Leicester General Hospital
Leicester LE5 4PW

clr22@leicester.ac.uk
Tel: 0116 258 8913
<date>

Dear <Name>

You recently took part in the Hypoglycaemia questionnaire study and said it was ok to invite you for future research. We are writing to ask if you would agree to be interviewed (asked some questions) about hypoglycaemia (low blood sugar).

An information sheet is enclosed which provides further details about the interview. If you would like to volunteer please complete the reply slip enclosed and return it using the freepost envelope.

We are extremely grateful for your participation so far and hope you will agree to take part in this further study.

If you have any questions please do not hesitate to contact the study co-ordinator Chloe Redshaw on 0116 2588913 or email clr22@le.ac.uk

Yours sincerely

Prof Kamlesh Khunti
(Professor of Primary Care Diabetes and Vascular Medicine)

THE HYPOGLYCAEMIA INTERVIEW STUDY LETTER PARTICIPANT INVITATION V1_01_12_13

Appendix 10: Consent form

PCDS
Primary Care Diabetes Society

hypostudy
interview

University *of* **Leicester**

**Please write
your initials in
each box**

Participant Consent Form (Patient)

The Hypoglycaemia Interview Study

1. I confirm that I have read and understood the participant information sheet
for the above study (**Version 1, 01/12/2013**) and have had the opportunity to ask questions.

2. I understand that taking part is voluntary and that I am free to withdraw at any time, without
giving a reason and without my medical care or legal rights being affected.

3. I understand that the interview will be audio-recorded but that the recording will be
destroyed at the end of the study and all information will remain strictly confidential.

4. I agree that any information collected as part of the study can be stored (computer and
paper records), analysed and reported anonymously by the research team at the University
of Leicester.

5. I understand that data collected during the study may be looked at by individuals from the
University of Leicester, regulatory authorities or the NHS Trust, where it is relevant to my
taking part in this research. I give permission for these individuals to have access to my
records.

6. I agree to take part in the above study.

7. I would like to receive a summary of the results of the study and agree to them being posted
to the address given below.

   (This is optional)   YES ☐   NO ☐

....
NAME OF PARTICIPANT (PRINT)   **SIGNATURE** (*or mark*)   **DATE**

....
NAME OF RESEARCHER (PRINT)   **SIGNATURE**   **DATE**

Participant Contact Details

Address..

....

Postcode.............................

| When completed: |
| 1 copy (original) for research file |
| 1 copy for patient |

THE HYPOGLYCAEMIA INTERVIEW STUDY PARTICIPANT CONSENT FORM
V1_01_12_13

References

1.   Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

2.   The NHS Information Centre for health and social care. (2011) National Diabetes Audit Executive Summary 2009-2010 Audit. Leeds UK: : The NHS Information Centre; .

3.   Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. Diabetologia. 1993;36(8):771-7.

4.   Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-72.

5.   Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-39.

6.   Graveling AJ, Frier BM. Hypoglycaemia: an overview. Prim Care Diabetes. 2009;3(3):131-9.

7.   Lopez JM, Annunziata K, Bailey RA, Rupnow MF, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of life, work productivity, and medication adherence. Patient Prefer Adherence. 2014;8:683-92.

8.   Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health. 2011;14(5):665-71.

9.   Geelhoed-Duijvestijn PH, Pedersen-Bjergaard U, Weitgasser R, Lahtela J, Jensen MM, Ostenson CG. Effects of patient-reported non-severe hypoglycemia on healthcare resource use, work-time loss, and wellbeing in insulin-treated patients with diabetes in seven European countries. J Med Econ. 2013;16(12):1453-61.

10.   Williams SA, Pollack MF, Dibonaventura M. Effects of hypoglycemia on health-related quality of life, treatment satisfaction and healthcare resource utilization in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2011;91(3):363-70.

11.   Whitehead.B.J. Older people's experience of driver licence cancellation: A phenomenological study. Australian Occupational Therapy Journal. 2006;53(3):173–80.

12.   Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. Diabet Med. 2012;29(7):855-62.

13.   Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med. 1988;318(23):1487-92.

14.   Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes. 1988;37(7):901-7.

15.   McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med. 2001;18(9):690-705.

16.   Canadian Diabetes Association Clinical Practice Guidelines Expert C, Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Can J Diabetes. 2013;37 Suppl 1:S1-3.

17.   European Agency for Evaluation of Medicinal Products (EMEA). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus 2012. 2012.

18.   Munshi MN, Segal AR, Suhl E, Staum E, Desrochers L, Sternthal A, et al. Frequent hypoglycemia among elderly patients with poor glycemic control. Arch Intern Med. 2011;171(4):362-4.

19.   Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wandell P. Self-reported experience of hypoglycemia among adults with type 2 diabetes mellitus (Exhype). Diabetes Res Clin Pract. 2011;92(1):19-25.

20.   Domgaard M, Bagger M, Rhee NA, Burton CM, Thorsteinsson B. Individual and societal consequences of hypoglycemia: A cross-sectional survey. Postgrad Med. 2015;127(5):438-45.

21.   MacLeod KM, Gold AE, Frier BM. Frequency, severity and symptomatology of hypoglycaemia: a comparative trial of human and porcine insulins in type 1 diabetic patients. Diabet Med. 1995;12(2):134-41.

22.   Nicolucci A, Pintaudi B, Rossi MC, Messina R, Dotta F, Frontoni S, et al. The social burden of hypoglycemia in the elderly. Acta Diabetol. 2015;52(4):677-85.

23.   Barendse S, Singh H, Frier BM, Speight J. The impact of hypoglycaemia on quality of life and related patient-reported outcomes in Type 2 diabetes: a narrative review. Diabet Med. 2012;29(3):293-302.

24.   Evans M, Khunti K, Mamdani M, Galbo-Jorgensen CB, Gundgaard J, Bogelund M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Outcomes. 2013;11:90.

25.   Driver and Vehicle Licensing Agency (DVLA). Current medical guidelines: DVLA guidance for professionals. 2013.

26.   Ragland DR, Satariano WA, MacLeod KE. Driving cessation and increased depressive symptoms. J Gerontol A Biol Sci Med Sci. 2005;60(3):399-403.

27.   B.M. F. The incidence and impact of hypoglycemia in type 1 and type 2 diabetes. International Diabetes Monitor. 2009;21:210-8.

28.   Briscoe.V.J. Hypoglycemia in Type 1 and Type 2 Diabetes: Physiology, Pathophysiology, and Management. 2006;24(3):115-210.

29.   Cnop M, Welsh N, Jonas JC, Jorns A, Lenzen S, Eizirik DL. Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: many differences, few similarities. Diabetes. 2005;54 Suppl 2:S97-107.

30.   Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55(6):1577-96.

31.   The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-86.

32.   Excellence NIfHaC. Type 2 diabetes: The management of type 2 diabetes. London: National Institute for Health and Care Excellence; 2009.

33.   Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373(9677):1765-72.

34.   Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes. 1997;46(2):271-86.

35.   Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854-65.

36.   Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53.

37.   Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA. 2010;303(14):1410-8.

38.   Schwarz PE. Report from the Congress of the American Diabetes Association (ADA): Orlando 2005 - 65th Annual Scientific Sessions in San Diego, CA, USA, June 10th-14th 2005. Exp Clin Endocrinol Diabetes. 2005;113(8):475-9.

39.   Choudhary P, Lonnen K, Emery CJ, MacDonald IA, MacLeod KM, Amiel SA, et al. Comparing hormonal and symptomatic responses to experimental hypoglycaemia in insulin- and sulphonylurea-treated Type 2 diabetes. Diabet Med. 2009;26(7):665-72.

40.   Group UKHS. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007;50(6):1140-7.

41.   Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. Diabetes Care. 2009;32(8):1513-7.

42.   Bramlage P, Gitt AK, Binz C, Krekler M, Deeg E, Tschope D. Oral antidiabetic treatment in type-2 diabetes in the elderly: balancing the need for glucose control and the risk of hypoglycemia. Cardiovasc Diabetol. 2012;11:122.

43.   Landstedt-Hallin L, Adamson U, Lins PE. Oral glibenclamide suppresses glucagon secretion during insulin-induced hypoglycemia in patients with type 2 diabetes. J Clin Endocrinol Metab. 1999;84(9):3140-5.

44.   Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care. 2003;26(5):1485-9.

45.   Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care. 1995;18(2):258-68.

46.   Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001;24(6):1069-78.

47.   Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. Int J Sports Med. 2000;21(1):1-12.

48.   Choudhary P, Amiel SA. Hypoglycaemia: current management and controversies. Postgrad Med J. 2011;87(1026):298-306.

49.   Browne DL, Avery L, Turner BC, Kerr D, Cavan DA. What do patients with diabetes know about their tablets? Diabet Med. 2000;17(7):528-31.

50.   Lund A, Knop FK. Worry vs. knowledge about treatment-associated hypoglycaemia and weight gain in type 2 diabetic patients on metformin and/or sulphonylurea. Curr Med Res Opin. 2012;28(5):731-6.

51.   Wijewickrama ES, Hewage UC, Fernando DJ. Knowledge of hypoglycaemia in patients with diabetes. Ceylon Med J. 2003;48(2):60.

52.   Cryer PE. Preventing hypoglycaemia: what is the appropriate glucose alert value? Diabetologia. 2009;52(1):35-7.

53.   Lawton J, Rankin D, Cooke DD, Elliott J, Amiel S, Heller S, et al. Self-treating hypoglycaemia: a longitudinal qualitative investigation of the experiences and views of people with Type 1 diabetes. Diabet Med. 2013;30(2):209-15.

54.   Schopman JE, Geddes J, Frier BM. Prevalence of impaired awareness of hypoglycaemia and frequency of hypoglycaemia in insulin-treated type 2 diabetes. Diabetes Res Clin Pract. 2010;87(1):64-8.

55.   Graveling AJ, Frier BM. Impaired awareness of hypoglycaemia: a review. Diabetes Metab. 2010;36 Suppl 3:S64-74.

56.   National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults. 2015.

57.   Malanda UL, Bot SD, Nijpels G. Self-monitoring of blood glucose in noninsulin-using type 2 diabetic patients: it is time to face the evidence. Diabetes Care. 2013;36(1):176-8.

58.   Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care. 2005;28(6):1510-7.

59.   Peel E, Parry O, Douglas M, Lawton J. Blood glucose self-monitoring in non-insulin-treated type 2 diabetes: a qualitative study of patients' perspectives. Br J Gen Pract. 2004;54(500):183-8.

60.   Franciosi M, Pellegrini F, De Berardis G, Belfiglio M, Cavaliere D, Di Nardo B, et al. The impact of blood glucose self-monitoring on metabolic control and quality of life in type 2 diabetic patients: an urgent need for better educational strategies. Diabetes Care. 2001;24(11):1870-7.

61.   Anderson RM. Patient empowerment and the traditional medical model. A case of irreconcilable differences? Diabetes Care. 1995;18(3):412-5.

62.   Jacobson AM, Hauser ST, Willett JB, Wolfsdorf JI, Dvorak R, Herman L, et al. Psychological adjustment to IDDM: 10-year follow-up of an onset cohort of child and adolescent patients. Diabetes Care. 1997;20(5):811-8.

63.   Cavan D. Giving power to the patients. . Modern Diabetes Management. 2001;2(4): 15–16.

64.   Matthews SM, Peden AR, Rowles GD. Patient-provider communication: understanding diabetes management among adult females. Patient Educ Couns. 2009;76(1):31-7.

65.   Fox S, Chesla C. Living with chronic illness: a phenomenological study of the health effects of the patient-provider relationship. J Am Acad Nurse Pract. 2008;20(3):109-17.

66.   Charlton CR, Dearing KS, Berry JA, Johnson MJ. Nurse practitioners' communication styles and their impact on patient outcomes: an integrated literature review. J Am Acad Nurse Pract. 2008;20(7):382-8.

67.   Heisler M, Bouknight RR, Hayward RA, Smith DM, Kerr EA. The relative importance of physician communication, participatory decision making, and patient understanding in diabetes self-management. J Gen Intern Med. 2002;17(4):243-52.

68.   Meetoo D, Meetoo L. Explanatory models of diabetes among Asian and Caucasian participants. Br J Nurs. 2005;14(3):154-9.

69.   Anderson RM, Funnell MM. Patient empowerment: myths and misconceptions. Patient Educ Couns. 2010;79(3):277-82.

70.   Khunti K, Gray LJ, Skinner T, Carey ME, Realf K, Dallosso H, et al. Effectiveness of a diabetes education and self management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. BMJ. 2012;344:e2333.

71.   Crasto W, Jarvis J, Khunti K, Skinner TC, Gray LJ, Brela J, et al. Multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: the Microalbuminuria Education and Medication Optimisation (MEMO) study. Diabetes Res Clin Pract. 2011;93(3):328-36.

72.   Cooper H, Booth K, Gill G. A trial of empowerment-based education in type 2 diabetes--global rather than glycaemic benefits. Diabetes Res Clin Pract. 2008;82(2):165-71.

73.   Tang TS, Funnell MM, Brown MB, Kurlander JE. Self-management support in "real-world" settings: an empowerment-based intervention. Patient Educ Couns. 2010;79(2):178-84.

74.   Castillo A, Giachello A, Bates R, Concha J, Ramirez V, Sanchez C, et al. Community-based Diabetes Education for Latinos: The Diabetes Empowerment Education Program. Diabetes Educ. 2010;36(4):586-94.

75.   Wong CK, Wong WC, Wan YF, Chan AK, Chan FW, Lam CL. Patient Empowerment Programme (PEP) and Risk of Microvascular Diseases Among Patients With Type 2 Diabetes in Primary Care: A Population-Based Propensity-Matched Cohort Study. Diabetes Care. 2015;38(8):e116-7.

76.   Adolfsson ET, Walker-Engstrom ML, Smide B, Wikblad K. Patient education in type 2 diabetes: a randomized controlled 1-year follow-up study. Diabetes Res Clin Pract. 2007;76(3):341-50.

77.   Hibbard JH GH. Supporting people to manage thier health: An introduction to patient activation. The King's Fund,; 2014.

78.   Hibbard JH, Cunningham PJ. How engaged are consumers in their health and health care, and why does it matter? Res Brief. 2008(8):1-9.

79.   UHL(NHS) UoHL. Type 2 diabetes referral criteria to specialist services: National service framework STANDARD 2. 2013.

80.   Rushforth B, McCrorie, C, Glidewell, L, Midgley, E and Foy, RC Barriers to effective management of type 2 diabetes in primary care: qualitative systematic review. British Journal of General Practice. 2015;(In Press)

81.   Farooqi A, Dodd L, Stribling B, Jarvis J, Davies M, Khunti K. Diabetes service provision in primary care: a baseline survey in a city primary care trust (PCT). Practical Diabetes International. 2004;21(1):13-7.

82.   McLean G, Guthrie B, Sutton M. Differences in the quality of primary medical care for CVD and diabetes across the NHS: evidence from the quality and outcomes framework. BMC Health Serv Res. 2007;7:74.

83.   Murrells T BJ, Cookson G, Maben J, Lee G, Griffiths P Managing diabetes in primary care: how does the configuration of the workforce affect quality of care? : National Nursing Research Unit, King's College London.; 2013.

84.   Bloomfield HE, Greer N, Newman D, MacDonald R, Carlyle M, Fitzgerald P, et al. Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes - A Systematic Review of the Evidence. VA Evidence-based Synthesis Program Reports. Washington (DC)2012.

85.   Inkster B, Zammitt NN, Frier BM. Drug-induced hypoglycaemia in type 2 diabetes. Expert opinion on drug safety. 2012;11(4):597-614.

86.   Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health technology assessment. 2010;14(36):1-248.

87.   Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2011(10):CD006423.

88.   Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2008(2):CD006739.

89.   Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2011(7):CD006383.

90.   Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2007(2):CD005613.

91.   Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes care. 2005;28(4):950-5.

92.   Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 2007;36(3):666-76.

93.   Project EPHP. Quality assessment tool for quantitative studies. Available from: http://www.ephpp.ca/Tools.html (2009) [

94.   Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. . The Cochrane Collaboration, ; 2011.

95.   Wong WC, Cheung CS, Hart GJ. Development of a quality assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. Emerging themes in epidemiology. 2008;5:23.

96.   Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

97.   DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials. 2007;28(2):105-14.

98.   Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet. 1991;337(8746):867-72.

99.   Light RJ, & Pillemer, D.B. . Summing up: The science of reviewing research. Cambridge, MA: Harvard University Press(1984). .

100.   Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

101.   Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycemia in insulin-treated type 2 diabetes: a literature survey. J Diabetes Complications. 2006;20(6):402-8.

102.   Allen KV, McAulay V, Sommerfield AJ, Frier BM. Hypoglycaemia is uncommon with a combination of antidiabetic drugs and bedtime NPH insulin for type 2 diabetes. Practical Diabetes International. 2004;21(5):179-82.

103.   Andel M, Grzeszczak W, Michalek J, Medvescek M, Norkus A, Rasa I, et al. A multinational, multi-centre, observational, cross-sectional survey assessing diabetes secondary care in Central and Eastern Europe (DEPAC Survey). Diabet Med. 2008;25(10):1195-203.

104.   Aung PP, Strachan MW, Frier BM, Butcher I, Deary IJ, Price JF. Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabet Med. 2012;29(3):328-36.

105.   Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab. 2012;14(7):634-43.

106.   Katon WJ, Young BA, Russo J, Lin EH, Ciechanowski P, Ludman EJ, et al. Association of depression with increased risk of severe hypoglycemic episodes in patients with diabetes. Ann Fam Med. 2013;11(3):245-50.

107.   Krnacova V, Kubena A, Macek K, Bezdek M, Smahelova A, Vlcek J. Severe hypoglycaemia requiring the assistance of emergency medical services--frequency, causes and symptoms. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2012;156(3):271-7.

108.   Lecomte P, Romon I, Fosse S, Simon D, Fagot-Campagna A. Self-monitoring of blood glucose in people with type 1 and type 2 diabetes living in France: the Entred study 2001. Diabetes Metab. 2008;34(3):219-26.

109.   Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care. 2003;26(4):1176-80.

110.   Leiter LA, Yale J, Chiasson J, Harris SB, Kleinstiver P, Sauriol L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. Can J Diabetes. 2005;29(3):186-92.

111.   Lin CH, Sheu WH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. Journal of internal medicine. 2013;273(1):102-10.

112.   Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. Diabetes Care. 2013;36(11):3535-42.

113.   Lundkvist J, Berne C, Bolinder B, Jonsson L. The economic and quality of life impact of hypoglycemia. The European journal of health economics : HEPAC : health economics in prevention and care. 2005;6(3):197-202.

114.   Maggi S, Noale M, Pilotto A, Tiengo A, Cavallo Perin P, Crepaldi G, et al. The METABOLIC Study: multidimensional assessment of health and functional status in older patients with type 2 diabetes taking oral antidiabetic treatment. Diabetes Metab. 2013;39(3):236-43.

115.   McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care. 2012;35(9):1897-901.

116.   McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. Endocr Pract. 2013;19(5):792-9.

117.   Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med. 2001;161(13):1653-9.

118.   Murata GH, Duckworth WC, Shah JH, Wendel CS, Hoffman RM, Diabetes Outcomes in Veterans S. Factors affecting hypoglycemia awareness in insulin-treated type 2 diabetes: The Diabetes Outcomes in Veterans Study (DOVES). Diabetes Res Clin Pract. 2004;65(1):61-7.

119.   Neil BJ BA, Clothier B , Nelson DB , Bloomfield HE. Self-Monitoring of Blood Glucose in Diabetic Patients Not Taking Insulin: Does It Affect Hypoglycemia? Fed Pract 24(8):27. 2007.

120.   Ooi CP, Loke SC, Zaiton A, Tengku-Aizan H, Zaitun Y. Cross-sectional study of older adults with type 2 diabetes mellitus in two rural public primary healthcare facilities in Malaysia. Med J Malaysia. 2011;66(2):108-12.

121.   Parsaik AK, Carter RE, Myers LA, Basu A, Kudva YC. Hypoglycemia requiring ambulance services in patients with type 2 diabetes is associated with increased long-term mortality. Endocr Pract. 2013;19(1):29-35.

122.   Rombopoulos G, Hatzikou M, Latsou D, Yfantopoulos J. The prevalence of hypoglycemia and its impact on the quality of life (QoL) of type 2 diabetes mellitus patients (The HYPO Study). Hormones (Athens). 2013;12(4):550-8.

123.   Samann A, Lehmann T, Heller T, Muller N, Hartmann P, Wolf GB, et al. A retrospective study on the incidence and risk factors of severe hypoglycemia in primary care. Fam Pract. 2013;30(3):290-3.

124.   Sarkar U, Karter AJ, Liu JY, Moffet HH, Adler NE, Schillinger D. Hypoglycemia is more common among type 2 diabetes patients with limited health literacy: the Diabetes Study of Northern California (DISTANCE). J Gen Intern Med. 2010;25(9):962-8.

125.   Skinner TC, Bruce DG, Davis TM, Davis WA. Personality traits, self-care behaviours and glycaemic control in type 2 diabetes: the Fremantle diabetes study phase II. Diabet Med. 2014;31(4):487-92.

126.   Stahl M, Berger W. Higher incidence of severe hypoglycaemia leading to hospital admission in Type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas. Diabet Med. 1999;16(7):586-90.

127.   Stargardt T, Gonder-Frederick L, Krobot KJ, Alexander CM. Fear of hypoglycaemia: defining a minimum clinically important difference in patients with type 2 diabetes. Health Qual Life Outcomes. 2009;7:91.

128.   Vexiau P, Mavros P, Krishnarajah G, Lyu R, Yin D. Hypoglycaemia in patients with type 2 diabetes treated with a combination of metformin and sulphonylurea therapy in France. Diabetes Obes Metab. 2008;10 Suppl 1:16-24.

129.   Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr., Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009;301(15):1565-72.

130.   Yun JS, Ko SH, Ko SH, Song KH, Ahn YB, Yoon KH, et al. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. Diabetes Care. 2013;36(5):1283-9.

131.   Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007;50(6):1140-7.

132.   Zhang Y, Ting R, Lam M, Lam J, Nan H, Yeung R, et al. Measuring depressive symptoms using the Patient Health Questionnaire-9 in Hong Kong Chinese subjects with type 2 diabetes. Journal of affective disorders. 2013;151(2):660-6.

133.   Schopman JE, Simon AC, Hoefnagel SJ, Hoekstra JB, Scholten RJ, Holleman F. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. Diabetes/metabolism research and reviews. 2014;30(1):11-22.

134.   Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in

metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes care. 2009;32(5):762-8.

135.   Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V, et al. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. Current medical research and opinion. 2009;25(1):65-75.

136.   Gallwitz B, Bohmer M, Segiet T, Molle A, Milek K, Becker B, et al. Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia. Diabetes care. 2011;34(3):604-6.

137.   Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med. 2009;3(3):e123-30.

138.   Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. J Clin Endocr Metab. 2013;98(5):1845-59.

139.   Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care. 2015;38(2):316-22.

140.   Amiel SA AP, Childs B, Cryer PE, de Galan B, Heller SR, Frier BM et al. Minimizing Hypoglycemia in Diabetes. Diabetes Care. 2015;38(8):1583-91.

141.   Rogers HA, de Zoysa N, Amiel SA. Patient experience of hypoglycaemia unawareness in Type 1 diabetes: are patients appropriately concerned? Diabet Med. 2012;29(3):321-7.

142.   Spencer JE, Cooper HC, Milton B. The lived experiences of young people (13-16 years) with Type 1 diabetes mellitus and their parents--a qualitative phenomenological study. Diabet Med. 2013;30(1):e17-24.

143.   Mandrik O, Severens JL, Doroshenko O, Pan'kiv V, Kravchun N, Vlasenko M, et al. Impact of hypoglycemia on daily life of type 2 diabetes patients in Ukraine. J Multidiscip Healthc. 2013;6:249-57.

144.   Tan PS, Chen HC, Taylor BJ, Hegney DG. Exploring the meaning of hypoglycaemia to community-dwelling Singaporean Chinese adults living with type 2 diabetes mellitus. Int J Nurs Pract. 2012;18(3):252-9.

145.   Smith JA. Qualitative Psychology: A Practical Guide to Research Methods. Great Britain: SAGE Publications; 2008.

146.   Leiter LA YJ-, Chiasson J-, Harris SB, Kleinstiver P, Sauriol L. . Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. . Canadian Journal of Diabetes 2005;29(3):186-92.

147. Rask KJ, Ziemer DC, Kohler SA, Hawley JN, Arinde FJ, Barnes CS. Patient activation is associated with healthy behaviors and ease in managing diabetes in an indigent population. Diabetes Educ. 2009;35(4):622-30.

148. Carnevale Schianca GP, Sola D, Rossi L, Fra GP, Bartoli E. The management of type 2 diabetic patients with hypoglycemic agents. ISRN endocrinology. 2012;2012:601380.

149. Conditions. TNCCfC. Type 2 Diabetes: national clinical guideline for management in primary and secondary care(update).   . London: Royal College of Physicians 2008.

150. Browne D, Avery L, Turner B, Kerr D, Cavan DA. What do patients with diabetes know about their tablets? Diabetic medicine. 2000;17(7):528-31.

151. Lund A, Knop FK. Worry vs. knowledge about treatment-associated hypoglycaemia and weight gain in type 2 diabetic patients on metformin and/or sulphonylurea. Current Medical Research & Opinion. 2012;28(5):731-6.

152. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. Diabetes technology & therapeutics. 2011;13(8):813-8.

153. Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes care. 2003;26(4):1153-7.

154. Given JE, O'Kane MJ, Coates VE, Moore A, Bunting BP. Comparing patient generated blood glucose diary records with meter memory in type 2 diabetes. Diabetes Res Clin Pract. 2014;104(3):358-62.