HYPOGLYCAEMIA IN OLDER PEOPLE WITH DEMENTIA AND DIABETES

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ABSTRACT

Objective

To explore the effect of hypoglycaemia on adverse events in older people with diabetes and dementia and determine the feasibility of using continuous glucose monitoring in this patient group.

Methods

Systematic review on continuous glucose monitoring in older people with diabetes: Hypothesis-generating systematic review to inform my feasibility study and to identify gaps in the evidence.

Feasibility study: I conducted a feasibility study of continuous blood glucose monitoring to explore continuous glucose monitoring in older people with diabetes and memory problems.

Pharmacoepidemiological study: Retrospective cohort study using the Clinical Research Practice Datalink database to test the effect of exposure to hypoglycaemia in older patients with dementia.

Systematic review and meta-analysis on the associations between hypoglycaemia and adverse events in older people treated with glucose-lowering agents: Updated systematic review and meta-analysis of serious adverse events associated with hypoglycaemia in older patients treated with glucose-lowering agents.

Findings

Systematic review on continuous glucose monitoring in older people with diabetes: 9 studies were included with a total of nearly 1000 patients. Hypoglycaemic episodes occurred in a sizeable proportion and most of

these episodes were asymptomatic. Some patients spent nearly 2 hours per day in the hypoglycaemic range. CGM is acceptable to patients and improved health-related well-being.

Feasibility study: 12 participants completed the study and found using CGM device acceptable. Data capture with this device varied considerably (3%-92%). The device captured hypoglycaemic episodes in 6 participants, two of which lasted for over 300 minutes.

Pharmacoepidemiological study: Older people with dementia and diabetes who have had a hypoglycaemic event are at substantially higher risk of death, cardiovascular events, falls, fractures and emergency department attendances, than those who have not had a hypoglycaemic event.

Systematic review and meta-analysis on the associations between hypoglycaemia and adverse events in older people treated with glucose-lowering agents: 42 included studies with over 2 million patients. Hypoglycaemia is associated with an 80% increased risk in vascular complications, a doubling in risk of all-cause mortality, a 55% increased risk in dementia, and a 78% and 68% increased risk in falls and fractures respectively.

Conclusions

My research has highlighted the complications associated with hypoglycaemia in older people with diabetes and dementia and set the ground work for future studies using continuous glucose monitoring in this patient group.

Table of Contents

List of Appendices

INDEX OF FIGURES AND TABLES

FOR AMY

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Finally, none of this would have been possible without the unwavering support from my partner Amy.

ABBREVIATIONS

ACEi= Angiotension-converting enzyme inhibitor

ADA = American Diabetes Association

AF= Atrial fibrillation

AGP= Ambulatory glucose profile

AGS= American Geriatrics Society

aHR= Adjusted Hazard Ratio

AMT= Abbreviated mini-Mental Test

ARB= Angiotension Receptor Blocker

AV block= Atrioventricular block

BMI= Body mass index

BP= Blood pressure

CAD= Coronary artery disease

CCI= Charlson co-morbidity index

CGM =Continuous glucose monitoring

CIS= Consultee Information Sheet

CKD=Chronic kidney disease

COPD= Chronic obstructive pulmonary disease

CPRD= Clinical Practice Research Datalink database

CV= Cardiovascular

CVD= Cardiovascular disease

DKA= Diabetic ketoacidosis

DM=diabetes mellitus

DPP-4=Dipetidyl-peptidase-4

ECG= Electrocardiogram

ED= Emergency department

eGFR=Estimated glomerular filtration rate

GDS= Geriatric Depression Scale

GFI= Groeningen Frailty Indicator

GLP-1= Glucagon-like peptide-1

GP= General Practitioner

HbA1C=Glycated haemoglobin

HDL-C= High-density lipoprotein cholesterol

HE=hypoglycaemic event

HES=Hospital Episode Statistic

HR=Hazard ratio

ICD= international classification of diseases

IFG= impaired fasting glucose

IGT= impaired glucose tolerance

iG= Interstitial glucose

ISAC= Independent Scientific Advisory Committee

LDL-C= Low density lipoprotein cholesterol

MACE= Major adverse cardiovascular events

MI=Myocardial infarction

MMSE=Mini-Mental State Examination

NHS= National Health Service

NSTEMI=Non-ST elevation myocardial infarction

NYHA= New York Heart Association

ONS= Office for National Statistics

OR= Odds ratio

PCGM= personal real-time continuous glucose monitoring

PIS= Patient Information Sheet

PPM= Permanent pacemaker

PVD= Peripheral vascular disease

QOL= Quality of life

RCT= Randomized controlled trial

RT-CGM= real-time continuous glucose monitoring

SGLT-2= Sodium-glucose transport 2

SH= Severe hypoglycaemia

SMBG=self-monitoring of blood glucose

STROBE= Strengthening the Reporting of Observation Studies in Epidemiology

STEMI=ST-elevation myocardial infarction

SU=Sulfonylureas

T1DM= Type 1 diabetes mellitus

T2DM= Type 2 diabetes mellitus

TIA= Transient ischaemic attack

TUG= Timed up and go test

UK=United Kingdom

VT= Ventricular tachycardia

WHO= World Health Organization

95% CI= 95% Confidence Interval

PUBLICATIONS AND STATEMENT OF AUTHORSHIP

The research reported is my own original work, which was carried out in collaboration with others as follows:

Chapter 1: written by Katharina Mattishent

Chapter 2: Katharina Mattishent was the lead author of the following published paper:

Detection of asymptomatic drug-induced hypoglycaemia using continuous glucose monitoring in older people - Systematic review.

Mattishent K, Loke YK. J Diabetes Complications. 2018 Aug;32(8):805-812. doi: 10.1016/j.jdiacomp.2018.05.005. Epub 2018 May 18.

KM designed the systematic review, carried out the data extraction, analysed the data and drafted the initial manuscript under YKL's supervision and expert input.

Chapter 3: Katharina Mattishent was the lead author of the following published paper:

Mattishent K, Lane K, Salter C, Dhatariya K, May H, Neupane S, Loke YK. Continuous glucose monitoring in older people with diabetes and memory problems: a mixed-methods feasibility study in the UK.

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Conception and design: KM YKL, CS, KL, KD, SN, HMM. Data acquisition: KM, KL, YKL Analysis and interpretation of data: YKL, KM, KL, KD, CS. Drafting, revision and final approval of the manuscript: KM, YKL, CS, KL, KD, SN, HMM. YKL is the guarantor.

Parts of this work have been presented at conferences before submission as:

Recruitment and retention in a trial of continuous glucose monitoring in older patients with memory problems and diabetes. **Mattishent K**, Lane K, Salter C, Dhatariya K, May H, Neupane S, Loke YK. *Alzheimer's Society Conference, London, May 2019.*
Author contributions: KM, KL and YKL – conduct of study and data collection. Specialist input from CL, KD, HMM and NP. All authors contributed to the study protocol development and revision, the interpretation of findings, and the revision of the abstract/poster.

Feasibility and acceptability of continuous glucose monitoring in older patients living with memory problems and diabetes – preliminary results. **Mattishent K**, Lane K, Salter C, Dhatariya K, May H, Neupane S, Loke YK.
Advanced Technologies and Treatments for Diabetes (ATTD) Conference, Berlin, February 2019.
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Chapter 4: Katharina Mattishent was the lead author of the following published paper:

The effects of hypoglycaemia and dementia on cardiovascular events, falls and fractures and all-cause mortality in older individuals: A retrospective cohort study. **Mattishent K**, Richardson K, Dhatariya K, Savva GM, Fox C, Loke YK. Diabetes Obes Metab. 2019 May 8. doi: 10.1111/dom.13769.

KM and YKL conceived and developed the initial study. KR and GS drafted the statistical analysis plan. KM, YKL and KR developed the code lists. YKL, KM and KR conducted the statistical analysis. All authors contributed to the study protocol development and revision, the interpretation of findings, and the revision of the manuscript.

Chapter 5: written by Katharina Mattishent. This chapter is an updated systematic review and meta-analysis of two previously published reviews:

Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. **Mattishent K**, Loke YK. Diabetes Obes Metab. 2016 Feb;18(2):135-41. doi: 10.1111/dom.12587

Meta-analysis: Association between hypoglycaemia and serious adverse events in older patients. **Mattishent K**, Loke YK. J Diabetes Complications. 2016 Jul;30(5):811-8. doi: 10.1016/j.jdiacomp.2016.03.018

Chapter 6: written by Katharina Mattishent

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STRUCTURE OF THESIS

This thesis contains two systematic reviews, a pharmacoepidemiological study using a large primary care database and a feasibility study.

The publications are listed on pages 17-19.

Each publication is incorporated in separate chapters with preambles before each and edits to remove repetition.

Chapter 2 presents a systematic review on the use of continuous glucose monitoring in older people with diabetes to consolidate the growing evidence base in that area

Chapter 3 presents a feasibility study on the feasibility and acceptability of flash glucose monitoring in older people with diabetes and memory problems.

Chapter 4 presents a pharmacoepidemiological study using the CPRD to evaluate the effect of hypoglycaemia on adverse events in older people with diabetes and dementia. The adverse events of interest were all-cause mortality, cardiovascular events and falls and fractures.

Chapter 5 presents an updated systematic review on the association between hypoglycaemia and adverse events in older people with diabetes, which will incorporate the findings from chapter 4.

Chapter 6 is the discussion chapter collating the core findings of my fellowship and setting out areas for future work.

AIMS OF THE THESIS

The idea for this thesis developed from the lack of existing evidence and guidelines for standardised care for older people with diabetes and other complex health problems, in particular dementia. Trials in diabetes have focused mainly on a younger, less complex population and do not take into account the clinical heterogeneity of older patients [1].

Other researchers have highlighted the lack of standardised care in older patients with diabetes [2]. To compound matters, older people with multiple comorbidities are faced with polypharmacy and frailty [3]. Whilst for younger adults, tight glycaemic control is recommended in order to reduce the risk of long-term complications, there are no clear guidelines for older people with diabetes [4], especially those with multiple comorbidities, including dementia. As a result, older people with diabetes are at risk of being overtreated with a view to achieving glycaemic control targets that are based on data from the younger population [5]. Consequently, they are at higher risk of hypoglycaemia, a side-effect of some of the medications prescribed to manage diabetes.

Studies involving older people with diabetes have identified significant associations between hypoglycaemia and subsequent cardiovascular events, falls, fractures and death [6]. In addition, those experiencing hypoglycaemia are at risk of worsening cognition [7]. However, we do not know the impact of hypoglycaemia in older people with co-existing dementia.

Based on the lack of evidence and lack of standardised care, there is a strong case that steps need to be taken to improve the care of this vulnerable group

with complex healthcare needs. Research into people living with dementia and diabetes is an area that has been identified as an area that should to be prioritised[8].

Hence, the aims of my thesis were to:

1. Carry out a systematic review on the use of continuous glucose monitoring (CGM) in older people with diabetes to contribute to the growing evidence base in that area. This was a hypothesis-generating systematic review to inform the design and conduct of my feasibility study and to identify gaps in the evidence and methodological challenges I might face when conducting my own study.
2. Conduct a feasibility study of CGM to explore closer glucose monitoring in older people with diabetes and memory problems. The specific question I was interested in was whether older people with diabetes and memory problems could tolerate wearing a CGM device for two weeks and the extent of data that I could capture.
3. Complete a retrospective cohort study using the Clinical Practice Research Datalink (CPRD) database to test the effect of exposure to hypoglycaemia in older patients with dementia. The question I was interested in answering was whether people with diabetes and dementia who experience a hypoglycaemic episode are at higher risk of adverse events (cardiovascular events, falls and fractures and all-cause mortality) compared to older patients with diabetes and dementia who do not have a hypoglycaemic episode. As a secondary aim, I wanted to determine whether risk of complications after hypoglycaemia is

different in patients with dementia compared to those without dementia.

4. Update previously published systematic reviews on the association between hypoglycaemia and adverse events in older people with diabetes, which will incorporate the findings from my retrospective cohort study. Whilst my previously published systematic reviews have established that older people are at higher risk of adverse events, such as cognitive impairment, cardiovascular events, falls and fractures, and mortality, my updated review and meta-analysis will include the findings from my retrospective cohort study and other studies published in the last few years. The updated review will provide the most up to date evidence on the associations of hypoglycaemia in older people and adverse events.

The findings will guide clinicians, patients and their carers in making evidence-based choices regarding intensity of drug therapy and strategies for better monitoring in this vulnerable and complex group of people.

CHAPTER 1 – INTRODUCTION

In this introductory chapter, I will outline the basic principles of the management of diabetes and the challenges older people, carers and clinicians face. In particular, I will discuss hypoglycaemia (a serious side effect of some medications used to manage diabetes) and the impact it has on older people with co-existing dementia.

1.1 DIABETES AND DEMENTIA IN OLDER PEOPLE

Diabetes mellitus is a very complex chronic illness often accompanied by co-morbidities and polypharmacy. It is characterised by a state of hyperglycaemia, due to insulin deficiency, insulin resistance or a mix of the two.

Worldwide, there are about 425 million people living with diabetes, of whom approximately 123 million are aged between 65 to 99 years. The figure for older people with diabetes is expected to rise to around 253 million in 2045[9]. The cost of diabetes will increase in the older age bracket by over 100 billion USD from 2017 to 2045[9]. The aim of diabetes management is to achieve optimum glycaemic control, in order to prevent long-term microvascular, macrovascular and neurological complications [10 11]. Optimum control can be achieved through lifestyle modifications, oral and/or injectable hypoglycaemic medications. The main classes of hypoglycaemic agents are: insulin, incretin mimics, sulfonylureas (SU), glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl-peptidase-4 (DPP-4) inhibitors, sodium-glucose transport 2 (SGLT 2) inhibitors, biguanides, and thiazolidinediones.

1.1.2 Dementia

It is estimated that around 50 million people across the world are living with dementia, which is expected to rise to 125 million by 2050 [12]. Dementia is a complex chronic progressive syndrome affecting the brain, in which there is disturbance of multiple brain functions, including the capacity to learn, language, calculation, planning and judgment [13]. The syndrome is present when there is an effect on a person's social and/or occupational functions. Typically, Alzheimer's dementia has an onset late in life with cognitive impairment and behavioural symptoms, all of which affect an individual's day-to-day functioning. The onset of symptoms is insidious and involves progressive loss of episodic memory due to hippocampal dysfunction (difficulty in acquiring and storing new information, whilst older memories are relatively spared). Language is affected, manifesting in word-finding difficulty, following a conversation, recognising and naming objects. Visuospatial orientation can become affected and an individual may feel insecure in unfamiliar places and get lost driving or walking home. As the disease progresses, individuals will find it difficult to use common objects (whilst retaining the motor skills to carry out these tasks). They will find it difficult to dress, eat and wash by themselves without assistance. Planning and carrying out tasks will become more and more challenging. Currently, there is no cure for dementia. Non-pharmacological and pharmacological measures for cognition and behavioural and psychological symptoms of dementia can be employed to manage the disease.

Given that the proportion of older people with dementia who have co-existing diabetes is approximately 13-20% [14], these projections indicate that comorbid diabetes and dementia are likely to pose a major healthcare burden.

Regarding life expectancy, Zilkens at al report that mean age of death was 82.4 years in patients with dementia and diabetes, as compared to 85.0 years in those with dementia but no diabetes [15]. People with dementia aged 65 to 84, who have had more than 15 years duration of diabetes, have a 40-50% increased risk of death, compared to those without diabetes.

1.1.3 Diabetes care in older people

The challenge regarding the management of diabetes in older people is that the evidence base is founded on studies that did not include older people, which unfortunately often is the case in clinical studies [10 16 17 18].

As a result, the targets regarding glycaemic control are applied for young and older patients with diabetes alike. Lipska et al highlighted that older people may not benefit from tight glycaemic control compared to younger adults and are more prone to hypoglycaemia as a result of intensive treatment strategies [4].

Various guidelines for the management of diabetes in older people have been developed, which contain recurring themes such as adopting a personalised approach taking into account each person's co-morbidities, frailty, polypharmacy and life expectancy [19 20]. The model below has been adapted from the *Standards of Medical Care in Diabetes - 2019* abridged for Primary Care Providers [21] and was developed for the management of people with T2DM – it does not differentiate or take into account the complexities of older frail people with dementia.

Figure 1 Goals of diabetes care

(adapted from American Diabetes Association (ADA) Standards of Medical Care – 2019)[21]

Whilst there is an emphasis on shared decision-making, it is an intensive model with a main goal of preventing complications, ie target-driven glycaemic control and monitoring of factors such as weight, blood pressure, cholesterol and glucose levels.

Specific areas which can be more challenging in the management of older people with co-existing dementia are around shared-decision making (if they lack capacity), monitoring of glucose levels (they may not be able to carry out finger-prick testing themselves and have to rely on carers). Older people might have to deal with administering insulin more than once per day and/or take a number of different oral medications to manage their diabetes, not taking into account any other co-morbidities for which they might be on a host of different

medications for. People with dementia may have difficulty recognising symptoms and/or side-effects, adhering to medication and complying with treatment[8]. In addition, older people with memory problems are at higher risk of hypoglycaemia, a serious side effects of some medications (in particular insulin and sulfonylureas) given to manage diabetes. Other challenges older people might face in managing their health (or daily activities for that matter) include impaired vision due to cataract, impaired motor skills due to arthritis, neuropathies secondary to diabetes, or difficulty accessing their general practitioner (GP) due to living in rural or socio-economically deprived areas. This is mirrored in a French longitudinal observational study, which revealed that incident dementia was associated with less frequent diabetes monitoring and an increased risk of complications compared with older people without dementia [22].

Despite all of this, there are as yet no standardised guidelines for older people who are having to juggle diabetes with co-existing dementia. A realist synthesis to identify theories, frameworks, and processes of care for patients living with dementia and diabetes, highlighted the need for a flexible service model prioritising patients and carers and better alignment of workforce and organisations[23]. The review included 89 papers, of which 79 were research papers and only ten out of the 89 focussed on people living with dementia and diabetes. Themes emerging from the review relate to dealing with the stigma of dementia and how it can affect patients and families accessing diabetes-related services, supporting and including families and carers in the management of each individual's needs, empowering health care professionals

to have the confidence to simplify medication regimes, and empowering patients and carers in the management of diabetes and dementia. Self-management of diabetes should be encouraged, especially in the earlier stages of dementia. Once the dementia progresses, there should be a shift to more monitoring by carers and healthcare professionals and making use of technological advances in the management of diabetes[2].

The American Geriatric Society (AGS) has also highlighted the lack of evidence in patients with diabetes and dementia. They remarked that older people were often excluded from trials in diabetes, resulting in guidelines not being based on reliable evidence in this group. The AGS has called for more research "to better understand the risks and benefits of tighter glycaemic control among older patients and those with comorbidities" because of "increasing observational evidence … that clinicians often do not differentiate treatments for older patients who differ widely in health status"[24].

In 2019, an international panel of clinicians, researchers and individuals with diabetes developed a consensus statement on clinical targets for CGM data interpretation. The need for a consensus statement arose to provide guidance to users of CGM, clinicians and researchers on how to interpret CGM data in clinical care and research [25].

The panel of experts produced a table setting out targets for different diabetes groups. Specifically, for older/high risk people they emphasised the need for minimizing the time spent in the hypoglycaemic range (ie <3.9 mmol/L). The recommendation is that this group should spend <15 minutes per day in the hypoglycaemic range.

Figure 2 Suggested targets for assessment of glycaemic control

	TIR		TBR		TAR	
Diabetes group	% of readings; time per day	Target range	% of readings; time per day	Below target level	% of readings; time per day	Above target level
Type 1*/type 2	>70%; >16h, 48 min	70–180 mg/dL (3.9–10.0 mmol/L)	<4%; <1 h <1%; <15 min	<70 mg/dL (<3.9 mmol/L) <54 mg/dL (<3.0 mmol/L)	<25%; <6 h <5%; <1 h, 12 min	>180 mg/dL (>10.0 mmol/L) >250 mg/dL (>13.9 mmol/L)
Older/high-risk# type 1/type 2	>50%; >12 h	70–180 mg/dL (3.9–10 mmol/L)	<1%; <15 min	<70 mg/dL (<3.9 mmol/L)	<10%; <2 h, 24 min	>250 mg/dL (>13.9 mmol/L)

Each incremental 5% increase in TIR is associated with clinically significant benefits for individuals with type 1 or type 2 diabetes (26,27). *For age <25 years, if the A1C goal is 7.5%, set TIR target to approximately 60%. See the section CLINICAL APPLICATION OF TIME IN RANGES for additional information regarding target goal setting in pediatric management. #See the section OLDER AND/OR HIGH-RISK INDIVIDUALS WITH DIABETES for additional information regarding target goal setting.

(taken from Battelino et al [25])

Of course, these targets have yet to be tested in a randomised controlled trial (RCT) or an observational study to evaluate whether they have a positive effect on patients' health and service use (eg, GP visits, ED attendances).

1.2 HYPOGLYCAEMIA AND ITS IMPACT

Hypoglycaemia is a serious adverse event of medications prescribed to manage diabetes, which can be fatal. It has been identified as one of the top three preventable adverse drug events by the US Department of Health and Human Services[26].

In the US, serious hypoglycaemic episodes resulted in nearly 300,000 emergency department (ED) visits in adults with either Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM)[26]. Insulin has been shown to be the second most common medication associated with accident and emergency visits or hospitalisation[27]. Population studies have confirmed that drug-induced hypoglycaemia is a growing burden in older patients with wide implications for patients, carers, healthcare professionals and healthcare service utilization. In

the UK, the East Midlands Ambulance Trust responded to 523 call outs for severe hypoglycaemia over a 3-month period (mean age 76 years for the non-insulin treated patients), with projected annual call out costs of over £235,000[28]. This is mirrored by evidence in older people in Asia where, there has been a 10-fold increase over the last decade in the risk of hypoglycaemic episodes in older people needing hospital admission [29 30]. This upsurge has been attributed to increased intensity of medical treatment, as well as greater co-morbidities and frailty.

A trend analysis on hypoglycaemia-related mortality in 109 countries from 2000-2014 using the World Health Organisation (WHO) mortality database, showed a 60% increase in hypoglycaemia-related deaths until 2010 and stable trends onwards, with most countries in South America, Central America and the Caribbean showing the highest rates of hypoglycaemia-related deaths[31].

1.2.1 Definition of hypoglycaemia

One of the challenges in addressing hypoglycaemia is inconsistent and varied definitions.

'Hypoglycaemia' can either be picked up biochemically by measuring glucose levels, or based on someone's symptoms (eg dizziness, confusion, sweating). Another clinical example might be picking up seizures via an electroencephalogram (EEG) measuring brain wave activity, or be observing a person having a seizure (without the need for a test).

Clinicians accept that certain conditions can be measured through doing a test, or through clinical diagnosis based on signs and symptoms (and this is reflected

in real-world epidemiology studies where laboratory verification may not be available at the time of the actual adverse event).

With regard to glucose levels, it is accepted throughout the world that the cut-off for the biochemical definition of the hypoglycaemic range is 3.9 mmol (70mg/dL) and below."

The 2017 Steering Committee on defining hypoglycaemia identified three levels[32]:

- Level 1 between 3.9 mmol/L (70 mg/dL) and 3.0 mmol/L (54 mg/dL);
- Level 2 <3.0 mmol/L (<54 mg/dL)
- Level 3 severe hypoglycaemia – altered mental state and/or requiring third party assistance.

A crude distinction used by clinicians is 'mild' hypoglycaemic events (which an individual self-treats) and 'severe' hypoglycaemic episodes, when an individual needs assistance from a third party in order to correct the glucose levels. 'Mild' or 'severe' does not give an indication as to the precise glucose levels an individual might have at the time of the hypoglycaemic event or the duration of the hypoglycaemic event. Someone might need help to treat their hypo at 3.9 mmol/L, whereas other individuals are still able to self-treat at levels <3 mmol/L.

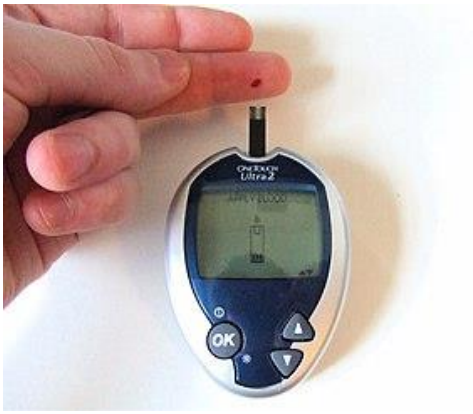
Interestingly, the cut off of <70 mg/dL (3.9mmol/L) for hypoglycaemia has been the subject of debate, as levels between 58-70 mg/dL (3.2-3.9 mmol/L) can be physiologically normal in a fasting non-diabetic person[33].

1.2.2 CAPTURING HYPOGLYCAEMIA

As with the definition of hypoglycaemia, there are a number of ways to capture these events, which in part will be influenced by whether a patient has T1DM or T2DM. Existing research on glucose monitoring has focused on markers of long-term efficacy or benefit[34] [35] for achieving optimum control to prevent long-term complications. Patients with T1DM carry out self-monitoring of blood glucose (SMBG) by means of capillary finger-prick testing, or CGM. SMBG in people with T1DM can range from a minimum of 4 times per day to 10 times per day [36]. The disadvantage of SMBG is that it will only provide a snapshot of an individual's glucose levels as and when that person makes a conscious decision to test. It gives no insight into trends and there are no continuous measurements.

SMBG accuracy is very much user and instrument-dependent [37].

Figure 3 Capillary finger prick testing



CGM is a device that sits just under a patient's skin (either on the back of an arm or on the stomach). The device has a sensor which can measure interstitial glucose (iG) levels continuously (day and night) throughout the lifetime of a sensor, which is usually around 10-14 days. Results can either be accessed by

the patient through swiping a reader over the sensor or can be transmitted via Bluetooth. Alarms can be set to indicate if glucose levels go too high or low and it is possible to see trends when glucose levels are rising or dropping. Data can be downloaded via software and summarised in a report (ambulatory glucose report) setting out daily glucose and insulin patterns. This can help in adjusting and optimising the management plan for that individual. Newer CGM devices allow for the user to share his/her data with either a carer or parents (in children with T1DM) – readings are transmitted to the third person giving him/her real time updates about the patient's glucose levels.

Figure 4 CGM device with Bluetooth

Figure 5 CGM device ("flash glucose meter") where readings are obtained by swiping the meter over the sensor

The disadvantages with CGM are cost, possible triggering of anxiety due to data overload, finger-prick testing is not completely eliminated, it requires a lot of motivation to make the most of the device and the data it collects, and the sensor can cause discomfort or evoke feelings of self-consciousness.

Whilst cost can be a barrier to access to CGM, recently, the National Health Service (NHS) announced its long-term plan, which included a pledge to enhance the support it offers people with diabetes. As part of this pledge, people with T1DM will benefit from flash glucose monitoring (a version of CGM)[38]. NHS England have published strict criteria for people with T1DM who might be able to get CGM on the NHS [39].

Studies have evaluated (and guidelines produced) the use of flash glucose monitoring in adults and children. A consensus group of diabetes specialists within Europe agreed that it is an effective standard for analysing glucose data in diabetes management and can assist people (or their carers) with diabetes understand daily life with their conditions[40 41].

The majority of randomised trials that have been conducted on CGM are in T1DM, which demonstrated overall improvement in glycated haemoglobin (HbA1c) and a reduction of time spent in the hypoglycaemic range (<3.9 mmol/L).

Whilst patients with T2DM are only recommended to use SMBG if they are on insulin, there is evidence of hypoglycaemia or they are on oral medication that increases the risk of hypoglycaemia whilst driving or operating machinery [42].

There is less evidence available about the use of CGM in type 2 diabetes, however, a few RCTs on CGM in T2DM have also shown improvement in time spent in hypoglycaemia and HbA1c [43 44], and a narrative review have highlighted that there are signals that its use promotes glycaemic and weight control and improves lifestyle[45].

Nevertheless, CGM use in T2DM is becoming more widespread, especially in the US. Fonda et al looked at the long-term cost-effectiveness of CGM use in an RCT involving people with T2DM not on insulin who had a reduction in HbA1c. The authors found that CGM is a cost- effective disease management option [46].

Anyone with T1DM or T2DM can opt to self-fund CGM.

Lastly, hypoglycaemic episodes requiring third party assistance, can be captured via capillary finger prick testing by a healthcare professional or venous sampling in a hospital setting.

Monitoring glucose levels can prove challenging in older people with co-existing dementia, who face difficulties in recognizing and managing changes in glucose levels. Recent studies of CGM technology in older adults (without dementia) have detected higher rates of hypoglycaemia compared to SMBG[47 48], in addition to capturing asymptomatic hypoglycaemic episodes[49]. However, to the best of my knowledge, there are no studies looking at the feasibility of the use of CGM technology in older people with memory problems and diabetes. In my thesis, the feasibility study captured hypoglycaemia based on CGM measured glucose levels. The cohort study identified hypoglycaemic events based on clinical diagnoses (the clinician attending the patient with hypoglycaemia will in all likelihood have measured the glucose levels, but as a researcher, I am not able to access these results). The studies in both systematic reviews used a mix of methods to identify hypoglycaemic episodes, ranging from capturing glucose levels, self-reporting by patients to review of healthcare records.

1.2.3 Incidence and prevalence of hypoglycaemia

The true incidence of hypoglycaemia in the older population is tricky to establish, especially when looking at people with diabetes in the community as compared to inpatients. Hypoglycaemic episodes are more common in T1DM, however people with insulin-treated T2DM can be prone to frequent hypoglycaemia, particularly at night[33]. Mild episodes of hypoglycaemia are

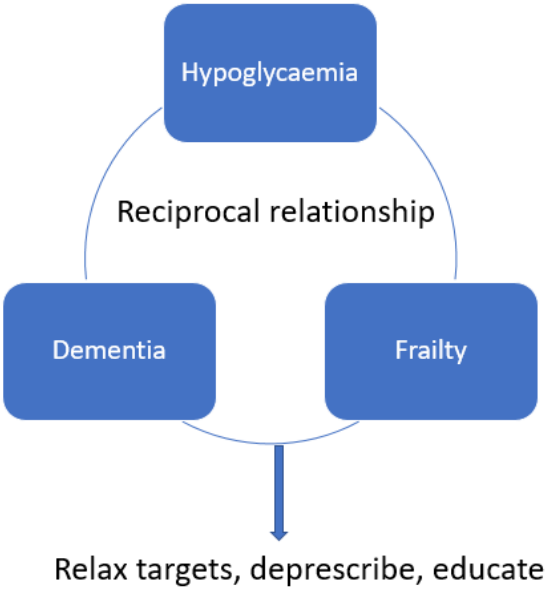
dealt with by the affected person without recourse to any medical help. In addition, such episodes may not have triggered measurement of glucose levels, via, for example, finger-prick testing. Instead, people manage *symptoms* as opposed to an objective glucose level [50]. Furthermore, it is possible to have asymptomatic hypoglycaemic episodes, especially at night [33]. Studies looking at the incidence and prevalence of hypoglycaemia can also be difficult to compare due to different hypoglycaemia definitions, heterogeneity of populations and varied modes of capture of hypoglycaemic episodes[33].

Looking at the general population, the UK Hypoglycaemia Study group carried out an observational study in patients with T1DM and T2DM. They relied on self-reporting of hypoglycaemic episodes and glucose capture via CGM. Severe hypoglycaemia rates in patients with T2DM on sulfonylureas or insulin ranged between 0.1 to 0.2 episodes per subject year [51]. In a further study, participants with T1DM and T2DM on insulin were recruited from a diabetes register in Scotland and asked to prospectively record the number of mild and severe hypoglycaemic episodes experienced over a one-month period. Patients with T1DM experienced hypoglycaemic events, at a rate of 43 events per patient per year. Patients with T2DM on insulin had an incidence of 16 hypoglycaemic events per patient per year. Duration of insulin treatment and previous hypoglycaemia were key predictors for hypoglycaemia in patients with T2DM[52].

Lastly, Akram et al carried out a questionnaire survey in Danish patients with insulin-treated T2DM asking about occurrence of hypoglycaemia, past hypoglycaemia awareness. Based on this survey, the incidence of severe hypoglycaemia was 0.44 episodes per person per year[53].

Focussing on the older population, Abdelhafiz et al carried out a comprehensive review exploring the relationship between hypoglycaemia, frailty and dementia[3]. The authors argue that the incidence of hypoglycaemia in older people is in all likelihood underestimated, although a substantive evidence-base for this is lacking. They put forward the argument that hypoglycaemia, frailty and dementia have a reciprocal relationship (Figure 6). Many frail older people are overtreated and are on hypoglycaemic medications that convey a high risk of hypoglycaemic events (insulin and sulfonylureas) [54 55].

Figure 6 Reciprocal relationship between hypoglycaemia, frailty and dementia



(adapted from Abdelhafiz et al 2016) [3]

Cross-sectional studies have shown that severe hypoglycaemia was more prevalent in patients with dementia and diabetes, in particular those taking insulin[56 57]. Feil et al's database study found that in participants taking insulin, hypoglycaemia was more common in patients with dementia (26.5%) and

cognitive impairment (19.5%) compared to those with neither condition (14.4%)[57]. Hypoglycaemia was identified from outpatient visits, emergency department and inpatient admission codes.

In Abbatecola's cross-sectional study, severe hypoglycaemic events were defined as a documentation of a plasma glucose of 50 mg/dL (2.8 mmol/L) or lower and symptoms requiring assistance from a third party to correct the low glucose. Severe hypoglycaemia was more prevalent in patients with dementia on sulfonylureas [56]. A further study using a German/Austrian diabetes registry found that older people with diabetes and co-existing dementia had a higher rate of hypoglycaemia and used insulin more often compared to those without dementia. Those with co-existing dementia and insulin therapy experienced 15 severe hypoglycaemic episodes per 100 patient years and 8 per 100 patient-years if taking sulfonylureas. In contrast, patients without dementia experienced 10 severe hypoglycaemic episodes per 100 person-years if on insulin and 5 per 100 person-years when taking sulfonylureas[58].

In a retrospective cohort study using a US insurance database, the incidence of serious hypoglycaemia (defined as requiring hospitalisation, emergency department attendance or death) was 2 per 100 person-years in older people aged 65 and above. The authors highlighted that increasing age, polypharmacy and frequent hospitalisations put patients at higher risk of severe hypoglycaemic episodes and that this vulnerable group needs close monitoring for adverse events[59]. Chen et al reported a higher occurrence of any kind of hypoglycaemic events in patients living in care homes. 41.9% of care home residents with diabetes who were being treated with medication experienced

hypoglycaemic episodes over a one-year period (26 out of 62 care home residents with diabetes with a mean age of 76 years).[60].

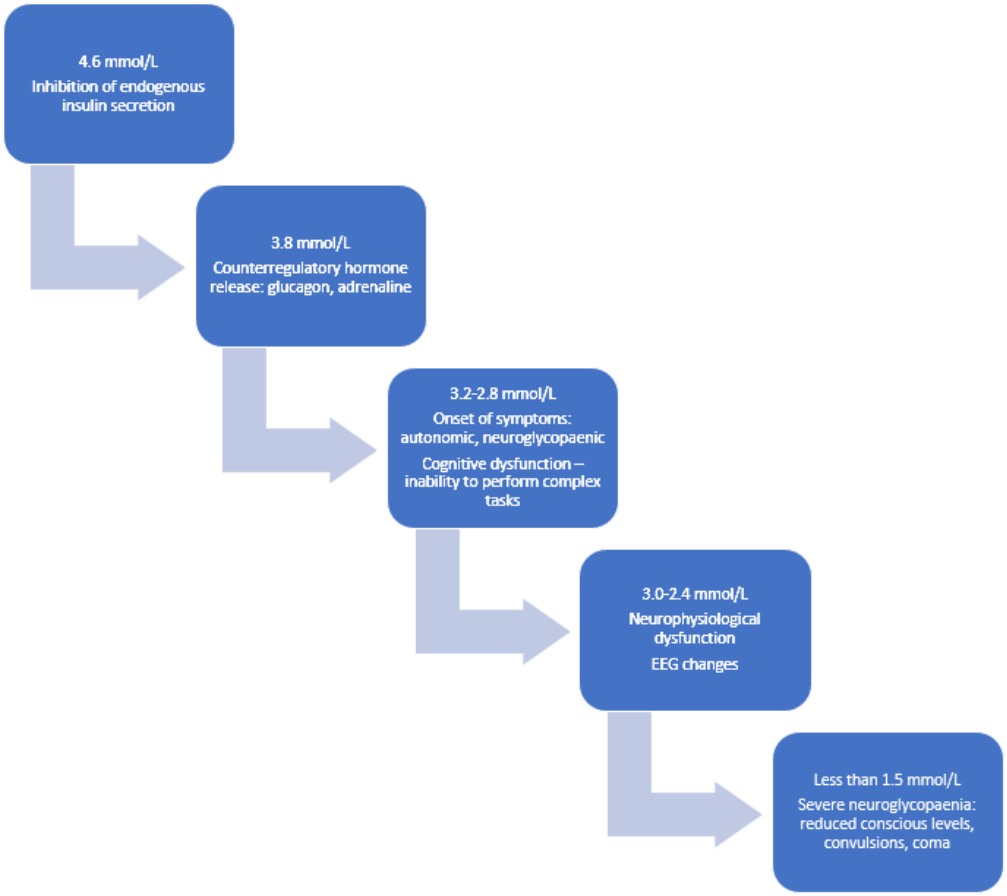
1.2.4 Risk factors for hypoglycaemia

Risk factors for hypoglycaemia for any person with diabetes include: use of insulin, sulfonylureas, kidney impairment, exercise, previous hypoglycaemic episodes, duration of diabetes and erratic meals [61]. Education around hypoglycaemia prevention, detection and management is essential both for patients and/or carers [20].

1.2.5 Physiology and symptoms

Hypoglycaemia is a state of glucose deficiency, often as a result of diabetes medication such as insulin or sulfonylureas. Counter-regulatory hormones (adrenaline, glucagon, glucocorticoids, growth hormone) are secreted in response to low glucose levels, in addition to the body suppressing endogenous insulin secretion (Figure 7).

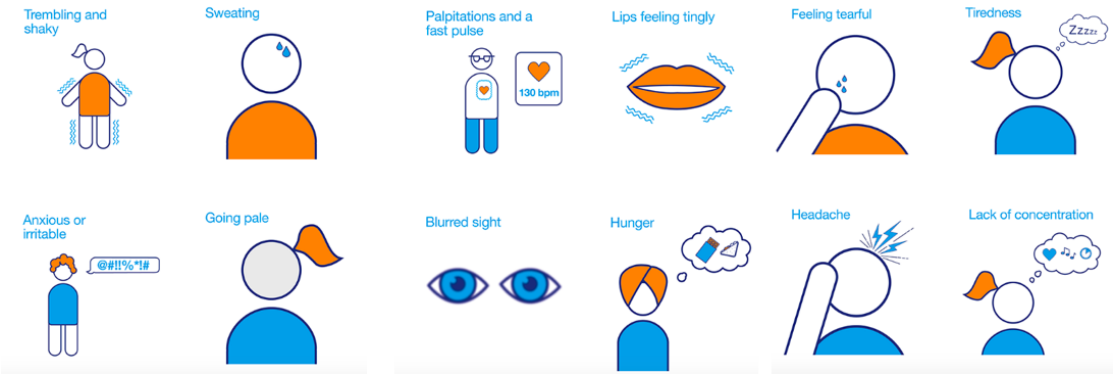
Figure 7 Glucose concentrations and physiological changes



(adapted from Zammitt et al)[61]

Symptoms of low glucose levels include irritability, hunger, sweating, light-headedness, palpitations, confusion (Figure 8). In the worst case scenario, it can lead to death, probably as a result of ventricular arrhythmias [20 33]. However, symptoms of hypoglycaemia are person-specific and can change with advancing age, due to changes in the counterregulatory response[61]. However, we do not know exactly at what age this occurs.

Figure 8 Signs and symptoms of hypoglycaemia



(taken from Diabetes UK webpage)[62]

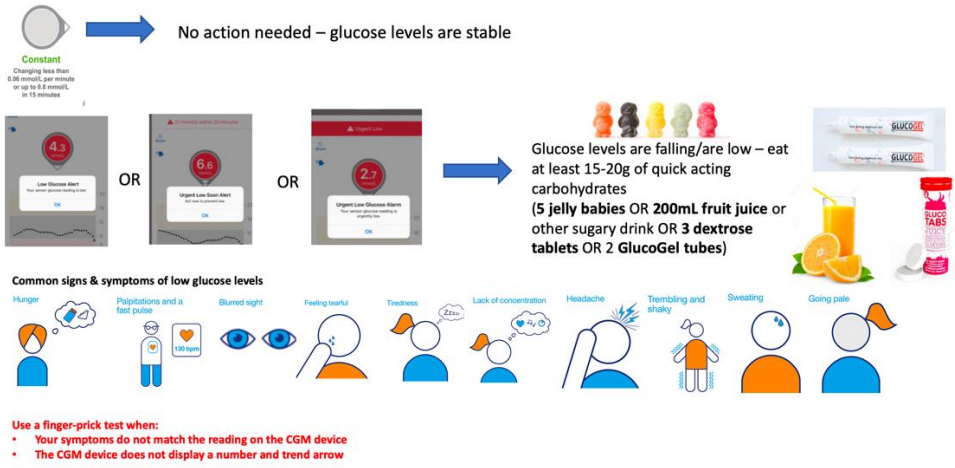
Being able to recognise falling glucose levels is crucial to self-management and preventing further deterioration. This recognition of hypoglycaemia and being able to efficiently self-manage hypoglycaemic events, becomes problematic in frail older people with co-existing dementia (and possibly further co-morbidities). They may experience reduced awareness of hypoglycaemic warning symptoms, reduced secretion of glucagon, may not be able to vocalize what they are experiencing, be impaired by altered psychomotor performance, all of which can lead to delays in treating the hypoglycaemic event[63]. Nocturnal hypoglycaemia is particularly tricky, as it is often asymptomatic and can last for hours [33].

1.2.6 Management of hypoglycaemia in older people

1.2.6.1 Acute management

A hypoglycaemic episode has to be treated with fast-acting carbohydrates (eg fruit juice, glucose tablets, jelly babies). 15-20g of quick-acting carbohydrates is usually an adequate amount. If the person experiencing the hypoglycaemic event is confused/uncooperative, but able to swallow, then 1.5-2 tubes of glucose gel is recommended. If a person is unconscious and/or is having a seizure, intramuscular glucagon can be administered, or, in the hospital setting, intravenous 10-20% glucose[64].

Figure 9 Simplified pictorial guide for making treatment decisions using CGM (Dexcom G6) in an older person when glucose levels are falling



1.2.6.2 Long-term management

The cornerstone of the long-term management has to be striking the right balance between adequate glycaemic control and avoidance of hypoglycaemic events. Patient education, glucose-monitoring and optimisation of prescribing will all play a part in this. However, Lash et al have identified a lack of resources to help clinicians and patients with diabetes reduce the risk of hypoglycaemic episodes[26].

Striking the right balance is particularly pertinent in older frail adults with multiple co-morbidities and the concept of deprescribing is gaining ever increasing momentum. Deprescribing consists of lowering doses of medications, switching medications or stopping medications altogether[65]. There is a lack of evidence, which shows that older, frail adults who have cognitive impairment or are nearing the end of life benefit from tight glycaemic control[65]. Farrell et al recommend deprescribing medications known to contribute to hypoglycaemia in older adults at risk (especially those with multiple co-morbidities and cognitive impairment) and individualising targets[65]. Other researchers have recently published findings of a systematic review, which suggest that overtreatment is common in frail older people with multiple co-morbidities and that deintensification appears safe [55].

There also needs to be a shift in how we carry out monitoring of glucose levels in older people with diabetes and dementia. We need to explore the use of CGM in this vulnerable group and I will discuss this in more detail in later chapters.

1.2.7 Adverse effects of hypoglycaemia

The immediate effect of hypoglycaemia can be confusion, visual disturbance, alteration in mood and lack of concentration. It also disrupts day-to-day activities, including exercise and driving. Confusion and visual disturbance can trigger falls and resulting injuries, such as fractures. There is also an increased risk in cardiovascular events, coma and death [6].

Longer term, both hypoglycaemia and T2DM are risk factors for dementia[66]. Persistent or severe hypoglycaemic episodes can lead to permanent neuronal

damage[3]. Gibas et al put forward the theory of "brain starvation" in patients with T2DM, due to concurrent hyperinsulinemia and relative hypoglycaemia due to insulin resistance resulting in apoptosis of healthy neurons from catabolic degeneration[67]. Radiological studies in patients who had suffered profound hypoglycaemia have shown that neurons in the hippocampal and temporal areas, cerebral cortex, substantia nigra and basal ganglia are particularly sensitive to hypoglycaemia [66]. Lee et al have found that hypoglycaemia was associated with smaller total brain volume on MRI [68]. Other studies have found a dose-response relationship between the frequency of severe hypoglycaemia and incidence of dementia[69], and a nearly three-fold increase in risk of dementia in older patients with diabetes and hypoglycaemia in a seven-year follow-up study in older Taiwanese patients with diabetes[70].

I carried out a systematic review and meta-analysis of 12 studies and 1.4 million participants, which revealed significantly greater likelihood of hypoglycaemia in patients with impaired cognition compared to those without. In addition, those affected by hypoglycaemia were more susceptible to worsening cognitive impairment and dementia, leading to a potentially vicious cycle of decline [7].

In a further meta-analysis, I found a significant association between hypoglycaemia and falls (Odds Ratio (OR) 1.89; 95% Confidence Interval (CI) 1.54, 2.32), or fractures (OR 1.92 95% CI 1.56, 2.38). Hypoglycaemia was also associated with cardiovascular complications, (OR 1.83; 95% CI 1.64, 2.05), microvascular complications (OR 1.77; 95% CI 1.49, 2.10), and increased likelihood of death, (OR 2.04; 95% CI 1.68, 2.47). This second meta-analysis was based on patients with diabetes in general, and there was insufficient data to

directly evaluate serious consequences of hypoglycaemia in those with co-morbid dementia [6].

Two more recent studies have shown that severe hypoglycaemia may influence cardiovascular risk and death independently of diabetes severity and general vulnerability, in addition to there being an association with higher risk of hip fracture [71] [72].

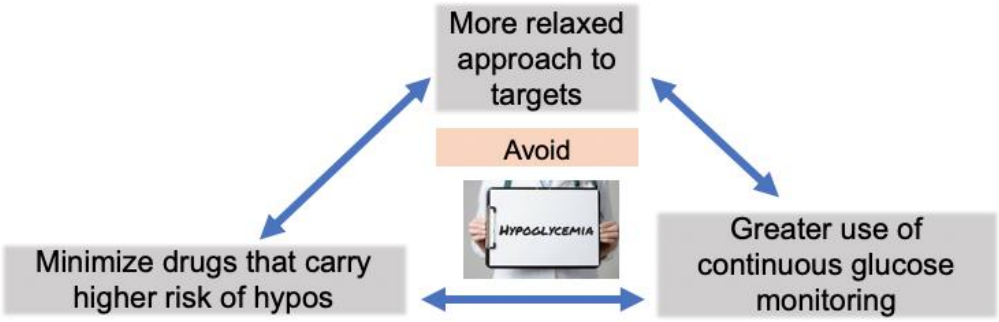
1.3 What needs to be done

The pressing need to address growing concerns about hypoglycaemia and its adverse effects, has led the Endocrine Society to develop a Hypoglycaemia Prevention Initiative [26]. Whilst clinical guidelines recommend personalised medicine and individualising goals in patients at risk of hypoglycaemia, this appears as yet not to have been translated into day-to-day clinical practice. Lash et al refer to a survey of healthcare professions carried out by the US Department of Veterans Affairs, in which 50% of the nearly 600 respondents reported no concerns over potential harms associated with tight glycaemic control in older people. The authors recommend advancing better management of hypoglycaemia though use of risk assessment and clinical support tools, patient education and shared decision-making [26].

It is becoming clear that new approaches or changes in mindset are needed when formulating monitoring strategies for older patients, aimed towards measuring harm from hypoglycaemia rather than just efficacy targets.

It is necessary to establish more robust evidence to support the principles set out in the figure below to guide the management of older people with diabetes and dementia.

Figure 10 Factors for hypoglycaemia minimization



CHAPTER 2 - A SYSTEMATIC REVIEW OF CONTINUOUS GLUCOSE MONITORING IN OLDER PEOPLE WITH DIABETES MELLITUS

2.1 PREAMBLE

The first chapter outlined the basic principles of the management of diabetes and the specific challenges that older people, clinicians and carers encounter. This chapter presents a systematic review on continuous glucose monitoring in older people with diabetes consolidating the growing evidence base in this area. It was published in Journal of Diabetes and its Complications in 2018[73]. Chapter 2 is largely a replication of the publication, whilst also expanding on background, results and discussion sections.

2.2 Chapter summary

2.2.1 Background

The presence of multiple comorbidities and cognitive decline poses major challenges for the self-management of older patients with diabetes. The best way to monitor glucose levels in this population and the extent of harm from hypoglycaemia is not known. The development of CGM over the last two decades has enabled a more comprehensive understanding of individual glycaemic profiles, however the focus has been on children and younger adults. Evidence on the use of CGM in older patients has started to emerge in recent years, but there has been no systematic review consolidating this growing evidence base.

This was a hypothesis-generating systematic review to inform my feasibility study (chapter 3). The parameters I was interested in were:

- Methods used in the studies and extent of overall capture of glucose readings;
- Quantitative estimates regarding time and depth of hypoglycaemia;
- Acceptability of CGM to participants;
- Adverse events and other patient outcomes associated with CGM use.

2.2.2 Methods

The protocol was registered on the international database of pre-registered systematic reviews, PROSPERO (CRD42017068523) (Appendix 1).

A literature search of SCI Web of Science, Ovid SP MEDLINE and EMBASE from January 2010 to June 2017 was conducted for observational studies and randomized controlled trials of CGM in older patients (mean age 65 or older) with diabetes. Studies that involved only hospitalized patients were excluded. Two reviewers independently extracted data (in particular, hypoglycaemic episodes) captured with the use of CGM. Adverse events and acceptability of CGM were also assessed.

2.2.3 Results

After screening 901 abstracts, I included nine studies with a total of 989 older patients with diabetes.

The CGM studies reveal that hypoglycaemic episodes were occurring in a sizeable proportion (28-79%) of participants. Most (80-100%) of these episodes were asymptomatic, with some patients spending nearly two hours per day in the hypoglycaemic range. Older people with diabetes found CGM acceptable and experienced improved health-related well-being.

2.2.4 Conclusions

CGM frequently picks up asymptomatic hypoglycaemic episodes in older patients with diabetes. Users of CGM report improved well-being, and reduction of diabetes-related stress.

2.3 Background

Chapter 1 outlined the challenges of self-management of diabetes mellitus in older people with co-existing dementia, in addition to the growing concerns about hypoglycaemia and its adverse effects in this vulnerable group of people. I also discussed how recent advances in CGM technology may uncover the true extent of hypoglycaemia (including asymptomatic hypoglycaemic episodes).

2.3.1 Evolution of CGM

CGM first became available nearly 20 years ago and provides a way to continuously measure interstitial glucose levels, as opposed to intermittent finger-prick testing, which measures capillary blood glucose levels. The overall goal of using CGM is to improve metabolic control and the evidence base to date is that it does lead to improvements in HbA1c, in addition to reducing hypoglycaemic events[74 75]. An open-label randomized controlled trial using the FreeStyle Libre in people with type 2 diabetes on a basal-bolus regime showed a significant reduction of time spent in the hypoglycaemic range, but no significant change in HbA1c[43]. More recently, Tyndall et al published a prospective observational study of 900 people with T1DM assessing change in HbA1c following flash glucose monitoring (compared to 518 not using flash glucose monitoring). Whilst there were significant improvements in HbA1c, an increase in symptomatic and asymptomatic hypoglycaemic episodes were also reported, which the authors thought could be related to greater capture of previously unrecognised hypoglycaemia[76].

Despite this, it is still not the norm for individuals to use CGM over SMBG via finger stick tests. Being relatively new and rapidly-evolving technology, barriers

to using CGM include cost, lack of standardised download of data, no standardised approach on how best to use the data, reliability of the glucose measurements and human factors[77].

2.3.1.1 Transmission of data

Depending on the manufacturer, CGM can transmit data continuously via Bluetooth to a receiver or smartphone, which then enables alarms to sound when readings are either high or low (Dexcom, Medtronic, Senseonics). In addition, readings provide users with trend arrows, indicating whether glucose levels are predicted to rise, fall or remain steady.

An alternative is 'flash' glucose monitoring such as the FreeStyle Libre (Abbott Diabetes Care), which has become available in 44 countries over the last few years and is licensed for adults and children. It provides a cheaper alternative to other CGM devices and is based on similar sensor functionality. The main differences are that whilst glucose levels are measured continuously, the data are not transmitted continuously from the sensor. Instead, the user has to swipe/scan ('flash') the sensor with a reader (based on Near Field Communication technology) at least eight-hourly in order to capture 24-hour data every day throughout the life time of a sensor (14 days) [77]. Anyone using the FreeStyle Libre has to physically scan the sensor in order to see glucose readings. Abbott have announced that they will be introducing a version 2, which includes a Bluetooth transmitter to enable optional alarms, although users will still need to scan the sensor regularly to obtain the full data.

Finally, some CGM devices are 'blinded', whereby a user is not able to see the readings and the data is transmitted directly to a healthcare professional.

Examples include the Freestyle Libre Pro, the Medtronic iPro and the Dexcom Seven Plus (blinded mode). Blinded CGM can be advantageous in a clinical trial setting, as trial participants will not be able to see their readings minimising any potential bias ('Hawthorn effect') that could arise. In a healthcare setting, blinded mode could facilitate maintenance of an individual's usual routines and behaviours.

2.3.1.2 Reliability of CGM measurements

CGM captures interstitial glucose levels, in contrast to capillary glucose. Interstitial glucose readings are known to lag behind capillary blood glucose readings, which relates to the diffusion time of glucose from capillaries to interstitial fluid and diffusion across sensor membranes [78]. There is an approximately 5-10 minute delay in interstitial fluid glucose response to changes in blood glucose[79] [80].

A 2013 study concluded that the physiological delay of 5-6 minutes between blood glucose and interstitial glucose levels should not be an obstacle to CGM sensor use in real-world treatment settings [80]. A study of time delay with CGM devices reported that factors other than delay have a larger influence on the overall performance of a CGM device [81].

Before 2016, CGM devices available in the US were only approved for use as adjunctive devices. This meant that user had to confirm the interstitial glucose reading with a capillary reading, before making a decision about insulin adjustment, although a survey of adult patients in the US T1DM Exchange Clinic registry revealed that only 26% of 999 participants in the survey carried out a capillary blood glucose test before making treatment decisions[82].

A randomized non-inferiority trial in adults with T1DM confirmed that it is safe to use CGM readings (Dexcom G4 Platinum) without confirmatory capillary blood glucose measurements. It should be pointed out though that the participants in this trial all had well-controlled T1DM at low risk of severe hypoglycaemia[82].

Research has also shown that interstitial glucose measurement with the FreeStyle Libre device differed on average by around 11% compared to capillary blood glucose values [79]. However, Abbott, the manufacturer of FreeStyle Libre, has reported their sensor may have less accuracy in the lower glucose ranges. Abbott's safety information discloses a clinical study showing that 40% of the time when the device indicated an interstitial glucose level of less than 3.3 mmol/L, the capillary reading was between 4.5 mmol/L to 8.9 mmol/L.

Older CGM devices required regular daily calibration (between 2 to 4 times per day) with capillary blood glucose measurements. FreeStyle Libre and Dexcom G6 do not require any calibration, although the product information does state that should symptoms not match with the interstitial readings, then the user is advised to double-check with a capillary test. The manufacturer of FreeStyle Libre point out that a capillary glucose reading is required during times of rapidly changing glucose levels when interstitial levels may not accurately reflect blood glucose, if hypoglycaemia or impending hypoglycaemia is reported or the symptoms do not match the interstitial reading (footnote 1 at https://freestylediabetes.co.uk/freestyle-libre/interstitial-vs-blood-glucose [83]).

Manufacturers of the newer CGM devices claim that their sensors are more accurate now at the extremes of glucose ranges.

The following factors influence the accuracy of CGM in a clinical setting:

- Intrinsic technical ability of the hardware;
- Performance of the software that picks up the sensor data and conducts processing to estimate the glucose concentrations;
- Age and batch of the sensor;
- Rate of change of glucose concentrations (which will be in turn be influenced by patient characteristics including age, physical activity, illness);
- Absolute glucose value, whether at low or higher end.

There is as yet no agreed standard for defining the performance of a CGM system. To start with, there are major methodological difficulties in obtaining a similarly large 'reference' set of glucose values from venous or capillary blood sampling concurrently for comparison against the hundreds of values captured by CGM over a 10-14-day period. There is also no single 'diagnostic accuracy' summary statistic that can be presented as a valid and generalizable depiction of the CGM performance in a dynamic environment subject to influence by a constantly evolving multitude of internal and external factors.

Performance of any glucose monitor (be it CGM or SMBG), can be described by either analytical or clinical accuracy. Analytical accuracy describes the difference between the glucose value captured by a device compared to a reference glucose value. Examples of measures that capture analytical accuracy are mean absolute relative difference (MARD) and diagnostic accuracy statistics. Importantly, measures describing analytical accuracy do not take into account of the clinical importance of any discrepant measurements.

A consensus error grid can be used to depict and describe clinical accuracy. Here, paired results from a glucose meter and the reference method are plotted on an error grid (see Figure 11) and risk zones are superimposed on the graph. The 'error' in this grid relates to the discrepancy between the referent value and the CGM value. The 'consensus' part relates to qualitative judgments (predefined by a consensus panel comprised of clinicians) about treatment decisions and clinical consequences that may arise due to the discrepancies between the CGM device and the referent glucose value.

The different risk categories in the consensus error grid (zones A to E) are defined as:

- A – no effect on clinical action (eg clinically accurate values within 20% of the reference sample);
- B - altered clinical action or little or no effect on clinical outcome (eg values outside 20% of the reference sample but would not lead to inappropriate treatment);
- C - altered clinical action (eg values that would lead to overcorrection of glucose levels);
- D – altered clinical action – could have a significant clinical risk (eg, dangerous failure to detect and treat high or low glucose);
- E – altered clinical action – could have dangerous clinical consequences (eg values that could lead to treatment contradictory to that needed) [84] [85] [86].

MARD

Put simply, MARD describes in percentage terms the disparity between the glucose level displayed by the CGM device compared to reference blood glucose results. A lower MARD reflects a smaller discrepancy between the CGM device and referent value, and is considered to represent better sensor performance. For example, if the CGM device consistently showed readings of 10.0mmol/L when reference blood glucose readings were 9.0 mmol/L, then the MARD would be 10%. Sophisticated statistical models are used in calculating and comparing single overall MARDs across studies based on summarizing the percentage difference seen in multiple samples across a wide range of glucose values. Typically, the MARD for CGM devices is better at normal glucose values, whereas the performance deteriorates outside range, thus resulting in larger MARDs[79].

Guidance published in the International Consensus on use of CGM, states that whilst "controversy exists regarding an exact cut-off point for accuracy, in silico testing has shown that a further lowering of MARD below 10% from reference values has little additional benefit for insulin dosing" [87 88]. Both the Freestyle Libre and Dexcom G6 CGM devices have MARD <10% and regulatory authorities have approved their use without having to conduct finger-prick tests (see Table 1).

The limitations of looking only at the overall MARD are that it does not tell us magnitude of errors at different glucose levels, nor the clinical importance of the discrepancies. In addition, MARD can vary during sensor life, for example, it can be higher during the first few days of a new sensor [86].

Table 1 CGM devices, MARDs and calibration requirements

Device	MARD (%)	Calibration requirements
Abbott Freestyle Libre	9.7	None, although user advised to check their glucose levels with a capillary reading if interstitial reading does not reflect symptoms
Dexcom G6	9.0	None, although user advised to check their glucose levels with a capillary reading if interstitial reading does not reflect symptoms
Medtronic Enlite	13.6	Every 12 hours
Medtronic Guardian Sensor 3	9.6 (abdominal insertion with 3-4 calibrations/day); 8.7 (arm insertion with 3-4 calibrations per day)	Every 12 hours
Professional Abbott Freestyle Libre (blinded)	12.3	None

Medtronic iPro2 (blinded)	13.6	None (but at least one capillary glucose level entry every 12 hours required for system uploads)

(adapted from ADA publication [89])

By way of comparison, in 2015 Freckmann et al evaluated the accuracy of four SMBG systems based on two datasets. One dataset evaluated 100 samples with blood glucose concentrations below 3.9 mmol/L and the second dataset evaluated 100 samples distributed following International Organization for Standardization (ISO) standard 15197 (in vitro diagnostic test systems – requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus). The authors reported MARD values ranging from 4%-13.4% for the first dataset that included low glucose value and 4.8% to 8.9% for the second ISO dataset [90].

Diagnostic Accuracy statistics at specific 'low' thresholds

For Freestyle Libre, the manufacturers report that 40% of the time when the device indicated an interstitial glucose level of less than 3.3 mmol/L, the capillary reading was between 4.5 mmol/L to 8.9 mmol/L.

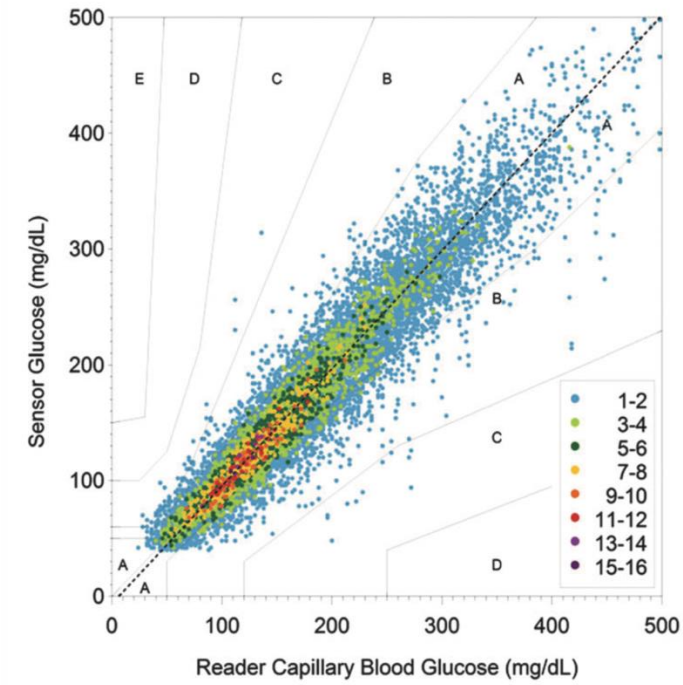
Wadwa et al have evaluated the alerts of the Dexcom G6 CGM system in a prospective multicentre study [91]. When the hypoglycaemia threshold alert was set to 3.9 mmol/L (70 mg/dL), the false alert rate was 15.6% whereas the false alert rate worsened to 30.1% when set to 3.3 mmol/L (60 mg/dL).

The main limitation of diagnostic accuracy statistics based on binary categories is that the actual size of the difference between the true and CGM value is not presented.

Clinical consensus error grids

A consensus error grid comparing CGM and the reference value has been reported for Freestyle Libre (Figure 11).

Figure 11 Error grid analysis – FreeStyle Libre[79]



In Figure 11, the percentage of results in Zone A (clinically accurate) of the consensus error grid was 86.7%. The percentage of sensor results in Zones A and B (clinically acceptable) of the consensus error grid was 99.7% [79].

In summary, each method of evaluating and reporting performance of CGM gives different but useful information and experts consider that interpretation of the MARD together with consensus error grids will present a more complete picture[90].

Looking at the clinical context, for users of any glucose monitoring device, it is vital that clinically important differences are identified rather than just numbers relating to % deviation. I recognise that CGM is a relatively new evolving technology that has limitations (like every evolving technology). However, clinical practice and technology should also move forward to harness the strengths of CGM whilst working around the recognized limitations.

CGM technology has evolved to address issues surrounding accuracy:

1. The ability to take multiple readings of the real-time glucose value (thereby avoiding spurious one-off errors) interpreted together with the trend display showing change in glucose over time;
2. Predictive software algorithms such as Urgent Low Soon (Dexcom G6) that analyse the pattern of change and generate alerts of impending hypoglycaemia.

These elements empower a person with diabetes to take taking corrective action BEFORE, for example, hypoglycaemia actually happens. Clinicians advocate this method to act on an impending hypo, rather than wait for notification of an actual hypo.

Hypoglycaemia has potentially very serious consequences, whereas corrective action is simple and likely to be very beneficial rather than harmful. The

predictive algorithm has also been implemented together with smart insulin pumps to suspend insulin delivery before low rather than stop only when the low has already occurred (discussed further in section 2.3.1.4.1).

In these instances, the clinicians do not feel that there is a need for highly precise measurements – action should be taken if the glucose value is 4.05 mmol/L or 3.75 mmol/L, or the true value of 3.9 mmol/L. There is no clinical rationale to wait until the exact threshold of 3.9 mmol/L is reached.

As discussed above, it is also necessary to bear in mind that SMBG systems have MARDs between 4-13%. Based on the currently accepted MARD of <10% with Dexcom G6 and FreeStyle Libre, the use of CGM would not necessarily be inferior to SMBG use because CGM has the added benefit of detecting asymptomatic hypoglycaemia, and can also sound alerts for impending hypoglycaemia.

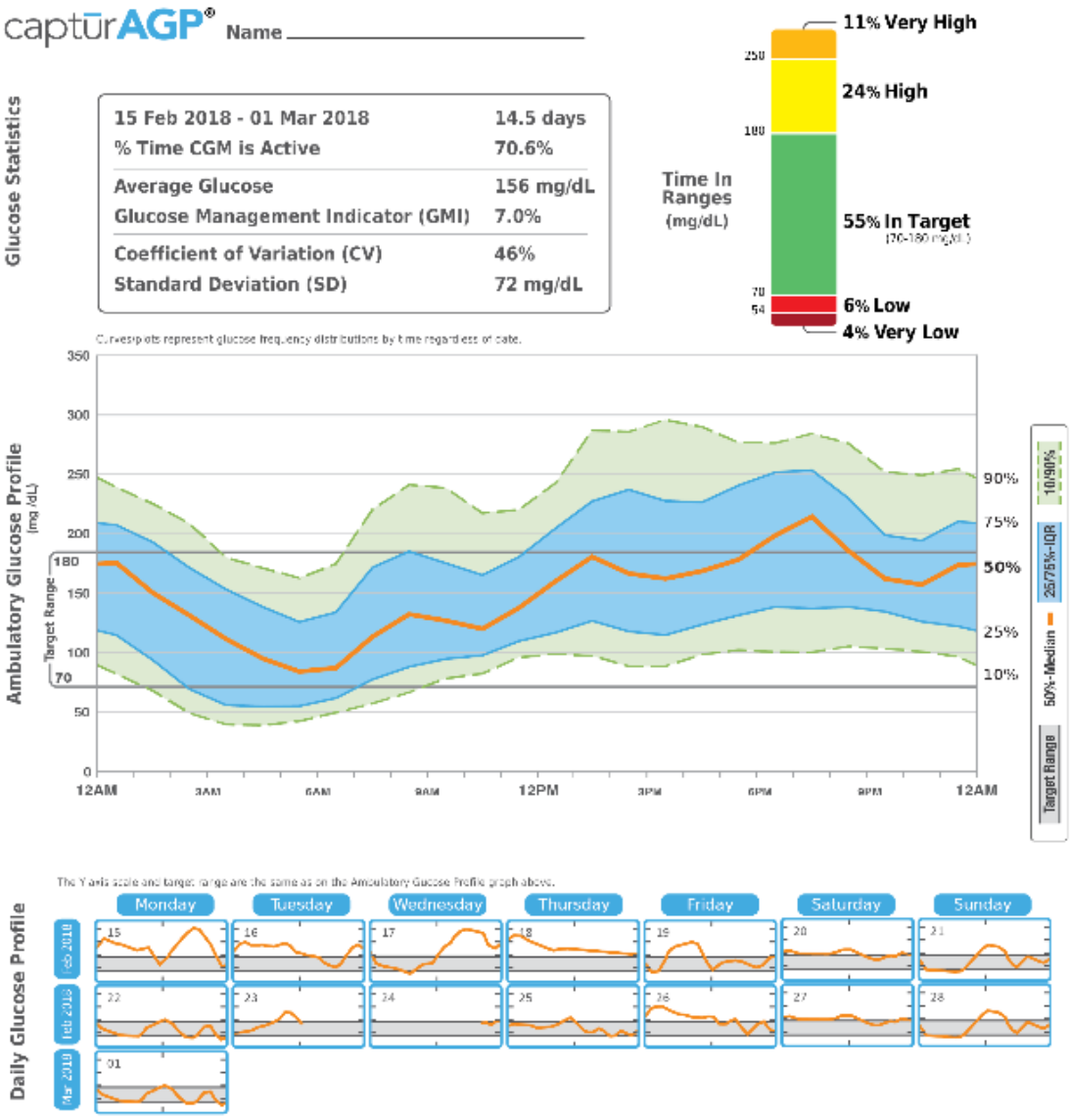
2.3.1.3 Lifespan of sensors

Depending on the manufacturer, sensors have a life span between 6 to 90 days, with implantable sensors (Eversense) lasting the longest.

2.3.1.4 Software and interoperability

The manufacturers of the various CGM devices provide free software, which enables users to download all the data that is collected throughout the life time of each sensor. Non-standardised reporting of data makes it more difficult to analyse different CGM devices in a trial setting or carry or systematic reviews and meta-analyses [77]. Nevertheless, ambulatory glucose profiles provide a useful summary and overview of a user's data.

Figure 12 Example of an ambulatory glucose profile



Users of CGM devices are unlikely to download data on a daily basis and it is not clear what information is used to make management decisions, eg based on an individual glucose level, the trend arrow (picture below), or the trend over the last few hours [77]. In addition to the software, users can download apps so that data can be viewed with their smartphone. It is also possible to share data with relatives or carers.

Figure 13 Picture of trend arrows – Dexcom G6 [92]

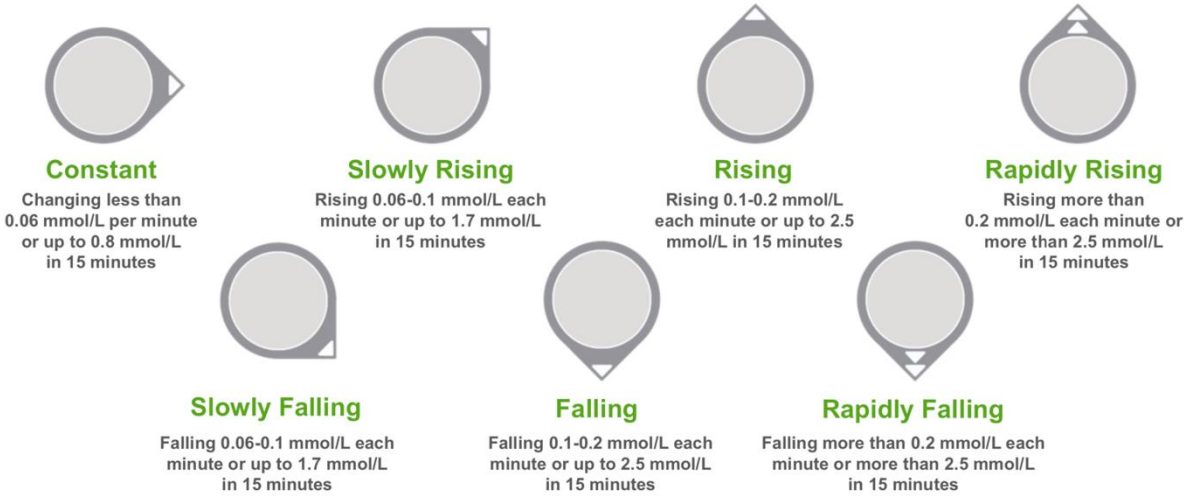
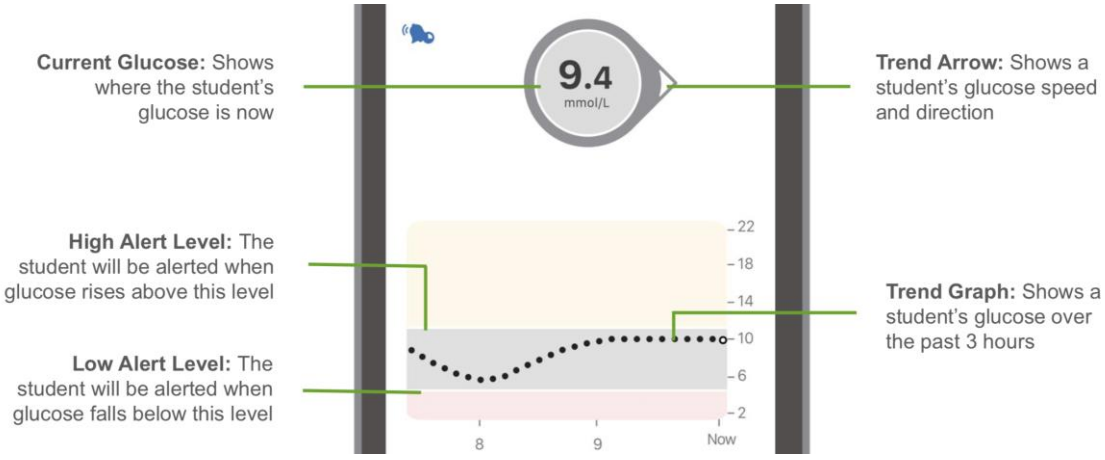


Figure 14 Display of individual glucose reading on a smartphone [92]



A further advantage of CGM systems is the capability of alarms, which warn users of high and low glucose levels.

Pictures of the types of alarm provided by the Dexcom G6 system are below:

Figure 15 Low glucose alert – Dexcom G6 [92]

Each student should have a set low and high glucose alert.

The display device will either vibrate or beep based on the student's alert settings.

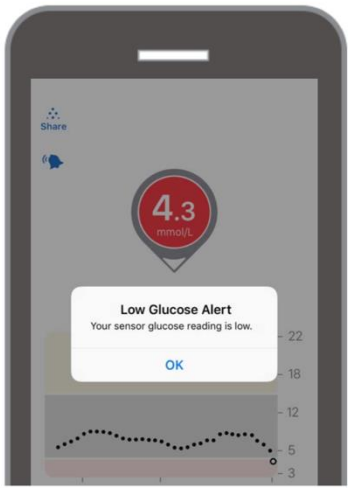


Figure 16 Urgent low soon alert – Dexcom G6 [92]

The Urgent Low Soon Alert sounds when a student will be 3.1 mmol/L in less than 20 minutes.

Depending on how quickly the student will be at 3.1, they will either get their Urgent Low Soon Alert or their Low Alert:

- Within 20 minutes = Urgent Low Soon Alert
- Not that fast = Low Alert

This alert can be turned on or off in settings.

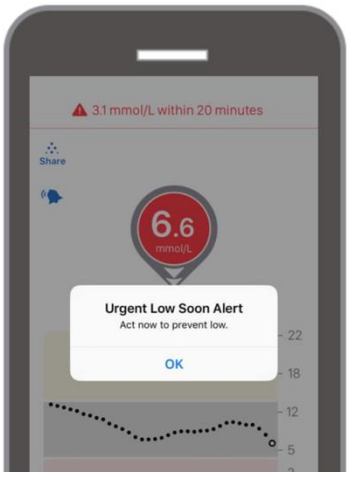
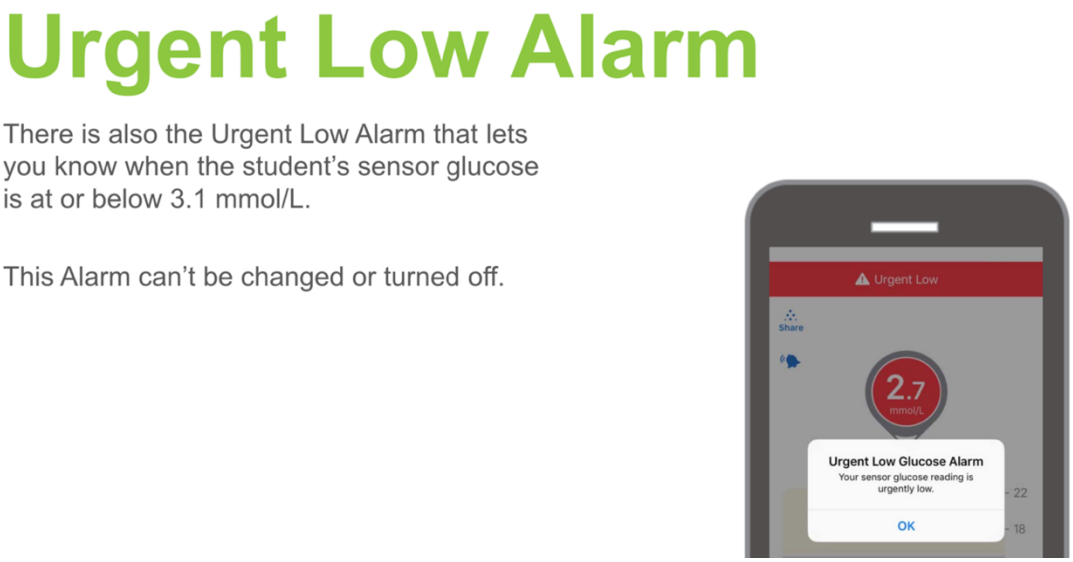


Figure 17 Urgent low alarm – Dexcom G6 [92]



2.3.1.4.1 Sensor augmented pump therapy systems and Tandem pumps

Medtronic have developed a system whereby a Medtronic CGM device is paired with a Medtronic pump (closed loop system – Medtronic 670G). Research has shown that sensor-augmented pump therapy can result in significant improvement in HbA1C levels [93] in adults and children with T1DM. The system is able to adjust basal (background) insulin rates every five minutes depending on the CGM reading and also has the feature of suspending insulin delivery up to 30 minutes before reaching hypoglycaemic levels.

More recently, Dexcom has worked with Tandem Diabetes Care to develop a so-called tandem pump (t:slim x2). The Dexcom G6 CGM device communicates in tandem with an insulin pump. The pump itself incorporates Basal-IQ technology, whereby software is able to predict hypoglycaemic events 30 minutes in advance resulting in automatic suspension of delivery of insulin, if glucose levels are expected to drop below a certain threshold. Insulin delivery

is then automatically restarted once glucose levels have sufficiently recovered. A RCT of 24 schoolchildren in the US with T1DM showed that those using the t:slim X2 pump paired with Dexcom G6 had a significantly improved time in range without increasing hypoglycaemia compared to those on sensor augmented pump therapy (71% versus 53%)[94].

Interestingly, the online diabetes community posted in March 2019 that Tandem have suspended their Control-IQ trial due to concerns about the software's behaviour resulting in hypoglycaemia.

Features of the tandem pump software include:

- An algorithm that is layered on top of the users' pump settings;
- Target range in normal use (6.25 mmol/L to 8.9 mmol/L);
- Target range for night-time (6.25 mmol/L to 6.7 mmol/L);
- Exercise settings;
- Adjustments to basal rates and automated bolus only occur when the predicted glucose level is expected to be higher than 8.9 mmol/l;
- Insulin delivery in a two-phase model, first adjusting basal rate every five minutes and then giving a single correction bolus per hour of 40% less than what the pump settings call for (but no bolus functionality when in sleep mode);
- Basic learning capability using total daily dose compared to current settings and adjusting based on this information.

In comparison, the closed loop Medtronic 670G uses a single target value instead of a range, there is no night time mode, there is no correction bolus and

the system learns about a user prior to being able to use auto mode (around two weeks).

Figure 18 T:slim X2 tandem pump

Figure 19 Medtronic 670G closed loop system

2.3.1.5 Costs

Cost of CGM devices is a barrier to access and whilst the NHS' long-term plan states that from April 2019, selected patients with T1DM will have access to flash glucose monitors, thus ending the variation patients in some parts of the

country are facing, many will still have to self-fund a CGM device especially if they have T2DM.

Abbott's FreeStyle Libre is the least expensive – the reader (which can be recharged) and each sensor cost around £50. The monthly cost for sensors for someone using the device all the time is approximately £100. The FreeStyle Libre has become so popular that its website is currently restricted to existing customers (https://www.freestylelibre.co.uk/libre/sign-in.html). Existing customers are only able to order three sensors every 25 days.

Dexcom have different payment plans for their G6 device. Customers can choose to sign-up for 12 months at £159 per month, which provides a user with 4 transmitters and 37 sensors over the 12-month period. Individually, transmitters cost £200 (last for 3 months) and a three-pack of sensors costs £153.75.

Patients who use the Medtronic Minimed 670G pump would have to pay between £210-£275 per box of five sensors.

2.3.1.6 Human factors

As alluded to above, human factors influence the use of CGM devices and there is a need to explore these more in a clinical trial setting. Users can find wearing a sensor all the time a burden. Inserting the sensor results in a small puncture site or may require a minor surgical procedure for implantable sensors [77].

Thinking of the older population whose skin will be thinner and more prone to damage, there is to the best of my knowledge no evidence as to how that might affect sensor usage. The impact of arthritis (in particular the hands) on an older

person's dexterity and strength has also not been explored in relation to being able to use sensor insertion devices.

Figure 20 Dexcom G6 insertion device

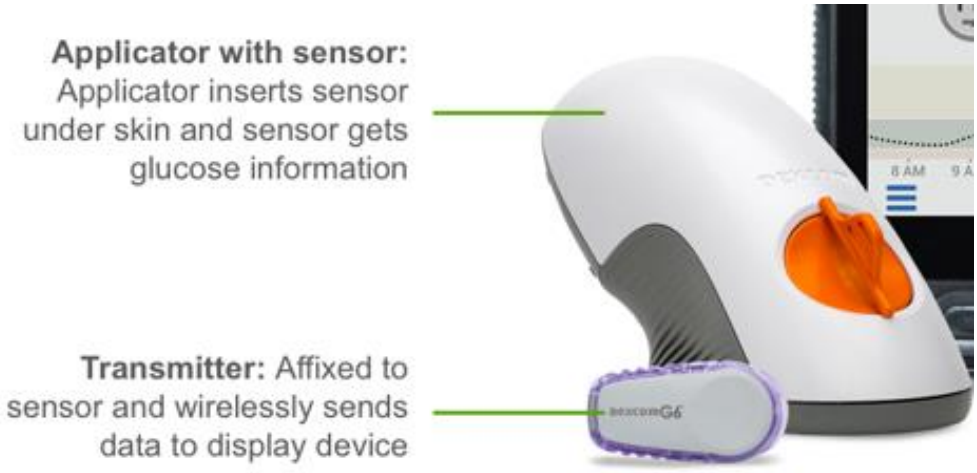
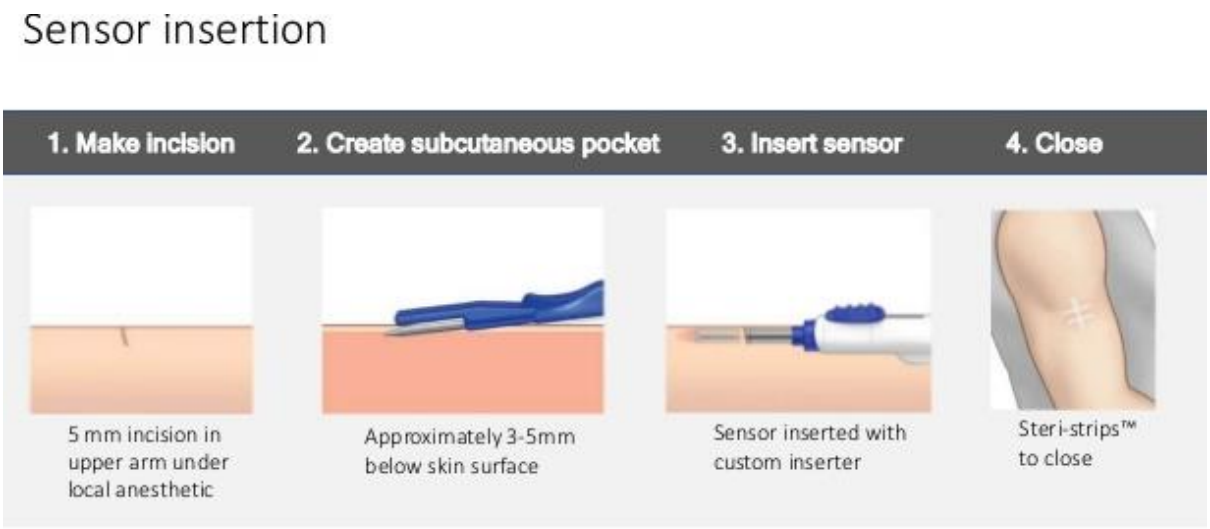


Figure 21 Eversense insertion (implantable sensor which lasts for 90 days)



The technology employed by the CGM manufacturers assume a high level of understanding and familiarity with smartphones, Bluetooth and apps. Again, this might be a barrier to anyone (irrespective of age) who is not used to such technology or who lives in a less-developed country where the technology is not as widely available, compared to countries in Europe or the United States.

There is limited scope to personalize the interface, which some may perceive as a disadvantage. Use of a CGM device will only be of benefit if the user and healthcare providers are able to analyse and interpret the data having had sufficient training. Consultations between patients/carers and healthcare professionals take time, in order to ensure that useful management decisions are made based on the data collated by the device. Such time, training and resources may be not available [77].

To sum up, the technology around CGM devices has rapidly evolved over the last couple of decades. Users are faced with an array of choices, but there are still a number of barriers preventing equitable access to this technology. Existing research in CGM has focussed on younger adults and children with diabetes and it is becoming clear that new approaches or changes in mindset are needed when formulating monitoring strategies for older patients, aimed towards measuring harm from hypoglycaemia rather than just efficacy targets. Hence, I conducted a systematic review on the role of CGM in older people, with specific focus on ascertainment of asymptomatic hypoglycaemia.

This was a hypothesis-generating systematic to inform my feasibility study (chapter 3). The parameters I was interested in were:

- Methods used in the studies and extent of overall capture of glucose readings;
- Quantitative estimates regarding time and depth of hypoglycaemia;
- Acceptability of CGM to participants;
- Adverse events and other patient outcomes associated with CGM use.

2.4 METHODS

The protocol was registered on PROSPERO (CRD42017068523) (Appendix 1).

2.4.1 STUDY SELECTION CRITERIA

I included observational studies and RCTs. Population of interest was older people, mean age >65 years. Studies based solely on inpatients or laboratory settings were excluded.

2.4.2 SEARCH STRATEGY

I searched three electronic databases: Web of Science, Ovid SP MEDLINE and EMBASE from January 2010 to June 2017.

No searches were conducted on unpublished or grey literature. Only human studies were included in the search.

The search strategy included terms related to the intervention (continuous glucose monitoring) and the population (older adults):

(Aged OR "older adult" OR "older adults" OR elderly OR geriatric OR veteran? OR senior?)

AND

(continuous-glucose-monitoring or CGM)

The full PubMed search strategy is reproduced below:

("aged"[MeSH Terms] OR "older adult"[All Fields] OR "older adults"[All Fields] OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields]) OR geriatric[All Fields] OR ("veterans"[MeSH Terms] OR "veterans"[All Fields] OR "veteran"[All Fields]) OR senior?[All Fields]) AND ("continuous glucose monitoring"[All Fields] OR CGM[All Fields]).

I also conducted a manual search by reviewing the reference lists of included studies and published systematic reviews on the same topic. The searches were also updated automatically on a monthly basis through electronic notifications from Pubmed.

2.4.3 Study Selection and Data Extraction

Two reviewers (YKL and KM) independently screened titles and abstracts to remove those that clearly did not fulfil selection criteria. Both reviewers then proceeded to check full-text versions of articles that were either of uncertain suitability or were judged as potentially relevant. Data extraction similarly involved two independent reviewers, with subsequent discussion to reach consensus.

I extracted the following information onto a spreadsheet: study design, geographical location, sample size, mean age, diabetes duration, model/make of CGM, selection of patients, loss to follow-up, missing data, selective reporting, summary statistics of blood sugar values captured, definition and number of hypoglycaemic episodes captured, adverse events, acceptability and adherence (Tables 2 and 3).

Table 2. Study design and characteristics

Study ID	Study design, setting, country	Patient Characteristics (numbers in each group, mean age overall, % male, type of diabetes, any inclusion/exclusion criteria, confounders adjusted for)	Intervention (which model/make of CGM), blinded or not
Argento 2014 [95]	Retrospective electronic health record review US adult endocrinology clinic. Any patient >65 years with CGM 15 June 2013	CGM (n=29) Age:68.8 (SD 3.5) years Male 12/29 (41%) T1DM 26/29 (90%) All patients used insulin	Device not stated No blinding
DuBose 2016 [96]	Post-hoc analysis of case-control study at the T1DM Exchange Clinic Network in US.	Non-CGM users, T1DM >60 years age, diabetes duration >20years. Exclusions: chronic kidney disease stage 4 or 5, moderate or advanced dementia, or pancreatic transplant. N=199 Mean age 68 Male 53% Mean duration of diabetes 40 years	Blinded participants using Dexcom SEVEN device, sampling glucose every 5 minutes for a week. Device replaced after that for further 7 days.
Ishikawa 2017 [97]	Retrospective observational study previously collected CGM data, Chiba University Hospital and Kashiwado Hospital Japan 2011-2016.	N=170 (83% outpatients) type II DM age>65 years. Mean Age 74 42.4% on DPP-4 inhibitors, 55.9% on with insulin) and 27.1% on SU.	Medtronic iPro v2 or System Gold

Litchman 2017 [98]	Two online surveys of CGM through Diabetes Online Community on Facebook. Convenience sample using snowball sampling technique	N=11 users T1DM >65 years, able to read/write English. Mean age 70 Male: 55% Diabetes duration 59.4 ± 6.4 y Control group N=11 who want to use CGM	Dexcom Gen4 =8 Dexcom Gen 5 =1 Medtronic Revel=1 Medtronic Enlite =1
Munshi 2011 [48]	Prospective observational study, Tertiary care diabetes clinic, USA.	N=40 Community-living patients aged ≥69 years with HbA1C>8%	blinded Medtronic iPro sampling every 5 minutes for a 3-day period
Pistrosch 2015 [99]	Cross-sectional study of tertiary centre, Germany	N=94 Frail patients with type 2 diabetes with a proven cardiovascular event Mean age 68 years	Medtronic iPro2 sampling every 5 minutes for a 5-day period
Polonsky 2016 [100]	Dexcom, Inc central database – email invites for participation in online survey in US	N=210 ≥ 65 years of age with Medicare as primary insurance or no health insurance coverage. Mean age 70 years M: 52.9% Duration of diabetes 35.7 years T1DM: 93.8% T2DM: 6.2%	Presumably Dexcom users
Ruedy 2017 [101]	Post-hoc analysis of multicentre RCT in US and Canada	N=63 on CGM, N =53 controls >60 years, receiving multiple daily insulin > 1 year, stable diabetes, compliant with self-monitoring. Excluded if recent use of CGM. Mean age 67 years Duration of diabetes 21 years T1DM: 20 (32%) T2DM: 43 (68%)	Dexcom G4 Platinum, unblinded There were two periods of blinded CGM use at baseline and week 24 follow-up to capture any change in hypoglycaemic episodes and their duration post-intervention

		Complex intervention involving CGM guided treatment strategy vs. SMBG strategy implemented by clinicians for 24 weeks	
Van Dijk 2017 [49]	Pilot study Primary care, Netherlands	N=23 Age ≥ 70 years, T2DM, HbA1c < 58 mmol/mol (7.5%), and a Groningen Frailty Indicator (GFI) score ≥ 4. Mean age 76 years Male 47% Median duration of diabetes 9 years	Blinded Medtronic IPro2

Table 3. Outcomes

Study ID	Summary statistics of blood sugar values captured (mean, median, range, standard deviation) Recording time	Definition and number of hypoglycaemic episodes captured	What types of adverse events of interest were specified or defined?	How and when were adverse events ascertained?	How complete was follow-up and reporting of adverse events? (duration, numbers for loss to follow-up, or selected sample only)	Was patient adherence and device acceptability ascertained?
Argento 2014 [95]	CGM duration 36.8 (range 4-68) months Pre- vs. post-CGM outcomes: Percent with hypo pre: 79% vs..31% (P = .0002). No. of hypos: pre- 52 episodes in 5 years prior vs. 12 episodes after initiating personal real-time continuous glucose monitoring (PCGM). (5 SH episodes occurred while patients not using PCGM). Yearly rate of SH 0.37 ± 0.38 vs. 0.12 ± 0.19 (P = .0007)	Severe if patient required third-party assistance and counted as present if there was at least 1 recorded episode. Individual reports of SH were counted as single episodes, and if plural or many episodes, then classified as several	Not stated	Not stated	38 prescribed PCGM; 29 were still regularly using PCGM, 2 were using professional CGM intermittently, and 7 never started PCGM (3 patients) or discontinued Intermittent users excluded	Not stated.
DuBose 2016 [96]	Median 286 hours out of potential maximum of 336 hours CGM in two weeks.	CGM recorded hypos; Minutes per 24 hrs (% time) <3.9 mmol: 91 (6.3%) <3.3 mmol: 55 (3.8%) <2.8 mmol: 31 (2.2%)	Not stated	Not stated	Missing data varied from 3 – 15 participants according to category of> 6 hours missing data per time	Not stated

		% days with at least one hypo event 38%			period (24 h, day only, night only) 199/201 patients followed-up	
Ishikawa 2017 [97]	Glucose recordings: < 3.9 mmol: 72/170 % of time in hypo: 2.3%	< 3.9 mmol, no mention of clinical event	Not stated	Not stated	Not stated	Not stated
Litchman 2017 [98]	10/11 users said they had it on all the time.	Hypoglycaemia glucose < 3.9 mmol;, severe hypoglycaemia hypoglycaemia episode requiring assistance form another person, hypoglycaemia unawareness is defined as occurring when an individual with diabetes is experiencing hypoglycaemia, but feels no symptoms.	Hospitalization	Online survey	Selected sample – self-identified as high technology users	Yes. why participants were using/wanted to use real-time continuous glucose monitoring (RT-CGM), and how RT-CGM was affecting/might affect diabetes management and safety
Munshi 2011 [48]	65% of patients with A1C >8% were found to have ≥1 hypoglycaemic episode over a 3-day period. 4 times a day finger-stick glucose checks did not coincide with CGM-detected hypoglycaemia	Symptoms – self-report. Analysis of CGM according to time, duration and magnitude of low glucose 65% (26/40 patients) ≥1 hypoglycaemia (median glucose 63 (42–69) mg/dl). 12 (46%) had glucose levels <50	Not stated	Not stated	Not stated	Not stated

		mg/dl, and 19 (73%) <60 mg/dl. Average number of episodes 4 with average duration of 46 minutes. Of a total of 102 hypoglycaemic episodes, 95 (93%) were unrecognized, either by finger-stick monitoring or by symptoms. 18/ 26 (69%) had ≥1 nocturnal episode (average duration 56 minutes).				
Pistrosch 2015 [99]	Patients perceived 39 % of HE during the day and 11 % of HE during the night. Patients with HE had significantly higher number of severe ventricular arrhythmias [ventricular tachycardia (VT) 32.8 ± 60 vs. 0.9 ± 4.2, p = 0.019], and multivariate regression analysis revealed the duration of severe HE and TSH level as independent predictors of the occurrence of a VT	<3.1mmol 26/94 patients had hypo. Fifty-four episodes of hypoglycaemia (average of 2.4 episodes per patient), with 171 minutes mean duration over 5 days. Eighteen events during daytime and 36 nocturnal <3.9 mmol 4.2 episodes per patient with 415 minutes mean duration over 5 days. Patients asked to record all symptoms of hypoglycaemia with date and time in diary	Cardiovascular events (VT)	24-hour electrocardiogram (ECG) monitoring	Not stated	Not stated

Polonsky 2016 [100]	154 (73.3%) in 6 months prior to CGM as compared to recent 6 months with CGM 121 (57.6%). Drops in the incidence of events requiring the assistance of another, hypoglycaemia-related hospitalizations, ED visits, paramedic visits to the home, and car accidents.	Hypoglycaemia frequency of low blood glucoses (<70 mg/dl) in the past month, with and without symptoms; over the past 6 months, the frequency of moderate hypoglycaemic episodes (symptoms of confusion, disorientation, lethargy or being unable to treat oneself) and the number of a variety of events associated with severe hypoglycaemia, including episodes requiring assistance. Comparison of frequency/number of events during the "retrospective baseline period," defined as the 6-month period before they first started RT-CGM vs. current period.	Healthcare use including paramedic visit, emergency department care, road accidents.	Online survey	Online survey conducted on behalf of Dexcom (CGM manufacturer)	Not stated
Ruedy 2017 [101]	Mean CGM use was 6.9 ± 0.2 days/week in month one; and 6.8 ± 1.1 in month 6. HbA1c reduction from baseline to 24 weeks was greater in the CGM group than Control group (−0.9 ± 0.7%	SH event that required assistance from another person to administer carbohydrates or other resuscitative action	Not stated	Not stated	Post-hoc analysis of multicentre RCT	Satisfaction with use of CGM mean score of 4.2 ± 0.4 on the CGM Satisfaction Survey (possible score range 1 to 5), with mean

	versus −0.5 ± 0.7%, adjusted difference in mean change −0.4 ± 0.1%, P < .001).	No hypos recorded during study.				scores of 4.3 ± 0.5 on the Benefits subscale and 1.8 ± 0.5 on the Hassles subscale
Van Dijk 2017 [49]	Monitoring period – 97 hours median (out of maximum of 120 hours)	Hypo < 3.0mmol: 5 patients had 15 events (245 minutes total) Hypo <3.5 mmol: 8 patients had 25 events (292 minutes total). None of the patients reported symptoms.	Not stated	Not stated	Not stated	Not stated

2.4.4 Quality assessment

Two reviewers (KM and YKL) assessed key parameters, including selection of patients, loss to follow-up, missing data, selective reporting and analysis.

2.4.5 Data synthesis/Analysis

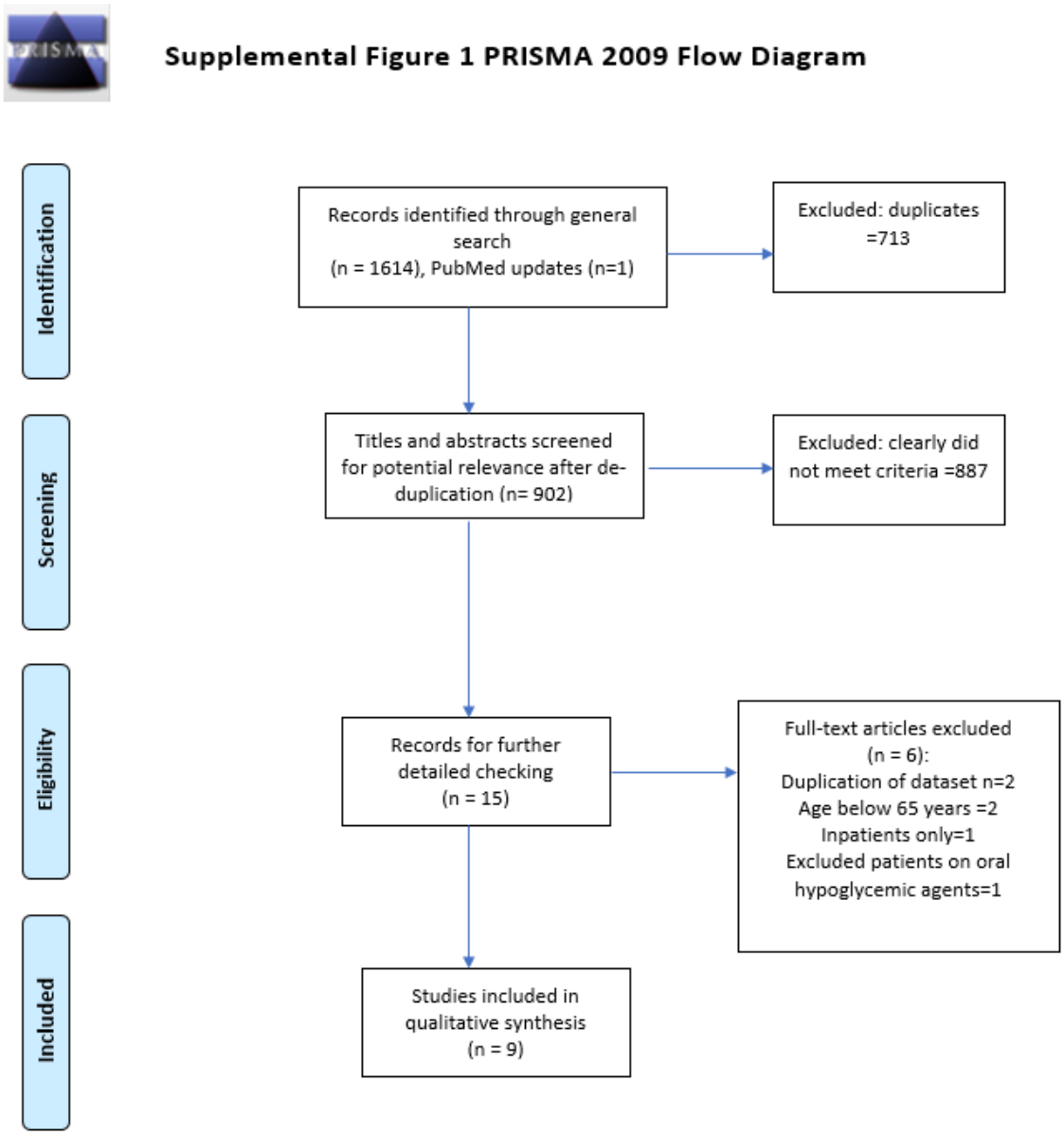
I aimed to perform meta-analysis if there was sufficient quantitative data and similarity in the reported outcome measures. Assessment of statistical heterogeneity would be through the I^2 statistic. I aimed to assess publication bias by examining funnel plots, if there were more than 10 included studies for a particular outcome, and there was no evidence of significant heterogeneity. Where studies were too heterogeneous to be pooled, a narrative analysis of the data would be undertaken.

2.5 Results

After de-duplication, we screened 902 citations and one citation from automated notification (Figure 23). I included nine studies [95 48 49 96-101].

The included studies had a total of 989 participants (sample size 22 to 285). Geographical locations were diverse and but were predominantly in economically developed countries such as North America, Japan, Canada, Germany and the Netherlands.

Figure 22. PRISMA Flow Diagram



2.5.1 Patient selection

Two studies used online surveys of already existing CGM users[98 100]. Users who were not able to tolerate CGM were not included in the surveys.

None of the studies included participants with cognitive impairment or dementia.

2.5.2 Age and Frailty

The mean age of all participants was 70 years, with six studies' participants' ages being between 67-69 years [101 99 48 98 95 96].

Two studies discuss frailty of their participants [49 99]. Van Dijk et al included patients with a GFI score of 5 (a score of 4 or above indicates moderate to severe frailty) [49 102]. The GFI takes into account physical problems (co-morbidities, mobility, hearing, eye sight), cognition, depression, anxiety and social factors. Answers are given either a score of 0 or 1, with 1 indicating a problem. The maximum score is 15 [102].

Pistrosch et al did not specify how they assessed frailty, but their participants had to have had a proven cardiovascular event[99].

2.5.3 Type of diabetes

Two studies only included participants who had T1DM [96 98], three studies included patients with T2DM[97 99 49] and the rest had a mix of T1DM and T2DM[48 95 100 101].

2.5.4 CGM devices

A range of CGM devices were used in the included studies (manufacturers were Dexcom and Medtronic). One study did not state which CGM device was used

[95]. Whilst Polonsky et al also did not expressly state what device(s) participants were using, it is likely that they were Dexcom devices, as participants were emailed using the Dexcom central database[100]. Four studies used blinded CGM, three of which used Medtronic iPro2 and one Dexcom SEVEN PLUS[49 99 48 96]. One study used both Medtronic iPro2 and Medtronic CGMS System Gold (also blinded) [97].

The participants who took part in Litchman et al's online survey used Dexcom G4, Dexcom G5, Medtronic Revel or Medtronic Elite [98], all unblinded. Ruedy et al's RCT used unblinded CGM (Dexcom G4 Platinum) [101].

2.6 Risk of Bias of Included Studies and Selective Outcome Reporting

There was a mix of types of studies, including a RCT, retrospective health record reviews, cross-sectional studies, pilot study and mixed-method study.

Most of the studies did not provide sufficient information on blinding of assessors and participants, drop-out rates, missing data and how missing data were addressed.

2.6.1 Definition of hypoglycaemia

There was considerable variation in the definition of hypoglycaemia amongst the included studies. Four studies looked at the occurrence of severe hypoglycaemia, defined as a patient requiring third party assistance [95 98 100 101]. Two studies used online surveys and relied on self-reporting of glucose levels and symptoms [100 98].

2.6.2 Pre-specification of adverse events

Six studies did not pre-specify any adverse events [95 96 97 48 101 49]. Polonsky et al captured healthcare use (paramedic visits, emergency department attendance) and road traffic accidents [100]. Pitrosch et al looked at the occurrence of ventricular arrhythmias [99] and Litchman et al's survey asked about hospitalization [98].

2.6.3 Completeness of follow-up

Four studies did not address completeness of follow-up or missing data at all [97 48 99 49]. One study was a post-hoc analysis of a randomized controlled trial [101], two studies were surveys which targeted already exciting CGM users or patients with diabetes who were keen to try out new technology [100 98]. DuBose et al provided incomplete information on missing data and follow-up [96]. Argento et al excluded intermittent users of CGM. Out of 38 participants who were prescribed CGM, nine stopped using it regularly during the study period [95].

2.6.4 Adherence

Seven studies did not state how patient adherence and acceptability were ascertained [95 96 97 48 99 100 49]. Ruedy et al evaluated acceptability with satisfaction surveys, and Litchman et al asked participants why they were using CGM and how CGM is affecting their diabetes management [101 98].

2.7 Evidence Synthesis

The nine included studies did not have sufficient quantitative data and similarity in the reported outcome measures for me to pool the data in a meta-analysis.

I therefore carried out a narrative synthesis under the following headings: capture of hypoglycaemia, CGM satisfaction, association of adverse events with hypoglycaemia, pre-and post CGM outcomes.

2.7.1 Capture of hypoglycaemia

Four studies report on the number of participants who had hypoglycaemic episodes recorded on CGM [48 49 97 99]. Figure 24 depicts the number of patients with and without hypoglycaemia.

The proportion of participants affected by at least one or more hypoglycaemic event varied between 28%-79%. This variation may have stemmed from differences in patient characteristics, nature of drug therapy and duration of monitoring (ranged from 3 to 5 days), nevertheless, the important unifying features of all of these studies is that CGM has demonstrated that a substantial proportion of older people are affected by hypoglycaemic events.

I extracted data from three studies regarding the symptomatic or asymptomatic nature of the hypoglycaemic episodes [48 49 99]. Figure 25 illustrates number of hypoglycaemic events with and without symptoms.

It is striking that between 80-100% of hypoglycaemic events were asymptomatic and arguably most if not all of these would have gone unnoticed had it not been for the use of CGM at that particular point in time.

Finally, I estimated the length of time participants spent in the hypoglycaemic range in minutes per day (Figure 26) [96 101 49 48 99].

Figure 23. Number of patients with and without hypoglycaemia

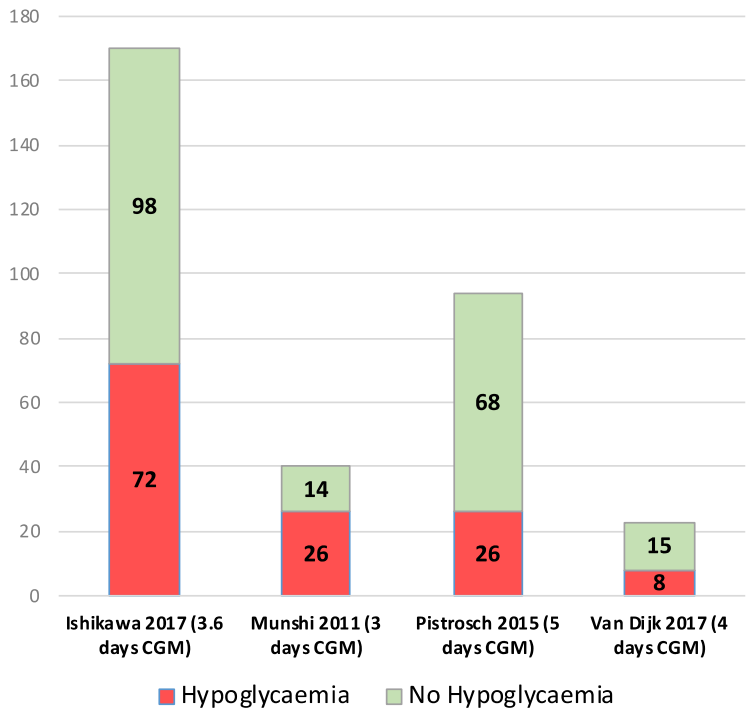


Figure 24. Number of hypoglycaemic episodes with and without symptoms

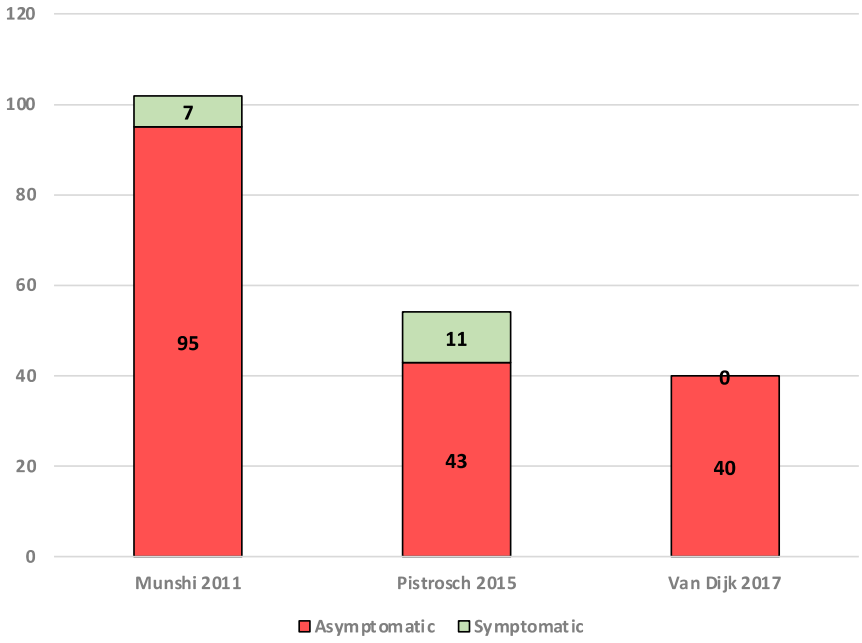
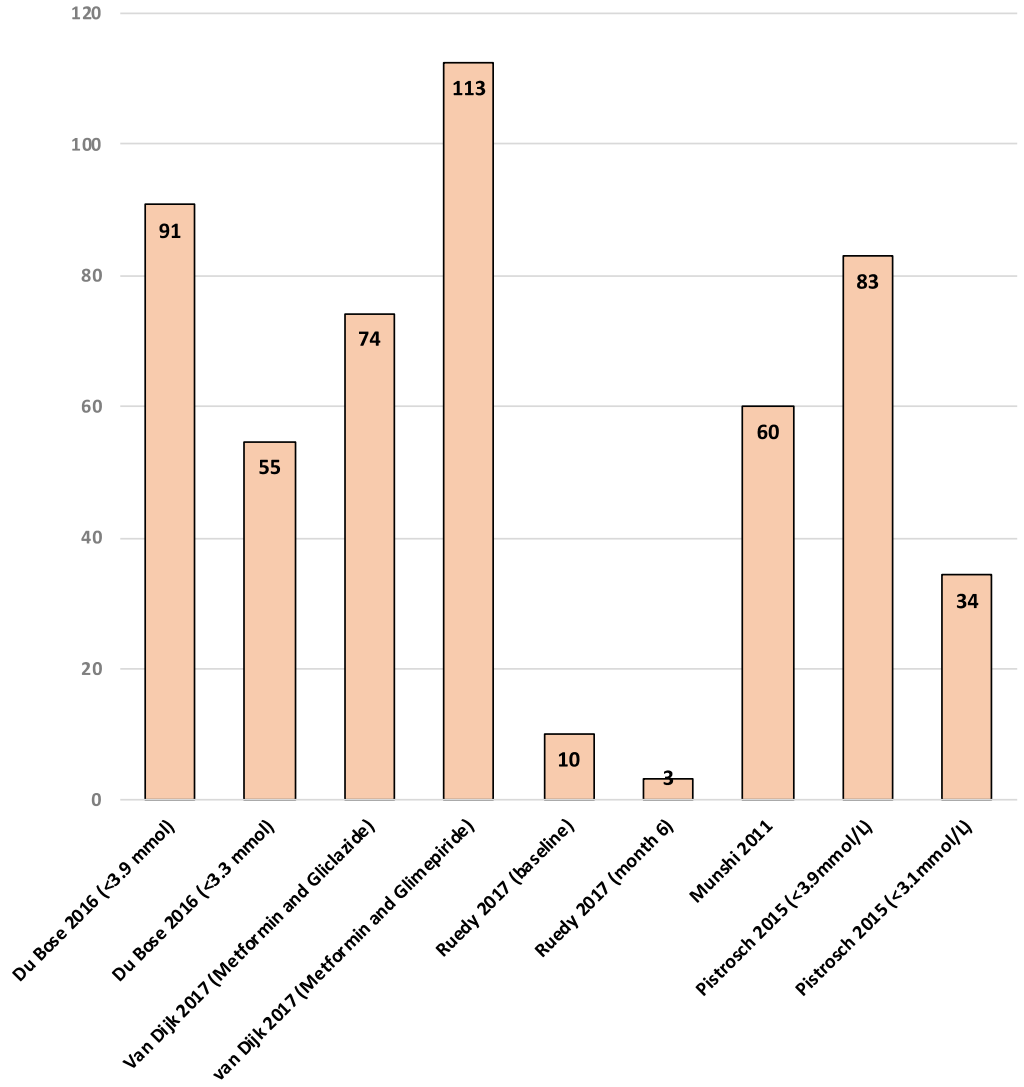


Figure 25 Minutes per day in the hypoglycaemic range



Participants in the observational studies spent between 34-112 minutes per day in the hypoglycaemic range, whereas those in the randomized trial spent only between 3-10 minutes in the hypoglycaemic range.

The RCT by Ruedy et al is notable outlier - it is a post-hoc analysis of older participants in the multi-centre DIAMOND RCT comparing CGM versus

SMBG [103]. The objective was to determine effectiveness of CGM in older adults with T1DM or T2DM, who were on multiple daily insulin injections. Participants in the DIAMOND trial had to have a stable diabetes regime for three months prior to study entry, and were performing self-monitoring three or more times daily, with no history of recurrent hypoglycaemia [103]. Co-morbidities such as recent cardiovascular disease, significant heart failure, conditions resulting in physical or cognitive decline, and renal impairment were listed as exclusion criteria. The participants selected for the DIAMOND trial were not frail older people with multiple co-morbidities and possible cognitive impairment. For the post-hoc analysis, patients had to be 60 years or older with T1DM or T2DM treated with multiple daily injections of insulin for at least one year. Exclusion criteria were use of CGM within three months of screening and any co-morbidities that would be deemed to make it unsafe to target an HbA1c of less than 7.0% - this was determined by the researchers. Prior to randomization to CGM or control (SMBG), each participant used blinded CGM for two weeks. After randomization, follow-up visits for both groups took place at 4, 12 and 24 weeks. The CGM group had an additional visit one week after randomization to troubleshoot potential use issues. The SMBG group had two additional visits at weeks 11 and 23 to initiate blinded CGM for one week.

Arguably, the participants were likely to have good hypoglycaemic awareness and ability to correct low blood sugars more quickly than those the frail older participants in, for example, van Dijk's study where all of the

hypoglycaemic episodes were asymptomatic[49]. In contrast to Ruedy et al, van Dijk et al's study included frail patients with T2DM aged 70 or older who were treated with metformin and a sulfonylurea. Pistrosch et al also included frail older patients with T2DM who already had a proven cardiovascular events, which included previous myocardial infarction (MI), ischaemic stroke, cardiac bypass surgery, peripheral artery disease with limb amputation or other endovascular procedures at the lower limb arteries[99].

The above three studies show how contrasting the included populations are – fit older patients with well-controlled diabetes versus frail older patients with multiple co-morbidities. It is therefore not surprising that the findings of the studies are quite different.

2.7.3 CGM SATISFACTION

Two studies report on CGM satisfaction[98 101].

Litchman et al's mixed-methods study, used convenience sample of older adults with T1DM aged 65 and older, using snowball sampling technique from the Diabetes Online Community within Facebook. A total of 22 participants were recruited – 11 who were using CGM and 11 'controls' who wished to start CGM use. Participants were asked to complete one of two online surveys about CGM. The first survey was aimed at current CGM users, whilst the second survey (one month after the first) was completed by the control group. The questions focussed on reasons for using CGM or wanting to use CGM and how it affected diabetes management. The

surveys also asked participants about hypoglycaemia occurrence and unawareness.

Emerging themes were that CGM use facilitates feelings of safety by preventing hypoglycaemia and improvement in well-being. CGM users felt that they were able to function better in their daily activities and that the device could assist in prolonging life by preventing injury and complication [98].

In Ruedy et a's study, CGM users (n=60) were asked to complete a CGM Satisfaction Survey at the 24-week follow-up visit. The questionnaire consisted of 44 items on how satisfied the participant was with using CGM. As discussed above, this was a post-hoc analysis of the DIAMOND study and included participants with no major co-morbidities and well-controlled diabetes. Overall satisfaction was high with mean score of 4.2 (range of scores 1-5), with mean scores of 4.3 on the Benefits subscale and 1.8 on the Hassles subscale, indicating that the perceived benefits outweighed the perceived hassles [101].

2.7.4 Adverse events

Three studies reported on adverse events, such as ED visits [100], falls, inability to operate a vehicle in the last year[98] and ventricular arrhythmias[99]. It is important to note that at this juncture, I cannot draw any conclusions regarding causality between the hypoglycaemic episodes and adverse events.

Litchman et al asked participants to complete an online survey which included a question on whether hospitalization had occurred in relation to

a participant's diabetes since they had started using CGM, which was compared to hospitalization on non-CGM users. The results of that particular question are not reported. However, CGM users (n=11) reported absence of severe hypoglycaemic episodes resulting in a fall or inability to operate a vehicle in the last year, compared to 6 non-CGM users (55%) [98].

Pistrosch et al looked at the occurrence of ventricular arrhythmias in patients with T2DM, who had hypoglycaemic events. The authors observed that 13 out of 26 patients in the hypoglycaemic group experienced ventricular arrhythmias, compared to 11 out of 68 participants in the non-hypoglycaemic group [99].

2.7.5 Adverse events pre- and post-CGM

Polonsky et al reported reduction of 5.3% of hospitalization in CGM users comparing hospitalization six months before starting CGM and over the past six months. This reduction of hospitalization was a within-group comparison [100]. There was no reduction in hospitalization in the non-CGM users in the same period. In addition, there was a 4.3% reduction in car accidents and 12.8% reduction in ED visits for CGM users within that time. This compares to a 4% increase in ED visits, 2.6% reduction in car accidents and 0% difference in hospitalization for non-CGM users within that same time period. The authors report unadjusted and adjusted ORs (and some p-values), but no confidence intervals, so it is not possible to properly comment on the statistical significance of the results.

Argento et al's study was a retrospective electronic health record review where the investigators looked at medically recorded hypoglycaemia (requiring assistance from a third party). Here, CGM users were shown to have a reduction in the rate of severe hypoglycaemia from 0.37 to 0.12 per year. Overall, the proportion of patients with any severe hypoglycaemia fell from 79% to 31% after initiation of CGM [95]. However, I am conscious of the major limitations of these studies which are non-randomized, unblinded, and without any specific treatment protocols involving glucose-lowering drugs.

2.8 Discussion

In this systematic review of CGM, I evaluated 9 studies with a total of 989 participants who had type 1 or type 2 diabetes. There were a diverse range of study designs, ranging from pilot studies, mixed method studies, database observational studies and one RCT. Despite the variation in study populations and geographical locations, I found consistent evidence that CGM was able to detect hypoglycaemic episodes in a sizeable proportion of older patients, many of which were asymptomatic. In particular, van Dijk et al's reported that 100% of the CGM recorded hypoglycaemic episodes were asymptomatic, with some patients having nearly two hours per day in hypoglycaemic range [49]. Munshi et al also highlighted that 95% of the captured hypoglycaemic episodes went unrecognized [48]. Clinicians and patients would probably have been completely unaware of these prolonged asymptomatic episodes in the pre-CGM era, and this may

represent a major unrecognized health burden in older people with diabetes.

Since the publication of my systematic review, further data confirms my findings. First, a Japanese study investigated the use of CGM in older people in an outpatient setting in Japan. Out of 326 participants, 7 used CGM. Asymptomatic hypoglycaemic episodes occurred in five out of the seven CGM users [104]. It was not possible to fully dissect the paper, other than the abstract, which is available in English. Secondly, a conference abstract was presented at Endo 2019 in New Orleans 23-26 March 2019 on the exposure to hypoglycaemia in older adults with type 1 diabetes. The authors analysed blinded CGM data in over 200 older adults (median age 68 years) with T1DM collected at baseline in an RCT assessing the effect of CGM on hypoglycaemia. The findings were that these older adults spent over one hour per day in the hypoglycaemic range and over 100 minutes per day in those with impaired hypoglycaemic awareness[105].

This supports my hypothesis that older patients (who may have cognitive problems and poor hypoglycaemic awareness) are spending longer in the hypoglycaemic range compared to patients with good hypoglycaemic awareness, who are able to correct their blood sugar levels in a short amount of time. Following on from this, an important area for further research is whether an increased risk of serious harm is associated with duration of time in hypoglycaemic range rather than discrete episodes of hypoglycaemic events.

In addition to picking up hypoglycaemic events, the included studies have highlighted that older people with diabetes find the use of CGM acceptable[101]and that it improved well-being[98]. Litchman et al also reported barriers regarding lack of accessibility, affordability and lack of insurance cover which can prevent older people from being able to make use of CGM technology[98]. Although many of the studies do not directly draw a link between hypoglycaemia and subsequent serious events that affect quality of life, we have found three studies that venture the possibility of an association with emergency department visits and ventricular arrhythmias[98 99 100].

I recognize important limitations of our systematic review. The data provided by the included studies was too heterogenous to provide an appropriate meta-analysis. I have therefore not been able to provide a quantitative analysis of the data. The included studies range to mixed-method online surveys to RCTs, which makes it difficult to provide a robust analysis of the quality of the data and we only included English-language articles. Some of the studies had a very select group of participants (Caucasian, highly educated and users of technological devices) and small sample sizes (<50). This limits the generalizability to the general older population with diabetes.

Rather than using CGM all-year round, it would be more cost-effective to use CGM to 'troubleshoot' (for example, two weeks every six months) and identify patterns in glucose variability (especially asymptomatic hypoglycaemia) in older patients. Intermittent finger-prick testing is not

useful in this group, because the vast majority of hypoglycaemic episodes seem to be asymptomatic, and the older patient or carer may not be alerted to the need to do the finger-prick test at that point in time. In addition, the duration of time spent in the hypoglycaemic range could not be reliably assessed through intermittent finger-prick testing. A recently published consensus statement on clinical target for CGM data interpretation recommends that older people with diabetes should spend less than 1% (less than 15 minutes) of time per day in the hypoglycaemic range[25].

Further studies should explore possible associations between CGM recorded hypoglycaemic episodes, duration of time in hypoglycaemic range and cognitive and cardiovascular outcomes. This could involve large cohorts of older people with diabetes (especially T2DM), with the aim of correlating asymptomatic hypoglycaemic episodes with subsequent serious adverse outcomes (for example patients could be asked to wear a 14-day ECG recorder, in order to capture possible arrhythmias occurring at the time of hypoglycaemic episodes).

In addition, trials of new glucose lowering therapies in older patients with diabetes should include the routine use of CGM, so that harmful effects are not missed. At present, the inconsistent definition and capture of hypoglycaemic episodes can lead to a misleadingly rosy picture of glucose lowering therapy in older people because the true extent of harm is difficult to analyse whilst the potential beneficial effects may be over-

emphasized[106]. CGM will make it possible to evaluate the cumulative effects of multiple minor hypoglycaemic episodes over the long-term. The monitoring strategy in older patients should focus on preventing imminent or acute harm, rather than long-term complications related to HbA1C which may only manifest in 10-20 years' time – this could be beyond the lifespan of some patients.

2.9 Conclusions

CGM is an innovative technology that can detect otherwise unrecognized hypoglycaemic events in older patients. CGM can provide more robust evidence to inform the careful balance of avoiding harm from hypoglycaemia and long-term diabetes control in such patients. It is anticipated that over the next few years there will be rapid technological changes leading to improved interoperability, apps, software and affordability. All of these factors should make CGM more accessible and potentially be a useful tool for older patients with diabetes and memory problems and their carers.

CHAPTER 3. CONTINUOUS GLUCOSE MONITORING IN OLDER PEOPLE WITH DIABETES AND MEMORY PROBLEMS – A FEASIBILITY STUDY

3.1 PREAMBLE

The second chapter outlined the findings of my systematic review on CGM in older people with diabetes. I found evidence that CGM was able to detect hypoglycaemic episodes, many of which were asymptomatic. The studies that were included in the systematic review also highlighted that older people found the use of CGM acceptable, in addition to experiencing improved well-being. However, my systematic review did not identify any studies of CGM specifically directed at older people with diabetes and co-existing memory problems, whilst at the same time exploring the experiences of these participants and their carers. Chapter 3 presents a feasibility study on the feasibility and acceptability of a CGM device in older people with diabetes and memory problems.

3.2 Chapter summary

3.2.1 Background

Older people with diabetes are at increased risk of harm from hypoglycaemia, particularly where there are co-existing memory problems. CGM offers important benefits in terms of detecting hypoglycaemia, but the feasibility of use and extent of data capture has not been tested in this patient group. The objective was to investigate the feasibility of trialling a CGM intervention in older people with diabetes and memory problems.

3.2.2 Methods

I evaluated the Freestyle Libre CGM device for two weeks in patients aged ≥65 with diabetes and abbreviated mini-mental test (AMT) score ≤8 or known dementia. Participants could obtain on-the-spot glucose readings (as well as readings from preceding 8 hours) by swiping a reader over the sensor. Feasibility criteria were numbers of eligible patients, recruitment, attrition, extent of capture of glucose readings and adverse events. I conducted qualitative interviews with participants (and their carers) regarding CGM.

3.2.3 Results

I identified 49 eligible participants. 17 subsequently consented, but 5 withdrew before recording of data because they, or their carers felt unable to manage study procedures. 12 participants (mean age 85 years) completed the study without any adverse events. Data capture across 14 days ranged between 3-92% (mean 55%); 6 participants had <60% capture. Hypoglycaemic events (some prolonged) were recorded in 6 out of 9 insulin users.

Qualitative interviews found the following themes: the device does not interfere with daily activities, usability and comfort was positive, and it was helpful for carers in monitoring participants' glucose concentrations.

3.2.4 Conclusions

The device was acceptable to participants, and carers reported greater ease in monitoring the participants' glucose concentrations. However, completeness of data capture varied considerably with this device due to the need for users to conduct ≥3 scans per day. Real-Time devices with automated data transfer may be more suitable in older people with memory problems.

3.3 Background

Following on from the results of my systematic review in chapter 2, it became apparent that is necessary to investigate in more detail whether older people with diabetes and co-existing memory problems could tolerate wearing a CGM device, especially as conventional methods, such finger-prick testing may not be appropriate in this population. These patients may not be able to recognise and/or act on symptoms stemming from major changes in blood sugars. In any event, finger-prick testing only provides a snap-shot of the glucose level at a particular point in time and is not able to provide a complete picture of the variability throughout the day and night.

A cohort study using registry data from German and Austrian diabetes centres, found that older people with diabetes and co-existing dementia had higher rates of severe hypoglycaemia (requiring third party assistance) and hypoglycaemia with coma compared to patients without dementia[58]. Hence, the adverse effects of hypoglycaemia may be of far more pressing concern to frail older people, rather than strict glycaemic targets for reduction of vascular complications.

Indications are the CGM can be a useful tool in uncovering the true magnitude of hypoglycaemia in older people. However, my systematic review of the literature did not identify any studies that have investigated the feasibility of the use of CGM in older people with diabetes and co-existing memory problems, in addition to exploring the experiences of both the participants and carers (where applicable).

3.4 Objective

To investigate the feasibility of using CGM in older people with diabetes and memory problems. Specifically, I investigated recruitment, retention, whether I could capture glucose data and what the participants' (and carers') experience was of the use of the device, and, finally, whether they experienced any adverse events.

The study was approved by an ethics committee (REC reference 17/EE/0388). Please refer to Appendix 2 for full details of the approved research protocol.

3.5 Methods

3.5.1 Design

I utilised mixed methods to conduct a feasibility study of CGM in older people with diabetes and co-existing diabetes living in the community.

3.5.2 Setting

Participants were identified and recruited whilst an inpatient under the Older People's Medicine and/or Acute Medicine Departments at the Norfolk and Norwich University Hospital Trust. Recruitment took place between 1 February 2018 to 31 January 2019. Data collection took place in the Community and the device was only used post-discharge from the acute setting.

3.5.3 Choice of device

At commencement of this feasibility study, there was only one CGM device (Abbott FreeStyle Libre), which does not require the user to conduct finger-

prick testing for calibration, and so this was the intervention of choice for my study. This device is licensed for use in children and adults and available direct to consumer via the internet or from pharmacies. The use of this device provides ambulatory glucose profiles, giving graphic and quantitative information on 24-hour glucose patterns. This information can be viewed on a computer using the manufacturer's software.

The system consists of a reader (although Android phones and certain ioS devices can download an app, which replaces the need for a reader) and a sensor (35mm x 5mm), which exchange data through Near Field Communication technology. The sensor is applied to the back of a person's arm. It is able to store blocks of glucose data spanning 8 hours and will function for 14 days. Whilst glucose levels are measured continuously, data are not transmitted continuously from the sensor. Instead, the user has to swipe the sensor with a reader (hence the term 'flash glucose monitoring' used by the manufacturer) at least eight-hourly in order to achieve complete capture of data throughout the two-week life-span of a sensor.

Figure 26 FreeStyle Libre sensor and reader

Figure 27 Illustration of attached sensor

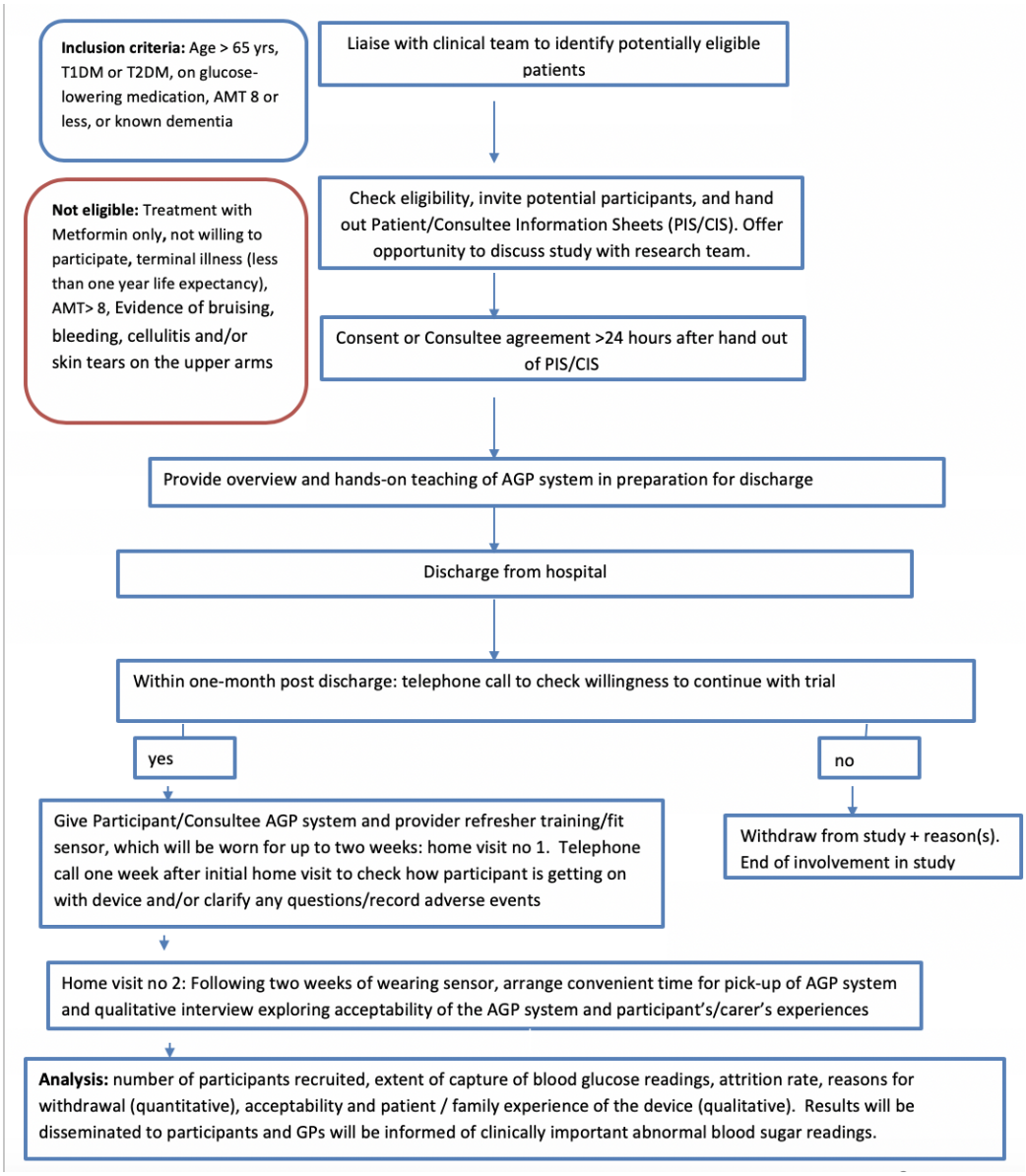
Figure 28 Illustration of obtaining a reading ('flashing' the reader over the sensor)

3.5.4 Recruitment of participants

Eligible participants were 65 or older with T1DM or T2DM. They needed to be on glucose-lowering medication (not diet or Metformin only), have an AMT

score equal or less than 8 (out of 10), or already have a formal diagnosis of dementia. I aimed to recruit up to 20 participants. As this was a feasibility study, there was no formal power calculation.

Figure 29 Identification of potential participants and study flow



Use of the AMT is mandated as a screening tool in the Norfolk and Norwich University hospital policy for all inpatients age 75 years and above. The value of AMT in hospital settings was confirmed in a systematic review and meta-analysis on screening for dementia in general hospital inpatients, where AMT

was reported to have good discriminant ability AUC 0.88[107]. I acknowledge however that the use of the AMT only covers three cognitive domains (memory, orientation, attention/calculation) and there are more rigorous cognitive tests available. The more rigorous test do not necessarily lend themselves to being carried out in an acute busy hospital setting [108]. However, my feasibility study was not about making new dementia diagnoses. Rather, I wanted to identify inpatients with memory problems during their hospital admission who might benefit from the use of CGM.

During the inpatient stay, information sheets were left at the bedside when it was not possible to speak to potential consultees (in cases where a patient did not have capacity) or a potential participant did not wish to discuss the study at the time of visit, but wanted to read the information sheet. Participants were asked to continue with their usual diabetes management (including any finger-prick monitoring) during the study period.

3.5.5 Measurements

3.5.5.1 Feasibility outcomes (quantitative)

I investigated eligibility, recruitment, retention, reasons for withdrawal, data capture and adverse events. For measure of "time in range" we set the reader to record it between 4mmol/L to 10mmol/L, which is similar to expert recommendations[25 109].

3.5.5.2 Patient outcomes (qualitative)

Semi-structured face-to-face interviews took place after the participants had worn the device for two weeks. A topic guide was used (Appendix 6) to ensure the same domains were covered in each interview. Participants and carers

were encouraged to talk about their experiences using the device. Domains covered in the interview were acceptability of the device, exploration of expectations, effectiveness, including experience of scanning the device and immediate or longer-term consequences for the user and their diabetes management, consequences, including impact on wider health and wellbeing, and overall opinion of the device. Detailed field notes were produced after each interview.

3.5.6 Data analysis

For categorical variables, the number and percentage will be presented. For continuous variables, the mean or median will be presented.

Thematic analysis was used, once the interviews had been transcribed[110].

Familiarisation took place by listening to the interview recordings and reading of the transcripts.

Framework analysis was applied to order[111], chart and search the data manually and with software (NVivo 12, MSWord). To ensure rigour and trustworthiness, coding was undertaken by two members of the research team (KM and KL) and transcripts were checked for accuracy.

3.6 Ethics

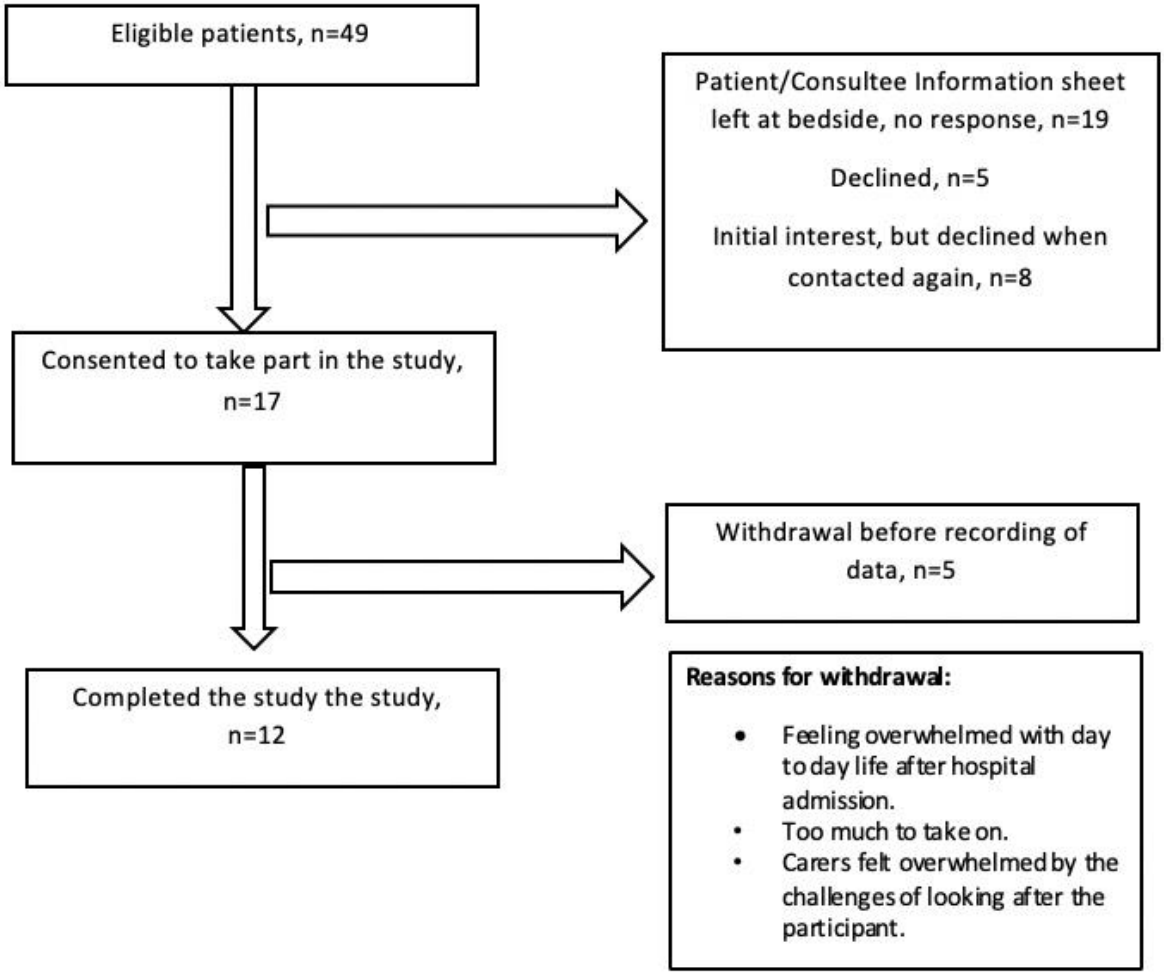
The study was approved by an ethics committee (REC reference 17/EE/0388).

The trial registration ID is ISRCTN29516623.

3.7 Results

The patient recruitment flowchart is set out in Figure 31.

Figure 30 Patient flowchart



3.7.1 Quantitative results

I identified 49 eligible participants. 17 people consented and twelve completed the study.

The main reason for deciding not to participate after discharge home, was that the participant or carer felt it was too much to take on. Participants living on their own were finding it challenging to cope with day to day life. Carers felt overwhelmed by the challenges of looking after the participant.

Table 4 sets out baseline characteristics and data captured with the FreeStyle Libre device for participants who completed the study period. 12 participants (mean age 85 years) completed the study without any adverse events (skin reactions and/or pain). All had T2DM apart from one participant with T1DM. Three participants had a formal diagnosis of dementia. The AMT for the nine participants who did not have a formal diagnosis of dementia ranged between five to eight out of ten.

Data capture across 14 days ranged between 3% to 92% (mean 55%); six participants had less than 60% capture. Nine participants were insulin users, of which six (66%) experienced hypoglycaemic events (some prolonged). The average duration of hypoglycaemic events ranged from 106 minutes to 437 minutes.

Figure 32 depicts the time in range for each participant, including the proportions spent below and above the target range (4-10 mmol/L). Figure 33 gives the FreeStyle Libre snapshot report for each participant who completed the study period.

Table 4. Baseline characteristics and data captured with FreeStyle Libre

	1	2	3	4	5	6	7	8	9	10	11	12
Gender M/F	M	M	M	M	M	M	F	F	M	M	M	M
Age	90	79	82	80	86	87	84	92	84	81	90	90
Type of diabetes	2	2	2	1	2	2	2	2	2	2	2	2
Insulin user, Y/N	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y
AMT, n/10	5	-	8	8	8	7	7	7	8	-	-	7
Dementia, Y/N	N	Y	N	N	N	N	N	N	N	Y	Y	N
Days sensor worn	14	14	14	14	14	14	14	14	14	14	14	14
Data capture, %	70	62	65	83	38	3	34	76	92	33	55	43
Scans over 14 days	57	45	34	166	27	4	24	75	183	22	40	182
Average glucose, mmol/L	16.8	8.8	8.4	11.9	10.8	9.6	12.2	7.3	6.6	16.0	6.6	10.4
Hypo events (<4mmol/L)	-	-	1	11	-	-	-	13	21	-	4	1
Average duration of low glucose events, min			109	113				106	182		437	348

Figure 31 Time in range (4-10mmol/L)

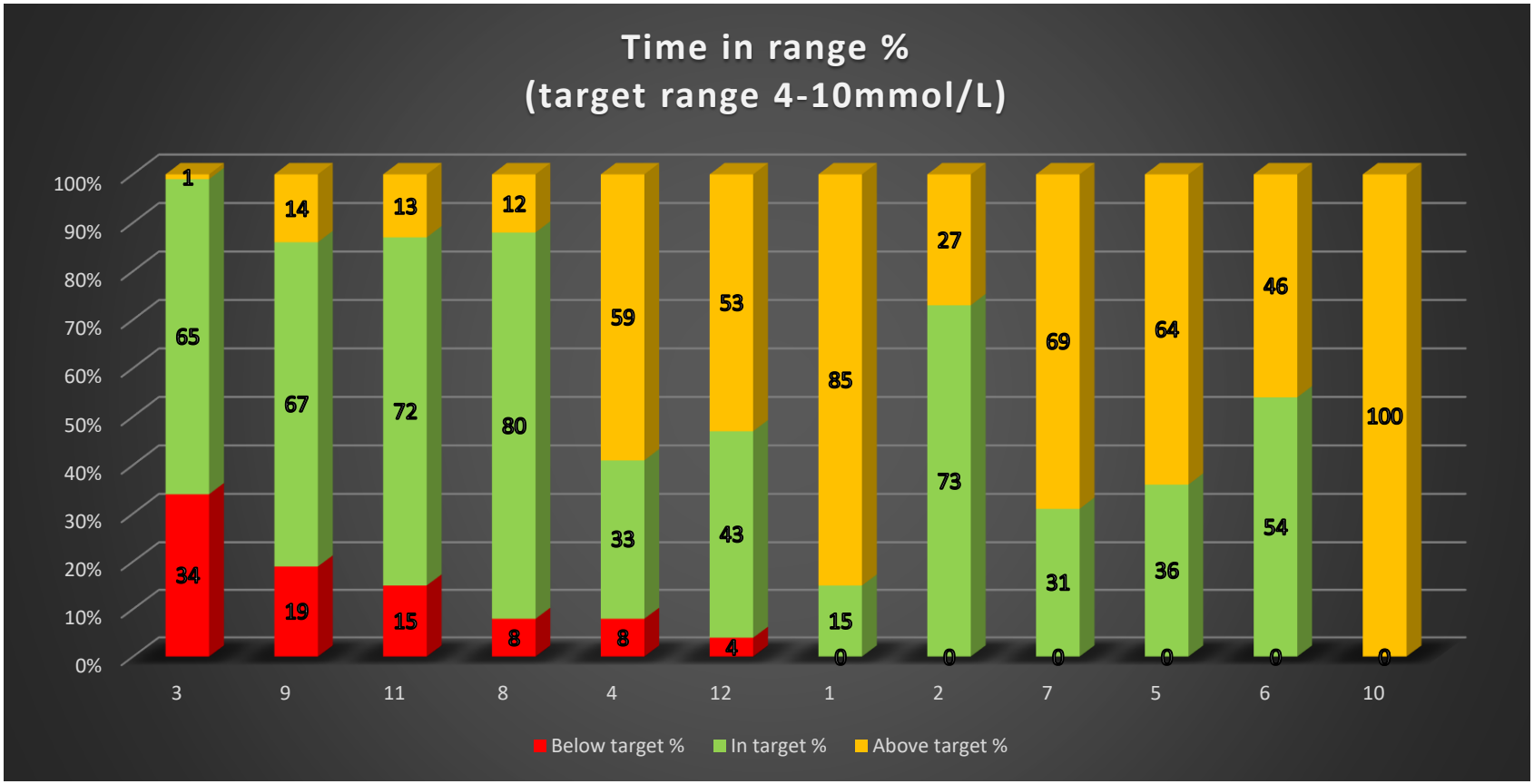
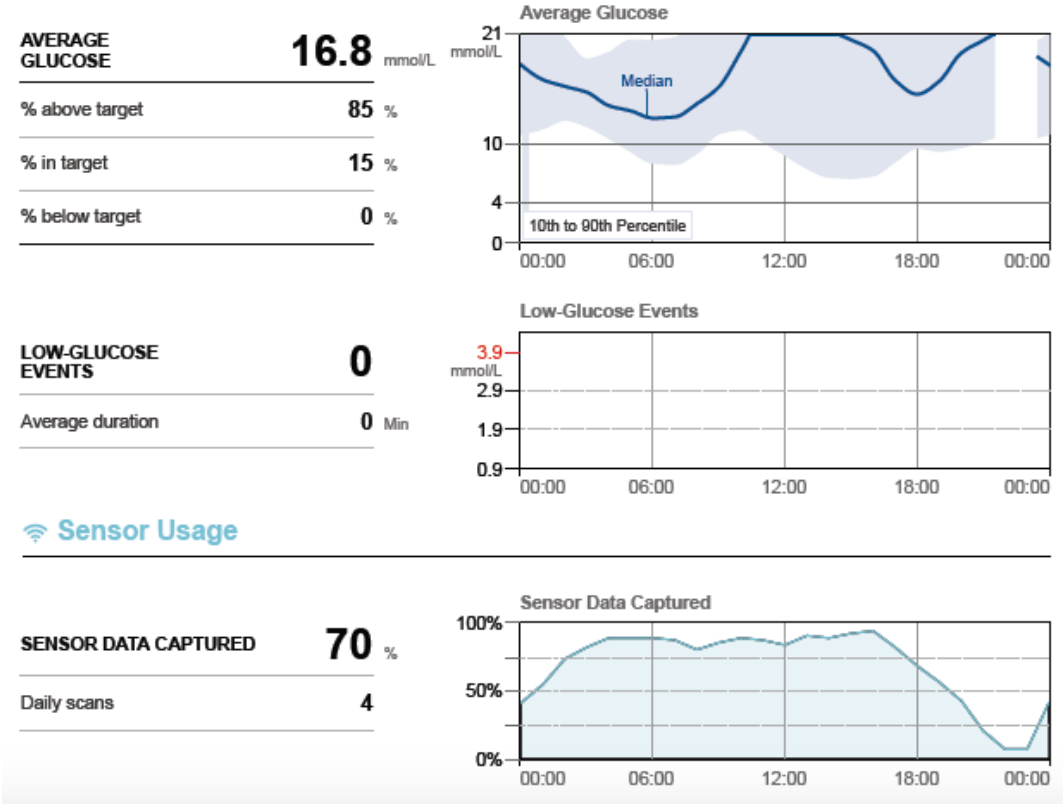


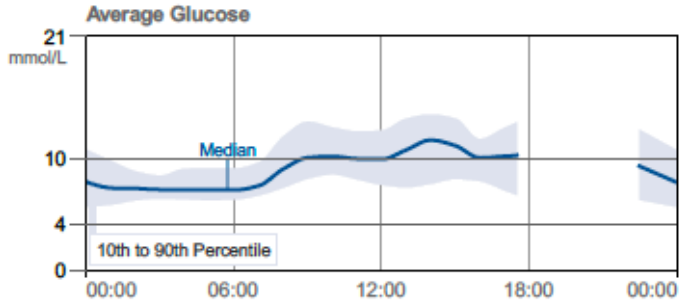
Figure 32 Participants' snapshot reports

Participant ID 001

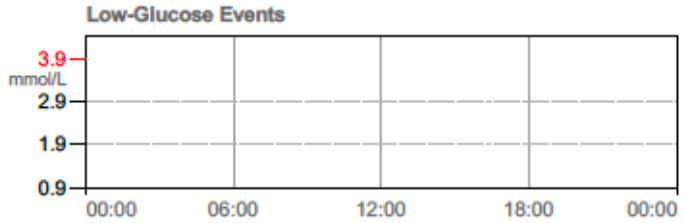


Participant ID 002

AVERAGE GLUCOSE	**8.8**	mmol/L
% above target	27	%
% in target	73	%
% below target	0	%

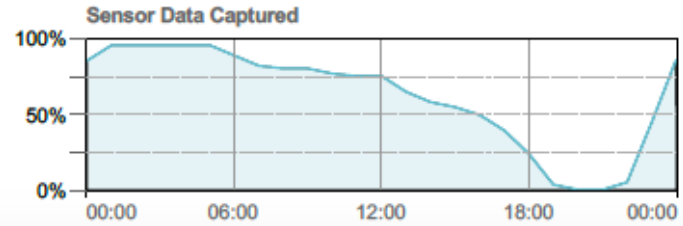


LOW-GLUCOSE EVENTS	**0**	
Average duration	0	Min



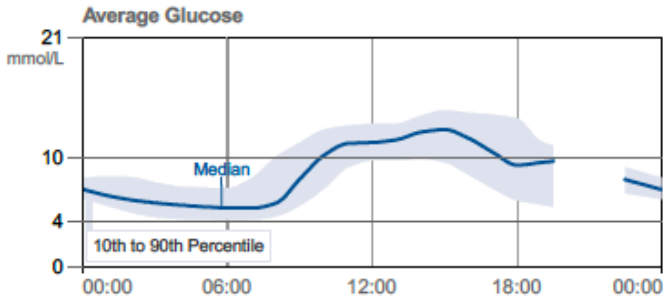
Sensor Usage

SENSOR DATA CAPTURED	**62**	%
Daily scans	3	

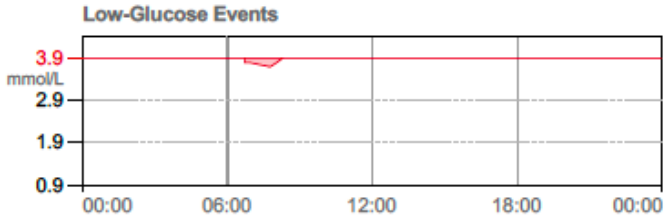


Participant ID 003

AVERAGE GLUCOSE	**8.4**	mmol/L
% above target	**34**	%
% in target	**65**	%
% below target	**1**	%

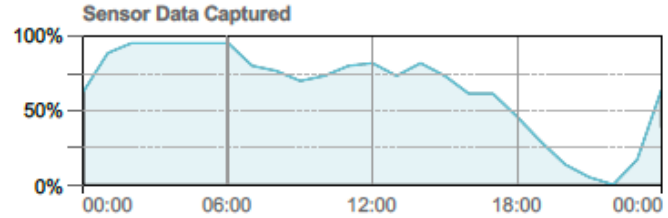


LOW-GLUCOSE EVENTS	**1**	
Average duration	**109**	Min



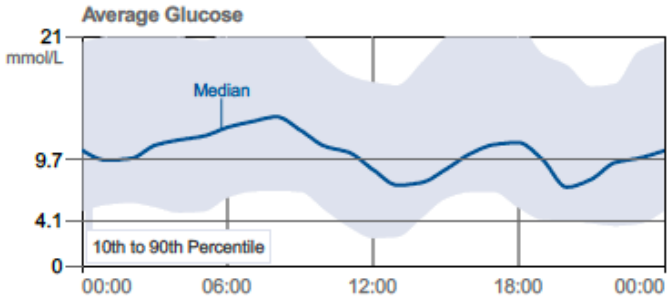
Sensor Usage

SENSOR DATA CAPTURED	**65**	%
Daily scans	**2**	

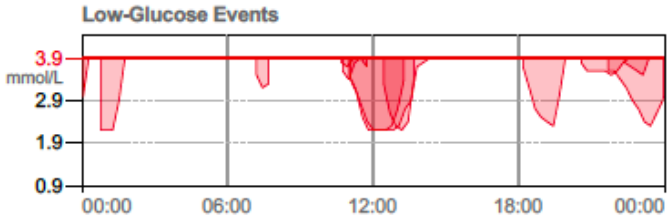


Participant ID 004

AVERAGE GLUCOSE	**11.9**	mmol/L
% above target	**59**	%
% in target	**33**	%
% below target	**8**	%

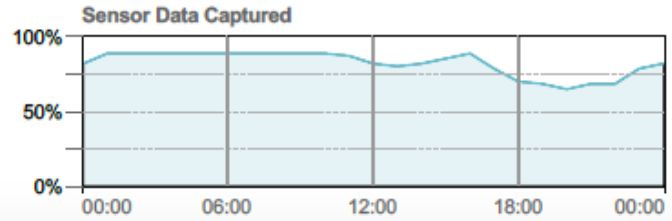


LOW-GLUCOSE EVENTS	**11**	
Average duration	**113**	Min



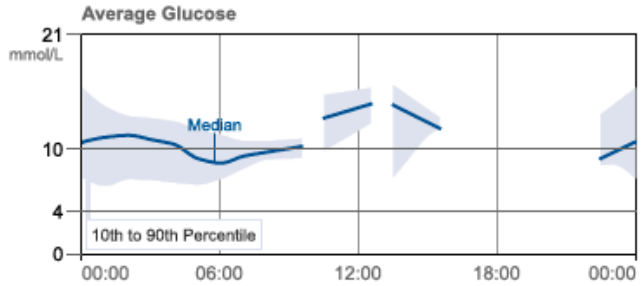
Sensor Usage

SENSOR DATA CAPTURED	**83**	%
Daily scans	**11**	

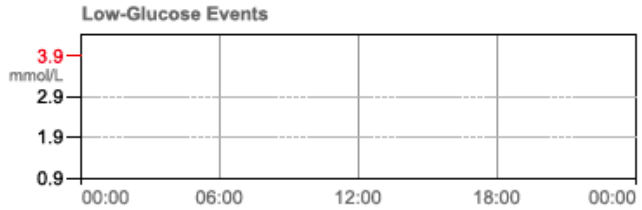


Participant ID 005

AVERAGE GLUCOSE	10.8	mmol/L
% above target	64	%
% in target	36	%
% below target	0	%

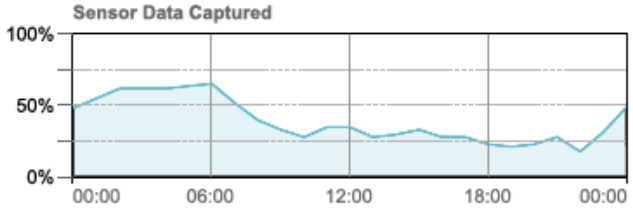


LOW-GLUCOSE EVENTS	0	
Average duration	0	Min



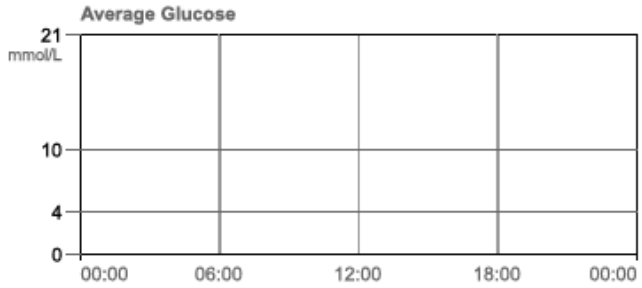
Sensor Usage

SENSOR DATA CAPTURED	38	%
Daily scans	2	

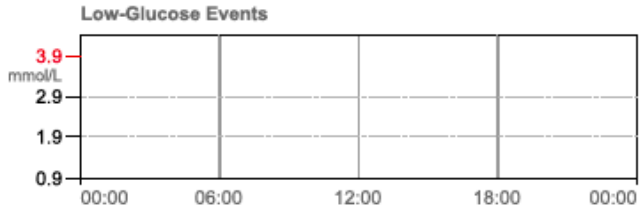


Participant ID 006

AVERAGE GLUCOSE	9.6 mmol/L
% above target	46 %
% in target	54 %
% below target	0 %

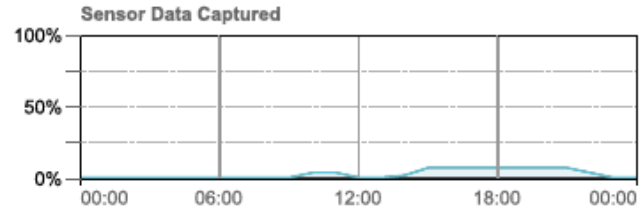


LOW-GLUCOSE EVENTS	0
Average duration	0 Min



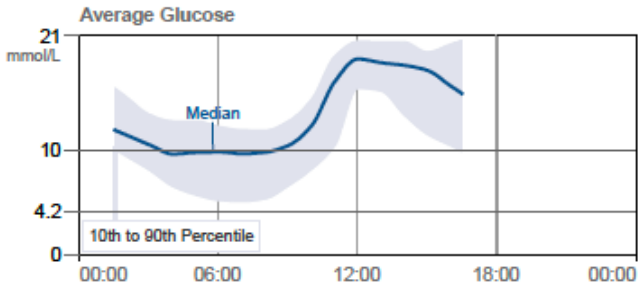
Sensor Usage

SENSOR DATA CAPTURED	3 %
Daily scans	0

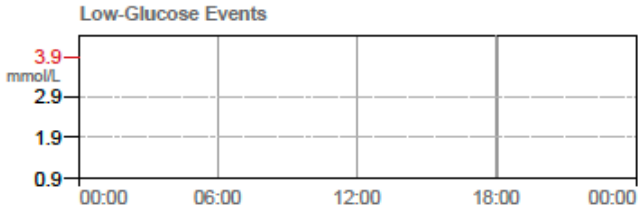


Participant ID 007

AVERAGE GLUCOSE	12.2 mmol/L
% above target	69 %
% in target	31 %
% below target	0 %

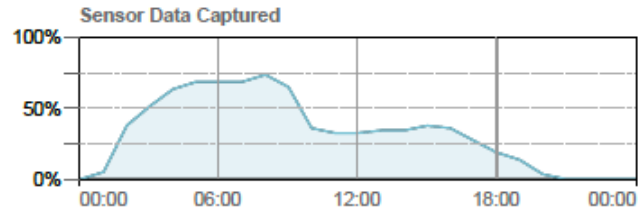


LOW-GLUCOSE EVENTS	0
Average duration	0 Min



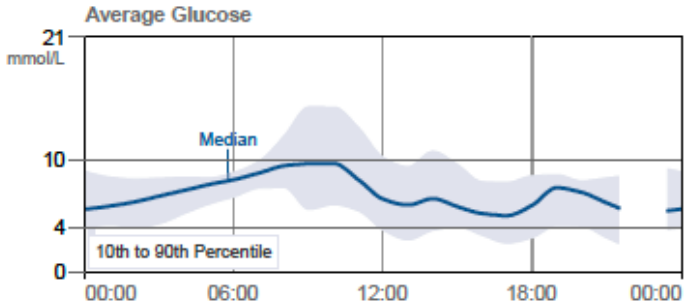
Sensor Usage

SENSOR DATA CAPTURED	34 %
Daily scans	2

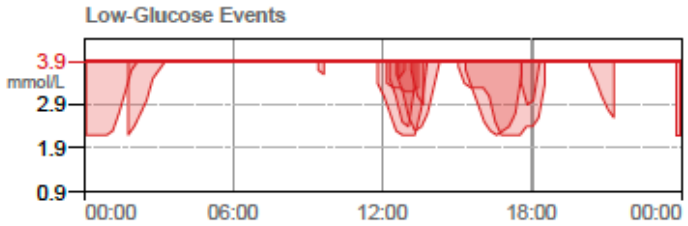


Participant ID 008

AVERAGE GLUCOSE	**7.3**	mmol/L
% above target	12	%
% in target	80	%
% below target	8	%

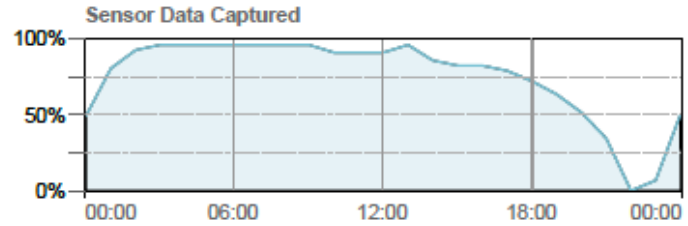


LOW-GLUCOSE EVENTS	**13**	
Average duration	106	Min



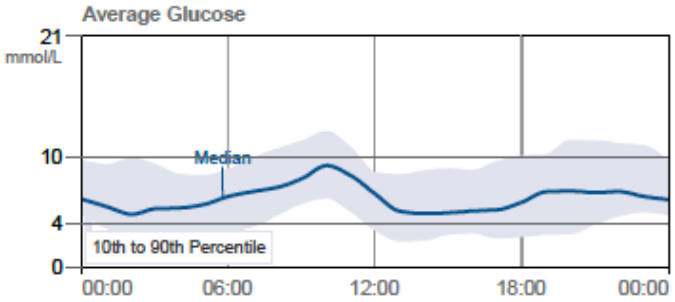
Sensor Usage

SENSOR DATA CAPTURED	**76**	%
Daily scans	5	

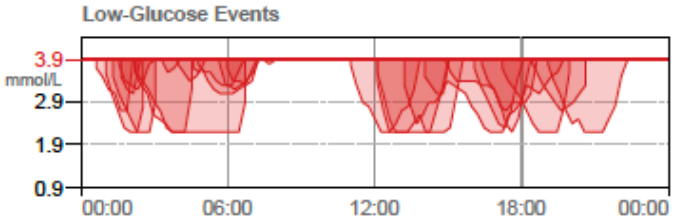


Participant ID 009

AVERAGE GLUCOSE	**6.6**	mmol/L
% above target	14	%
% in target	67	%
% below target	19	%

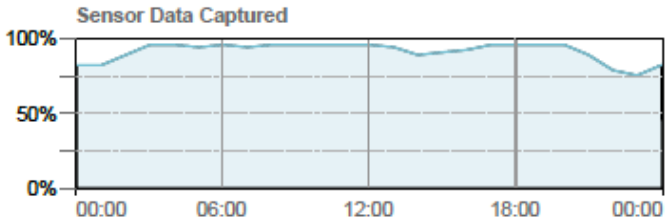


LOW-GLUCOSE EVENTS	**21**	
Average duration	182	Min



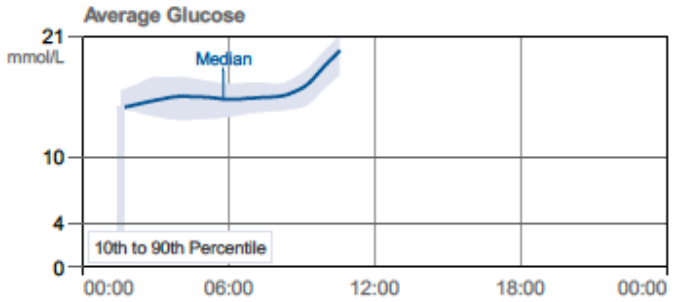
Sensor Usage

SENSOR DATA CAPTURED	**92**	%
Daily scans	12	

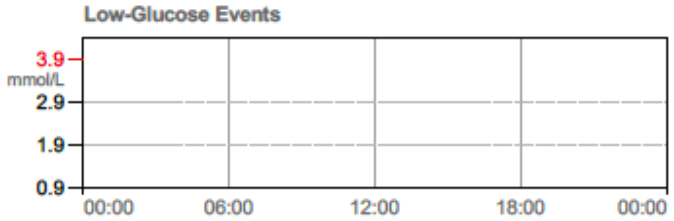


Participant ID 010

AVERAGE GLUCOSE	**16.0**	mmol/L
% above target	**100**	%
% in target	**0**	%
% below target	**0**	%

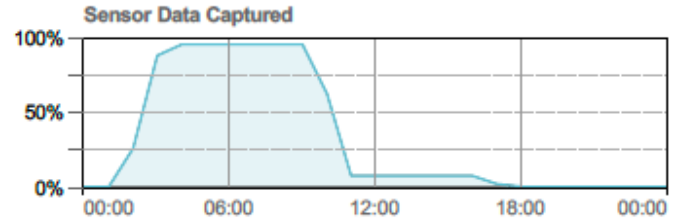


LOW-GLUCOSE EVENTS	**0**	
Average duration	**0**	Min



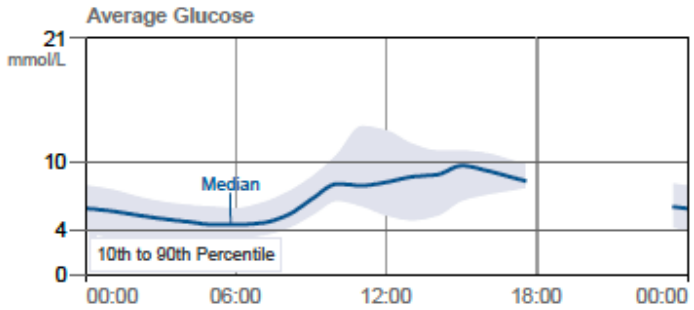
Sensor Usage

SENSOR DATA CAPTURED	**33**	%
Daily scans	**1**	

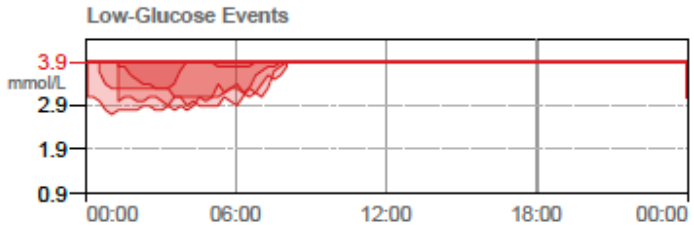


Participant ID 011

AVERAGE GLUCOSE	**6.6**	mmol/L
% above target	13	%
% in target	72	%
% below target	15	%

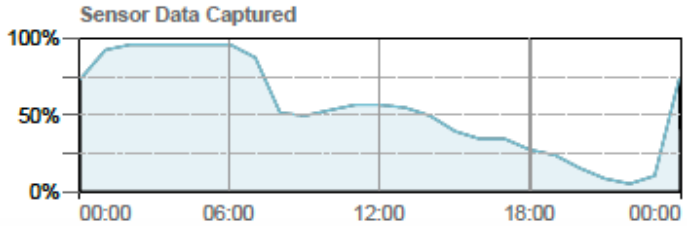


LOW-GLUCOSE EVENTS	**4**	
Average duration	437	Min



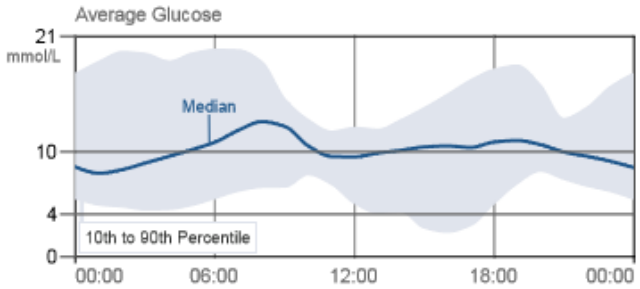
Sensor Usage

SENSOR DATA CAPTURED	**55**	%
Daily scans	3	

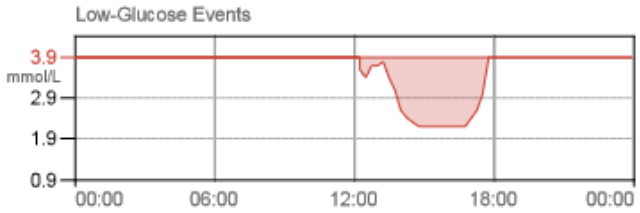


Participant ID 012

AVERAGE GLUCOSE	10.4	mmol/L
% above target	53	%
% in target	43	%
% below target	4	%

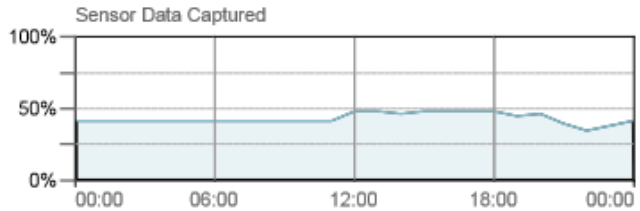


LOW-GLUCOSE EVENTS	1	
Average duration	348	Min



Sensor Usage

SENSOR DATA CAPTURED	43	%
Daily scans	12	



3.7.2 Results from the interviews

All participants (and, where applicable, carers) agreed to take part in the semi-structured interview. The 12 interviews all took place in the participants' homes, apart from three. Two were nursing home residents (IDs 001 and 012), and one participant (004) was in a community hospital for rehabilitation during the study period. The demographics of the participants who completed the study period are set out in Table 5. Analysis of the main findings are presented below under key domains including acceptability, expectations, effectiveness and consequences. Representative data extracts are presented verbatim (Table 6) with all participant and carer identifiers removed and replaced by the participants' and carers' IDs.

Acceptability

Participants and carers overwhelmingly found using the device acceptable. Almost without exception participants reported not knowing or being conscious of wearing the device throughout the two weeks and that it did not interfere with day-to-day activities (Table 6). In addition, participants confirmed that they were not aware of the device at night when they were sleeping.

Many participants described what they considered advantageous about the device. The most common example given was the elimination of finger-pricking. Participant 007 described that her fingers got sore from doing finger prick tests.

Exploration of expectations

When asked about expectations they had about wearing the device, many participants stated that they had had none. Participants were also asked if any expectations had

come to mind about what it meant for their diabetes: again, they replied they had none.

One participant revealed an altruistic motivation to his joining the study (Table 6). Carer 011 also exhibited altruistic motivations when describing her expectations of being on the study, explaining that the findings will be positive for other people[112]. Other expectations showed an interest in contributing to science and a natural curiosity of being part of a research study (Table 6). For another participant, joining the study meant that he had an opportunity to "join the 21st century" (Participant 004).

A distinct perspective was provided by the carer 002 - she admitted wondering if this was "a scam or something", however, became reassured upon hearing details about the device and the feasibility study (Table 6).

Effectiveness

Interviews explored the experience of participants/carers using the device for two weeks and whether they felt they found any effectiveness for the user and their diabetes health. Participants/carers found using the device effective, some preferring it over SMBG.

Carers spoke favourably about the simplicity of the device, being "handy at night-times" (Carer 002) for checking glucose levels without disturbing the participant and about the participant not being limited to the number of times they could check their glucose levels.

Consequences

The impact on participants' and carers' wider health and wellbeing was explored. In particular, I was interested whether they found any aspects of the experience positive

or negative. This included their views on whether the device had an impact on their symptoms, their experiences of living with diabetes and co-existing memory problems, and on their socialising and day-to-day activities.

Although no participant reported anxiety or stress in wearing the device, a few reported that they wondered about the different results obtained from the device compared with finger-pricking. Participant 012 expressed disappointment that the readings from the device did not always match the readings from the finger-prick test.

Carers found the device particularly useful as it made them feel reassured and safer being able to check glucose levels, without having to use SMBG. No reports of anxiety or stress in using the device were given by carers (Table 6).

Another carer made the point of Participant 002 not always understanding the need for SMBG due to his underlying dementia (Table 6).

One participant reported that wearing the device "made her feel confident" and, now that the two-week episode had ended, she would "miss it … it was a boon to have it" (Participant 008).

Overall

Participants were asked if they would recommend the device to others or what would they would say about their attitude to device to anyone who was considering it. They all responded positively about recommending the device.

One drawback mentioned was financial (Table 6). Some participants remarked on discrepant readings provided by the device compared with finger-pricking. One participant was explicit that he would like the device "to be more accurate", comparing its readings less favourably with finger-pricking the results of which, he said, set his mind "more at rest" (Participant 009). Nevertheless, his overall view of the device remained positive.

Table 5 Demographics and care arrangements of participants who completed the study period

ID	Age	M/F	Accommodation	Social situation at time of interview
1	90	M	Room in Nursing Home	Lives in nursing Home, nurse present at interview
2	79	M	House	Lives with wife (present at interview); package of care four times per day
3	82	M	Bungalow	Lives with wife (present at interview; she is his main carer
4	80	M	Bungalow	In community hospital; wife present at interview
5	86	M	Cottage	Lives alone, independent
6	87	M	Bungalow	Lives alone, cleaner, supportive family
7	84	F	House	Lives alone, daughter helps
8	92	F	House	Lives alone, package of care three times per day
9	84	M	Bungalow	Lives with wife (present at interview); she is main carer
10	81	M	House	Lives with wife (present at interview); she is main carer
11	90	M	House	Lives with wife (present at interview); she is main carer
12	90	M	Room in Nursing Home	Nursing home

Table 6 Illustrative quotes

Theme	Illustrative quotes
Acceptability	"I don't even know it's on" (ID 007); "Easy to take a reading" and "it was silent and stayed in place" (ID 010).
Exploration of expectations	"What they do with it, they can do what they like with me" (ID 001); "You've got to work with science and progress" (ID 003*);* *"*I found out what it did and I thought, this is fantastic" (Carer ID 002).
Effectiveness	"Well it's better than pricking your finger cos my fingers got like sore" (ID 007). "If I wanted to go and check [009's] blood and say [009] was partly asleep I could check it and find out if everything was all right you know" (Carer ID 009)
Consequences	"…when it was low and then when I then give him something, it had then gone up so I knew it was working, so I was happy, more than happy with it. Yes, I felt happy and I felt safer." (Carer ID 011); "I just think it like I say with the whole package of the Alzheimer's and dementia he's not always understanding and doesn't want it done and will pull his hand away and you know sometimes it's just all too much" (Carer ID 002).
Overall opinion	"I'd tell them that it does away with the needle" (ID 003); "We both think it's progress and it's going to help people in the future" (Carer ID 003); "I'd do it [take part] again" because it had been a positive experience (ID 005); "I really can't see any [drawbacks], apart from the price I can't think of any drawbacks" (Carer ID 002).

3.8 Discussion

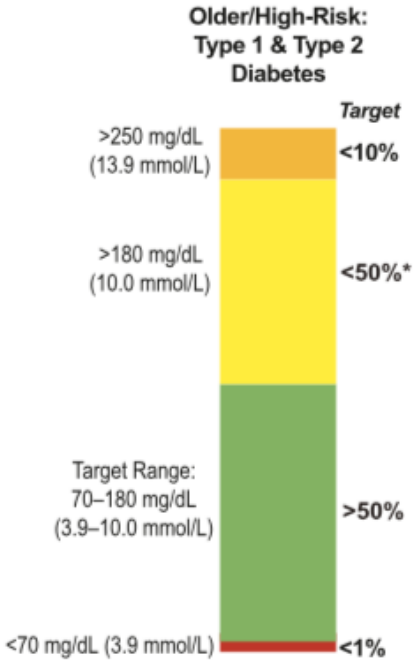
This study has shown that whilst the participants found wearing the sensor acceptable, data capture varied, depending on how many times the reader was used to scan the sensor during the study period. Possible reasons for this include self-management skills, whether or not the participant had a carer living with them, and experience of glucose self-monitoring. Nevertheless, some carers found it to be a useful and reassuring tool in managing this complex group of patients without having to resort to finger prick testing in a person who may not be able to understand the reasons for it.

Only four of my twelve participants reached the target of 70% or more data capture in fourteen days as specified in a recently published international consensus on clinical targets for CGM data interpretation[25].

The living arrangements of the participants were not were not a clear-cut indicator regarding data capture. 4 of the 12 participants lived alone (data capture 3-76%), 2 were in a nursing home (data capture 57% and 43% respectively), 1 in a community hospital (data capture 83%), and 5 participants had the support of spouses at home during the study period (data capture 33-92%). Further work needs to be done to investigate which can of device can provide the most reliability regarding data capture. For example, a CGM device with Bluetooth technology and continuous data transfer may result in higher data capture, irrespective of the living arrangements/packages of care.

The consensus statement for CGM targets in older people is that they should spend more than 50% in the target range (3.9-10 mmol/L), less than 1% below the target range (<3.9 mmol/L) and less than 10% above target (>13.9 mmol/L)[25]. In my study, six participants reached the above 50% time in range target and six reached the target of <1% below the target range.

Figure 33 CGM targets as set out by international consensus on time in range



(taken from Battelino et al)[25]

Recruitment proved challenging in this vulnerable group, particularly because we chose to identify and recruit potential participants whilst they were inpatients in an acute hospital setting. Challenges arose when a potential participant lacked capacity and consultee information sheets were left with the patient. Often it was not possible to speak to next of kin, relatives or friends who could have been consultees, due to the unpredictability of visiting and some patients not being visited at all whilst in hospital. In addition, it became

apparent that on discharge some participants found getting back into a daily routine and coping with day-to-day life overwhelming and therefore decided to withdraw from the study, despite showing interest in principle when approached in hospital.

3.8.1 Strengths and limitations

My study used a mixed-methods approach exploring participants' and carers' experiences during the study period.

With regards to the capture of hypoglycaemia, the manufacturer of FreeStyle Libre has reported their sensor may have less accuracy in the lower glucose ranges when compared to SMBG. Abbott's safety information discloses clinical study, which found that 40% of the time when the device indicated an interstitial glucose level of less than 3.3 mmol/L, the capillary reading was between 4.5 mmol/L to 8.9 mmol/L. A further study carried out in France with older patients with type 2 diabetes (on insulin) in care homes, found that 51% of hypoglycaemic episodes captured with FreeStyle Libre were associated with values equal or greater than 3.9 mmol/L on capillary readings[113].

Despite limitations of the Freestyle Libre in data capture, our findings are supported by two recent pieces of research. A conference abstract presented at Endo 2019 in New Orleans 23-26 March 2019 on the exposure to hypoglycaemia in older adults with T1DM analysed blinded CGM (Dexcom G4 Platinum) data in over 200 older adults (median age 68 years) collected at baseline in a randomised controlled trial, assessing the effect of CGM on hypoglycaemia. These older adults spend over one hour per day in the

hypoglycaemic range and over 100 minutes per day in those with impaired hypoglycaemic awareness[105].

In addition, a 2019 Japanese study investigated the use of blinded CGM (Medtronic iPro2) in older people in an outpatient setting in Japan. Out of 326 participants, 7 used CGM. Asymptomatic hypoglycaemic episodes occurred in 5 out of the 7 CGM users [104].

Whilst the study took place within one area of the United Kingdom, I believe that the results are potentially generalizable to the rest of the older population in the UK with diabetes and memory problems.

3.8.2 Meaning of findings and potential for future work

Meaning of findings and potential for future work

CGM has gained momentum in the last few years, with more affordable devices being freely available for people with diabetes to purchase. However, the focus has very much been on adults and children with T1DM and pregnant women. More recently, the National Health Service published its long-term plan, making reference to the fact that from April 2019, patients with T1DM benefit from flash glucose monitors ending the variation patients in some parts of the country are facing. This includes patients T1DM, who are unable to routinely carry out finger prick testing due to disability (which would arguably include cognitive problems) and require carer support for their diabetes management (ie checking glucose levels and insulin administration). No mention is made in the long-term plan of people with T2DM on medications which carry a high risk of hypoglycaemia (insulin, sulfonylureas), who may need carer support (for example due to underlying dementia) with the management of their diabetes.

There appears to be a disconnect by the commissioners by placing too much emphasis on the type of diabetes, rather than focussing on the class of anti-diabetic medication a patient might be on. One of the questions should be whether an individual is at high risk of hypoglycaemia and needs support with the management of their glucose levels, due to underlying frailty (including cognitive impairment), not what type of diabetes they have or how many times per day they carry out finger prick testing. We know the older people with dementia and diabetes are at much higher risk of severe hypoglycaemia[8].

There is a need to seriously think about older frail people (especially those on insulin and/or with memory problems) and how best to manage diabetes in later life focussing on avoidance of hypoglycaemia and its adverse effects. This will require an enormous shift in mindset by healthcare professionals and policy makers.

A key area for investigation is what type of CGM (i.e. intermittent scanning/flash glucose monitoring, continuous transmission via Bluetooth or blinded and retrospective CGM) would be most appropriate in this group of patients? Secondly, how often should CGM be employed (all the time, when there is a change in drugs, or intermittently for troubleshooting)? Thirdly, should it be limited to insulin and sulfonylurea users, which carry a higher risk of hypoglycaemia?

In the first instance, it will be necessary to carry out a large-scale study using CGM to assess its true potential impact in this vulnerable group. CGM would be used to capture hypoglycaemic episodes and guide the hypoglycaemia minimization strategy. In addition, CGM may be a useful and supportive tool for

carers in their day to day care of this vulnerable group of older people, especially those on drugs that carry a high risk of hypoglycaemia. Further work is needed to explore whether older people with memory problems will be able to deal with the technology for continuous Bluetooth capture and reacting to the data that is produced by the software, including alarms for high and low glucose levels.

3.9 Conclusions

It is potentially feasible for older people with diabetes and memory problems to operate a CGM device that requires users to conduct intermittent scans. However, the added benefit of real-time transmission CGM devices that do not require active scanning needs to be explored further in this group of patients.

CHAPTER 4. THE EFFECTS OF HYPOGLYCAEMIA AND DEMENTIA ON CARDIOVASCULAR EVENTS, FALLS AND FRACTURES AND ALL-CAUSE MORTALITY IN OLDER PEOPLE – A RETROSPECTIVE COHORT STUDY

4.1 PREAMBLE

The second and third chapters outlined existing evidence regarding CGM use in older people and the detection of hypoglycaemia, in addition to my feasibility study of using the FreeStyle Libre CGM device in older people with memory problems. Two-thirds of the insulin users in my feasibility study experienced hypoglycaemic events, two of which lasted over 300 minutes. The consequences of hypoglycaemia in patients with co-morbid diabetes and dementia are unknown. Hence, this fourth chapter presents a retrospective cohort study exploring the association between hypoglycaemia and serious adverse events in older patients with diabetes and dementia, and whether the consequences of hypoglycaemia were affected by presence of dementia. It was published in Diabetes Obesity and Metabolism in 2019 (https://www.ncbi.nlm.nih.gov/pubmed/31069922). Chapter 4 is a more comprehensive and detailed expansion of the publication.

4.2 Chapter summary

4.2.1 Aims

I aimed to test the association between hypoglycaemia and serious adverse events in older patients with diabetes and dementia, and whether the consequences of hypoglycaemia were affected by the presence of dementia.

4.2.2 Materials and Methods

Retrospective cohort study using Clinical Practice Research Datalink in England (1997-2016). I selected participants, intervention (exposure) and follow-up to mirror two hypothetical target randomised controlled trials. Target trial 1's exposure was hypoglycaemia in patients with dementia. Target trial 2 examined adverse effects of hypoglycaemia according to dementia status.

I used Cox proportional hazard regression to estimate adjusted hazard ratios for falls, fractures, cardiovascular events and mortality.

4.2.3 Results

In target trial 1, hypoglycaemia was associated with an increased risk during 12 months follow-up of falls and fractures – adjusted Hazard Ratio (aHR) 1.94 (95% CI 1.67 to 2.24), cardiovascular events - aHR 2.00 (95% CI 1.61 to 2.48) and mortality - aHR 2.36 (95% CI 2.09 to 2.67).

In target trial 2, presence of dementia was associated with increased risk of adverse events after hypoglycaemia (12 months follow-up): falls & fractures - aHR 1.72 (95% CI 1.51 to 1.96) and mortality - aHR 1.27 (95% CI 1.15 to 1.41), but had no effect on cardiovascular events - aHR 1.14 (95% CI 0.95 to 1.36).

4.2.4 Conclusions and Relevance

Hypoglycaemia is associated with an early increased risk of serious adverse events in older people with diabetes and dementia.

4.3 Introduction

In the preceding chapters, I have discussed the major healthcare burden comorbid diabetes and dementia are likely to pose over the next decades and how the self-management of diabetes is particularly challenging for older patients because they have limited recall of the dangers of hypoglycaemia and what remedial action to take[114], and because they are more prone to hypoglycaemia from their medication[115 6].

Existing evidence has already highlighted the potentially serious consequences of hypoglycaemia (e.g. cardiovascular events, falls, fractures and death), however, none of the previous studies have specifically focused on the risks associated with hypoglycaemia among older people with dementia.

My aim was to test the effect of hypoglycaemia in older people with dementia and diabetes on serious adverse events (myocardial infarction, ischaemic stroke, falls and fractures, and all-cause mortality). I also examined whether dementia modified the effect of hypoglycaemia. A more comprehensive understanding of the consequences of hypoglycaemia in this vulnerable and complex group will help optimise the clinical management.

4.4 Methods

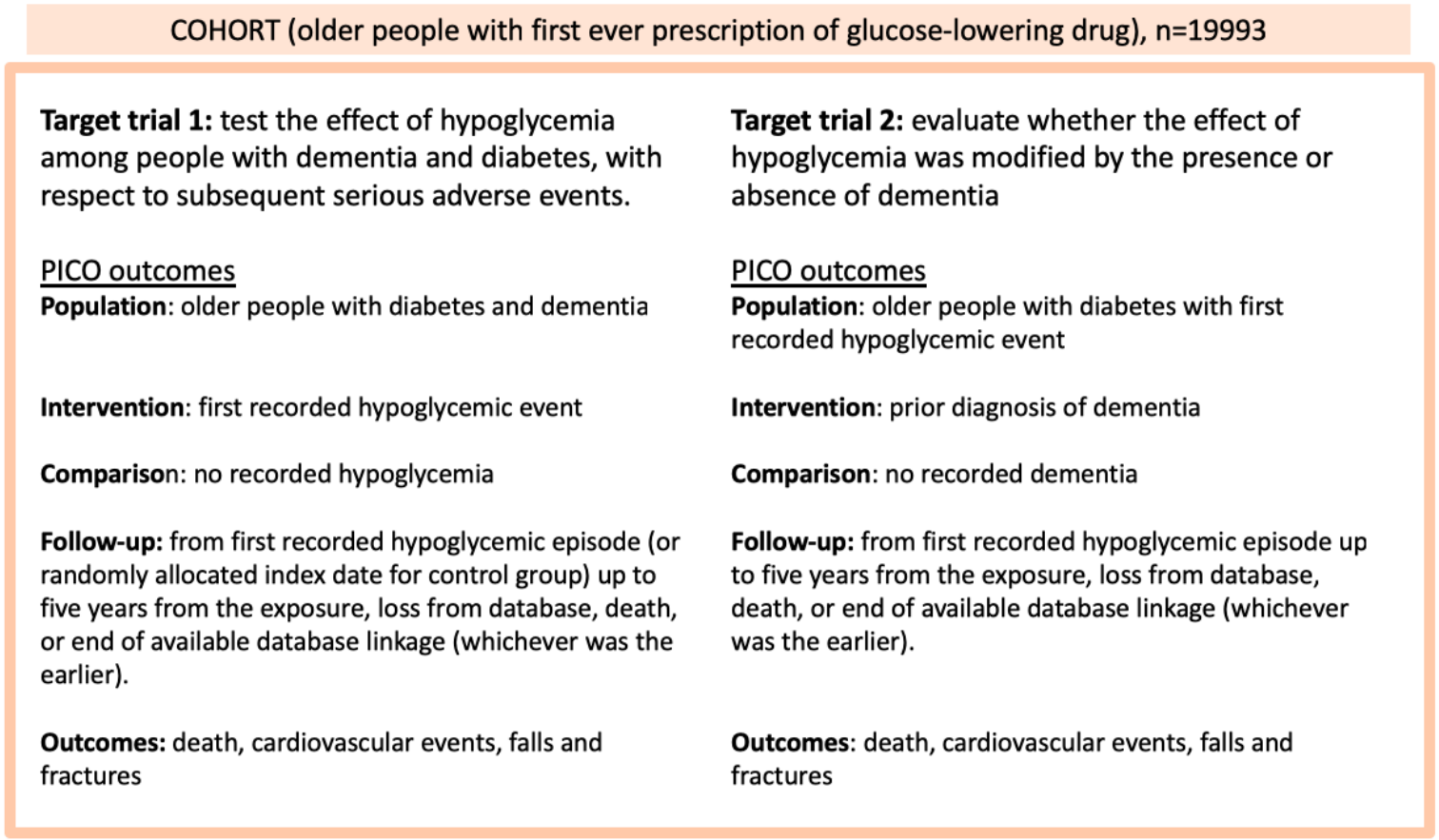
4.4.1 Study design

I performed a retrospective cohort study using data from CPRD. I designed two hypothetical target trials within a cohort of older patients with diabetes. The concept of "target trials" was formalised by Hernan et al as a means of using

observational data to emulate a RCT[116]. Whilst it would be preferable to carry out an RCT to assess or compare the effectiveness of an intervention, this is not always feasible, due to issues relating to time, funding, and/or ethics (particularly in studies of harmful effects). For instance, it would neither be feasible nor ethical to randomize participants to hypoglycaemia or no hypoglycaemia, for assessment of long-term adverse effects. Hence, researchers have to resort to observational data sets to try and emulate a target trial. Hernan et al set out a framework which mimics the design and analysis of a target trial and tries to address potential sources of bias. This enables a systematic and methodological evaluation of observational data, which will assist in analysing causal inferences[116].

My first target trial aimed to test the effect of hypoglycaemia among people with dementia and diabetes, with respect to subsequent serious adverse events. I also conducted a second target trial to evaluate whether the effect of hypoglycaemia was affected by the presence or absence of dementia. I selected participants, intervention (exposure) and follow-up to mirror the two hypothetical target randomised controlled trials[116](Figure 35).

Figure 34 Schematic presentation of study



4.4.2 Study data and Setting

I chose to use CPRD because it holds anonymised primary care records from GPs, encompassing over 11 million patients from 674 practices in the UK and is broadly representative of the UK general population in terms of age, sex and ethnicity [117]. Another advantage of CPRD is the data linkage with other databases, thus enabling me to ascertain hospital, national mortality, and socioeconomic data relating to the patient. A subset of primary care datasets is linked with Hospital Episode Statistics (HES), which covers ED attendances and hospitalization. Linkage with the Office for National Statistics (ONS), allows me to record date of death of the participants, whilst the Index of Multiple Deprivation and Townsend scores is a record of socioeconomic deprivation status [117].

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC); protocol number 16_184R (Appendix 8). I submitted proposed amendments to the Protocol in November 2017, which were approved in December 2017 (Appendix 9 and 10).

I followed the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) guidelines in writing up the published manuscript[118].

4.4.2.1 Sample size calculation

Preliminary feasibility estimates were that there would be at least 960 patients with diabetes and dementia experiencing hypoglycaemia, and potentially up to 9000 without hypoglycaemia. Based on an estimated baseline event rate of 6% for fractures [119], my study had>99% power to detect a clinically important relative risk increase of 2.0 for fracture between groups (alpha 0.05) i.e.

absolute increase of 12% in the hypoglycaemic group. I contacted CPRD beforehand to confirm that their database was potentially able to yield sufficient numbers of records to meet this sample size calculation.

4.4.3 Participants

The cohort consisted of patients aged 65 or older with diabetes, defined as a first ever prescription of any oral or injectable glucose-lowering agent between April 1997 and March 2016. I considered initiation of a glucose-lowering drug to be a proxy for diagnosis and treatment of diabetes mellitus because there are no other clinical indications (e.g. polycystic ovary syndrome) for such drugs in this age group.

Eligible participants also needed HES-linked data available. Dementia status was ascertained based on presence of CPRD Read Code or HES International Classification of Diseases (ICD) code (Appendix 11). Brown et al showed that dementia recorded in routinely collected in HES has 85% diagnostic agreement with a GP survey[120], and a recent systematic review has confirmed that large health-care datasets can achieve a high positive predictive value for dementia identification[121].

Read Codes have been used by the NHS since the 1980s and are a thesaurus of clinical terms.

4.4.4 Exposure and Outcomes

The exposure was defined as the first hypoglycaemic episode recorded on the primary (CPRD) or secondary (HES) healthcare database from April 1997 onwards following initiation of a glucose-lowering agent. Hypoglycaemic

episodes are recorded in primary care (CPRD) via Read codes and in secondary care (HES) via ICD codes:

Hypoglycemia	**Read codes:** C112100, C11y100**,** C116.00**,** C110z00**,** C112z00**,** C116000**,** C112000, C112.00**,** C110.00 **ICD9/10:** 251.0, 251.1, 251.2, E249.8 and E250.8, E10.64, E11.64, E16.0, E16.1, E16.2

Combined use of CPRD and HES broadens the capture of hypoglycaemia to include events recorded by medical personnel in both the primary and secondary care settings; a similar approach has been used in previous research on the association between hypoglycaemia and cardiovascular events in insulin users[122]. I have to concede at this juncture that I am only able to capture hypoglycaemic episodes which have resulted in an entry on a patient's medical record, which are those which require assistance from another person and are therefore flagged up to the medical team or result in an attendance in an emergency department. I will further discuss the rationale and implications of this approach in the Strengths and Limitations section.

For target trial 1, the exposed group's (dementia, hypoglycaemia) first coded hypoglycaemic episode occurred a median of 13 (interquartile range: 2-34) months after meeting the study eligibility criteria. The patients in the control group do not have hypoglycaemic events. I therefore had to allocate the start date to be similar to the exposed group based on the time interval between meeting the study criteria and actually experiencing a hypoglycaemic event[123]. The outcomes were falls, fractures, cardiovascular events (myocardial infarction, ischaemic stroke) and all-cause mortality. I chose these, based on a previous systematic review I published, which identified signals of elevated risk for these

outcomes in older people experiencing hypoglycaemic events[6].

In addition, I assessed the rate of ED attendances for patients who had their point of exposure after 1 April 2007 (HES Accident & Emergency data is only available for the time period April 2007 to 31 March 2016).

The start of follow-up was the first hypoglycaemic episode, or the randomly allocated exposure date for the control group in target trial 1. Follow-up continued for up to five years from the exposure, loss from database, death, or end of available database linkage (HES 31 March 2016 and ONS 17 April 2017), whichever was the earlier.

4.4.5 Covariates

The covariates I chose for the adjusted analysis are based on previous literature[124 125]. Important confounders are the ones that are likely to affect the probability of the exposure and the outcome of interest, hence the adjusted models are specifically tailored to each outcome of interest. For example, Hippisley-Cox et al used a specific list of confounders in their study assessing associations between risks of cardiovascular disease and all-cause mortality and different drugs used in the treatment of T2DM[124]. My choice of covariates for the adjusted models assessing associations for those outcomes in my target trials was based on this paper.

Driessen et al assessed bone fracture risk associated with the use of GLP-1 receptor agonists and I was able to base my choice of covariates for the adjusted models assessing fracture risk in my target trials on Driessen's study[125].

I extracted information on a range of patient characteristics, including year of birth, gender, index of multiple deprivation quintile, year of glucose-lowering drug initiation, duration of dementia and diabetes, medications, co-morbid conditions (hypertension, peripheral vascular disease, valvular heart disease, cardiovascular disease, chronic kidney disease, atrial fibrillation), complications (severe kidney failure, amputation, blindness), body mass index (BMI) and HbA1c. CPRD does not provide the month of birth for patients aged over 16, only the year of birth. I therefore allocated the date of birth as the middle of the year of birth.

Regarding ethnicity, Mathur et al demonstrated that in primary care there is good capture, which is largely comparable to the general population. Linkage of datasets (ie HES inpatients) shows nearly 100% completeness, although there was poor completeness for HES A&E and poor consistency for HES outpatient records[126]. I used HES categories, however, replaced with CPRD categories when HES was 'other', 'unknown' and 'missing'. Data extraction showed 10 patients as 'others', which I then combined to make a 'mixed/other' category, in addition to 'white', 'asian', 'black', 'unknown'.

For alcohol, I extracted the last date on/before the exposure of drinking alcohol and the last date on/before the exposure of not drinking alcohol. I then generated a variable for 'alcohol status' (yes/no).

Looking at the smoking status for patients, I extracted three dates: last date on/before the exposure of being (a) current (b) ex or (c) non-smoker. From those three dates, I generated a 'smoking status' variable with 'yes' being allocated to current and ex-smokers and 'no' allocated to non-smokers.

Covariates were measured at the point of exposure or the allocated index date for controls. I took into account the medication history for the past 90 days, most recent BMI within the last three years and most recent HbA1c within the last 18 months.

4.4.6 Statistical analysis

To estimate the association between the timing of hypoglycaemic episodes and defined outcomes, I used Cox proportional hazard regression models with adjustment for appropriate confounders to generate HRs and 95% CIs for each outcome. Modelling the time for events (outcomes) to occur (survival time) is known as survival analysis. The Cox proportional hazards model is a commonly used tool to investigate survival time and the relationship of predictor variables through the hazard function, for example, the hazard of the occurrence of myocardial infarction over a particular time period in relationship to various covariates[127]. The assumption for this model is that the effect of predictors is constant over time. However, the effect of the intervention (hypoglycaemia for target trial 1 and dementia for target trial 2) may be short-lasting or diminish with time, so it is necessary to check proportionality. One way of doing this is, is to visually inspect log-log plots of survival to assess the proportional hazards assumption, ie the assumption that the relative effect of covariates on the hazard function does not change over time[128]. If the proportional hazards assumption is met, then this should result in the log-log plot displaying parallel lines. Log-log plots display the log survival versus log survival times.

The proportional hazard assumption was not met in several of the outcomes, as a result of which I estimated the hazards at shorter and longer follow-up

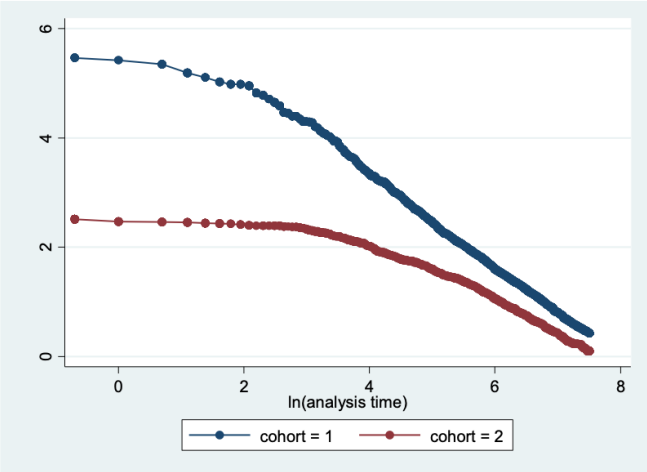
periods. An example of log-log plots where the proportional hazards assumption was met, and one were where it was not are in Figures 36 and 37.

I used negative binomial regression to estimate the adjusted rate ratios of emergency department attendances for patients who had their point of exposure after 1 April 2007. The aim of negative binomial regression is to model the relationships between predictors and the likelihood of a count outcome (ie here the emergency department attendances).

It is similar to Poisson regression, however, the assumption with Poisson regression is that the mean and variance are the same, which often is not the case. Negative binomial regression takes into account the variability of the counts.

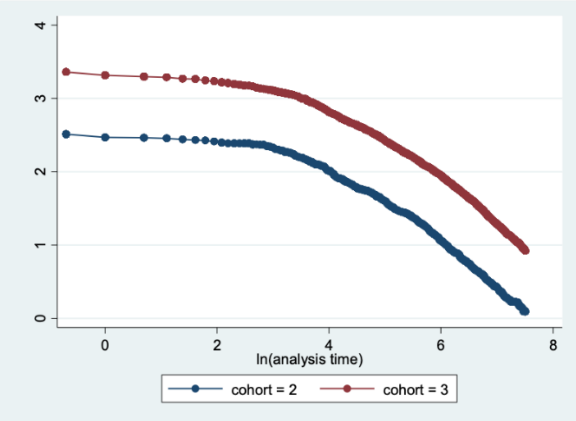
Analyses were performed with STATA version 14.2 software (StataCorp LP, College Station, TX).

Figure 35 Example where proportional hazards assumption was not met (target trial 1 – falls/fractures composite)



	Number of events, n		Adjusted HR (95% CI) Up to one-year follow-up	Adjusted HR (95% CI) 12-60 months follow-up
	Dementia, no hypoglycaemia (n=6134)	Dementia, hypoglycaemia (n=1679)	Complete case analysis (n=5607)	
Adverse events				
Falls & Fractures (composite)	1771	555	1.94 (1.67 to 2.24)	1.16 (0.97 to 1.40)

Figure 36 Example where proportional hazards assumption was met (target trial 2 - falls/fractures composite)



	Number of events, n		**Adjusted HR (95% CI) Up to one-year follow-up**	**Adjusted HR (95% CI) 12-60 months follow-up**
	Dementia, hypoglycaemia (n=1679)	No dementia, hypoglycaemia (n=12180)	Complete case analysis (n=11683)	
Adverse events				
Falls & Fractures (composite)	555	2642	1.72 (1.51 to 1.96)	1.71 (1.44 to 2.04)

4.4.7 Missing data

Missing data is unavoidable when analysing datasets, which can lead to bias and imprecise analysis. Different approaches have been developed to address missing data and there is a lot of discussion around which technique is the most appropriate to employ dependent on the type of missing data.

Data can be missing for different reasons:

- Missing completely at random: there are no systematic differences between the missing and observed data [129], for example, people with missing blood pressure readings do not differ systematically from other people in the dataset [130].

- Missing at random: there might be systematic differences between the observed and missing data, but they can be explained by other observed variables [129]. For example, if glycated haemoglobin (HbA1c) data are missing at random, conditional on age and gender, then the distributions of missing and observed HbA1c data will be similar among people of the same age and gender [130].

- Missing not at random: associations with the observed data cannot explain systematic differences between observed and missing data [129].

Two techniques which have been developed in order to address missing data are:

- Complete case analysis: only individuals with complete information on all variables are considered in the main analysis;

- Multiple imputation: missing values are imputed (replaced by plausible values – statistical packages create multiple datasets with imputed values to address uncertainty surrounding imputed values).

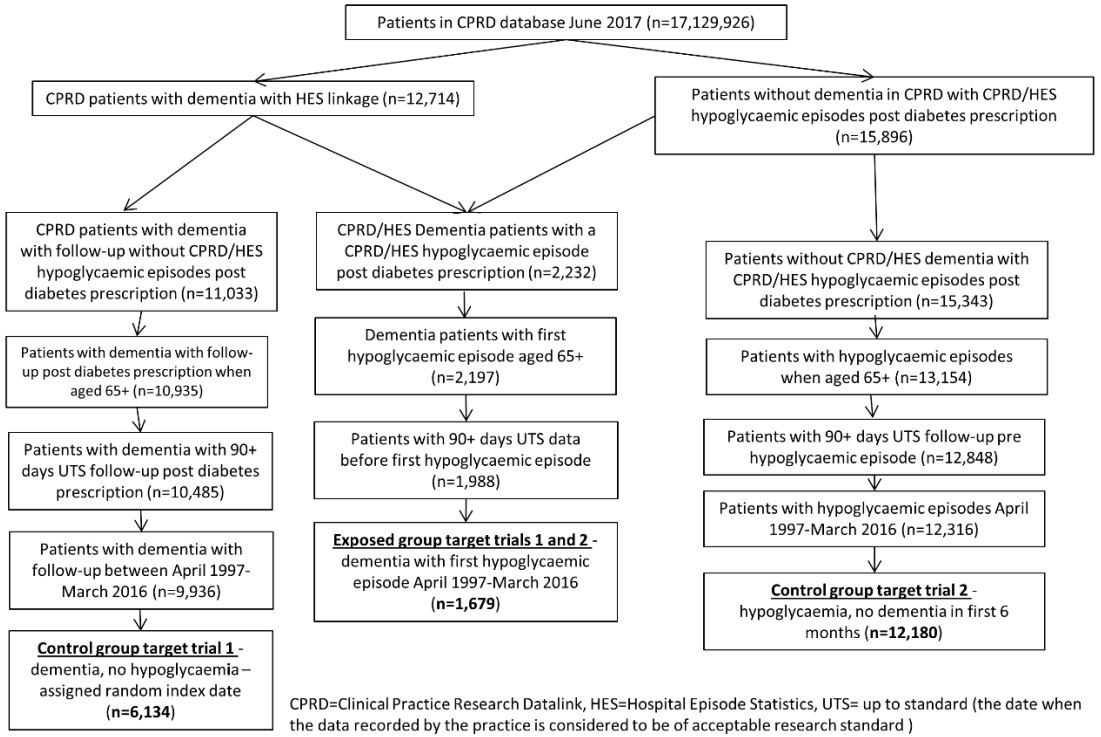
There is no single optimal choice, however, researchers have argued that if data is not missing at random, then a complete case analysis can be a valid approach, whereas multiple imputation is valid for data missing at random and data missing completely at random [129].

I used complete-case analysis for both hypothetical target trials, because I could not be certain that data were missing at random or not. Due to not knowing the reason for missingness, I also carried out sensitivity analyses using different methods (multiple imputation, use of a missing data category, and exclusion of lifestyle covariates).

4.5 Results

The cohort consisted of a total of 19,993 patients with diabetes. The patient flowchart can be seen in Figure 38.

Figure 37 Patient flowchart



Patient demographics are set out in Table 7.

Table 7 Baseline characteristics

	Dementia, no hypoglycaemia (n=6134)	Dementia, hypoglycaemia (n=1679)	Hypoglycaemia, no dementia (n=12180)
Characteristics			
Age (years), mean (SD)	81.61 (6.88)	82.77 (6.59)	76.97 (7.31)
Male gender, n (%)	2600 (42.39)	691 (41.16)	6105 (50.12)
Ethnicity, n (%)			
Asian	188 (3.1)	59 (3.5)	541 (4.4)
Black	156 (2.5)	59 (3.5)	261 (2.1)
White	5409 (88.2)	1489 (88.7)	10787 (88.6)
mixed/other	29 (0.5)	9 (0.5)	45 (0.4)
unknown	352 (5.7)	63 (3.8)	546 (4.5)
Documented smoking history, n (%)			
Yes	2984 (48.65)	852 (50.74)	7300 (59.93)
No	3150 (51.35)	827 (49.26)	4880 (40.07)
Body mass index (kg/m2), mean (SD)	26.63 (5.29)	26.32 (5.15)	28.67 (5.92)
IMD quintile score, mean (SD)	2.88 (1.37)	3.03 (1.38)	3.01 (1.36)
Documented alcohol history, n (%)			
Yes	3638 (59.31)	964 (57.42)	8601 (70.62)
No	2496 (40.69)	715 (42.58)	3579 (29.38)
Haemoglobin A1c (mmol/L), mean (SD)	56.71 (17.10)	62.46 (20.89)	60.51 (17.74)
Haemoglobin A1c (%), mean (SD)	7.3 (3.7)	7.9 (4.1)	7.7 (3.8)
Diabetes therapy duration (years), mean (SD)	5.22 (5.53)	8.55 (6.66)	8.62 (5.77)
Dementia duration (years), mean (SD)	1.64 (2.24)	1.90 (2.31)	N/A
Comorbidities, n(%)			
Atrial fibrillation (AF)	951 (15.50)	309 (18.40)	1829 (15.02)
Blindness	385 (6.28)	132 (7.86)	873 (7.17)
Chronic obstructive pulmonary disease	448 (7.30)	138 (8.22)	1442 (11.84)
Heart failure	482 (7.86)	190 (11.32)	1583 (13.00)
Liver disease	89 (1.45)	31 (1.85)	258 (2.12)
Hypertension	4023 (65.59)	1101 (65.57)	8515 (69.91)
Inflammatory bowel disease	78 (1.27)	23 (1.37)	176 (1.44)
Neuropathies	195 (3.18)	103 (6.13)	693 (5.69)
Osteoporosis	405 (6.60)	137 (8.16)	725 (5.95)
Parkinson's disease	224 (3.65)	56 (3.34)	149 (1.22)
Peripheral vascular disease	247 (4.03)	111 (6.61)	829 (6.81)
Valvular heart disease	150 (2.45)	60 (3.57)	363 (2.98)

Renal disease	389 (6.34)	230 (13.70)	1524 (12.51)
Rheumatoid arthritis	141 (2.30)	57 (3.39)	429 (3.52)
Thyroid disease	884 (14.41)	267 (15.90)	1754 (14.40)
Retinopathy	1438 (23.44)	653 (38.89)	4709 (38.66)
Lower limb amputation	69 (1.12)	46 (2.74)	418 (3.43)
Previous fractures	1143 (18.63)	397 (23.65)	1753 (14.39)
Cancer that metastasizes to the bone	349 (5.69)	113 (6.73)	847 (6.95)
History of previous MI	973 (15.86)	366 (21.80)	2643 (21.70)
Prescription in past 90 days, n (%)			
Renin-angiotensin blockers	2790 (45.48)	825 (49.14)	7597 (62.37)
Thiazide diuretic	763 (12.44)	137 (8.16)	2039 (16.74)
Loop diuretics	1371 (22.35)	525 (31.27)	4165 (34.20)
Betablocker	1304 (21.26)	367 (21.86)	3327 (27.32)
Antiplatelets	3322 (54.16)	952 (56.70)	6367 (52.27)
Anticoagulation	437 (7.12)	120 (7.15)	1154 (9.47)
Lipid lowering medication	3608 (58.82)	974 (58.01)	7657 (62.87)
Steroids	278 (4.53)	111(6.61)	1212 (9.95)
Calcium channel blocker	1556 (25.37)	406 (24.18)	4011 (32.93)
PD meds	216 (3.52)	54 (3.22)	185 (1.52)
Antiarrhythmics	49 (0.80)	24 (1.43)	278 (2.28)
Antidepressants	2006 (32.70)	598 (35.62)	2560 (21.02)
Antipsychotics	904 (14.74)	253 (15.07)	468 (3.84)
Hypnotics	429 (6.99)	121 (7.21)	565 (4.64)
Drugs affecting bone metabolism	475 (7.74)	166 (9.89)	810 (6.65)
Sulfonylureas	2511 (40.94)	786 (46.81)	5662 (46.49)
Insulin	794 (12.94)	801 (47.71)	5974 (49.05)
Other oral hypoglycaemics	3512 (57.25)	678 (40.38)	5528 (45.39)
Dementia drugs	1027 (16.74)	180 (10.72)	Not applicable

[1]Bisphosphonates, Calcitonin, Calcium and Vitamin D supplements

The mean age of the dementia group was 82 years and the non-dementia group was 77 years. Insulin use was higher in those with dementia and hypoglycaemia compared to those with dementia and no hypoglycaemia (48% versus 13%).

In several instances, the proportional hazards assumption was not met in the statistical analysis. In order to identify any changes in the hazard during the follow-up period I have stratified the analysis according to less than or more than 12 months of follow-up (Tables 8 and 9).

The number of events is reported in Tables 8 and 9 and the median time to event is reported in Table 10.

Target trial 1 – the effect of hypoglycaemia on outcomes in patients with dementia (Table 8)

During the first 12 months, adverse events occurred at about twice the rate among those with hypoglycaemia compared to those without - all-cause mortality (aHR 2.36 [95% CI 2.09 to 2.67]), cardiovascular events (aHR 2.00 [95% CI 1.61 to 2.48)] and falls and fractures (aHR 1.94 [95%CI 1.67 to 2.24]). Hypoglycaemia was associated with an increase in subsequent myocardial infarction (MI) (aHR 2.24 [95% CI 1.59 to 3.15]) and ischaemic stroke (aHR 1.80 [95% CI 1.37 to 2.36]) among people with dementia. Falls and fracture risks individually were also both increased (aHR 1.96 [95% CI 1.69 to 2.29] and aHR 1.62 [95% CI 1.25 to 2.08]).

However, the associations diminished with longer follow-up. During the 12-60 months follow-up, there remained an association with mortality (aHR 1.33 [95% CI 1.19 to 1.48), but not the other outcomes.

Target trial 2 – the effect of co-morbid dementia on outcomes in patients with hypoglycaemia (Table 9)

During the first 12 months, co-morbid dementia was associated with an increased risk of falls and fractures (aHR 1.72 [95% CI 1.51 to 1.96]) and mortality (aHR 1.27 [95% CI 1.15 to 1.41]) in older people with hypoglycaemia. The risk of mortality increased to more than double during the 12-60 months follow-up period (aHR 2.15 [95% CI 1.94 to 2.37]).

Dementia did not show a statistically significant association on cardiovascular events (aHR 1.14 [95% CI 0.95 to 1.36]). It was associated with a significant increase in the risk of ischaemic stroke (aHR of 1.41 [95% CI 1.12 to 1.78]), but not myocardial infarction (aHR 0.84 [95% CI 0.64 to 1.10]).

	Number of events, n		Adjusted HR (95% CI) Up to one-year follow-up	Adjusted HR (95% CI) 12-60 months follow-up
	Dementia, no hypoglycaemia (n=6134)	Dementia, hypoglycaemia (n=1679)	Complete case analysis (n=5607)	
Adverse events				
Cardiovascular (composite)	815	271	2.00 (1.61 to 2.48)	1.11 (0.85 to 1.47)
MI	311	119	2.24 (1.59 to 3.15)	1.28 (0.86 to 1.91)
Stroke	543	163	1.80 (1.37 to 2.36)	1.01 (0.71 to 1.43)
Falls & Fractures (composite)	1771	555	1.94 (1.67 to 2.24)	1.16 (0.97 to 1.40)
Falls	1640	514	1.96 (1.69 to 2.29)	1.10 (0.91 to 1.34)
Fractures	720	207	1.62 (1.25 to 2.08)	1.09 (0.83 to 1.43)
Mortality	3860	1370	2.36 (2.09 to 2.67)	1.33 (1.19 to 1.48)

Table 8 Target trial 1 – effect of hypoglycaemia in patients with diabetes and dementia

The model for cardiovascular events was adjusted for age, gender, ethnicity, BMI, duration of diabetes therapy, HbA1c, smoking status (ever/never), alcohol use (ever/never), index of multiple deprivation, co-morbidities (amputation history, atrial fibrillation, blindness, liver disease, heart failure, hypertension, neuropathies, Parkinson's disease, peripheral vascular disease, renal disease, retinopathy, rheumatoid arthritis, valvular heart disease, history of MI), medications (insulin, sulfonylureas, other oral hypoglycaemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, Angiotensin-converting enzyme inhibitor (ACEi), dementia drugs)

The model for falls and fractures was adjusted for age, gender, ethnicity, BMI, duration of diabetes management, HbA1c, smoking status (ever/never), alcohol use (ever/never), index of multiple deprivation, co-morbidities (amputation history, atrial fibrillation, blindness, chronic obstructive pulmonary disease (COPD), liver disease, inflammatory bowel disease, heart failure, hypertension, neuropathies, osteoporosis, previous fractures, Parkinson's disease, peripheral vascular disease, renal disease, retinopathy, rheumatoid arthritis, thyroid disease, valvular heart disease, history of cancer that metastasises to the bone), medications (bone protection medications, insulin, sulfonylureas, other oral hypoglycaemics, hypnotics, antipsychotics, antidepressants, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, steroids, Parkinson's medications, ACE-i), dementia drugs

The model for mortality was adjusted for age, gender, ethnicity, BMI, duration of diabetes management, HbA1c, smoking status (ever/never), alcohol use (ever/never), index of multiple deprivation, co-morbidities (amputation history, atrial fibrillation, blindness, COPD, liver disease, heart failure, hypertension, neuropathies, Parkinson's disease, peripheral vascular disease, renal disease, retinopathy, rheumatoid arthritis, valvular heart disease, history of MI, history of cancer that metastasises to the bone), medications (insulin, sulfonylureas, other oral hypoglycaemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i), dementia drugs

	Number of events, n		Adjusted HR (95% CI) Up to one-year follow-up	Adjusted HR (95% CI) 12-60 months follow-up
	Dementia, hypoglycaemia (n=1679)	No dementia, hypoglycaemia, (n=12180)	Complete case analysis (n=11683)	
Adverse events				
Cardiovascular (composite)	271	2297	1.14 (0.95 to 1.36)	0.91 (0.71 to 1.17)
MI	119	1366	0.84 (0.64 to 1.10)	0.70 (0.75 to 1.00)
Stroke	163	1097	1.41 (1.12 to 1.78)	1.22 (0.89 to 1.69)
Falls & Fractures (composite)	555	2642	1.72 (1.51 to 1.96)	1.71 (1.44 to 2.04)
Falls	514	2266	1.82 (1.59 to 2.09)	1.69 (1.40 to 2.03)
Fractures	207	1208	1.36 (1.09 to 1.71)	1.39 (1.08 to 1.80)
Mortality	1370	6142	1.27 (1.15 to 1.41)	2.15 (1.94 to 2.37)

Table 9 Target trial 2 – the effect of presence or absence of dementia

The model for cardiovascular events was adjusted for age, gender, ethnicity, BMI, duration of diabetes therapy, HbA1c, smoking status (ever/never), alcohol use (ever/never), index of multiple deprivation, co-morbidities (amputation history, atrial fibrillation, blindness, liver disease, heart failure, hypertension, neuropathies, Parkinson's disease, peripheral vascular disease, renal disease, retinopathy, rheumatoid arthritis, valvular heart disease, history of MI), medications (insulin, sulfonylureas, other oral hypoglycaemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i).

The model for falls and fractures was adjusted for age, gender, ethnicity, BMI, duration of diabetes management, HbA1c, smoking status (ever/never), alcohol use (ever/never), index of multiple deprivation, co-morbidities (amputation history, atrial fibrillation, blindness, COPD, liver disease, inflammatory bowel disease, heart failure, hypertension, neuropathies, osteoporosis, previous fractures, Parkinson's disease, peripheral vascular disease, renal disease, retinopathy, rheumatoid arthritis, thyroid

disease, valvular heart disease, history of cancer that metastasises to the bone), medications (bone protection medications, insulin, sulfonylureas, other oral hypoglycaemics, hypnotics, antipsychotics, antidepressants, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, steroids, Parkinson's medications, ACE-i).

The model for mortality was adjusted for age, gender, ethnicity, BMI, duration of diabetes management, HbA1c, smoking status (ever/never), alcohol use (ever/never), index of multiple deprivation, co-morbidities (amputation history, atrial fibrillation, blindness, COPD, liver disease, heart failure, hypertension, neuropathies, Parkinson's disease, peripheral vascular disease, renal disease, retinopathy, rheumatoid arthritis, valvular heart disease, history of MI, history of cancer that metastasises to the bone), medications (insulin, sulfonylureas, other oral hypoglycaemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i)

Table 10 Median time to outcome

	Median time to outcome, median days (25th to 75th percentile)		
	Dementia, no hypoglycaemia	**Dementia, hypoglycaemia**	**Hypoglycaemia, no dementia**
Outcome			
Cardiovascular (composite)	397 (152 to 762)	153 (21 to 574)	326 (53 to 793)
Falls & Fractures (composite)	359 (136 to 751)	145 (4 to 461)	341 (50 to 863)
Mortality	618 (266 to 1047)	334 (80 to 779)	350 (80 to 877)

Sensitivity analyses (Tables 11 and 12)

Certain lifestyle variables such as BMI, alcohol, smoking status and HbA1c were not regularly measured or necessarily measured close to the exposure. My findings did not substantially change when using different methods to account for the missing data.

Table 11 Models used to investigate missing or incomplete data for target trial. 1 (12 months follow-up)

	Unadjusted HR (95% CI)	Model 1*† aHR (95% CI)	Model 2* aHR (95% CI)	Model 3* aHR (95% CI)
Adverse events during follow-up				
Cardiovascular (composite)	2.11 (1.77 to 2.52)	1.79 (1.48 to 2.16)	1.78 (1.48 to 2.16)	1.77 (1.45 to 2.14)
Falls & Fractures (composite)	1.98 (1.76 to 2.23)	1.80 (1.58 to 2.05)	1.80 (1.59 to 2.06)	1.79 (1.58 to 2.04)
Mortality	2.58 (2.35 to 2.83)	2.34 (2.13 to 2.59)	2.33 (2.11 to 2.57)	2.32 (2.10 to 2.56)

Model 1: Regression model excluding the following covariates: BMI, HbA1c, smoking status and alcohol status
Model 2: Regression model with BMI and HbA1c as categorical covariates with missing category
Model 3: Regression model with multiple imputation of continuous covariates HbA1C and BMI

* The amount of missing lifestyle data for continuous variables was as follows: HbA1c within the last 18 months: 2042 (10.2%), BMI within the last three years: 2916 (14.6%).

†An up to date (within 3 years of index date) record of smoking or alcohol history was not available in 2570 (12.9%) participants and 5667 (28%) participants respectively.

Table 12 Models used to investigate missing or incomplete data for target trial 2 (12 months follow-up)

	Unadjusted HR (95% CI)	Model 1* † aHR (95% CI)	Model 2* aHR (95% CI)	Model 3* aHR (95% CI)
Adverse events during follow-up				
Cardiovascular (composite)	1.20 (1.03 to 1.40)	1.03 (0.88 to 1.21)	1.00 (0.85 to 1.17)	0.99 (0.84 to 1.16)
Falls & Fractures (composite)	2.32 (2.07 to 2.60)	1.61 (1.43 to 1.82)	1.62 (1.44 to 1.83)	1.60 (1.42 to 1.81)
Mortality	1.84 (1.69 to 1.99)	1.39 (1.28 to 1.51)	1.35 (1.25 to 1.47)	1.35 (1.24 to 1.47)

Model 1: Regression model excluding the following covariates: BMI, HbA1c, smoking status and alcohol status
Model 2: Regression model with BMI and HbA1c as categorical covariates with missing category
Model 3: Regression model with multiple imputation of continuous covariates HbA1C and BMI

* The amount of missing lifestyle data for continuous variables was as follows: HbA1c within the last 18 months: 2042 (10.2%), BMI within the last three years: 2916 (14.6%).

† An up to date (within 3 years of index date) record of smoking or alcohol history was not available in 2570 (12.9%) participants and 5667 (28%) participants respectively.

Emergency department attendances (Table 13)

The rate of ED attendances in patients with dementia and hypoglycaemia was 113 per 100 patient-years. The rate in those with dementia but no hypoglycaemia was 64 per 100 patient-years (aRR 1.43 [95% CI 1.30 to 1.57]).

Table 13 ED attendances across entire study duration

	Patients exposed	Numbers of outcomes	Events per 100- person years	Target trial 1 aRR (95% CI)	Target trial 2 aRR (95% CI)
ED attendances				1.43 (1.30 to 1.57)	1.22 (1.10 to 1.34)
Dementia, no hypoglycaemia	6134	9156	64		
Dementia, hypoglycaemia	1679	3110	113		
Hypoglycaemia, no dementia	12180	16451	51		

Adjusted for age, gender, index of multiple deprivation quintile, ethnicity, HbA1c, medications (insulin, sulfonylureas, antipsychotics, hypnotics), co-morbid conditions (amputation, atrial fibrillation, blindness, COPD, liver disease, heart failure, hypertension, inflammatory bowel disease, neuropathies, osteoporosis, Parkinson's disease, peripheral vascular disease, previous fractures, renal disease, rheumatoid arthritis, thyroid disease, retinopathy, cancers that metastasise to bone, diabetes duration)

4.6 Discussion

I have shown that older people with dementia and diabetes who have had a hypoglycaemic event have substantially higher risk of death, cardiovascular events, falls, fractures and emergency department attendances, than those who have not had a hypoglycaemic event.

The hazard ratios of complications were found to be greatest within the first 12 months of follow-up, which would be consistent with a clinically and biologically plausible relationship. The magnitude of risk diminished with longer follow-up time, which indicates that our findings are probably not related to residual confounders. This is because persistent residual confounding (such as greater frailty) would more likely be associated with constantly elevated hazard ratios for adverse outcomes across the entire duration of follow-up.

The results underscore the importance of management strategies tailored towards avoidance of hypoglycaemic episodes rather than just chasing tight glycaemic targets in this vulnerable group. This is of particular significance in the light of recent findings that asymptomatic hypoglycaemic episodes are often missed in older people with diabetes[73], as this study may only be looking at the tip of the iceberg regarding the impact of hypoglycaemia.

Furthermore, the higher risk in the first 12 months would be clinically consistent with the potential impact of an acute episode of hypoglycaemia, especially if the underlying harm stems from cardiac damage. For example, Pistrosch et al's study of CGM and ambulatory cardiac monitoring found a link between hypoglycaemia and the occurrence of ventricular arrhythmias[99]. A recently published meta-analysis confirmed that hypoglycaemia can result in

ECG changes associated with cardiac arrhythmias that are markers of increased risk of mortality and cardiovascular events[131]. Cardiac arrhythmias may be an underlying factor to explain our findings of increased risk of myocardial infarction, stroke, falls and death following hypoglycaemia. Nevertheless, the effects of hypoglycaemia on the cardiovascular physiology of frail, multi-morbid older patients with diabetes remains unclear.

More recent studies estimated the link between hypoglycaemia and accelerated cognitive decline. Hypoglycaemia in older people is linked to an increased risk in cognitive decline[7] and another recent study found that hypoglycaemia was associated with smaller total brain volume on MRI[68]. Cognitive decline may in turn pre-dispose older frail people to falls, fractures and death following hypoglycaemia. This ties in with my findings that dementia contributes to greater hazards in terms of mortality, falls and fractures in older patients with hypoglycaemia. My study demonstrates that co-morbid dementia and diabetes is a particularly challenging, high-risk condition in older people where carefully tailored strategies will be needed to minimize the serious consequences of hypoglycaemia.

However, the effect of co-existing dementia on subsequent risk of myocardial infarction in older people with hypoglycaemia has not been established here. Diagnostic difficulty or misclassification may be a source of bias towards the null because of under-ascertainment of coronary events. Older people with myocardial infarction can present with vague symptoms such as shortness of breath, nausea, sweating or collapse, which may result in an acute cardiac event going unrecognised. Alexander et al found that only 40% of over 85-year-

olds presented with the typical symptom of chest pain when experiencing an acute myocardial infarction[132 133]. Patients with co-morbid dementia may not be sufficiently able to communicate their symptoms, and symptoms such as shortness of breath and sweating could, for example, be misdiagnosed as pneumonia on initial presentation. Bronchopneumonia is reported as the most common cause of death in older patients with dementia[134 135]. Presence of cognitive impairment may also affect rates of diagnosis for other outcomes including fractures and strokes.

4.6.1 Strengths and limitations

The strengths of this study include the size of the cohort of nearly 20,000 patients and the number of covariates that I used to address confounding. I am aware that differences in patient characteristics and medication could be potentially important contributors to risk of adverse outcomes. Hence, the registered protocol specified the inclusion of several key variables (such as age, insulin use and co-morbidities) to reduce confounding in the adjusted statistical model. As I am presenting the results of an observational study, I am not able to prove a causal link, however, this study does demonstrate that hypoglycaemia is a marker of risk for subsequent adverse events.

The three areas which carry some risk of bias in my study are: reliability of capture of potential confounders, missing data and classification of intervention. I am aware that in some patients, covariates such as BMI, HbA1c, smoking and alcohol status may not have been regularly documented in the preceding period before the exposure. However, I used three different

methods to address this issue in our sensitivity analyses, all of which yielded similar results.

My findings are principally applicable to severe hypoglycaemic events, which require medical assistance and hence result in an entry on an individuals' medical records. Large trials have used the same methodology in assessing severe hypoglycaemia and its complications, and my approach is therefore compatible with current research practice[136 137]. I recognize that risk of subsequent complications may be of greater magnitude due to the severity of the hypoglycaemia and I cannot determine whether self-managed or asymptomatic hypoglycaemia are associated with a similar or lower risk of serious consequences. However, in the absence of large CGM trials in older people with diabetes and dementia, there are no means of reliably detecting mild or asymptomatic hypoglycaemic episodes for research purposes. Hypoglycaemic episodes documented in primary and secondary care healthcare records are currently the only available source.

In addition, I am not able to accurately ascertain from the database the precise timing of the hypoglycaemic episode and what the blood glucose concentrations were, although, by virtue of the fact that these hypoglycaemic episodes have been recorded on the medical database, one would assume that they were of a severity that warranted being brought to the attention of the patient's healthcare team. Moreover, I have not attempted to analyse the effects of recurrent hypoglycaemia because very few patients experienced recurrent events in previous studies using the same database [138 31].

Similarly, I am not able to accurately determine dementia severity or duration from onset due to the insidious onset and substantial variation in clinical presentation which makes it difficult to reliably capture and code in a GP database.

A combination of less rigorous management regimes, but greater intensity of monitoring should be considered to reduce hypoglycaemia in this vulnerable population. Simply changing or loosening HbA1c targets for the older frail population may not help in reducing hypoglycaemic events. The risk of hypoglycaemia may also have some relationship to variability, rather than low absolute values of HbA1c, as demonstrated in a recent paper reporting that a slight change in HbA1c variability resulted in a more than five-fold risk of hospitalization due to hypoglycaemia[138].

Future research has to focus on a RCT (in older people with diabetes and dementia), where the treatment strategy would be aimed at minimizing hypoglycaemic episodes. An essential component of the trial would be the use of CGM, in order to capture hypoglycaemic episodes that may otherwise go unrecorded and guide the hypoglycaemia minimization strategy (by means of analysing ambulatory glucose profiles obtained through CGM), in addition to being a useful and supportive tool for carers in their day to day care of this vulnerable group of older people.

To sum up, hypoglycaemia is associated with greater risk of subsequent complications such as falls, fractures and death in patients with dementia. Future work should focus on personalized management of diabetes and

monitoring strategies in those with co-morbid dementia, aiming for an optimal balance of treatment effect whilst minimizing risk of hypoglycaemia.

Chapter 5 - Meta-Analysis: Association between Hypoglycaemia and Serious Adverse Events in Older Patients Treated with Glucose-Lowering Agents

5.1 Preamble

The fourth chapter explored the association between hypoglycaemia and serious adverse events in older patients with diabetes and dementia. I have previously published meta-analyses on adverse events (dementia, macro- and micro-vascular events, falls and fractures, and death associated with hypoglycaemia[6 7]. However, since those publications in 2016, I am aware of the publication of several new studies on adverse events associated with hypoglycaemia, including my study discussed in the previous chapter. Hence, I have updated my meta-analyses and present a comprehensive review of the up to date evidence regarding the association between hypoglycaemia and adverse events in older people.

5.2 Chapter summary

5.2.1 Aims:

I aimed to conduct a meta-analysis of serious adverse events (dementia, macro- and micro-vascular events, falls and fractures, death) associated with hypoglycaemia in older patients treated with glucose lowering drugs.

5.2.2 Methods:

Meta-analysis of studies reporting on hypoglycaemia and adverse events. My search included searches from two previous systematic reviews I published, and I updated the search of MEDLINE and EMBASE for a five-year period between April 2014 to April 2019. I assessed study validity based on ascertainment of hypoglycaemia, adverse events and adjustment for confounders and conducted random effects inverse variance meta-analyses, assessing heterogeneity using the I^2 statistic. Hypoglycaemia was assessed in different ways by the included studies, from relying on hospital or claims data records for hypoglycaemia requiring hird party assistance, to relying on self-reported hypoglycaemic episodes or questionnaires completed by patients.

5.2.3 Results:

I included 42 studies involving 2,137,211 participants.

Meta-analysis of eight studies demonstrated that hypoglycaemic episodes were associated with dementia – pooled OR 1.55 (95% CI 1.33 to 1.79).

Meta-analysis of eighteen studies demonstrated that hypoglycaemic episodes were associated with macrovascular complications, pooled OR 1.81 (95% CI

1.69 to 1.95), and microvascular complications in two studies pooled OR 1.77 (95% CI 1.49 to 2.10).

Meta-analysis of six studies demonstrated an association between hypoglycaemia and falls and fractures, pooled OR 1.78 (95% CI 1.44 to 2.21) and 1.68 (95% CI 1.37 to 2.07) respectively.

Hypoglycaemia was associated with increased likelihood of death in a meta-analysis of eighteen studies, pooled OR 2.02 (95% Confidence Interval 1.75 to 2.32).

5.2.4 Conclusion:

My meta-analysis raises major concerns about a range of serious adverse events associated with hypoglycaemia. Clinicians should prioritize individualized therapy and closer monitoring strategies to avoid hypoglycaemia in susceptible older patients.

5.3 INTRODUCTION

I have previously conducted meta-analyses to analyse the evidence on the relationship between hypoglycaemia and adverse events in older patients treated with glucose lowering drugs[6 7].

My first systematic review looked at the bi-directional relationship between hypoglycaemia and dementia. The key findings of my meta-analyses were a 70% increased risk of deterioration in cognition following hypoglycaemia and conversely a 60% increased risk of hypoglycaemia in older people with dementia. However, this review did not include other major adverse events that may be associated with hypoglycaemia. Hence, I conducted a second systematic review which focused on vascular adverse events, falls and fractures and all-cause mortality. I found a 1.5 times increased risk in macrovascular events (ischaemic strokes, myocardial infarctions) and a doubling of risk in falls, fractures and death.

However, this second review did not find any studies that specifically looked at the effects of hypoglycaemia in older patients who also have dementia. The gaps in the evidence, helped me design the CPRD study, which I discussed in chapter 4.

I am now able to do a more comprehensive systematic review and meta-analysis, which addresses the evidence gaps I identified.

5.4 Material and Methods

I worked from the methods described in my previously published meta-analyses[6 7].

5.4.1 Data sources and searches

The population I was interested in was older adults (above the age of 55 years, which is an arbitrary cut-off). I used the arbitrary cut-off of 55 years because there is no accepted value, and I aimed to be broad rather than too restrictive. The intervention was 'hypoglycaemia' and the comparator 'no hypoglycaemia'. The outcomes of interest were cardiovascular events, falls and fractures, death and dementia.

The searches I ran only included terms for the population and the intervention. The outcomes are too diverse and non-specific for me to be confident that I would capture all the relevant papers if I focused on particular outcomes. For instance, myocardial infarction could be described under a multitude of terms as acute coronary syndrome, ST-elevation myocardial infarction (STEMI) or non-ST elevated myocardial infarction (NSTEMI).

Three searches fed into this systematic review and meta-analysis.

For both previously published reviews, I searched MEDLINE and EMBASE for a ten-year period up to March 2015 with English language restriction and checked the bibliographies of included studies for any potentially suitable studies. In addition, I signed up for the PubMed automated update email notifications of any newly published articles on hypoglycaemia in older patients.

The search strategies were as follows:

Search software: Ovid SP

1. diabetes-mellitus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. older-patient?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. older-adult?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. elderly.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. geriatric.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. veterans.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. hypoglyc?emia.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 2 or 3 or 4 or 5 or 6
9. 1 and 7 and 8
10. limit 9 to (english and last 10 years)

PubMed update

((("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND ("hypoglycaemia"[All Fields] OR "hypoglycemia"[MeSH Terms] OR "hypoglycemia"[All Fields]) AND (("aged"[MeSH Terms] OR "aged"[All Fields] OR ("older"[All Fields] AND "adult"[All Fields]) OR "older adult"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields]) OR geriatric[All Fields] OR ("veterans"[MeSH Terms] OR "veterans"[All Fields]) OR older-patient?[All Fields]))

The updated search I ran was for a five-year period from April 2014 to April 2019. I decided to go back five-years, to make sure that I had not missed studies when conducting the previous two searches.

The search strategy was as follows:

PubMed

("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND ("older patients"[All Fields] OR "older patient"[All Fields] OR "elderly"[All Fields] OR geriatric?[All Fields] OR "veterans"[MeSH Terms] OR "Aged"[MeSH Terms] OR "veterans"[All Fields] OR "older adults"[All Fields]) AND ("hypoglycaemia"[All Fields] OR "hypoglycemia"[MeSH Terms] OR "hypoglycemia"[All Fields]) AND ("2014/04/10"[PDat] : "2019/04/08"[PDat] AND English[lang]).

5.4.2 Study selection

In my analysis, I included cohort studies (prospective and retrospective), which examined the association between hypoglycaemia and serious adverse events in participants aged 55 years and older on glucose-lowering medications. I treated post-hoc analyses of randomized controlled trials as cohort studies, as the analysis is no longer on a prospective randomized basis due to post-hoc classification of patients (with and without hypoglycaemia). I excluded cross-sectional studies. The reason I excluded cross-sectional studies was that it would be impossible to determine whether the intervention (hypoglycaemia) or outcome (adverse events) occurred first.

I included only full journal publications because abstracts are limited in word count and cannot fully describe the statistical models and confounding variables that are of key interest in non-randomized studies.

5.4.3 Data extraction and quality assessment

Study screening and data extraction was performed by me and YKL, by independently scanning all titles and abstracts for relevant articles, before obtaining full text versions for further checking. YKL and I resolved uncertainties and discrepancies through discussion.

Data collection was completed by using a standardized form, which included details of the study design, date of the study and country of origin, setting, selection criteria, participants' characteristics and outcome measures. I extracted relative measures of effect such as odds ratios, risk ratios, and hazard ratios for the outcomes of interest in the group with hypoglycaemia as compared to the controls.

The outcomes (adverse events) of interest were dementia, falls and fractures, composite cardiovascular (macrovascular) and microvascular events and all-cause mortality.

In order to assess study validity, YKL and I independently checked the methods used for recording hypoglycaemia and determining serious adverse events, as well as adjustment for potential confounding factors.

5.4.4 Data synthesis and analysis

I performed a random effects meta-analysis of the relative effect measures using the generic inverse variance method (Revman 5.3, Nordic Cochrane Centre, Kobenhavn). As adverse events are rare, odds ratios and risk or hazard

ratios will yield similar estimates of relative effect, and I have pooled all of them using a random effects model. I chose to perform a random effects meta-analysis, as this method takes heterogeneity into account. The model estimates an average effect and considers differences in intervention effects as random, rather than the single true effect pooled estimate that arises from the fixed effect model.

Heterogeneity is a description of the extent to which the results of studies are consistent with each other.

Heterogeneity was assessed by using the I^2 statistic and visual inspection of the forest plots. The I^2 test was developed to assess the potential extent of heterogeneity in the meta-analysis. The Cochrane Collaboration[139] has issued the following rough guide on interpreting heterogeneity using I^2:

- 0% to 40%: might not be important;
- 30% to 60%: moderate heterogeneity;
- 50% to 90%: substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

I planned to construct a funnel plot if I had more than 10 studies in the meta-analysis (without evidence of statistical heterogeneity - I^2 <50%). Funnel plots are a means of assessing possible bias, in particular that intervention effects of smaller studies differ from intervention effects of bigger studies [139]. It presents a scatter plot of intervention effect estimates of studies included in the meta-analysis and should resemble a funnel. If there is bias, then the scatter plot will appear asymmetrical, although the interpretation/visual inspection of the scatter plots is inherently subjective.

5.5 RESULTS

I screened 3134 citations in addition to the 29 papers that were included in the previous reviews. I included 42 studies with a total of 2,137,211 participants [137 140-146 147 148 149-151 152 68 70-72 122 153-159 160-169 69 170-174].

The flow chart of the study selection is shown in Figure 39. Characteristics of the included studies and participants are shown in Table 14.

Figure 38 PRISMA Flow Diagram

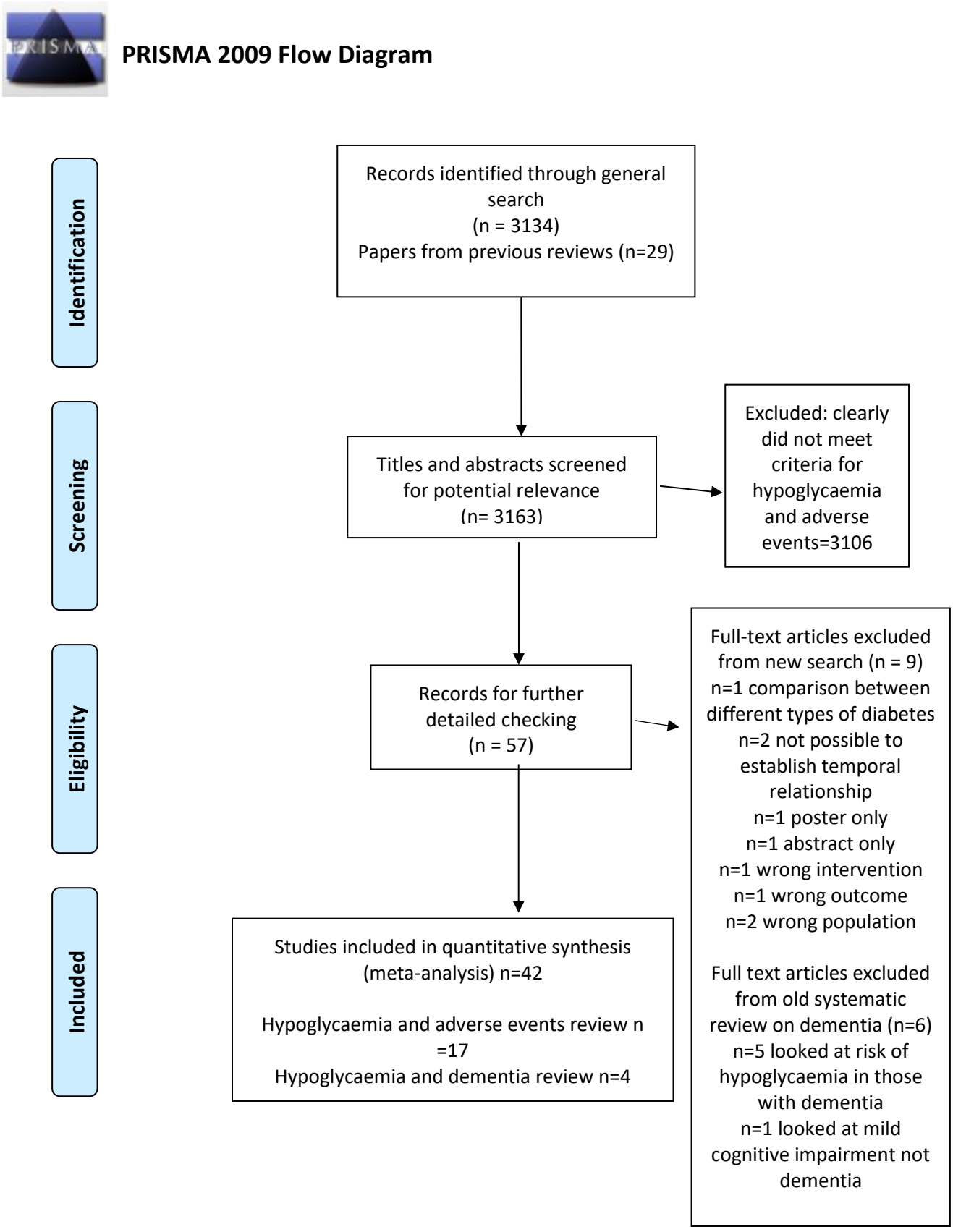


Table 14 Study design and characteristics (new papers highlighted in bold)

Study ID	Design	Data source Number of patients, setting, dates	How were the patients selected for study	Diabetes definition & Patient Characteristics, age, sex (or Selection of Cases and Controls)	Type of glucose lowering agents
Bedenis 2014[140]	Prospective cohort	Edinburgh type 2 Diabetes Study, 1066 participants, Lothian Region Scotland 2006-2010	Lothian Diabetes Register	Type 2 diabetes, mean age 68 years, male 51% 31% previous coronary heart event, 8.7% previous cerebrovascular event, 14% previous MI, 5.8% previous stroke	Oral hypoglycaemic agents, insulin
Bonds 2010[137]	Post hoc analysis of RCT	10,251 77 clinical centres in North America	RCT (ACCORD) in patients with Type 2	Type 2 diabetes, mean age 62.2 years, male 62%. Had either established cardiovascular disease or additional cardiovascular risk factors. Exclusions: past severe hypoglycaemia, BMI >45, serum creatinine >133 micromol/L, other serious illness	Insulin, oral hypoglycaemic agents
Cha 2016[141]	Prospective cohort	Vincent Type 2 Diabetes Registry enrolled between January 2000 to December 2010 (follow-up until May 2015), 1260 participants, South Korea	Consecutive patients attending Diabetes Centre at St. Vincent's hospital	Type 2 diabetes, mean age 55 years, female 59% Exclusions: older than 75 years, mental health illness, unable to undertake self-care, previous episodes of SH, cognitive impairment, alcohol excess, malignancy, end-stage renal disease, severe infection, liver cirrhosis	Insulin, oral hypoglycaemic agents
Chiba 2015[142]	Retrospective	211 Tokyo, Japan, Dec 2009-Apr 2011	Outpatient diabetes clinic attended for ≥one year.	>60 years 168 T2DM patients and 43 age-matched, non-diabetic controls	Oral hypoglycaemic agents Insulin

				Exclusion: blindness, wheelchair/bedridden, end-stage renal disease, adrenal insufficiency, hypopituitarism, hypo/hyperthyroid, uncontrolled hypertension	
Chin 2016[143]	Prospective cohort	Korea National Diabetes Program, 1957 participants, Korea 2006-2014	Korea National Diabetes Program database and Health Insurance Review and Assessment Service of Korea (HIRAS)	Type 2 diabetes, mean age 68 years, 47% male, mean diabetes duration 8 years Exclusions: history of hypoglycaemia. cognitive impairment, previous history of drug misuse, head injury, depression.	Oral hypoglycaemic agents insulin
Cukierman-Yaffe 2019[144]	Post-hoc analysis form ORIGIN trial (RCT)	11,495 participants recruited between 2003 to 2005, 573 sites in 40 countries	ORIGIN trial of insulin glargine versus standard care.	Individuals with impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes who also had additional cardiovascular risk factors Mean age 66 years (SH), 63 years (non-SH), female 26% (SH), 33% (non-SH), baseline mini-mental state examination (MMSE) >24 Median follow-up 6.2 years	Oral hypoglycaemic agents insulin
Davis 2019[145]	Post-hoc analysis of Veterans Affairs Diabetes Trial (VADT)	1791 military veterans 20 Veterans Administration Hospitals across the United States	VADT trial	Type 2 diabetes, 97% male, median follow-up 5.6 years, inadequate response to maximal doses of oral agents or insulin therapy. Exclusions: HbA1c <7.5%, occurrence of a cardiovascular event during previous 6 months, advanced congestive heart failure, severe angina, life expectancy <7 years, BMI>40, serum creatinine level >141	Oral hypoglycaemic agents insulin

				micromol/L, alanine aminotransferase level > three times the upper limit of normal	
Duckworth 2011[146]	Posthoc analysis of RCT	1791 US 1 December 2000 – 30 May 2008	RCT (VADT)	Mean age 60.3 years 97% male T2DM Exclusions: recent cardiovascular event, serious co-morbidities, renal or liver impairment, BMI>40	Insulin, oral hypoglycaemic agents
Escalada 2016[147]	Retrospective cohort	Medicare Advantage claims database 31035 patients 1 January 2007 to 31 December 2012 US	Medicare Advantage claims database	Patients with type 2 diabetes making first pharmacy claim for basal insulin, included if previously on GLP-1 analogs/ oral hypoglycaemic agentes and had at least 2 years of Medicare Advantage coverage. Excluded: previous insulin use (prandial insulin use during follow-up was permitted)	Oral hypoglycaemic agents, insulin
Freemantle 2016[148]	Post hoc analysis of CREDIT study (longitudinal study in patients starting insulin in routine clinical practice)	3601 participants enrolled between 4 December 2006 and 20 April 2008 314 centres in 12 countries	CREDIT study	Primary inclusion criteria: men and women with type 2 diabetes, age >40 years, who had started insulin therapy >1 month and <6 months prior to study entry and who had HbA1c measurement within the 3 months prior to beginning insulin. Mean age 62 years, diabetes duration 11 years, type 2 diabetes.	Oral hypoglycaemic agents, insulin
Goto 2016[149]	Retrospective cohort	Health insurance database 58223 patients Japan	Japan Medical Data Centre Co Ltd database	Inclusion criteria: T2DM or unspecified diabetes, prescription of glucose-lowering agent, observation for a continuous period of at least.6 months from January 2005 to July 2014.	Oral hypoglycaemic agents, insulin

				Exclusions: <18 years or >75 years, type 1 diabetes, severe hypoglycaemia, history of cardiovascular disease (CVD).	
Haroon 2015[150]	Prospective	Canada, Ontario 225045 with newly diagnosed diabetes 668070 without diabetes	Provincial health administrative databases	Seniors with newly diagnosed diabetes and matched comparison cohort without diabetes aged 66-105 between 1 April 1995 to 31 March 2007. Followed until 31 March 2012 for a new diagnosis of dementia. Exclusions: dementia at baseline, individuals living in long-term care facilities	Insulin, oral agents
Heller 2017[151]	Post-hoc analysis of EXAMINE trial (RCT)	5380 patients 49 countries	EXAMINE trial of alogliptin versus standard care and placebo	Type 2 diabetes requiring anti-hyperglycaemic medications with a baseline HbA1c of 6.5% to 11.0% (48-97 mmol/mol or 7.0%-10.0% [53-86 mmol/mol] if on insulin therapy).	Oral hypoglycaemic agents, insulin
Hsu 2013[152]	Prospective cohort	77,611 Taiwan, 1998-2009	Enrolled in National Health Insurance	>60 years, newly diagnosed T2DM (with ≥3 outpatient claims ICD-9-CM code 250) Hypoglycaemic patients with randomly selected and matched non- hypoglycaemics.	Insulin, SU, other drugs
Hung 2017[72]	Cohort	Insurance claims database 2001 to 2009 7761 patients Taiwan	National health Insurance Research Database	Type 2 diabetes, mean age 70 years, male 43%. Controls were frequency matched on age within 5 years, on gender and on duration of diabetes at a ratio of 1:2. Exclusions: pathological fractures, transportation accident before the index date. Median follow-up 3.9 years.	Oral hypoglycaemic agents, insulin

Johnston 2011[154]	Retrospective cohort	860,845 US, 30 September 2006 to 30 September 2008	Thomson Reuters MarketScan Commercial Claims and Encounters (Commercial) database and Medicare database	Age>65 years with T2DM (≥1 claim with diagnosis code) and ≥2 prescriptions claims for antidiabetic drugs. Continuous enrolment and pharmacy benefits throughout 24-month study period, except in case of inpatient death due to acute cardiovascular event. Exclusion: claim with diagnosis code for T1DM.	Oral glucose-lowering agents, insulin
Johnston 2012[153]	Retrospective cohort	361,210 1 April 2008 to 31 March 2010	Thomson Reuters MarketScan Commercial Claims and Encounters (Commercial) database and Medicare Database.	Mean age 75, 52% male, T2DM (≥1 claim with diagnosis code) and ≥2 prescriptions claims for antidiabetic drugs. Continuous enrolment and pharmacy benefits throughout 24-month study period, except in case of disenrolment due to fracture.	Any antidiabetic drugs
Kacharoo 2015[155]	Retrospective cohort study	43,226 US, 2008-2011	Truven Health Market Scan Medicare Supplemental Database, 21,613 hypoglycaemia patients matched with 21,613 non-hypoglycaemia patients.	T2DM Randomly matched to controls 1:1 by age, gender. Age >65 at index date (first T2DM date in the study period). Male 48%	Metformin, SU, Thiazolodinediones, Insulin

Khunti 2015[122]	Retrospective	Total: 265,868 T2DM: 10,422 England & Wales, 2001-2007	CPRD with hospital episode statistics datalink.	All insulin users, age >30 years. T2DM sample mean age 63, male 56% Exclusion: patient without linkage to HES, , pre-index period ≤180 days, hypoglycaemia before index, no diabetes classification, CV event at index.	Insulin, with or without other hypoglycaemic drugs
Kong 2014 - chronic kidney disease (CKD) [156]	Post-hoc analysis of prospective cohort study	Diabetes Registry 8767 patients Hong Kong	Hong Kong Diabetes Registry (Kong 2014 cancer/mortality)	Type 2 diabetes with and without SH in the 12 months before enrolment Exclusions: type 1 diabetes, missing variables used in the analysis	Oral hypoglycaemic agents, insulin
Lee 2018 (CV mortality) [71]	Prospective cohort	1209 patients with diabetes who had been recruited for the Artherosclerosis Risk in Communities study (ARIC) (4th study visit in 1996-1998 Is baseline for this analysis) US	ARIC study	Participants with diabetes identified by self-report of a physician diagnosis or use of glucose lowering medication at 4th ARIC study visit.	No glucose lowering medications, oral hypoglycaemic agents, insulin
Lee 2018 (dementia) [68]	Cross-sectional study (cognitive status) 'Prospective study'-dementia	2011 patients with diabetes who had been recruited for the Artherosclerosis Risk in Communities study (ARIC)	ARIC study.	Participants with diagnosed diabetes by self-report of diagnosis or diabetes medication use at 4th ARIC study visit.	No glucose lowering medications, oral hypoglycaemic agents, insulin

		'Prospective incident dementia' analysis included 1263 participants; the baseline was visit 4 (1996–1998), with follow-up to the end of 2013.			
Leong 2016[157]	Longitudinal cohort	Primary care Network, 9137 participants Massachusetts, US.	Primary care Network.	Type 1 or type 2 diabetes patients without coronary artery disease before 1 January 2006; Follow-up until earliest incident of coronary artery disease (CAD), last clinic visit, death or 30 June 2012. Patients with 1 or more hypoglycaemic events in 200-2005 considered exposed; patients without a reported hypoglycaemic episode before 1 January 2006 were considered unexposed. Exclusions: patients with CAD before 1 January 2006.	Oral hypoglycaemic agents, insulin
Lin 2013[70]	Prospective cohort	Taiwan 15404	National Health Insurance Database	Type 2 diabetes (ICD9-CM), no prior dementia. 45% male, mean age 64. [2% had prior hypoglycaemia – not in baseline characteristics].	Oral hypoglycaemics or insulin
Lu 2015[158]	Cohort study	National Health Insurance Database	Insurance database	Type 1 and type 2 diabetes plus other group without diabetes.	Medications not listed in Table 1

		Taiwan 31049 enrolled in each of three groups, 2000 to 2008.	covering those with at least two outpatient visits for diabetes.	Mean age in patients with diabetes and hypoglycaemia 63 years, 46% male Exclusions: admissions to hospital with cancer or any diagnoses of accident between 1997 and index date.	
Majumdar 2013[159]	Retrospective cohort	85,810 Canada, 2004-2009	Alberta Kidney Disease Network and the provincial health ministry (Alberta Health)	Outpatients age>66 years (mean 75) who had administrative data for both serum creatinine and HbA1c within 6 months of each other 51% female 50% diabetic	Oral hypoglycaemic drugs (mono therapy or combination), insulin
Mattishent 2019[160]	Retrospective cohort	Primary care database 1997-2016 19993 patients	CPRD database	Patients aged 65 or older with diabetes, defined as a first ever prescription of any oral or injectable glucose-lowering agent between April 1997 and March 2016. Eligible participants also needed HES-linked data available. Follow-up continued for up to five years from the exposure, loss from database, death, or end of available database linkage (HES 31 March 2016 and ONS 17 April 2017), whichever was the earlier	Insulin, oral hypoglycaemic drugs
McCoy 2012[161]	Retrospective cohort	1013 Diabetes Clinic, single centre, US August 2005 – July 2006	Medical records	Type 1 and Type 2 diabetes, mean age 60.5 years, male 55%, history of hypoglycaemia established prior to index clinical encounter Exclusions: seven lost to follow-up	Insulin, oral hypoglycaemic drugs
Mehta 2017 [162]	Retrospective cohort	Primary care database	CPRD	New diagnosis of type 2 diabetes from 2003-2012, >65 years on drug therapy.	Oral hypoglycaemic agents, insulin

		53055 patients 2003-2012 UK		Exclusions: dementia diagnosis in a year prior to index date.	
Mellbin 2013[164]	Posthoc analysis of RCT	12,537 40 countries, 2003-2005	International multicentre randomized controlled trial of two different interventions in dysglycaemic individuals with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), newly detected diabetes, or established diabetes	50 years or older (mean age 63.5, 65% male) with cardiovascular risk factors 60% had prior cardiovascular event, 80% had prior diagnosis of diabetes, 6% had newly detected Type2 diabetes, 12% had impaired glucose tolerance or impaired fasting glucose. Median baseline HbA1c 6.4% and fasting plasma glucose 6.9mmol/L.	Insulin glargine, oral hypoglycaemic drugs
Ntouva 2019[163]	Retrospective cohort	Primary care database 1995-2016 41163 participants UK	The Health Improvement Network (THIN)	Type 2 diabetes aged 18 and older, registered in general practices contributing to THIN between 1 January 1995 to 1 May 2016 Follow-up: earliest of transfer date, death date, first documentation of outcome (fracture) or study end date). History of hypoglycaemia=exposed cohort (follow-up from date of hypoglycaemic episodes=index date).	Oral hypoglycaemic agents, insulin

				No history of hypoglycaemia=unexposed cohort. For each exposed patients up to 2 unexposed controls were randomly selected Exclusions: history of fracture.	
Pieber 2018[165]	Post hoc analysis of RCT	DEVOTE RCT – multicentre, double-blind, cardiovascular outcomes trial 7637 patients randomised to either insulin degludec or insulin glargine.	DEVOTE trial	Type 2 diabetes with at least one oral or injectable glucose-lowering agent with HbA1c >7.0% (53mmol/L) or with >20 units/day basal insulin. Eligible for trial if they either had at least one co-existing cardiovascular or renal condition and were aged >50 years or had at least one of a list of pre-specified cardiovascular risk factors and were aged >60 years. NOT excluded if experienced SH prior to randomisation.	Oral hypoglycaemic agents, insulin
Rajpathak 2015[166]	Retrospective cohort	42,747 US, (1 January 2002 to 31 December 2005), with 13195 propensity matched pairs	OptumInsight, medical claims database	>65 years (mean 72.5) with T2DM 1:1 propensity matching score (Sulfonylurea v non-sulfonylurea users). Exclusion criteria: drug supply <30 days, insulin use, prior hip fracture, SU initiation among non-users or discontinuation among users after the index date.	SU
Rathmann 2013[167]	Retrospective	19184 DPP-4 and 31110 SU users (total: 50294) Germany (1201 general practices), April 2007 to July 2010	Primary care data: Disease Analyzer Database (IMS HEALTH)	T2DM with first time prescription (index date) of either DPP-4 inhibitors or SU from Continuous treatment in same practice Mean age 64 (DPP-4) and 69 (SU) Excluded: use of both SU and DPP-4 inhibitor; insulin use at baseline or follow-up, or any other antidiabetic drugs except metformin.	DPP-4 SU

Signorovitch 2013[168]	Retrospective	33,492 US, 1998-2010	Claims database from self-insured companies	T2DM who had filled ≥2 prescriptions for oral hypoglycaemic drugs Mean age 60; Male 50%. Random sample without hypoglycaemia 5:1 ratio to hypoglycaemic patients Exclusion: evidence of insulin use	Oral hypoglycaemic drugs
Standl 2018[169]	Post-hoc analysis of RCT	14671 participants; multi-national, double-blind, placebo-controlled, randomized, trial designed to assess CV safety of sitagliptin vs placebo.	TECOS trial	T2DM, pre-existing coronary, cardiovascular or peripheral atherosclerotic disease, >50 years, baseline HBA1c 6.5-8% (48-64mmol/L) Exclusion: those on DPP4 inhibitor, GLP-1 agonist, Rosiglitazone during the preceding three months, >2SH episodes in the previous 12 months, estimated glomerular filtration rate (eGFR) <30mL/min Follow-up median of 3 years.	Oral hypoglycaemic agents, insulin
Whitmer 2009[69]	Prospective	US 16667	Kaiser Permanente Northern California Diabetes Registry (1980-2007)	T2DM Mean age 66 Male 55% No prior diagnoses of dementia, mild cognitive impairment, or general memory complaints.	Insulin, oral agents
Yaffe 2013[170]	Prospective	US 783	Participants with DM enrolled in Health, Aging, and Body Composition Study. Excluded those with	DM (self-report, use of hypoglycaemia meds, or biochemical testing) Mean age 74 47% black ethnicity 52.4% male Baseline modified MMSE >80 (no pre-existing cognitive impairment)	Insulin, oral agents

			evidence of possible cognitive impairment at study baseline		
Zhao 2012[171]	Retrospective cohort study	44,261 (unmatched sample), 761 hypoglycaemia matched to 761 controls US, January 2004-September 2010	Electronic medical and pharmacy records Veteran Health Administration	T2DM, mean age 63, male 96%. Excluded: patients with 1-year pre-index records of hypoglycaemia, cardiovascular, and microvascular diseases, patients with T1DM	Oral glucose lowering agents, insulin
Zhao 2015[172]	Retrospective cohort study	Cohort 4215 with hypoglycaemia matched to controls US January 2004-July 2010	Electronic medical and pharmacy records Veteran Health Administration	Mean age 76.5, T2DM Excluded: patients with T1DM, patients with 6-month pre-index record of fall.	Oral glucose lowering agents, insulin
Zinman 2018[173]	Post-hoc analysis of RCT	9430 patients Multi-centre, double-blind, placebo-controlled RCT of liraglutide	LEADER trial	Type 2 diabetes; age 50 years or older and established CV disease or chronic renal failure OR age >60 years and risk factors for CV disease, HbA1c >7%. Patients were randomized 1:1 to receive liraglutide or placebo both in addition to standard-of-care treatment and followed for 3.5-5 years. Exclusions: type 1 diabetes, use of GLP-1 agonist, DDP-4 inhibitors, pramlintide, or rapid-acting insulin, history of MEN type 2 or medullary thyroid cancer and occurrence of	Oral hypoglycaemic agents, insulin

				an acute coronary or cerebrovascular event within 14 days before screening and randomization.	
Zoungas 2010[174]	Posthoc analysis of RCT	11,140, 215 centres in 20 countries June 2001 to March 2003	ADVANCE randomized controlled trial of intensive glucose lowering (between)	T2DM, age ≥55 years, diagnosis after the age of 30 and had a history of macrovascular or microvascular disease or at least one other cardiovascular risk factor. Excluded if clear indication for long-term insulin at baseline.	Gliclazide together with other oral glucose lowering agents

The included studies consist of nineteen retrospective, eleven prospective and twelve post-hoc analyses. The studies had a total of 2,137,211 participants (sample size from 211 to 860,845). Geographical locations were diverse and included North America, Canada, Asia and Europe.

Twenty-seven studies focused on patients with T2DM, whereas the remaining studies had a mix of T1DM, T2DM and impaired glucose tolerance/impaired fasting glucose. Four studies looked only at oral agents [166 167 174 168]. The remaining studies included patients with injectable as well as oral antidiabetic drugs.

I report details of study validity (ascertainment of adverse outcomes, and confounding factors) in Table 15 and summarize the key features below.

5.5.1 Measurement of hypoglycaemic events

Most of the studies relied on hospital or claims data records for severe hypoglycaemic events, ie hypoglycaemia that requires help from another person to be managed/treated.

Eleven studies rely on either a history of self-reported hypoglycaemic episodes, questionnaires, or provided participants with diaries and glucometers [164 137 142 161 173 151 169 148 140 141 145]. These studies would be considered to be lower quality because of lack of medical documentation and high risk of recall bias.

5.5.2 Measurement of adverse events

Twelve studies used pre-specified outcomes from RCTs and one non-interventional study[148 137 144-146 148 156 164 165 169 173 174].

27 studies measured adverse events through database or medical records codes, one study relied on a professional interviewer with questionnaire [142]and one study on self-report/GP questionnaires [140].

A diverse variety of tests were used to ascertain dementia for the research studies, which reflects the reality of there not being one single agreed diagnostic test for dementia. Some studies relied on diagnostic coding in medical or insurance records, where it was unclear if any specific validation based on cognitive testing had taken place.

5.5.3 Confounding factors

All studies attempted to account for potential confounding through the use of multivariate logistic regression models, and in addition four studies used Propensity Score Matching [152 164 171 175].

Table 15 Study outcomes, results and risk of bias (new papers highlighted in bold)

Study ID	Method of diagnosing each type of adverse event	Method of diagnosing or determining that patients had hypoglycaemia	Statistical adjustments for confounding factors (if any)	Results
Bedenis 2014 [140]	Primary outcomes were MI (fatal or nonfatal), angina, transient ischaemic attack (TIA), stroke (fatal or nonfatal). Composite macrovascular disease outcome defined as one or more episodes of MI, angina, TIA or stroke. Coronary heart disease defined by occurrence of MI or angina. Cerebrovascular disease defined by occurrence of stroke or TIA. Self-report questionnaire or via GP questionnaire, WHO chest pain questionnaire, ECG and hospital discharge data linkage from Information and Services Division of NHS Scotland	Self-report questionnaire of events within past 12 months (severe hypoglycaemia only)	Univariate and multivariate-adjusted regression models adjusting for age, sex, blood pressure, HbA1c, total cholesterol, HDL cholesterol, BMI, eGFR, duration of diabetes, smoking status, diabetes treatment, cardiovascular medications, microalbuminuria.	Macrovascular disease events aOR 2.11 (1.06 to 4.21); Coronary heart disease events aOR 2.44 (1.13 to 5.26); Cerebrovascular disease events aOR 1.01 (0.29 to 3.61); MI aOR 4.02 (1.54 to 10.48); Stroke aOR 0.86 (0.21 to 3.56).
Bonds 2010 [137]	Pre-specified primary outcome: non-fatal MI or non-fatal stroke and cardiovascular (CV) death Pre-specified secondary outcome: all cause mortality	Investigators asked patients about hypoglycaemic events at each visit. Patients were given home glucose monitors: -symptomatic severe hypoglycaemic event requiring medical assistance (HMA);	Cox regression models (stepwise procedure) Confounders: baseline covariates, age, gender, ethnicity, education, BMI, alcohol, smoking, cardiovascular disease, diabetes	Association between any hypoglycaemic event and mortality intensive arm aHR 1.41 (1.03, 1.93); standard care arm aHR 2.30 (1.46, 3.65).

	Blinded independent adjudication of outcomes	blood glucose <2.8mmol/L or symptoms resolved with treatment -symptomatic severe hypoglycaemic event requiring any assistance (HA)	duration, diabetic complications, cardiovascular risk factors, medication, trial treatment assignment	
Cha 2016 [141]	Primary outcome: death from any cause or cardiovascular death (deaths resulting from acute MI, sudden cardiac death, death due to heart failure, other CV causes) CVD based on review of medical records and diagnosis confirmed by cardiologist, neurologist or neurosurgeon. Causes of death determined from death certificates, clinical records and hospital records	SH – hypoglycaemic episodes requiring medical care in an emergency department or hospitalization. Patients were asked if they had experienced SH and medical records were reviewed for confirmation.	Cox proportional hazards regression with adjustments for: sex, age, duration of diabetes, hypertension, diabetic nephropathy, mean HbA1c, insulin, ACE inhibitor, Angiotension Receptor Blocker (ARB), CVD history	Cardiovascular mortality aHR 6.34 (2.02 to 19.87) All-cause mortality aHR 2.64 (1.39 to 5.02).
Chiba 2015 [142]	Professional interviewer with questionnaire about frequency and type of falls (defined as unexpected event in which the person came to rest on the ground, floor, lower level. Complicated with a head injury or fractures).	Professional interviewer with validated questionnaire regarding hypoglycaemic symptoms. Severe: coma, convulsion, inability of self-management and recovery from symptoms. Mild: hypoglycaemic symptoms with recovery within 10 minutes by self-administered sugar or glucose.	Multiple regression analysis: age, sex, cognitive impairment (MMSE <26), Timed up and go test (TUG) score, Geriatric Depression Scale (GDS)-15 scores, Falls Risk Index, presence of hypoglycaemia.	Presence of hypoglycaemia OR 3.62 (1.24, 10.53), associated with presence of multiple falls, and any fall OR 2.05 (0.93-4.535). Prevalence of falls increased as the frequency of hypoglycaemia increased.

Chin 2016 [143]	Incident cases of dementia and organic mental disorder were identified form HIRAS claim database (ICD-10 codes)	HIRAS claims database (ICD-10 codes). Data on severity or need for hospital admission was not captured.	Cox proportional hazards regression models adjusting for age, sex, smoking status, alcohol status, BMI, diastolic blood pressure, medications, diabetes duration, dyslipidaemia, CVD, cerebrovascular disease	Any events of hypoglycaemia and risk of dementia aHR 2.689 (1.080 to 6.694). Two or more hypoglycaemic events and risk of dementia aHR 4.065 (1.099 to 15.039)
Cukierman-Yaffe 2019 [144]	Incident cognitive dysfunction defined either as reported dementia (first occurrence of an affirmative answer to a case report form question) or a post-randomization MMSE score of <24. Sensitivity analysis conducted using a more restrictive definition of cognitive dysfunction (reported dementia or two consecutive MMSE scores <24 or last available MMSE score <24)	Self-reported, based on questioning of participants and patient diary of capillary glucose. Non-severe hypoglycaemia defined as an event associated with symptoms consistent with hypoglycaemia and confirmed by a capillary glucose reading of <54mg/dL (3mmol/L). SH defined as a symptomatic events requiring assistance of another person and there was prompt recovery after oral carbohydrate, IV glucose or glucagon and/or documented self-measure or laboratory-measured plasma glucose level of <36 mg/dL (2 mmol/L)	Cox proportional hazards regression adjusting for baseline CVD, diabetes status, allocation to glargine, allocation to b-3 fatty acids, HbA1c as a time-varying covariate, age. Accounted for competing risk of death.	Relationship between SH and incident cognitive impairment after adjusting for baseline CVD, diabetes status, treatment allocation: aHR 1.16 (0.89 to 1.52) Model with propensity score for SH: aHR 1.00 (0.76 to 1.31). Sensitivity analysis with more restrictive definition of cognitive impairment: aHR 1.21 (0.90 to 1.63). Non-SH and risk of incident cognitive impairment aHR 0.59 (0.52 to 0.68); Model with propensity score for non-SH aHR 0.58 (0.51 to 0.67). Sensitivity analysis with more restrictive definition of cognitive impairment aHR 0.62 (0.52 to .073).

Davis 2019 [145]	Primary outcome: adjudicated by an end point committee that was unaware of study group assignments. Cardiovascular events were documented MI, stroke, death as a result of cardiovascular causes, new or worsening congestive cardiac failure, surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease, inoperable coronary artery disease and amputation for ischaemic gangrene. Total mortality pre-specified secondary outcome.	SH defined as a self-reported episode of a low blood glucose value accompanied by confusion requiring assistance from another person of loss of consciousness.	Cox proportional hazards regression adjusting for treatment group, overall cardiovascular risk (including factors such as diabetes duration, HbA1c), prior cardiovascular event, insulin use, eGFR	SH within prior three months and association with cardiovascular events and mortality Cardiovascular events aHR 1.90 (1.06 to 3.52); Cardiovascular mortality aHR 3.7 (1.30 to 10.40); All-cause mortality aHR 2.40 (1.10 to 5.10).
Duckworth 2011 [146]	Cardiovascular event is pre-specified composite: MI, stroke, CV death, cardiac failure, vascular surgery, inoperable coronary artery disease, amputation for gangrene Blinded independent adjudication of outcomes	Routine trial monitoring	Multivariate regression analysis Confounders: prior cardiovascular event, age, baseline insulin, ethnicity, smoking status, HbA1c, lipids, creatinine, diabetes treatment and duration	HR for composite cardiovascular event 1.88 (1.03, 3.43).
Escalada 2016 [147]	Hospitalization Secondary outcome: mortality	Medically attended hypoglycaemia events identified from claims database – ICD-9 codes	Cox proportional hazards regression for risk of hospitalization with medically attended hypoglycaemia as the time-varying covariate, adjusting for demographic, comorbidity and medication history factors	Medically attended hypoglycaemia after initiation of basal insulin and risk of hospitalization aHR 1.59 (1.53 to 1.65). Hypoglycaemia and risk of death aHR 1.50 (1.40 to 1.60)

			Three sensitivity analyses for mortality modelling after hypoglycaemia: 1) mortality risk amongst the population with an MI, congestive heart failure, peripheral vascular disease or stroke; 2) population with MI, CHF, peripheral vascular disease (PVD), stroke, dementia or renal disease,3) population without cancer	Sensitivity analyses of hypoglycaemia in patients with different baseline comorbidities: 1) aHR 1.46 (1.34 to 1.58) 2) aHR 1.44 (1.34 to 1.56) 3) 1.48 (1.37 to 1.58)
Freemantle 2016 [148]	Primary outcomes: composite of stroke of myocardial infarction or cardiovascular-specific death; Outcome events reported by investigator in clinical report forms at 6-month intervals; supportive documents requested and adjudicated by three reviewers (ECG, hospital records, biochemistry, radiology reports, medication charts) Cardiovascular events: MI, stable angina, severe unstable angina leading to hospitalization, stroke, TIA, PVD, limb amputation, myocardial revascularization.	Reported by participants based on symptoms, recorded capillary values, and need for assistance. Data were gathered in routine clinical practice, and treating physicians were asked to report updated participant data every 6 months	Cox proportional hazards regression Time-to-event endpoints calculated from date of insulin initiation and were restricted to 54 months	Relationship between reported severe hypoglycaemia and CV death or all-cause mortality CV death and SH aHR 1.10 (0.34 to 3.57) All-cause mortality and SH 1.22 (0.59 to 2.53).
Goto 2016 [149]	Primary outcome: CVD CVD defined as conditions during hospitalization with both a diagnosis of	Severe hypoglycaemia defined by ICD 10 code and prescription	Cox proportional hazards models to evaluate association of SH with CVD risk, adjusted	Association between SH and CVD risk aHR 3.39 (1.25 to 9.18);

	CVD (ischaemic heart disease, stroke, peripheral artery disease) and either a medical procedure performed or a prescription to treat CVD	for either 50% dextrose or glucagon infusion	for age, sex, duration of diabetes, history of microvascular disease, Charlson Co-morbidity index, medications. 5:1 propensity score matching	Propensity-score matched cohort: aHR 7.31 (1.87 to 28.6).
Haroon 2015 [150]	Dementia: defined based on one or more hospitalisation records or two outpatient physician billing claims (within six months) listed relevant ICD-9 claim	Healthcare administrative database records of hospitalisation or emergency department visits for hypoglycaemia	Cox proportional hazard modelling Sensitivity Analyses to examine whether detection bias could explain elevated risk of dementia Models were adjusted for baseline income and co-morbidities, including hypertension, chronic kidney disease and vascular diseases of varying aetiologies. Cumulative incidence functions were used to estimate the probability of occurrence of dementia	Hospitalisation and emergency department visits for hypoglycaemia were significant predictors of dementia aHR 1.73 (1.62 to 1.84) based on comparison of one or more episodes versus none.
Heller 2017 [151]	Primary endpoint in EXAMINE trial: composite of death from cardiovascular causes, nonfatal MI or non-fatal stroke. Independent central adjudication committee adjudicated all suspected	Assessed at study visits at 1, 3, 6, 9 and 12 months post-randomization during the first year of the study and every 4 months during subsequent years of participation. Hypoglycaemic events	Cox proportional hazards models with adjustments for age, sex, treatment, HbA1c, glycaemic medication and stratified by screening renal function and geographic region	Risk of major adverse cardiovascular events (MACE) after reported serious hypoglycaemia aHR 1.60 (0.80 to 3.20); MACE after any hypoglycaemia aHR 1.05 (0.79 to 1.40).

	primary end-point events and other cardiovascular and points, as well as all deaths.	characterised by local investigators according to their intensity (mild to severe) and seriousness (hospitalization or ED management)		
Hsu 2013 [152]	Cancer, stroke, coronary heart disease and cardiovascular disease identified from hospital claims dataset, ICD-9-CM codes Death status ascertained according to discharge reasons with death or critically ill at discharge, or if insurance cover stopped due to death.	Hospital claims dataset for severe hypoglycaemia Outpatient claims dataset for mild hypoglycaemia ICD-9-CM codes	Propensity score, Cox proportional hazard model, Kaplan-Meier Variables in propensity score matching: age, sex, diabetes duration, hypertension, heart disease, renal and liver disease, cancer, mental disease, socio-economic status, treatment adherence.	HR 2.09 (1.63, 2.67) for cardiovascular diseases, HR 2.51 (2.00, 3.16) for all-cause hospitalisation, HR 2.48 (1.41, 4.38) for total mortality
Hung 2017 [72]	Primary outcome: hip fracture after SH Insurance claims ICD-9	Index date was first date of hospitalization or ED hypoglycaemic visit Insurance claims ICD-9.	Cox proportional hazards regression models adjusted for sex, ESRD, COPD, epilepsy, CAD, stroke, dementia, Parkinson's, osteoporosis, retinopathy, neuropathy, alcohol misuse, TZD, oestrogen, acarbose, glinide, metformin, SU, DPP4i, beta blocker, corticosteroid, anti-depressants, NSAIDs, anti-osteoporosis	Risk of hip fracture higher in relation to SH aHR 1.71 (1.35 to 2.16)

Johnston 2011 [154]	Acute cardiovascular events: coronary artery bypass graft, revascularisation, percutaneous coronary intervention – ≥one inpatient or outpatient claim ICD-9-CM code Acute MI, incident unstable angina – ≥1 inpatient claim with an ICD-9-CM code	≥1 outpatient claim with ICD-9-CM diagnosis code for hypoglycaemia (hypoglycaemic events were allowed to occur at any time during the evaluation period, including after acute cardiovascular events)	Multiple logistic regression and backwards stepwise selection Adjusted for age, sex, geography, insurance type, comorbidity scores, cardiovascular risk and prior events, diabetes complications, total baseline medical expenditures.	OR 1.79 (1.69, 1.89) for acute cardiovascular events; Patients >age 65 years OR1.78 (1.65, 1.92)
Johnston 2012 [153]	Emergency department claim with ICD-9-CM diagnosis code	≥1 outpatient claim with ICD-9-CM diagnosis code for hypoglycaemia (hypoglycaemic events allowed to occur at any time during evaluation period, including after fracture)	Multiple logistic regression Confounders: patient demographics, baseline co-morbid conditions, baseline medications, Charlson Co-morbidity Index (CCI), medical encounters for diabetes, total baseline medical expenditures, number of medical codes	aOR for fall-related fractures 1.70 (1.58, 1.83).
Kacharoo 2015 [155]	Admin claim data Fall-related events defined as ICD-9-CM codes 800.x-995.x, with a fall being the external cause defined as ICD-9-CM E-codes E880-E888 which were recorded within +/-2 days of each other in any order. Composite fall events (e.g. fall with head injury or fracture) identified based on two or more claims codes occurring within 2 days.	Admin claim data ICD-9-CM codes 250.8, 251.0, 251.1 and 251.2	Logistic regression analysis Patients matched on age and gender; statistical adjustment on CCI	Risk of fall-related events aOR 1.95 (1.70, 2.2); Fracture – aOR 2.16 (1.74 -2.67).

Khunti 2015 [122]	Cardiovascular event defined as a composite of MI, stroke or cardiovascular death (cause of death obtained through linkage to Office for National Statistics).	Data on hypoglycaemic episodes were obtained from HES via ICD-10 codes 9E16.0, E16.2).	Mutivariate Cox regression models Covariates: age, sex, smoking status, geographical region, history of cardiovascular events before index date, use of oral antidiabetic medications, Charlson comorbidity index, BMI, HbA1c	All-cause mortality for T2DM: HR 1.94 (1.52, 2.47) and 2.39 (2.13, 2.67) for those with and without a history of CVD. Cardiovascular events for T2DM: HR 1.70 (1.09, 2.64) and 1.50 (1.19, 1.88) for those with and without a history of CVD.
Kong 2014 [156]	Ascertained though Hospital Authority Central Computer Management System, which records diagnoses of all hospital discharges, including mortality based on ICD-9 codes. Mortality data cross-checked with Hong Kong Death Registry.	SH defined as one or more hospitalizations for hypoglycaemia in the 12 months before enrolment or during the follow-up period from enrolment to death or 31 January 2009.	Cox proportional hazards regression models with adjustments for age, sex, BMI, smoking satus, alcohol use, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (BP), HbA1c, duration of diabetes, urinary albumin to creatinine ratio, prior CVD, prior cancer, medications at enrolment.	Hazard ratios of severe hypoglycaemia for the risk of all-cause death in patients without CKD aHR 1.81 (1.38 to 2.37).
Lee 2018 [71]	An expert committee adjudicated all coronary heart disease and stroke events (ICD-9 codes). Mortality was assessed via proxy, coroner reports, and the National Death Index through 2013.	Severe hypoglycaemic events were identified from hospitalizations, emergency department visits, and ambulance calls with a validated algorithm, using ICD-9	Cox proportional hazards regression models adjusting for age, sex race-centre, diabetes medication use, duration of diabetes, tertiles of fructosamine, low eGFR,	Association between SH and CV events and all-cause mortality (Model 3); Coronary heart disease aHR 2.02 (1.27 to 3.20); Stroke aHR 0.81 (0.40 to 1.63)

		codes in the primary position through 31 December 2013. Hospitalization records were available from ARIC surveillance of local hospitals. Linked Medicare claims for were also assessed.	albumin-urea ratio, income, disability, systolic BP, hypertension, LDL-C, HDL-C, medications, smoking status (Model 3)	All-cause mortality aHR 1.73 (1.38 to 2.17).
Lee 2018 [68]	Assessment of cognitive status (normal, mild cognitive impairment or dementia) was based on available cognitive test scores from visits 2 (1990–1992), 4 (1996–1998) and 5 (2011–2013), the Clinical Dementia Rating (CDR), based on interviews with participants and informants, the Modified Telephone Interview for Cognitive Status (TICS), hospitalisation records and death certificates. Diagnoses standardised using algorithm, with expert panel review who could clinically over-ride algorithm. For the analysis of incident dementia, a date of dementia diagnosis was assigned as the date of hospitalisation with a dementia ICD-9 code or, if no hospitalisation with dementia occurred, the first date of detection via the TICS or CDR, or visit 5.	Severe hypoglycaemic episodes were identified from hospitalisations, emergency department visits and ambulance calls by a widely used algorithm that employs primary position ICD-9 codes.	Multinomial logistic regression to compare the odds of having mild cognitive impairment or dementia by history of severe hypoglycaemia Prospective incident dementia analysis, based on Cox regression model for the outcome of incident dementia, with severe hypoglycaemia as a time-varying exposure (4 models used, adjusting for covariates).	Prospective association of severe hypoglycaemia with incident dementia among ARIC participants with diagnosed diabetes at visit 4 in the prospective incident dementia analysis Model 4 aHR 2.28 (1.58 to 3.29).

Leong 2016 [157]	Electronic health record repository, including outpatients, emergency department and inpatient visits. iCD-9 code-cased algorithm	Hypoglycaemia defined as hypoglycaemia brought to medical attention. ICD-9 code-based algorithm capturing healthcare use.	Three Cox models for incident CAD constructed, Model 3 fully adjusted adjusting for sex, age, educational attainment, CAD risk factors, insulin, oral hypoglycaemics, total medication count, retinopathy, neuropathy, renal failure, eGFR, LDL < HDL, cancer, dementia, dysrhythmias, hospitalizations, weight loss within a year, HbA1c measurements per year.	Hypoglycaemia and associated CAD risk aHR 1.90 (1.09 to 3.31) Risk diminished with time after event. Fully adjusted model aHR 1.65 (0.95 to 2.87).
Lin 2013 [70]	Dementia: ICD9-CM Method of diagnosing not stated	ICD9-CM Method of diagnosing not stated	Multivariable Cox proportional hazard analysis Age, gender, co-morbidities (Ischaemic heart disease, cardiovascular disease, hyperlipidaemia, chronic renal disease, hypertension), insulin use.	Adult diabetic patients with prior hypoglycaemia had a significantly increased risk dementia: aHR 1.45 (1.07 to 1.97);
Lu 2015[158]	Falls needing admission to hospital – fall-related diagnosis code in discharge diagnosis during the follow-up (ICD-9 codes). Unable to distinguish between the falls occurring before or during hospitalization.	SH defined as presence of ICD-9 codes in outpatient and inpatient visits before the index date.	Proportional hazards regression models. Fine & Gray competing risks model to account for mortality. Sequential construction of multivariate regression. Adjustments for age, sex, type of diabetes, geographic area,	Risk of falls in diabetes with hypoglycaemia group - Patients with diabetes but without hypoglycaemia as referent category: Age>65 years aHR 1.35 (1.25 to 1.45)

			urbanization status, obesity, mental health problems, neurological, cardiovascular, endocrine, renal, ophthalmic disorders epilepsy, stroke, substance abuse.	
Majumdar 2013[159]	Primary outcome: all-cause mortality Secondary end points included all-cause hospitalisations and hypoglycaemia-associated hospitalisations. Mortality and dates of hospitalisation determined by linkage to provincial health ministry databases.	Defined severe hypoglycaemia by the presence of any inpatient discharge diagnosis of hypoglycaemia (ICD-10 code E15 or E16)	Multivariable Cox proportional hazard methods Adjusted for age, sex, socioeconomic status (based on individual health insurance premium level and median neighbourhood income), index eGFR, prevalent hypoglycaemia, co-morbidities, use of diabetes medications	Mortality associated with any hospitalisation with hypoglycaemia in patients with diabetes: aHR 2.46 (2.17 to 2.80)
Mattishent 2019 [160]	Outcomes were falls, fractures, cardiovascular events (myocardial infarction, ischaemic stroke) and all-cause mortality. Data obtained from CPRD using Read codes and HES with ICD codes	First hypoglycaemic episode recorded on the primary (CPRD) or secondary (HES) healthcare database from April 1997 onwards following initiation of a glucose-lowering agent. Data on hypoglycaemic episodes were obtained from CPRD using Read codes and HES with ICD codes	Cox proportional hazard regression models with adjustments for medications, age, gender, co-morbidities, Townsend deprivation index	Hypoglycaemia was associated with an increased risk during 12 months follow-up of: Falls 1.96 (1.69 to 2.29) Fractures 1.62 (1.25 to 2.08) Cardiovascular events - aHR 2.00 (1.61 to 2.48) Mortality - aHR 2.36 (2.09 to 2.67)
McCoy 2012 [161]	Ascertainment of mortality from medical records and social security death index	Investigator asked patients about hypoglycaemic events	Logistic regression	OR 3.38 (1.55 to 7.39)

		-mild hypoglycaemia: symptoms consistent with hypoglycaemia not requiring any assistance -severe hypoglycaemia: similar symptoms requiring external assistance	Confounders: age, gender, type of diabetes and duration, CCI, HbA1c	Association between severe hypoglycaemia and 5-year mortality
Mehta 2017 [162]	Outcome variable was time to dementia – defined by diagnosis codes from electronic medical records.	Hypoglycaemia defined based on previously defined algorithm for CPRD using Read and Med codes.	Cox multivariable model taking into account competing risks. Adjustments for: age, sex, HbA1c, alcohol use, smoking status, diabetes treatment, co-morbidities associated with dementia.	Association of hypoglycaemia with dementia Fully adjusted model aHR 1.27 (1.06 to 1.51)
Mellbin 2013 [164]	-Composite of cardiovascular death (any death for which no non-cardiovascular cause could be identified), non-fatal MI (based on clinical presentation, elevated cardiac markers, and /or new electrocardiographic changes), or stroke (based on clinical presentation and imaging) -Mortality Blinded independent adjudication of outcomes	Participants recorded hypoglycaemic events with glucose meters and diaries. Investigators asked patients about hypoglycaemic events at each study visit. Non-severe hypoglycaemia: relevant symptoms confirmed by glucose reading <3mmol/L. -severe hypoglycaemia: symptomatic hypoglycaemia requiring assistance of another person with (i) prompt recovery after oral carbohydrate and/or	Propensity score matching, as well as Cox regression models addressing potential confounders: age, gender, ethnicity, education, prior cardiovascular events, hypertension, depression, current smoking, alcohol intake, albumin/creatinine ratio >30 mg/g, diabetes and cardiovascular drugs, BMI, waist-hip ratio, HbA1c, fasting plasma glucose, lipids, serum	In those with severe hypoglycaemia aHR 1.58 (1.24 to 2.02) for composite event. aHR 1.71 (1.27 to 2.30) for cardiovascular death. HR 1.74 (1.39 to 2.19) for total mortality.

		(ii) documented plasma glucose level <2mmol/L	creatinine, mini-mental status, prior diabetes mellitus	
Ntouva 2019 [163]	Primary outcome: any fracture; secondary outcome: fragility fracture Read codes obtained from database	Read codes obtained from database	Incidence Rate Ratios derived using Poisson regression adjusting for covariates: age, sex, BMI, Townsend deprivation index, smoking, CCI, HbA1c, insulin, bisphosphonates, steroid, hyperthyroidism, Graves disease, renal impairment, antihypertensive medications.	Risk of all fractures in patients with documented hypoglycaemia compared to those without aIRR 1.20 (1.12 to 1.30)
Pieber 2018 [165]	Primary outcome: MACE (cardiovascular death, non-fatal MI, non-fatal stroke)	Adjudication-confirmed SH was pre-specified, multiplicity-adjusted secondary outcome as defined by ADA as an episode requiring the assistance of another person to actively administer carbohydrates or glucagon, or to take other corrective action.	Cox regression models Adjustments for age, sex, HbA1c, BMI, diabetes duration, insulin, hepatic impairment, renal status, cardiovascular risk group	Risk of MACE for individuals who had vs those who had not experienced SH aHR 1.38 (0.96 to 1.96); All-cause mortality aHR 2.51 (1.79 to 3.50).
Rajpathak 2015 [166]	Hip fracture defined as an ICD-9 code 820.xx	ICD-9 codes based on validated algorithm	Multivariable logistic regression based on propensity score as well as adjustment for confounders:: age, sex, Medicare cover, region, coronary heart disease, stroke, osteoporosis, dementia, CKD	aOR 2.42 (1.35 to 4.34) for hip fractures in those with documented hypoglycaemia

Rathmann 2013 [167]	Macrovascular complications were determined based on primary care diagnoses (ICD-10 codes) for coronary heart disease (I20, I24 and I25), MI (I21, I22, I23 and I25.2), stroke (I63, I64, G45) and peripheral vascular disease (E10.5, E11.5, E14.5 and I73.9)	ICD-10 coding (E16.0, E16.1, E16.2) Frequency of patients with >1 hypoglycaemic event assessed 30, 90, 183, 365 and 730 days after index date	Adjusted for age, sex, type of practise (diabetologist), practise region, health insurance status (private), antidiabetic co-medication, episodes of hypoglycaemia, microvascular complications, hypertension, hyperlipidaemia, antihypertensive, lipid-lowering and antithrombotic drugs and Charlson co-morbidity index	aHR 1.6 (1.1 to 2.2) for incident macrovascular complications
Signorovitch 2013 [168]	Inpatient and emergency department claims based on ICD9-CM codes, grouped into three codes: accidental falls, motor vehicle accidents and other accidents	ICD-9-CM codes for hypoglycaemia at any place of service	Multivariable Cox-proportional hazard models adjusted for age, gender, demographics, co-morbidities of diabetes, accident risk factors, CCI, inpatient admissions, use of oral hypoglycaemics.	Hypoglycaemia associated with accidental falls aHR 1.36 (1.13 to 1.65) For age >65: aHR 1.52 (1.18 to 195)
Standl 2018 [169]	Primary 4-point composite MACE: first confirmed event of CV death, non-fatal MI, nonfatal stroke or hospitalization for unstable angina Secondary outcome: 3-point MACE (CV death, nonfatal MI/nonfatal stroke), fatal/nonfatal MI, fatal/nonfatal stroke, all-cause death, hospitalization for heart failure	Proactive enquiry at screening/enrolment, 4-month, 8-month visits and then annual visits. SH episodes were recorded systematically as prespecified events of clinical interest: episodes in which a participant was sufficiently disorientated or incapacitated as to require help.	Cox regression models Adjustments for age, sex, race, ethnicity, HbA1c, New York Heart Association (NYHA) class, smoking, MI, COPD, CAD, stroke, >50% stenosis of carotid artery, atrial flutter/fibrillation, insulin, amputation, diabetic neuropathy, foot ulcer, blood pressure, heart rate, height, BMI, eGFR, randomized	SH association with primary composite CV end point aHR 1.55 (1.06 to 2.28); All-cause mortality aHR 1.83 (1.22 to 2.75); CV death aHR 1.72 (1.02 to 2.87).

	Adjudicated by independent clinical events classification committee		treatment, diabetes duration, geographical region.	
Whitmer 2009 [69]	Dementia: inpatient and outpatient databases based on ICD9-CM	Hospitalisation and ED diagnoses of hypoglycaemia using hospital/ED databases ICD9-CM	Cox proportional hazard regression models, adjusted for age, sex, race/ethnicity, education, BMI, duration of diabetes, 7-yr mean HbA1c, diabetes treatment,	History of severe hypoglycaemic episodes was associated with a greater risk of dementia: aHR 1.44 (1.25 to 1.66)
Yaffe 2013 [170]	Dementia: hospital records indicating an admission associated with dementia or the use of prescribed dementia medications	Hospital records: severe hypos requiring admission and identified as primary or secondary diagnosis related to overnight hospitalisation. No information on milder hypos not requiring admission	Cox Proportional Hazard Regression. Adjustments for age, educational level, race/ethnicity, and any other covariates significantly associated with severe hypoglycaemia or dementia in bivariate analysis	Hypoglycaemia associated with increased risk of dementia: aHR 2.09 (1.00 to 4.35)
Zinman 2018 [173]	Primary composite outcome: first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Adjudicated by blinded, external, independent committee.	Self-reported hypoglycaemia was a secondary safety endpoint, reported using patient diaries and transcribed into case report form. SH defined as requiring assistance of another person to administer fast-acting carbohydrates, glucagon or other resuscitative action – reported as a medical event of special interest.	Cox regression to analyse time to first MACE, CV death, non-CV death or all-cause mortality with either SH at any time (yes/no) as a factors or with hypoglycaemia (SH or confirmed, yes/no) as a time-dependent covariate. Adjustments for randomized treatment, baseline covariates, concomitant insulin use, HbA1c during trial, concomitant	MACE up to one year with SH aHR 1.90 (1.30 to 2.90) All-cause death up to one year with SH aHR 2.70 (1.90 to 3.90).

		Confirmed hypoglycaemia defined as SH or minor hypoglycaemia (<3.1mmol/L). Nocturnal hypoglycaemia defined as episodes occurring between 00:01 and 05:59h. Patients asked to check blood glucose whenever a hypoglycaemic episode was suspected.	sulfonylurea/glinide use, eGFR and event adjudication committee-confirmed hospitalization for heart failure during the trial (time-dependent covariates)	
Zhao 2012 [171]	ICD-9-CM codes. Macrovascular: MI, stroke, congestive heart failure, peripheral vascular disease. Microvascualr: renal, ophthalmic or neurologic manifestations with diabetes.	ICD-9-CM codes	Propensity score matching (greedy 5 to 1 method) for noncomparable baseline characteristics Cox proportional hazard regression models controlling for covariates, including baseline demographic and illness characteristics, vital signs, prior medication, and index drug	aHR 2.00 (1.63 to 2.44) for cardiovascular events, aHR 1.76 (1.46 to 2.11) for microvascular complications aHR 1.29 (0.94 to 1.77) for mortality.
Zhao 2015 [172]	ICD-9-CM codes for fall-related events (fractures, head injuries) with a fall being the external cause within a two-day window.	ICD-9-CM codes	McNemar tests, Generalised estimating equation (GEE). Matching on age, gender, ethnicity and medical service. Adjustments for social demographic and illness characteristics, vital signs and medication use.	aOR 2.70 (1.64 to 4.47) for fall-related events in the hypoglycaemia group

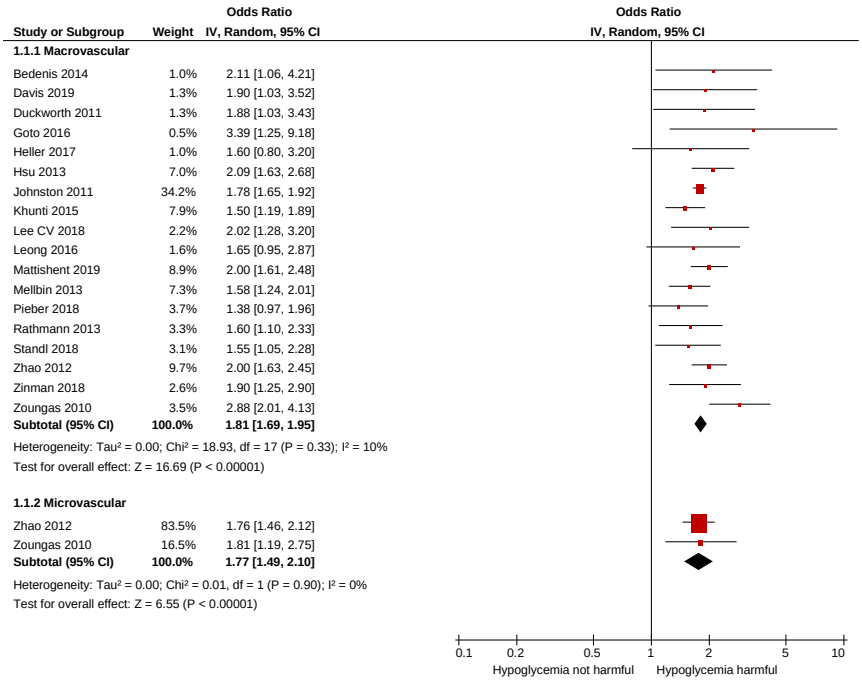
Zoungas 2010 [174]	First major macrovascular event=death from cardiovascular cause, non-fatal MI, non-fatal stroke First major microvascular event=new or worsening nephropathy or retinopathy Secondary outcomes=death from any cause and death from a cardiovascular event Independent adjudication by blinded committee	Blood glucose level <2.8 mmol/L or typical symptoms/signs without other apparent cause. Those with transient neurological dysfunction who required help from 3rd party were considered to have severe hypoglycaemia. Minor hypoglycaemia if transient dysfunction of CNS and able to treat themselves.	Cox proportional-hazard models adjusted for covariates. Baseline: sex, duration of diabetes, treatment allocation, history of macrovascular or microvascular disease, ever smoker. Time dependent covariates during follow-up: age, HbA1c, body mass index, creatinine, urine albumin to creatinine ratio, systolic blood pressure, diabetes and blood pressure drugs.	aHR 2.88 (2.01 to 4.12) major macrovascular events, aHR 1.81 (1.19 to 2.74) major microvascular events, aHR 2.68 (1.7 to 4.19) death from cardiovascular cause, aHR 2.69 (1.97t o 3.67) death from any cause

5.5.4 META-ANALYSIS

5.5.4.1 ASSOCIATION BETWEEN HYPOGLYCAEMIA AND VASCULAR DISEASE

I included eighteen studies in the meta-analysis for macrovascular complications[140 145 146 149 151 152 71 122 154 157 160 164 165 167 169 171 173 174]. The pooled odds ratio was 1.81 (95% CI 1.69 to 1.95). There was low heterogeneity (I^2=10%). Hypoglycaemia was significantly associated with macrovascular complications. There are two studies in the meta-analysis which reported on the association between hypoglycaemia and microvascular complications [174 171]. The microvascular complications covered in the study were nephropathy or retinopathy [174] and a composite endpoint of several complications [171]. The pooled odds ratio was 1.77 (95% CI 1.49 to 2.10) with no evidence of heterogeneity (I^2=0%) (Figure 40).

Figure 39 Meta-analysis of association between hypoglycaemia and vascular events

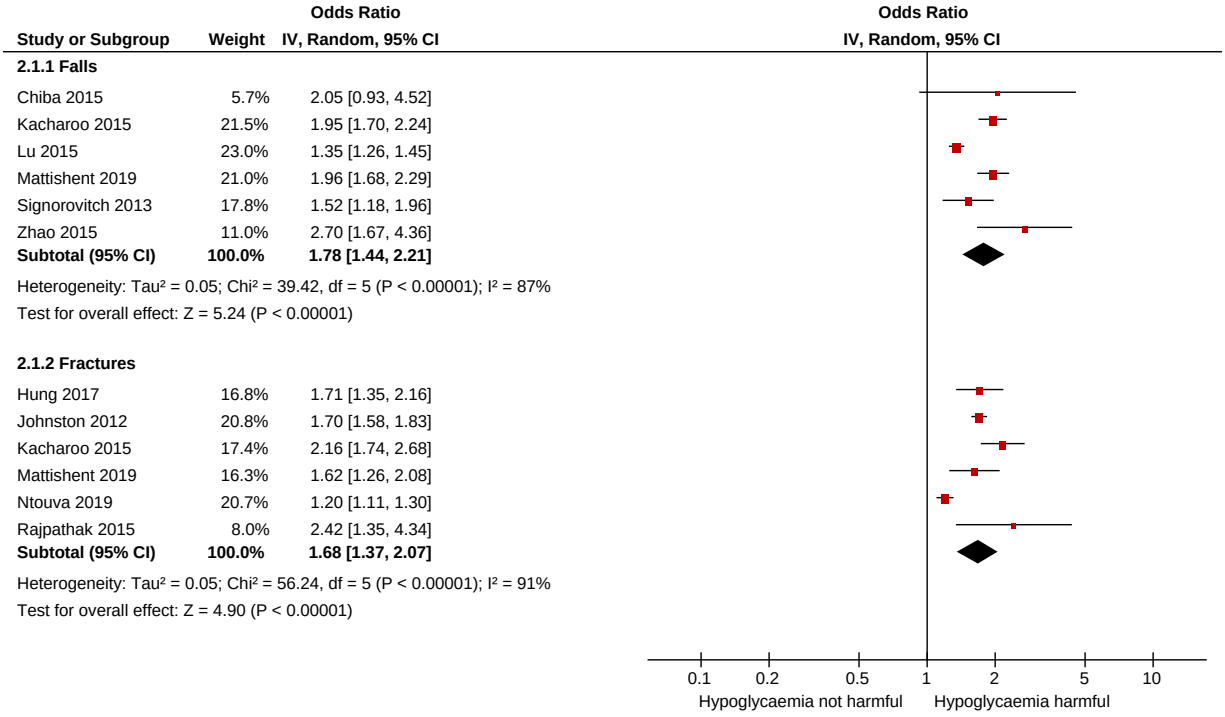


5.5.4.2 Association between hypoglycaemia and falls or fractures

There are six studies reporting on falls[142 155 160 158 168 172]with a pooled odds ratio of 1.78 (95% CI 1.44 t0 2.21) and substantial heterogeneity (I^2=87%).

I included six studies for fractures with a pooled odds ratio of 1.68 (95% CI 1.37 to 2.07) and considerable heterogeneity (I^2=91%) [160 72 153 155 163 166] (Figure 41).

Figure 40 Meta-analysis of association between hypoglycaemia and falls and fractures



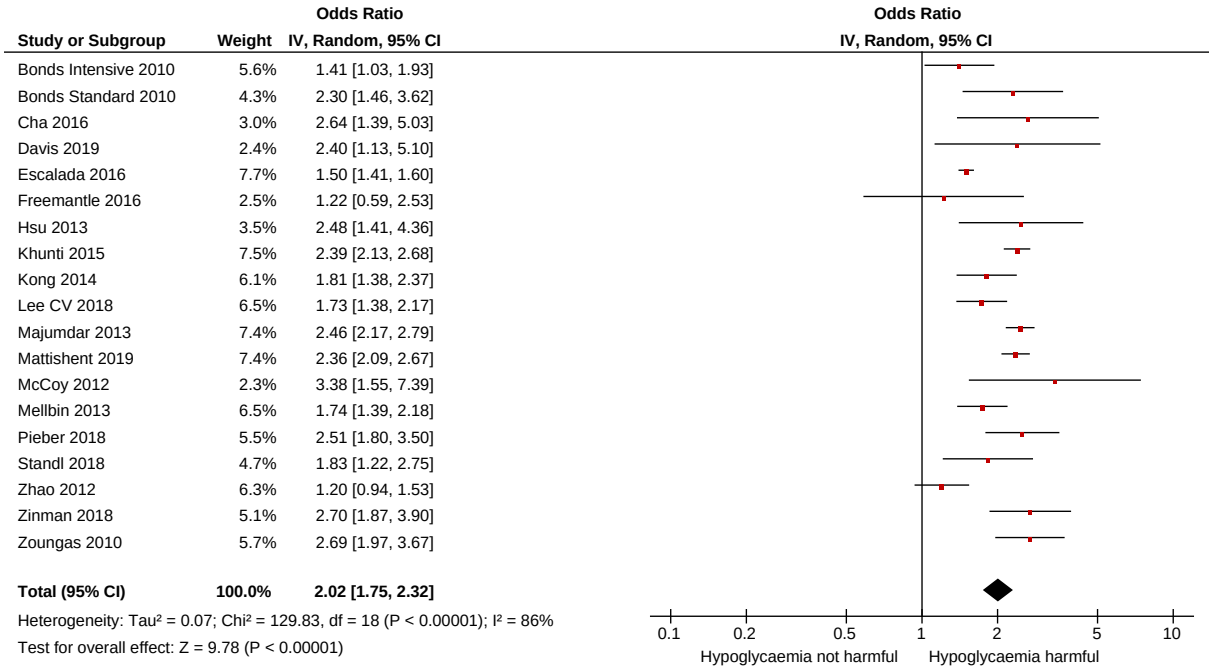
5.5.4.3 Association between hypoglycaemia and mortality

There are eighteen studies reporting on overall mortality with a pooled odds ratio of 2.02 (95% CI 1.75 to 2.32) with substantial heterogeneity (I^2=86%)[71 122 137 141 145 147 148 152 156 159-161 164 165 169 171 173 174] (Figure 42).

Despite the heterogeneity, the direction of association was consistent across all the studies in the Forest plot.

Two studies did not find a statistically significant association between hypoglycaemia and mortality [148 171]. I explored the contribution of these two studies to the heterogeneity, by removing them, one at a time, and found that it made no difference to the heterogeneity.

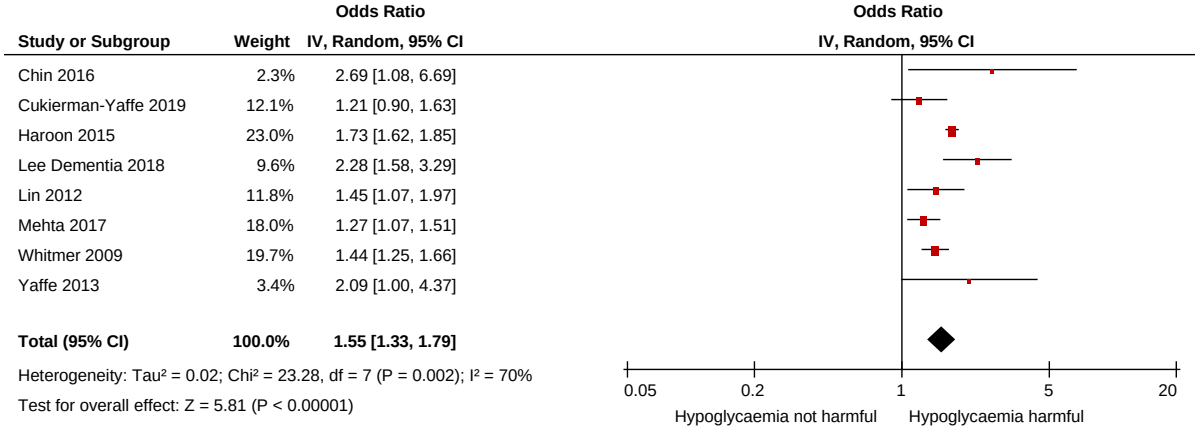
Figure 41 Meta-analysis of association between hypoglycaemia and mortality



5.5.4.4 Hypoglycaemia as a predictor for dementia

I identified eight relevant studies that evaluated the relationship of hypoglycaemia as a predictor of dementia [143] [144] [68] [69] [150] [162] [170]. The meta-analysis shows an increased risk of dementia in patients known to suffer from hypoglycaemic episodes, with a pooled odds ratio of 1.55 (95% CI 1.33 to 1.79). I detected substantial heterogeneity with I^2 = 70% (Figure 43).

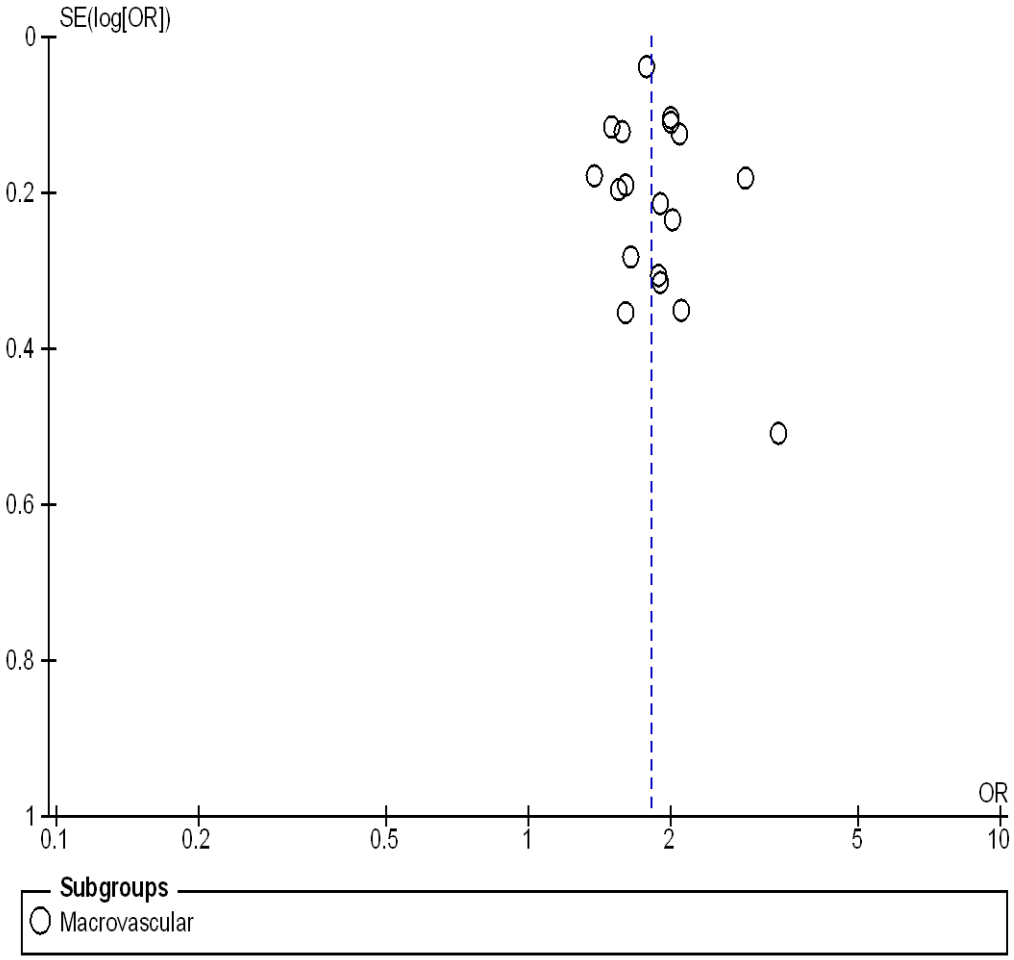
Figure 42 Meta-analysis of association between hypoglycaemia and dementia



5.5.5 Publication bias and selective outcome reporting

I constructed a funnel plot for the meta-analysis on the association between hypoglycaemia and vascular events, as more than ten studies were included in the analysis. On visual inspection of the funnel plot there are very few small studies that contributed to the meta-analysis, and it is difficult to judge presence or absence of asymmetry. As such, I cannot rule out the possibility of selective reporting or publication bias.

Figure 43 Funnel plot



For completeness, at Appendix 14, I have produced a supplemental table listing the pooled odds ratios using both random and fixed effects methods. Effect estimates were not substantially altered whether a fixed effect model was used, or a random effects model that distributed a greater proportion of weight to smaller studies.

5.6 Discussion

My meta-analysis of 42 observational studies (involving a total of over 2 million participants) confirms the major concerns about a range of serious adverse

events associated with hypoglycaemia in older patients treated with glucose-lowering drugs. I found consistent evidence of an 80% relative increase in the likelihood of vascular events (both macro- and microvascular complications) with hypoglycaemic episodes.

My meta-analysis also reveals a significant relationship between hypoglycaemia and risk of falls and fractures, as well as a doubling in the likelihood of death**.** There is also evidence from eight studies identifying the increased likelihood of dementia in those with a history of hypoglycaemic events.

The abundance and consistency of evidence regarding serious harm supports my argument that treatment strategies aimed at minimizing hypoglycaemia should be prioritized in older patients who are already prone to suffer from cardiovascular events, falls, and fractures. In addition, an international consensus on clinical targets for continuous glucose monitoring data was published in June 2019, which highlights that older adults with diabetes should spend less than 15 minutes per day in the hypoglycaemic range (<3.9mmol/L)[25]. What is still debated is the physiological mechanism behind the adverse impact of hypoglycaemia on, for example, the cardiovascular system and cognition. I have discussed different theories in chapters 1 and 4. Of course, hypoglycaemia may simply be a surrogate marker/indicator for greater disease burden or frailty in older patients, and there may actually be no direct mechanistic pathway linking hypoglycaemia to cardiovascular events or death[137 164]. Given the multi-factorial nature of adverse events in older people, it seems prudent to consider that hypoglycaemia may be one factor amongst a host of others that can contribute to serious harm, and that all efforts should be

made to reduce this risk. It is also tempting to speculate whether hypoglycaemia episodes that trigger acute cardiovascular events may be the unifying factor in explaining the associated falls and increased mortality.

5.6.1 Strengths

My systematic review and meta-analysis provide a comprehensive synthesis of the most up to date evidence covering a range of adverse events that are a major burden in older patients with diabetes.

My review also extends to assessing adverse events in two subgroups of older people; those with chronic kidney disease[156] and dementia[160].

5.6.2 Limitations

I am aware of limitations in my meta-analyses, in particular the inability to prove causality due to the observational nature of the studies. However, I do not consider it ethical or feasible to conduct a randomized trial in older patients to expose them to hypoglycaemia. There is some heterogeneity, especially regarding the association between hypoglycaemia and mortality and falls and fractures. Factors which could be influencing heterogeneity include different classes of medications, different geographical locations, different study designs and ascertainment of hypoglycaemic episodes. The temporal relationships are not always clear and my search was limited to English-language articles.

Detection of hypoglycaemia is a major issue that may have biased the estimates in either direction. For instance, poor recording or failure to accurately capture hypoglycaemia can bias the results towards the null.

Another limitation is the studies included in the systematic review employ a very wide definition of adverse events, particularly when constructing a

composite endpoint. This stems from the variation in the use of administrative codes for the definition of cardiovascular events, as well as hypoglycaemia.

I considered summarizing the evidence using GRADE, however, this tool is mainly designed for recommendations on healthcare intervention and not for aetiology and prognostic studies. The two main areas within GRADE that cannot be applied here are 'measure of indirectness' and 'estimation of absolute effect size'.

Finally, I am conscious of potential publication and selective outcome reporting biases where null or negative findings are not fully reported, thus resulting in inflated estimates of association in the meta-analyses. However, the funnel plot analysis I performed in relation to cardiovascular events, did not show obvious asymmetry, which can be interpreted as no definite evidence of underlying publication bias, or bias due to missing studies.

5.7 Conclusions

My updated systematic review and meta-analysis provide a strong evidence base to support and strengthen my argument about the importance of adopting a hypoglycaemia minimization strategy. The new search added 21 studies to my already existing systematic reviews.

Adopting a hypoglycaemia minimization strategy is especially true in older patients with diabetes mellitus and other co-morbidities, as they are at risk of serious adverse events associated with hypoglycaemic episodes. With regard to patients with co-morbid diabetes and cognitive impairment, they may find

themselves in an awkward spiral descent resulting in ever-worsening cognitive decline and more frequent hypoglycaemic episodes at the same time, which is something I highlighted in my previously published review. In addition, older people with dementia and diabetes may have difficulty with self-management due to their cognitive decline, greater susceptibility to hypoglycaemia and having poorer access to diabetes services and monitoring [2].

The next big step has to be to conduct an RCT in older people with diabetes. The intervention arm would be managed with a hypoglycaemia minimization strategy (using continuous glucose monitoring) and the control arm with standard care. I envisage a follow-up for 6 months and the outcomes would be adverse events, such as cardiovascular events leading to hospitalization.

CHAPTER 6. DISCUSSION

This chapter presents an overall discussion of my research, how it should be interpreted by the clinical community and its impact for future work.

I have highlighted the complexities of hypoglycaemia in older people with diabetes and dementia and the take home messages from my research are:

- This vulnerable group is at higher risk of cardiovascular events, falls and fractures and mortality following hypoglycaemia, especially in the first 12 months after a medically recorded hypoglycaemic episode (requiring third party assistance), compared to those without medically recorded hypoglycaemia.
- I have demonstrated through my feasibility study that it is feasible to pick up hypoglycaemic episodes through the use of CGM in older people with memory problems and diabetes.

My work should also contribute to the growing evidence around managing diabetes and dementia in older people leading to the implementation of a common pathway, rather than trying to manage each condition in isolation.

Whilst I have discussed strengths and limitations for each aspect of my research in the individual chapters (chapters 2-5), here I will also discuss overarching areas for improvement and further development.

6.1 HOW SHOULD MY FINDINGS BE INTERPRETED BY THE CLINICAL COMMUNITY?

My findings should help guide clinicians, patients and their carers in making evidence-based choices regarding intensity of drug therapy, and strategies for

better monitoring in this vulnerable and complex group. There are important implications for different sectors covering the provision of healthcare:

6.1.2 Health Economics

My research has focussed on medical adverse events, however, the cost implications of hypoglycaemic events and the effect on quality of life are also crucial to consider. Studies have shown that hypoglycaemia impacts heavily on a person's quality of life and my systematic review on CGM in older people also flagged up papers which commented on an improvement in quality of life when using CGM[176 73]. In addition, existing evidence has demonstrated the high economic burden and healthcare utilization resulting from hypoglycaemia[177-179]. Between December 2014 and April 2016, there were more than 2000 ambulance call-outs for severe hypoglycaemia in the East of England, 24% of which were from callers aged over 80 years and 44% from callers aged over 70 years. The severe hypoglycaemic events in the older population were associated with insulin use[180]. In the East Midlands, the annual estimated costs of call-outs for hypoglycaemia is approximately £235,000[28].

With this in mind, the main driver from an economics point of view should be minimising the risk of hypoglycaemia. There needs to be an enormous shift in thinking by commissioners regarding how we can best minimise hypoglycaemia, especially in frail older people, combined with the use of CGM. We know that the use of CGM can significantly reduce the time spent in the hypoglycaemic range[43].

At this point in time, there is a general perception that older people do not need to test their glucose levels as much and I have already argued that

intermittent finger-prick testing is not helpful to fully capture hypoglycaemic episodes. The work that I will need to carry out in the future will have to include health economic modelling to show that the costs of using CGM technology will be recouped due to reduction in ED attendances, hospitalisations, falls and fractures and cardiovascular events, in addition to the improvement in quality of life for patients and carers. I would like to assess whether the benefits of intermittent use of CGM could outweigh the costs of it. CGM technology has seen so much development in the last two decades, I would expect the devices to become more affordable and user-friendly over the next 10 years.

Older people with dementia are at higher risk of hypoglycaemic episodes[8] and I alluded to this already in my discussion in chapter 3. It should not matter what type of diabetes a person has or how often he or she checks glucose levels. The important question has to be whether an individual is at high-risk of hypoglycaemia, be it because of the medication they are on (insulin and sulfonylureas) and/or the fact that they are frail, have memory problems or other disabilities, which makes the management of their diabetes more complex.

6.1.3 Social Care

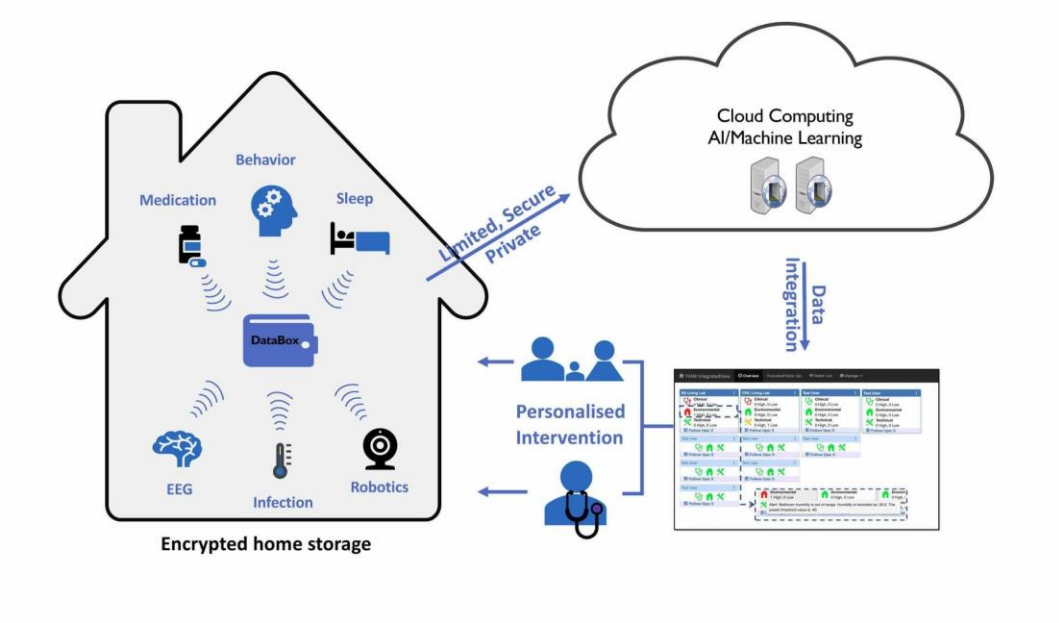
An advantage of using CGM in frail older people would be less need for District Nurses to drive to lots of homes to carry out finger-prick testing, although chances are that they may still need to administer insulin. It is already possible to remotely share CGM data via smartphone apps.

In order to be able to implement the use of CGM effectively, areas that need to be explored are around who (if the patient is unable to, due to, for example,

dementia) would monitor glucose levels and react to alarms: a next of kin, doctors, carers? Cloud-based services enable patients and carers to set up "followers" to share the data. For example, parents of young children can set up their smartphone so that they receive their child's glucose readings and alarms. By analogy, similar scenarios with relatives and/or carers could apply to older frail people who need support with the management of their diabetes. What would need to be explored is how the care network can be set up to deal with low glucose alerts that need addressing sooner rather than later. Ideally (if NHS and Social Care resources were not an issue), older people with memory problems and high-risk of hypoglycaemia would have access to tailored packages of care, taking into account nutrition (composition of meals, in particular carbohydrates, timing of meals) and hydration (avoiding dehydration), in addition to CGM. The ADA recommends that the composition of meals (carbohydrates, protein and fat) should be individualised, reflecting eating patterns, personal preferences, the individual's culture, traditions and religion, economics and metabolic goals [21].

There are interesting developments around remote monitoring in the home, led by the Care Research & Technology Centre at Imperial College, using artificial intelligence and robotics to enable people with dementia to live in their own home for longer. It involves monitoring aspects such as sleep, behaviour, possible markers of impending infection and even EEG which is transmitted from encrypted home storage to Cloud Computing leading to data integration and intelligent decision-making (Figure 45). It would be fascinating to explore whether CGM could also be incorporated into such a set up.

Figure 44 The 'Healthy Home'



(taken from Imperial College website)[181]

6.1.4 Clinical care

For clinicians, when managing a frail older person with diabetes and other complex co-morbidities, the focus has to be on minimisation of hypoglycaemia rather than achieving a HbA1c target. This can be achieved by deintensification of medications and also (paradoxically) greater monitoring through CGM. A recently published systematic review found that the benefits of deintensification outweigh the harms in older people with type 2 diabetes with or without co-morbidities[182]. The outcomes the authors were interested included measures of glycaemia, admission rates, hospitalizations, complications, mortality, quality of life and patient satisfaction. Most of the data in the review appears to relate to glycaemic outcomes. Only two studies report adverse events and three reported on mortality. It would be more accurate to state that the relative paucity of data of adverse events and mortality outcomes means that we cannot conclusive make statements on

deintensification outweighing harms. The authors acknowledge that the studies were of poor methodological quality with short follow-up durations of only a few months, which makes it impossible to draw robust conclusion.

Using CGM is really the only way to pick up hypoglycaemic episodes, especially at night, in addition to variability in glucose readings throughout day and night. In older frail patients I envisage that CGM could be used as a troubleshooting tool, for example, if someone on insulin or sulfonylureas has required the help of another person to manage a hypoglycaemic episode, or when there has been a change in dose of medications. In those cases, CGM could be used over a period of, for example, a month, in order to obtain an ambulatory glucose profile. Treatment decisions, including deintensification of medication can then be made with the help of the ambulatory glucose profile before and/or after any planned changes in management.

I concede that for healthcare professionals this may result in more and longer consultation times with this group of patients, which poses a challenge in itself in an already stretched NHS. However, the benefits of this approach in the long term are likely outweigh the challenges (however, this again will need to be assessed).

6.2 Areas for improvement

The strengths and limitations for each aspect of my fellowship are discussed in chapters 2-5. Here I will outline more generally some limitations that still need to be overcome in future research.

I have not yet assessed the optimal strategy of hypoglycaemia minimization. Should this be done through modification of pharmacotherapy or better monitoring, or better social care, or a combination of all of these factors.

With regard to better monitoring, I need to assess which device is most acceptable to older people and their carers. The different CGM devices are constantly undergoing modifications and innovations and my thesis data relate to a device that has since been made more accurate and refined.

I have not assessed whether reduction of hypoglycaemia leads to improved patient and health service use outcomes, or indeed adverse effects. I will also need to assess which older patient group is the most appropriate to target, for example, should it be nursing home residents, older people who are still living alone, those on insulin and/or sulfonylureas or those with carers.

I have not yet been able to assess the factors that can lead to older people not being able to use a CGM device, for example, the presence or absence of carers, past experience of self-monitoring glucose levels, type and severity of memory problems, other co-morbidities such as arthritis and visual problems. I have not been able to confirm improvements in diabetes-related psychological and physical health.

6.2.1 Pharmacoepidemiological study

Whilst I can only work with the data that is available through a particular dataset, I would have liked to have been able to gather information on the following aspects:

- A&E data (other than being able to extract that someone has attended A&E) - A&E is good at coding for trauma injuries, but not specific enough for hypoglycaemia.

Figure 45 Extracts from HES Data Dictionary – Accident & Emergency

A&E diagnosis: 2 character (DIAG2_NN)	
Field	DIAG2_NN
Field Name	A&E diagnosis: 2 character
NHS Field Name	N/A
Category	Clinical diagnoses
Length and format	2n
Availability	2007-08 onwards
Description	The A&E diagnosis description at 2-character level covering the diagnosis condition. This field contains a description based on the diagnosis condition (first 2 characters) of the A&E diagnosis and only displays a code where it is unclassifiable against the A&E Diagnosis classification.

30 = Diabetes and other endocrinological conditions

A&E diagnosis: 3 character (DIAG3_NN)	
Field	DIAG3_NN
Field Name	A&E diagnosis: 3 character
NHS Field Name	N/A
Category	Clinical diagnoses
Length and format	2n or 3n
Availability	2007-08 onwards
Description	The A&E diagnosis description at 3-character level, covering the diagnosis condition and the sub-analysis. Note that if no sub-analysis has been provided or is not applicable then the 2-character description will be displayed if available. This field contains a description based on the diagnosis condition and sub-analysis (first 3 characters where applicable) and only displays a code where it is unclassifiable against the A&E Diagnosis classification.

301 = Diabetes and other endocrinological conditions - diabetic

- Free text written by GPs for individual patient visits: I would have liked to have been able to check free text, as this may have revealed further hypoglycaemic episodes, which I would have missed due to not being able to do that.

- Data on social care packages and whether or not someone has had to move into a care/nursing home as these can be interpreted as proxies for frailty.
- Information on aspects such as delayed discharges (which are often linked to the challenges of finding and starting a care package).
- Severity of dementia: this is a tricky area and impossible to reliably code on a database, however, ideally it would be useful to be able to extract information on whether an individual is not able to live independently anymore, has limited communication, whether or not they are still able to wash/dress/eat themselves and what their mobility is like.

During the preparatory work of extracting raw data from the database, I noticed that the date of death in CPRD at times did not match the date of death in ONS, or HES dates occurred after the death date. This could be a reflection of the time it can take for discharge letters to be completed and sent to primary care and for primary care then to code the diagnoses listed in the discharge documentation.

6.2.2 Feasibility study

One of the findings of my feasibility study was the variability of data capture, as some participants did not remember to scan the sensor. Data capture was less than 60% in six participants. Since my study started, a new CGM device became widely available, which is licensed for use in adults and children (Dexcom G6). With this device, data is constantly being transmitted to a reader via Bluetooth and does not require active scanning. It also does not require any calibration

via finger-prick testing and has greater accuracy in glucose measurements than the older Freestyle Libre.

I would have liked to have used the Dexcom G6 device to assess whether data capture improved and whether participants (and carers) were able to work with the Bluetooth technology. Another aspect to investigate is the use of alarms (for high/low glucose readings) which Dexcom employs and how this may or may not have affected participants and carers. I am however planning a new study using Dexcom G6, which is discussed below.

6.3 Personal reflections

6.3.1 Feasibility study

The feasibility study was my first opportunity to carry out a clinical trial from start to finish. The entire process was fascinating and at times frustrating, especially regarding the bureaucracy that is involved in setting up any study, from inception through to getting paperwork signed off by the sponsor before submitting to and attending an Ethics Committee. It made me realise how much of a challenge it is to try and get a study up and running and why clinicians who do not have protected research time and do not understand/are not aware of the intricacies of the different steps involved might be put off carrying out research.

A further aspect I found challenging on a personal level was the recruitment of participants. I felt quite conflicted when approaching potential participants, especially as I was very aware of their vulnerability exacerbated by being in an acute hospital, which in itself can be a stressful and scary experience for each

affected individual. If anything, I probably discouraged some participants from taking part, as I did not want them to feel pressured.

Saying that, once participants had consented and I carried out study visits, this gave me a chance to build rapport and trust, which in turn resulted in getting to know fascinating individuals. I felt quite humbled being able to spend time with them and incredibly grateful that the participants were prepared to take part in my study. It highlighted to me how much older people still want to be involved in furthering scientific and medical advances and that they are so often wrongly excluded from primary research. On the flip side, in some cases it was also a stark reminder of just how vulnerable this patient population is, especially in rural Norfolk, where access to anything from food shops to social clubs to GP surgeries can be extremely limited when someone does not have a car or friends/family who could provide transport. On a few occasions, I visited a participant whose front door was left unlocked leaving them incredibly vulnerable to anyone walking into their house.

Despite all the bureaucratic hurdles that have to be overcome (and that is after the hurdles of securing funding in the first place), I am determined to carry out further studies which naturally flow on from my fellowship, which I discuss below.

As a research community I feel there needs to be a much greater effort in including older frail people in research studies.

6.3.2 Pharmacoepidemiological study

I was keen to carry out a database study, partly because of the intellectual challenge of dealing with a big dataset. It was a very steep learning curve,

especially as I am not naturally drawn to complex statistical models or large sets of numbers. This is exactly why I wanted to incorporate such a study into my fellowship.

Learning about how to approach a large dataset and all the groundwork (around carefully examining the data) before any statistical models can be applied was a real eye-opener for me.

A huge amount of preparatory work went into extracting raw data and putting it into a format that is suitable for software analysis. I spent a lot of time putting together lists using the CRPD code browser to collate codes for hypoglycaemia (exposure), co-morbidities, lifestyle factors, outcomes (all Read codes), medications (BNF codes). I also had to identify ICD-10 codes for the A&E/HES data (Appendix 11).

Working with a big dataset also made me realise just how imperfect they are and how much we rely on the accuracy of coding of diseases, medications and patient characteristics. Any dataset is only going to be as good as the coding, which is inconsistent.

My view is that observational research continues to be a very important part of evidence synthesis, especially as it may not always be feasible to carry out an RCT due to time, funding and/or ethical issues. However, rigour around the construct of observational studies is vital. In that context, I was fascinated by the theoretical constructs created by Miguel Hernan (target trials to emulate a theoretical RCT).

6.4 Future research

My research to date has set the ground work for future studies on CGM in frail older people with diabetes. I am already working on a pilot study where I will capture data on the time spent in range using CGM in older people with diabetes living in care and/or nursing homes. I am setting up the research team and have consulted lay members of the Alzheimer's Society Research Network about the planned study. I will submit an application for Research for Patient Benefit funding within the next 12 months.

A key area for investigation is what type of CGM (i.e. intermittent scanning/flash glucose monitoring, continuous transmission via Bluetooth or blinded and retrospective CGM) would be most appropriate in older people with memory problems? Can older people with memory problems (or their carers) deal with the technology for continuous Bluetooth capture and react to the data that is produced by the software, including alarms for high and low glucose levels.

Secondly, how often should CGM be employed (all the time, when there is a change in drugs, or intermittently for troubleshooting)?

Thirdly, should it be limited to insulin and sulfonylurea users, which carry a higher risk of hypoglycaemia?

Finally, it would be important to identify facilitators and barriers to CGM use in older people with memory problems, with specific focus on factors such as dementia severity, functional status, availability of carers, familiarity with self-monitoring etc. that can influence extent of data capture.

There is a clear need for a large-scale prospective study using CGM to assess its true potential impact in this vulnerable group. CGM would be used to capture hypoglycaemic episodes and guide a hypoglycaemia minimization strategy. In addition, CGM may be a useful and supportive tool for carers in their day to day care of this vulnerable group of older people, especially those on insulin.

With regards to patient outcomes and hypoglycaemia, I would need to conduct a cluster-randomised trial. This could be done either at GP practice level or nursing home level. The population of interest would be older people with diabetes treating either with insulin and/or sulfonylureas, which confer a higher risk of hypoglycaemia. CGM would be part of a complex intervention in combination with implementing a hypoglycaemia minimisation strategy. The control group would continue with their standard diabetes care (plus blinded CGM). The main outcome would be health service use (including ambulance call-outs and emergency department visits). The secondary outcome would be time in range.

6.5 Statement of impact

Based on my work on diabetes and dementia, I presented oral and written evidence at the All-Party Parliamentary Group (APPG) on Dementia, which led to the publication (and launch in Parliament) of their report in 2016: *'Dementia rarely travels alone: Living with dementia and other conditions'* (https://www.alzheimers.org.uk/sites/default/files/migrate/downloads/appg_on_dementia_2016_report.pdf).

More recently, two of my systematic reviews on adverse events of hypoglycaemia in older people with diabetes formed part of the evidence behind a Position Statement of Primary Care Diabetes Europe on the management of type 2 diabetes in older people (Factors influencing safe glucose-lowering in older adults with type 2 diabetes: a PeRsOn-centred ApproaCh To IndiVidualisEd (PROACTIVE) Glycemic Goals for older people. A position statement of Primary Care Diabetes Europe (https://www.primary-care-diabetes.com/article/S1751-9918(18)30300-0/pdf).

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PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

Continuous glucose monitoring in older patients: systematic review

Katharina Mattishent, Yoon Loke

Citation
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Review question
The objective is to examine the use of continuous glucose monitoring in older adults in the community and its effects on capturing blood sugar values and adverse events.

Searches
We will conduct a search on published literature using the electronic databases SCI Web of Science, Ovid SP MEDLINE and EMBASE from January 2010 to June 2017.
No searches will be conducted on unpublished or grey literature. Only human studies will be included in the search.
The search strategy will include terms related to the intervention (continuous glucose monitoring) and the population (older adults) as follows:
(Aged OR "older adult" OR "older adults" OR elderly OR geriatric OR veteran? OR senior?)
AND
(continuous-glucose-monitoring or CGM)
We will also conduct a manual search by reviewing the reference lists of included studies and published systematic reviews on the same topic. The searches will also be updated automatically on a monthly basis through electronic notifications from PubMed.

Types of study to be included
We will include observational studies and randomised controlled trials (RCT).

Condition or domain being studied
Diabetes mellitus

Participants/population
Humans, mean age 65 years or older. We will exclude studies that were solely conducted on inpatients or in laboratory settings.

Intervention(s), exposure(s)
Continuous glucose monitoring devices.

Comparator(s)/control

Comparator(s)/control

Not required for this review.

Context

Older patients living diabetes face a challenge in the self-management of their condition, having to recognise and manage changes in blood sugars, in particular, low blood sugars (hypoglycemia).
Harm from hypoglycemia is a rapidly growing problem for health services. Older people have a 10-fold increased risk of hypoglycaemic episodes needing hospital admission [Chen 2015] [Kim 2011], whereas East Midlands Ambulance Trust had 523 call outs for severe hypoglycemia (mainly in older people) over a 3-month period, with projected costs > £235,000 per year [Khunti 2013]. Severe hypoglycemia has serious health consequences, but even mild episodes can cause significant distress and disruption to quality of life and daily activities. The American Geriatric Society and American Diabetes Association have recommended relaxing glycemic control for older vulnerable patients [Munshi 2011].
Mattishent et al have identified the potentially enormous impact of hypoglycemia on patients with memory problems and diabetes and their carers. Their systematic review and meta-analysis of 12 studies and 1.4 million participants revealed significantly greater likelihood of hypoglycemia in patients with impaired cognition (pooled odds ratio (OR) 1.61 (95% Confidence Interval (CI) 1.25, 2.06)) compared to those without. In addition, those affected by hypoglycemia were more susceptible to worsening cognitive impairment and dementia (OR 1.68; 95% CI 1.45, 1.95), leading to a potentially vicious cycle of decline [Mattishent 2016].
Management of diabetes in older people with comorbidities is challenging, because the extent of harm from hypoglycemia, and the best way to monitor blood glucose in this population, is not known. The development of continuous glucose monitoring (CGM) has paved the way to better understanding individuals' glycaemic profiles. A study of CGM technology in 40 older adults (mean age 75 years) picked up 102 hypoglycaemic events over a 3-day period, whereas conventional monitoring failed to detect 95/102 (93%) of these hypoglycaemic events [Munshi 2011].
A more recent study employed CGM in 23 well-controlled older patients (mean age 76 years) with Type 2 diabetes mellitus and monitored them for a median period of 97 hours. Subsequent analysis found that five patients had a total of 15 hypoglycaemic events with a glucose level <3.0mmol/L recorded with the CGM device (the cut-off for a hypoglycaemic episode is <4mmol/L). Eight patients experienced a total of 25 events with a glucose level <3.5mmol/L. None of these patients reported experiencing symptoms of hypoglycemia [van Dijk 2017]. This study shows that asymptomatic hypoglycaemic episodes (which might otherwise go unnoticed unless CGM was performed) are an issue in older people.
Ishikawa et al published the findings of their study in April 2017, in which CGM technology was used to analyse the relationship between low blood sugars and diabetes treatment in older patients (>65 years) with Type 2 diabetes. They concluded that patients aged 65 and older with Type 2 diabetes had a higher risk of low blood sugars if they had higher blood sugar variability and lower average glucose levels [Ishikawa 2017].
To date, there has been no systematic review which has consolidated the emerging evidence on the use of continuous glucose monitoring in older patients with diabetes.

Main outcome(s)

To assess the extent to which blood sugar values (in particular, hypoglycaemic episodes) can be captured in older patients with diabetes with the use of continuous glucose monitoring. We will also assess adherence and acceptability, as well as any adverse events that are recorded during the study.

Additional outcome(s)

None

Data extraction (selection and coding)

Two reviewers will separately screen the titles and abstracts of the identified papers to determine their adequacy to the selection criteria. The eligible studies will be separately scrutinized for inclusion in the meta-analysis by two reviewers. Any disagreement will be resolved through consensus with an independent clinical expert in continuous glucose monitoring.
Two reviewers will independently extract data from each eligible study. Any disagreements or discrepancies will be resolved through contacting authors and consensus.
Data will be extracted using a standardised, pre-piloted data extraction form and will include information on study design, setting, country, number of participants, mean age, percentage of males, study duration, type of device (exposure definition), abnormal glucose concentrations (outcome definition), confounders adjusted for, and main study results.
For the study results, we will extract summary statistics of blood sugar values that were captured ((e.g. mean, median, range, standard deviation), the number of hypoglycaemic episodes captured, and recording time. We will also extract any reported results on patient adherence, device acceptability, drop-outs or withdrawals, and adverse events during the study period.
We will contact study authors for further information/clarification where necessary.

Risk of bias (quality) assessment

Two reviewers will assess key parameters, including selection of patients, loss to follow-up, missing data, selective reporting and analysis.

Strategy for data synthesis

If there are sufficient quantitative data and similarity in the reported outcome measures, then we will use the appropriate analytical meta-analysis model to combine the data. In that case, we will measure statistical heterogeneity across studies using the I-squared statistic. Sources of heterogeneity will be assessed by subgroup analysis. We will assess publication bias by examining funnel plots, if there are more than 10 included studies for a particular outcome, and there is no evidence of significant heterogeneity. Where studies are too heterogeneous to be pooled, a narrative analysis of the data will be undertaken.

Analysis of subgroups or subsets

At this point it is not possible to specify subgroups or subsets in advance.

Contact details for further information

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Organisational affiliation of the review

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Review team members and their organisational affiliations

Dr Katharina Mattishent. Norwich Medical School
Professor Yoon Loke. Norwich Medical School

Type and method of review

Systematic review

Anticipated or actual start date

01 May 2017

Anticipated completion date

01 August 2017

Funding sources/sponsors

The Alzheimer's Society UK (Grant number 324 (AS-CTF-16-001)

Conflicts of interest

None known

Language

English

Country

England

Stage of review

Review Completed not published

Details of final report/publication(s)

Mattishent K, Loke YK. Detection of asymptomatic drug-induced hypoglycemia using continuous glucose monitoring in older people - Systematic review.
J Diabetes Complications. 2018 Aug;32(8):805-812. doi: 10.1016/j.jdiacomp.2018.05.005. Epub 2018 May 18.
https://www.ncbi.nlm.nih.gov/PubMed/29887300
https://www.ScienceDirect.com/science/article/pii/S1056872718302290?via%3Dihub

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Blood Glucose; Blood Glucose Self-Monitoring; Humans

Date of registration in PROSPERO

05 June 2017

Date of publication of this version

24 April 2019

Revision note for this version

Publication details submitted

Publication details submitted

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Publication details submitted

Versions

05 June 2017
24 April 2019

F**ea**sibility and acceptability of monitoring ambulatory **gl**ucose profil**e** in older patients living with memory problems and diabetes (**EAGLE**)

Version	Version 3.0
Date	March 2018
Sponsor	University of East Anglia

Authorisation: Chief Investigator

Name	Dr Katharina Mattishent
Role	Chief Investigator

Authorisation: Sponsor

Name	Sarah Green
Role	Project Officer

1 Administrative information

This document describes the Feasibility study: feasibility and acceptability of ambulatory glucose profile (AGP) in older patients with memory problems and diabetes, sponsored by the University of East Anglia.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, the medical device, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

1.2 Sponsor

The University of East Anglia is the trial sponsor and has delegated responsibility for the overall management of the EAGLE study to the Chief Investigator. Queries relating to sponsorship of this trial should be addressed to the Chief Investigator, or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	TBC
Date of Registration in Primary Registry	TBC
Secondary Identifying Numbers	Funding reference number: Grant number 324 (AS-CTF-16-001) IRAS reference number: 221757
Source of Monetary or Material Support	Clinician and Healthcare Professional Training Fellowship, Alzheimer's Society
Sponsor	University of East Anglia
Contact for Scientific Queries	Dr Katharina Mattishent Norwich Medical School University of East Anglia Bob Champion Research and Education Building Norwich NR4 7TJ. e-mail: k.mattishent@uea.ac.uk
Public Title	EAGLE study
Scientific Title	Feasibility and acceptability of monitoring ambulatory glucose profile in older patients living with memory problems and diabetes
Countries of Recruitment	England
Health Condition(s) or Problem(s) Studied	Patients with memory problems and diabetes
Intervention(s)	Use of ambulatory glucose profile system (AGP – FreeStyle Libre Flash Glucose Monitoring System, Abbott)
Key Inclusion and Exclusion Criteria	Inclusion Criteria: Patients 65 years and older, Type 1 or Type 2 Diabetes mellitus, on glucose-lowering medication, Abbreviated Mental Test (AMT) equal to or less than 8 or formal diagnosis of dementia. **Exclusion criteria**: treatment with metformin only, not willing to participate, terminal illness (less than one-year life expectancy), AMT>8. Evidence of bruising, bleeding, cellulitis and/or skin tears on the upper arms
Study Type	Feasibility study of a medical device
Date of First Enrolment	Anticipated 01/02/2018
Target Sample Size	20 participants

Feasibility objectives	• Estimate size of eligible patient population • Estimate recruitment and retention pattern of patients • Estimate proportion of captured blood glucose readings
Feasibility Outcome(s)	1. Numbers of potentially eligible patients who meet the selection criteria 2. Number of participants subsequently recruited into the study 3. Extent of capture of blood glucose readings 4. Attrition rate and reasons for withdrawal 5. Adverse events
Patient outcome measure	This is a feasibility study, as such no primary outcome has been defined. The following patient outcomes will be collected by means of a qualitative interview • Acceptability of ambulatory glucose profile system to patients • Acceptability of ambulatory glucose profile system to family and carers (both informal and formal) • Patient and carer experience

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

Protocol contributors

Name	Affiliation	Role
Professor Yoon Loke, Professor of Medicine and Pharmacology	Norwich Medical School, UEA	Initiated and developed the trial question and study development. Lead the writing of the protocol and funding application.
Dr Katharina Mattishent, Alzheimer's Society Doctoral Research Fellow	Norwich Medical School, UEA	Contributed significantly to the development of the trial question, and the drafting of the protocol.
Dr Ketan Dhataryia, Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	Contributions on the study design with emphasis on the clinical aspects of management of diabetes.
Dr Sankalpa Neupane, Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	Contributions on the study design with emphasis on the clinical aspects of management of diabetes.
Professor Chris Fox, Professor of Clinical Psychiatry and Honorary Consultant Psychogeriatrician	Norwich Medical School, UEA	Contributions on the study design with emphasis on the clinical aspects of management of dementia.
Professor John Potter, Professor of Ageing and Stroke Medicine	Norfolk & Norwich University Hospital NHS Trust	Contributions on the study design with emphasis on the clinical aspects of management of older people with multiple co-morbidities.
Dr Helen May, Consultant Geriatrician	Norfolk & Norwich University Hospital NHS Trust	Contributions on the study design with emphasis on the clinical aspects of management of older people with multiple co-morbidities.
Dr Charlotte Salter	Social Gerontologist, Norwich Medical School, UEA	Contributions on the study design with emphasis on the qualitative data collection

Dr George Savva	Senior Lecturer Applied Statistics, School of Health Sciences, UEA	Contributions on the study design with emphasis on the quantitative data collection
~~Matthew Lariviere~~ Dr Kathleen Lane	~~Anthropologist of Health, Ageing & Technology,~~ Senior Research Associate, School of Health Sciences, UEA	Contributions on the study design with emphasis on the qualitative data collection

Role of trial sponsor and funders

Name	Affiliation	Role
Trial sponsor	University of East Anglia	Approval of: trial design, data collection methods, conduct and monitoring with ultimate authority over these.
Funder	Alzheimer's Society	Approval of: trial design, data collection methods, conduct, monitoring and analysis with ultimate authority over these the responsibility of the sponsor.

Trial Team

Name	Affiliation	Role and responsibilities
Dr Katharina Mattishent, Alzheimer's Society Doctoral Research Fellow	Norwich Medical School	*Chief investigator* with responsibility for the: conduct, data analysis, interpretation and reporting. Recruitment of participants.
Professor Yoon Loke, Professor of Medicine and Pharmacology	Norwich Medical School	*Co-Chief investigator* with overall responsibility for the: design, conduct, monitoring, analysis, interpretation and reporting of the trial. Recruitment of participants.
Dr Ketan Dhataryia, Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	*Clinical advisor* on management of patients in the trial.
Dr Sankalpa Neupane, Locum Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	*Clinical advisor* on management of patients in the trial. Recruitment of participants.

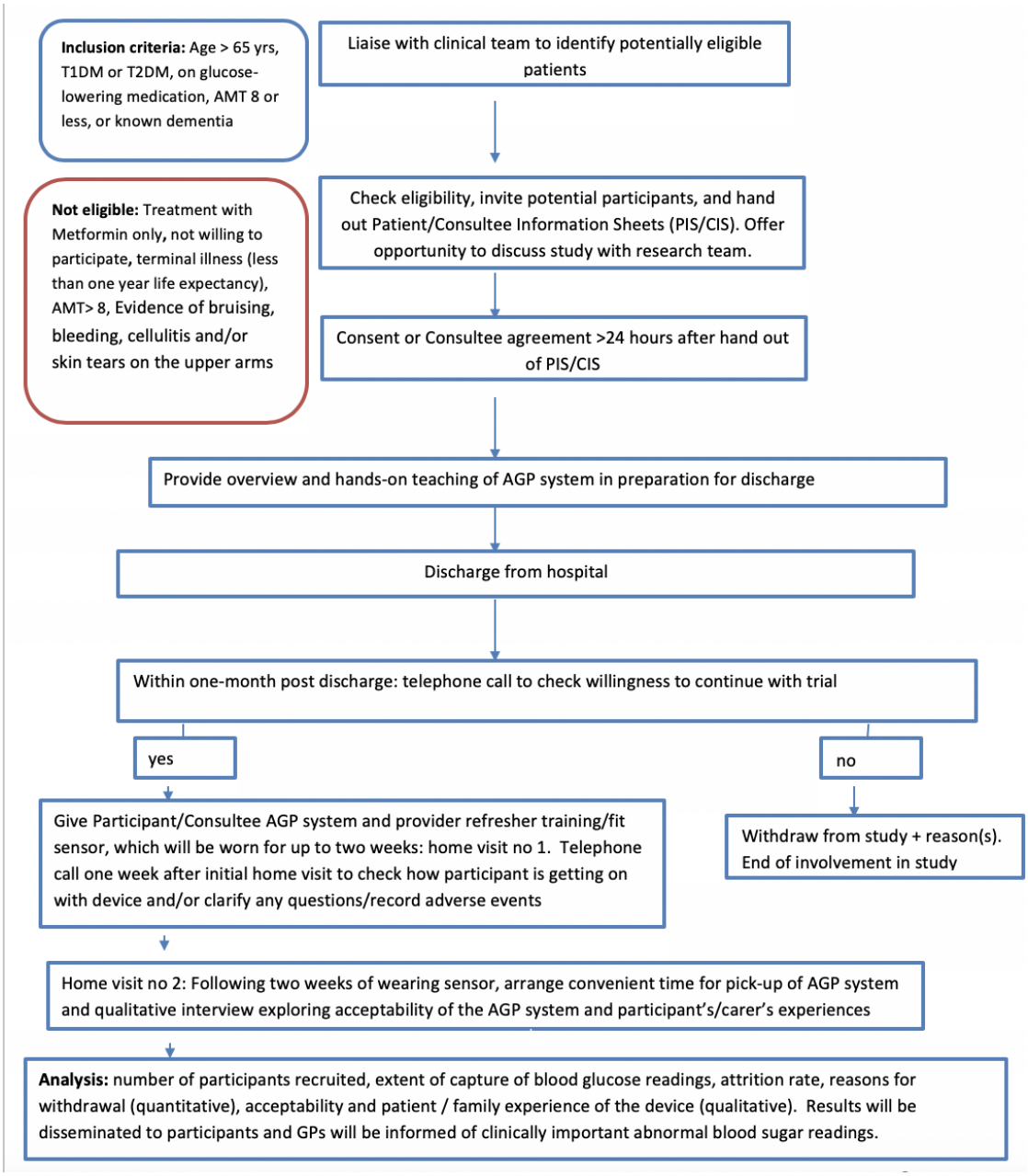
Dr Helen May, Consultant Geriatrician	Norfolk & Norwich University Hospital NHS Trust	*Clinical advisor* on management of patients in the trial. Recruitment of participants.
Dr Charlotte Salter	Norwich Medical School, UEA	*Advisor* on the study design with emphasis on the qualitative data collection.
Dr George Savva	Senior Lecturer Applied Statistics, School of Health Sciences, UEA	*Study Statistician*

Trial Steering Committee

Name	Affiliation	Role and responsibilities
Dr Chris Atkins, NIHR Doctoral Research Fellow	Norwich Medical School	*Independent Chair Person*
Professor Yoon Loke, Professor of Medicine and Pharmacology	Norwich Medical School	*Co-chief research investigator* with overall responsibility for the: development, conduct, progress, administration and monitoring of the work in all centres, plus analysis and production of the final manuscript.
Dr Katharina Mattishent, Alzheimer's Society Doctoral Research Fellow	Norwich Medical School	*Chief investigator* with responsibility, with the trial manager, for the management of the trial including: conduct and progress, responding to clinical inquiries, data analysis and interpretation and production of the final manuscript.
Dr Helen May, Consultant Geriatrician	Norfolk & Norwich University Hospital NHS Trust	*Clinical advisor* on management of patients in the trial, particularly in relation to older people with multiple co-morbidities
Dr Ketan Dhataryia, Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	A *clinical advisor* on aspects of management of participants in the trial particularly relation to the management of diabetes and hypoglycaemia
Paul Miliac	Alzheimer's Society	*Patient Representative*
Dick Abbott	Alzheimer's Society	*Patient Representative*

Sarah Green	University of East Anglia	*Sponsor Representative*

2 Flow Diagram



3 Abbreviations

AGP	Ambulatory glucose profile
AMT	Abbreviated Mental Test
AR	Adverse reaction
CA	Consultee agreement
CI	Chief Investigator
CIS	Consultee Information Sheet
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTRG	Clinical Trials and Research Governance
EAGLE	Feasibility and acceptability of ambulatory glucose profile in older patients living with memory problems and diabetes.
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
IRAS	Integrated Research Application System
NHS	National Health Service
NMS	Norwich Medical School
NNUH	Norfolk and Norwich University Hospital
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Safety Committee
SOP	Standard Operating Procedure

SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee

4 Introduction

4.1 Background and Rationale

Older patients living with memory problems and diabetes face a specific burden due to the high cognitive load in self-management of diabetes, resulting in substantially increased risks of low blood sugars (hypoglycaemia) from decreased food intake or inability to adjust drug doses. Patients and carers have to recognize and respond to acute, dangerous changes in blood sugar (e.g. hypoglycaemia) necessitating urgent treatment, but this is difficult because patients with memory problems may not be able to relay how unwell they feel.

Harm from hypoglycaemia is a rapidly growing problem for health services. Older people have a 10-fold increased risk of hypoglycaemic episodes needing hospital admission (1) (2), whereas East Midlands Ambulance Trust had 523 call outs for severe hypoglycaemia (mainly in older people) over a 3-month period, with projected costs > £235,000 per year (3). Severe hypoglycaemia has serious health consequences, but even mild episodes can cause significant distress and disruption to quality of life and daily activities.

Mattishent et al have identified the potentially enormous impact of hypoglycaemia on patients with memory problems and diabetes and their carers. Their systematic review and meta-analysis of 12 studies and 1.4 million participants revealed significantly greater likelihood of hypoglycaemia in patients with impaired cognition (pooled odds ratio (OR) 1.61 (95% Confidence Interval (CI) 1.25, 2.06)) compared to those without. In addition, those affected by hypoglycaemia were more susceptible to worsening cognitive impairment and dementia (OR 1.68; 95% CI 1.45, 1.95), leading to a potentially vicious cycle of decline. (4)

The National Institute of Health Research has also funded a realist (literature) synthesis on theories, frameworks, and processes of care for patients with diabetes and memory problems. The American Geriatric Society has called for more research "to better understand the *risks* and benefits of tighter glycaemic control among older patients and those with comorbidities" because "clinicians often do not differentiate treatments for older patients who differ widely in health status. (5)

Management of comorbid diabetes in people with memory problems is challenging, because the extent of harm from hypoglycaemia, and the best way to monitor blood glucose in this population is not known. The development of continuous glucose monitoring (CGM) has paved the way to better understanding individuals' glycaemic profiles. A study of CGM technology in 40 older adults (mean age 75 years, no dementia) picked up 102 hypoglycaemic events over a 3-day period, whereas conventional monitoring failed to detect 95/102 (93%) of these hypoglycaemic events. (6)

A more recent study employed CGM in 23 well-controlled older patients (mean age 76 years) with Type 2 diabetes mellitus and monitored them for a median period of 97 hours. Subsequent analysis found that five patients had a total of 15 hypoglycaemic events with a glucose level <3.0mmol/L recorded with the CGM device (the cut-off for a hypoglycaemic episode is <4mmol/L). Eight patients experienced a total of 25 events with a glucose level <3.5mmol/L. None of these patients reported experiencing symptoms of hypoglycaemia. (7) This study shows that asymptomatic hypoglycaemic episodes (which might otherwise go unnoticed unless CGM was performed) are an issue in older people.

Ishikawa et al published the findings of their study in April 2017, in which CGM technology was used to analyse the relationship between low blood sugars and diabetes treatment in older patients (>65 years) with Type 2 diabetes. They concluded that patients aged 65 and older with Type 2 diabetes had a higher risk of low blood sugars if they had higher blood sugar variability and lower average glucose levels(8) .

Noteably, neither of these recent studies explored CGM's value in patients with memory problems and diabetes. The technology is under-researched in this vulnerable group.

More recently, flash glucose monitoring has been introduced, which obtains ambulatory glucose profiles (AGP) as a novel method of analysing glycaemic profiles. The device enables patients and healthcare professionals to retrospectively look at data collected over a two-week period. It stores glucose readings every 15 minutes over the last eight hours (for a complete picture, the sensor should be scanned approximately three times a day). It is possible to download all the glucose readings via free software. The downloaded report enables identification of patterns in the glucose levels and when they are occurring.

The main advantages of the flash glucose monitoring system compared to standard CGM are:

- Cost: Flash glucose monitors are significantly cheaper than CGM systems (*see below section 4.1.2).*
- AGP systems do not require finger-prick testing for calibration, whereas CGM systems do.
- The sensor for the AGP system lasts for 14 days. Standard CGM sensors last for a maximum of seven days (there has been a development of a recently approved implantable sensor (Eversense), which lasts for up to 90 days, but still requires finger-prick testing for calibration)(9).

Studies have already evaluated and guidelines produced for the use of flash glucose monitoring with adults and children (10). A consensus group of diabetes specialists within Europe agreed that AGP is an effective standard for analysing glucose data in diabetes management and can assist people (or their carers) with diabetes understand daily life with their conditions (11).

However, to date there are no studies looking at the feasibility of this device in adults with memory problems and diabetes.

Technology can be liberating offering enhanced safety and freedom but can also leave people vulnerable, create increased expectation of services and be stigmatising (Kang *et al*., 2010). Whilst older people are known to be far from passive when it comes to using and adapting technology to suit their needs (12) there are some important issues in relation to personal health monitoring technologies (PHM) such as the AGP System. Research suggests PHM can lead to social isolation and over reliance on technology can give a false sense of safety especially where resources remain scarce (13). A recent review of the literature found issues such as privacy, autonomy, visibility and impact on health providers were all highlighted as potential consequences of PHM (14).

It will therefore be important to try to understand the patients' experiences as well the carers' (both informal and paid). Interviews will cover personal experience of the AGP System and seek to understand longer-term issues regarding the value of using such devices in patients with diabetes and memory problems. Different personal situations and their contextual elements that affect the use of the APG System will be explored.
This feasibility study of new technology for flash glucose will pave the way for further development and implementation of improved monitoring in this vulnerable group. This research will help develop strategies for better monitoring.
Before a full RCT to assess efficacy of the use of the AGP system in patients with memory problems and diabetes can be conducted, important feasibility criteria need to be assessed to justify its development and inform its design and conduct, which include eligibility, recruitment, retention, successful capture of blood glucose readings and qualitative assessment of value and acceptability.
Topics for discussion are likely (but not exclusively) to include: factors that have had an impact on the acceptability of the AGP System including design and usability; and, the impact of the device on daily life and routines including physical, emotional and social health; current and perceived practical, emotional and theoretical issues with wearing the device and the associated health monitoring. In addition, we will gather participants' views on the quality and quantity of communication received concerning information, explanations and on-going and follow-up care needs; and, recommendations for inclusion in the design of future patient and carer-facing information and explanations.
The feasibility criteria will determine whether a full RCT could be conducted, which would look at whether patients with memory problems and diabetes can correctly use the device and act on the results to potentially improve clinical outcomes and quality of life.

4.1.1 Background to the fellowship

This feasibility study forms part of an Alzheimer's Society funded doctoral research fellowship, which commenced in January 2017. The focus of the fellowship is to investigate hypoglycaemia and serious adverse events in older people living with memory problems and diabetes.
The feasibility study is complementary to a pharmacoepidemiological (database) study that looks at the consequences of hypoglycaemia in patients with dementia and diabetes. The results of both studies will provide a multi-faceted approach towards tackling the difficult challenges faced by patients with dementia and diabetes, and their carers.

4.1.2 Explanation for choice of device

The introduction of flash glucose monitoring using the factory-calibrated meter has emerged as a novel method to study glycaemic patterns. The system that is currently publicly available for patients to purchase is the FreeStyle Libre Flash Glucose Monitoring System-Abbott. The website also provides video tutorials on the use of the system (https://www.freestylelibre.co.uk/libre/).
The use of the flash glucose system provides AGP, giving graphic and quantitative information on 24-hour glucose patterns. This can enable patients, carers and clinicians to identify patterns in glycaemic control and when they are occurring. The

use of the AGP system has been evaluated and recommended both in adults and children aged 4-17.
The system consists of a reader (although Android phones can download an app, which replaces the need for a reader) and a sensor (approximately the size of a £2 coin):

Sensor applicator Sensor pack Sensor

LibreLink App

You can now scan the FreeStyle Libre sensor using the FREE LibreLink app on your Android smartphone[5,6].

More information

GET IT ON Google play

The starter pack consists of the reader and two sensors (each sensor lasts for two weeks) and costs £159.95. Each subsequent sensor costs £57.95. Patients with diabetes ordering the products will be exempt from VAT. Importantly, if a patient or carer owns an Android smartphone, it will not be necessary to purchase a reader, as they can download a free app instead.

The flash glucose monitoring system does not require finger-prick testing for calibration (in contrast to CGM systems, which do require calibration via finger-prick testing).

This feasibility study has not received any sponsorship from Abbott. The device received the CE mark for use in adults in 2014 and for children (4-17 years) in 2016.

4.2 Objectives

The objectives of this study are to assess if the use of AGP system is feasible and acceptable for older patients with memory problems and diabetes.

- Participant eligibility: how many patients with memory problems and diabetes are potentially eligible?
- Participant recruitment: how many patients are subsequently enrolled in the study?
- Participant retention: what proportion of participants will take part until the end of the study? For withdrawals, what are the reasons?
- How many hours of glucose data will successfully be recorded?
- Do participants find the use of the AGP system acceptable?
- Are there any adverse events related to wearing the sensor (for example pain or skin reactions)?
- Are there any other adverse events, for instance, hospitalisation or events that require medical attention?

The data from this feasibility study will help guide further plans for a RCT, including recruitments plans and power calculations.

4.3 Trial Design

This study is a single-centre medical device study to determine the feasibility and acceptability of the use of the AGP system in older patients with memory problems and diabetes.

We will invite and recruit patients aged 65 and over, whilst they are inpatients under the Older People's Medicine Department, Acute Medicine Unit, or the Diabetes and Endocrinology Department. The use of the AGP system will take place around one-month after discharge from the acute setting, to ensure that the participants have had a chance to fully recover from their hospital admission and are settled back into their usual routine at their usual place of residence. We aim to recruit up to 20 participants.
The AGP system will be given to the participants for up to two weeks. At the first home visit, the researcher will fit the sensor and provide training on how to use the device. The research team will contact the participants one week after the first home visit (telephone call) to check whether any questions have arisen and whether the participant is still happy to be part of the study. At the end of the study period, participants and/or their carers will take part in an in-depth interview to explore the acceptability of the medical device.

5 Methods

5.1 Site Selection

5.1.1 Study Setting

Participants will be identified & recruited whilst an inpatient under the Older People's Medicine and/or Acute Medicine Departments at the Norfolk and Norwich University Hospital Trust. The trial itself will take place in the Community and AGP system will only be used post-discharge from the acute setting.

5.2 Participants

5.2.1 Eligibility Criteria

The population of interest is older people (≥65 years old) with memory problems and diabetes.

5.2.2 Participant Inclusion Criteria

- Patients aged 65 and older
- Type 1 or Type 2 diabetes mellitus
- On glucose-lowering medication
- Abbreviated Mini-Mental Test (AMT) score equal or less than 8 (out of 10) or already has formal diagnosis of dementia

With regard to the use the AMT, this is part of standard clinical care at the NNUH where it has been implemented as a short screening test to identify memory problems in inpatients. If a patient scores 8 or less out 10 on the AMT, this triggers an established Trust protocol called Memory Matters. The result of the AMT is logged on the Trust's reporting software (ICE) and automatic referrals to the Memory Matters Team and GP are triggered for further follow-up in the Community post-discharge. The value of AMT in hospital settings was confirmed in a systematic review and meta-analysis on screening for dementia in general hospital inpatients, where AMT was reported as a reasonable tool with good discriminant ability AUC 0.88 (15).

5.2.3 Participant Exclusion Criteria

The participant may not enter the trial if any of the following apply:

- Treatment with Metformin only;
- Not willing to participate;
- Terminal illness (less than one-year life expectancy);
- AMT above 8
- Evidence of bruising, bleeding, cellulitis and/or skin tears on the upper arms

5.2.4 Eligibility Criteria for Individuals Performing the Interventions

The Co-chief investigator will provide hands on teaching to participants and/or their carers on the use of the AGP system, including how to fit the sensor. She has met with the local Abbot representative who provided hands-on teaching. In addition, there are freely available instruction videos available at http://www.freestylelibre.co.uk.

5.3 Intervention

This is a one-arm feasibility study on the acceptability of wearing the Freestyle Libre AGP system. All participants will be issued with the AGP system. The trial team will buy the readers and sensors from the Freestyle Libre website and provide the participants with all the necessary equipment.

Participants will be shown how to wear the Freestyle Libre AGP system, which they will be asked to wear for up to two weeks (=the lifespan of one sensor). This two-week period will commence one month of discharge from the acute setting. The period between discharge and starting to wear the AGP system is intended to give participants time to recover from their acute admission and settle back into their normal daily routines. The blood glucose readings that are captured will, therefore, be a more realistic reflection of usual care (as opposed to capturing blood glucose readings whilst a participant is being treated or recovering from an acute illness). There will be no change in the standard care of the participants' diabetes management.

In order to gain the most information about the acceptability of use of the AGP system, there will be no blinding of the blood glucose readings. If participants and/or carers have any concerns about prolonged or recurrent blood glucose trends that indicate the patient is running significantly out of their individual target range, they can either contact their usual clinical team (e.g. GP or diabetes team) that provides their care, or alternatively alert the trial team (via a helpline) who will then assess the readings and make appropriate referrals. The trial team includes two Consultants in Diabetes who will be able to evaluate glucose patterns and make recommendations for any further care through usual channels.

We will encourage participants (and/or caregivers) to keep a diary of events, when there were concerns about blood sugar readings and the clinical or research team was contacted.

No adjustment to the diabetes medication should be made by the participants/carers, unless advised by a medical practitioner.

The trial team will look at the data retrospectively (after the participant has worn the device for up to two weeks). The readings that the Flash Glucose Monitor records are not real-time, as the blood sugar readings are taken from the interstitial fluid (thin layer that surrounds the cells of the tissues below the skin), as

opposed to blood. There is an approximate 10-minute delay in interstitial fluid glucose response to changes in blood glucose. Nevertheless, glucose readings on interstitial fluid have been shown to reliably reflect glucose levels(16).

5.4 Discontinuation

Participation in this study is completely voluntary and participants can choose to discontinue at any stage. If so, they (or their nominated consultee) will be informed they: do not need to give a reason (although they will be voluntarily asked to supply one) and that their medical and legal rights are not affected. In addition, if a participant is admitted to hospital during the study period, we would stop the glucose data collection from the date of the admission onwards.

5.5 *Concomitant Care*

This medical device study is testing the feasibility of the use of the Freestyle Libre AGP system. Whilst wearing the sensor, participants will be advised to continue with the standard care for their diabetes as recommended by their healthcare team.

5.6 *Outcomes*

Feasibility outcome measures

- Numbers of potentially eligible patients who meet the selection criteria
- Number of participants subsequently recruited into the study
- Extent of capture of blood glucose readings
- Attrition rate and reasons for withdrawal
- Adverse events related to wearing device and other adverse events

Patient outcome measures

Participants and/or their carers will be asked to take part in one interview, which will take place during the second home visit. It will focus on the acceptability of use of the AGP system following completion of the study period.

5.7 Participant Timeline

Participants will remain in the study for 6-8 weeks from providing consent.
Participants will undergo the following steps:

- Receipt of invitation letter and PIS/CIS whilst an inpatient at Norfolk and Norwich University Hospital, which will cover taking part in the study and one interview.
- If interested, the research team will fully explain the study and answer and questions. The chief investigator will assess whether there is any evidence of bruising, bleeding, cellulitis and/or skin tears on the upper arms. Should that be the case, then the potential participant will not be eligible to take part in the study.
- Consent will be taken (or consultee agreement sought) prior to discharge from hospital.
    a. In case of discharge before consent is obtained, potential participants will also have been given a reply slip and pre-paid envelope to confirm whether or not they are prepared to be contacted about the study.

- An introduction to the AGP system will be given to the patient and or carer by the co-chief investigator prior to discharge.
- Within one month after discharge, participants (or their carers) will be contacted to check willingness to continue with the study
    a. If no, then participant will be withdrawn and this will be the end of involvement for that particular person
    b. If yes, the chief investigator will arrange a home visit to deliver the AGP system and fit the sensor. Prior to fitting the senor, the chief investigator will again assess whether there is any evidence of bruising, bleeding, cellulitis and/or skin tears on the upper arms. Should that be the case, then the potential participant will not be eligible to take part in the study. The home visit will also be an opportunity to provide refresher teaching on the use of the AGP system. Understanding and health literacy may well be barriers to usability and participants (and care givers) will be encouraged to ask questions and be given a contact name and number in the event of any subsequent questions arising or concerns.
- After one week, the research team will telephone the participant (or carer) to check how they are getting on with the AGP system and whether they are still happy to continue being part of the study. If not, the participant will be withdrawn, however, the data collected by the AGP system up to the date of withdrawal will still be analysed. The reason for withdrawal will be documented on the case record form (anonymised).
- After wearing the sensor for two weeks, members of the trial team will contact the participant to arrange a convenient time for a 2nd home visit, in order to collect the AGP system and carry out a semi-structured face-to-face interview (lasting up to one hour) to explore patient and carer experiences of using the AGP system and the acceptability of the medical device and the participant's/carer's experiences.

5.7.1 Withdrawal

Participants will have the right to withdraw from the study at any time without giving reason. Identifiable data already collected with consent will be retained and used in the study.

5.7.2 Participant Transfers

If a participant moves from the area during the trial period, this will be considered a discontinuation from the study. Identifiable data already collected with consent will be retained and used in the study.

5.7.3 Trial Closure

Trial closure will be after the last participant has returned the AGP system.

5.8 Sample Size

This feasibility study aims to estimate the important parameters for the sample size calculation for a full trial; no sample size calculation has been undertaken at this stage. We aim to recruit up to 20 participants. This is a size that the research team consider to be pragmatic and sufficient as indicative quantitative data upon which to base the sample size for a full trial.

5.9 Recruitment and Retention

5.9.1 Recruitment

Potential participants will be identified whilst an inpatient under either the Acute Medicine or Older People's Medicine Departments:

- Patients aged 65 years and older
- Type 1 or Type 2 diabetes mellitus
- On glucose-lowering medication
- AMT equal or less than 8 (out of 10) or already has formal diagnosis of dementia

The research team will liaise with their colleagues on the clinical teams to identify if there are any potentially suitable participants/care givers who could be given the invitation letter. If there is interest in taking part, the investigator will go on to provided information sheets and offer verbal explanations of what the study involves.

If the patient lacks capacity to give informed consent to participate in the study, the research team will seek advice form a nominated consultee. The nominated consultee will be given a Consultee Information Sheet (CIS).

If the patient consents or the nominated consultee confirms that in his/her opinion the patient would be willing to participate in the study, the research team will obtain consent/consultee agreement. Consent/Consultee Agreement will be obtained >24 hours after provision of the PIS/CIS.

We will record the numbers of patients who decline participation, and any reasons given.

The Chief Investigator will then provide an overview of the AGP system by way of introduction. Participants will also be given a fridge magnet with contact numbers as a reminder/aide memoire.

In case of discharge from hospital prior to the potential participant consenting, the Chief Investigator will also hand out a pre-paid envelope, contact telephone number and reply slip stating that the trial team can contact the patient/carer to discuss recruitment into the trial. Consent would then take place at the first home visit.

No financial or non-financial incentives are offered to participants.

5.9.2 Retention

Within a month from discharge back home (or usual place of care), the Chief Investigator will contact the participants/the nominated consultee to check willingness to continue with the study. If the participant is willing (or the nominated consultee confirms agreement), the PI will carry out a home visit, in order to supply the AGP system, provide refresher training and fit the sensor.

Following fitting of the sensor, participants will receive a follow-up telephone call after one week to check on progress and willingness to continue with the study. A

note will be made of any issues for potential follow up at the 2nd home visit interview to ensure continuity.

Participants will have the right to withdraw from the study at any time without giving reason. Identifiable data already collected with consent will be retained and used in the study.

5.10 Data Collection, Management and Analysis

5.10.1 Data Collection Methods

Each participant will be given a unique trial Participant Identification Number (PIN).

The preferred method of data collection is direct online entry of data by trial staff onto the central database, stored on servers based at the University of East Anglia. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database (but this is not essential).

Data collection, data entry and queries raised by a member of the trial team will be conducted in line with the University of East Anglia's Data Management Standard Operating Procedure.

Baseline data (demographics, gender, age, medical history, medications) will be collected by medical case note review.

Quantitative data will be collected by downloading reports from the AGP system. These reports will capture the blood glucose readings during the two-week period when the AGP system was being used.

Qualitative data will be collected by means of one in depth interviews with participants and/or carers. The interview will take place after the two-week period of wearing the AGP system and will explore the experiences and acceptability of its use in this patient population and/or their carers where appropriate. An iterative topic guide will be prepared in advance to ensure key areas of importance both to the study and to the participants are followed up and reflect issues that may have arisen.

A sample topic guide is included in Appendix X with indicative questions and prompts. It will be a guide to discussion to ensure key areas are covered. The interview will take place at the participant's home or a location of their choosing and will last up to one hour. The interview and will be audio-recorded and transcribed in full.

Participant identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room. Clinical trial team members will receive trial protocol training. Regular central monitoring will assess data quality and completeness during progression of the trial. All data will be handled in accordance with the Data Protection Act 1998.

5.10.2 Data Management

All data will be stored in a database on a secure server, provided and maintained by the University. The server environment is protected by a firewall and is patched and maintained according to best practice. The physical location of the server is protected by CCTV and security door access. Access to the database will be controlled via unique, personally attributable (i.e. not generic) usernames, password protected, and accessible only to members of the trial team, and external regulators if requested.

Data will be entered in the approved database by a member of the trial team. The database software provides a number of features to help maintain data quality,

including; maintaining an audit trial, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/missing data. After completion of the trial the database will be retained on the servers of University for on-going analysis.
The identification, screening and enrolment logs, linking participant identifiable data to the pseudoanonymised Participant Identification Number (PIN), will be stored securely at the database, with access controlled on a per-user basis. Access to identifiable and pseudoanonymised data will be stored separately within the database and permissioned accordingly.

Participant contact details will be collected by a member of the research team at the time that the participant calls to express an interest in being part of the study.

Interviews will be recorded by the investigators. Interviews will be transcribed, coded and anonymised by members of the research team at the University of East Anglia after the interview has taken place. Typed data will be kept on a password protected University-owned computer. Data may be accessed only by the research team who may listen to recordings or read about them to check the work. After completion of the trial the personal data will be stored for 12 months and pseudoanonymised data for 10 years. Paper documents will be stored in a locked filling cabinet and electronic data on the university secure server.

5.10.3 Analysis plan

This study is a single-centre medical device study to determine the feasibility and acceptability of the use of an AGP system for two weeks in PWDD.

5.10.3.1 Statistical Analysis Plan (SAP)

Baseline characteristics for each participant will be presented in a Table. For categorical variables, the number and percentage will be presented. For continuous variables, the mean (and standard deviation) or median (and interquartile range) will be presented depending on the distribution.

5.10.3.2. Statistical Methods

Feasibility outcomes (quantitative)

- Hours of captured glucose data will be presented with numbers and percentages.
- Participant eligibility: how many patients with memory problems and diabetes are potentially eligible?
- Participant recruitment: how many patients are subsequently enrolled in the study?
- Participant retention: what proportion of participants will take part until the end of the study? For withdrawals, what are the reasons?
- How many hours of glucose data will successfully be recorded?
- Do participants find the use of the AGP system acceptable?
- Are there any adverse events?

Patient outcomes (qualitative)

One semi-structured face-to-face interviews will take place during the study period. Topics for discussion are likely (but not exclusively) to include: factors that have had an impact on the acceptability of the AGP System including design and usability; and, the impact of the device on daily life and routines including physical, emotional and social health; current and perceived practical, emotional and theoretical issues with wearing the device and the associated health monitoring. In addition, we will gather participants' views on the quality and quantity of communication received concerning information, explanations and on-going and follow-up care needs; and, recommendations for inclusion in the design of future patient and carer-facing information and explanations.
An interpretive inductive approach will be used based on the six phases outlined by Braun and Clarke (17): Data familiarisation, initial coding, themes identification, review, definition and, reporting.

5.11 Data Monitoring

5.11.1 Data Monitoring Committee

This feasibility study looking in to the acceptability of the use of AGP system in older people with memory problems and diabetes minimal or no risks. The device simply enables glucose concentrations to be recorded in a less invasive and more frequent manner than conventional finger-prick testing. This study does not involve delivery of a therapeutic intervention that exerts physiological effect. The medical device has already received CE mark/approval for the adult population with diabetes and can be purchased from the Freestyle Libre website (https://www.freestylelibre.co.uk/libre/), and, depending on local clinical commissioning groups (CCG) may also now be available on prescription (since November 2017).
A recent feasibility and acceptability study of the device in children showed that about 60% of the participants were willing to wear the sensor again. Five out of 46 participants complained of pain while wearing the sensor. In 16 out of 46, the sensor lasted for less than two weeks. Four out of those 16 rejected wearing the sensor again. One child developed a pustule at the insertion site (18).

Any adverse events reports will be assessed by the Trial Steering Committee. Therefore, the trial team submit that a separate data monitoring committee is not necessary.

5.11.2 Data Monitoring for Harm

5.11.2.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.
Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.

Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • or is another important medical condition***

* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (eg a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- continuous persistent disease or a symptom present at baseline that worsens following use of the device

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event.
- Pre-existing disease or a condition present before treatment that does not worsen.
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery.

5.11.3 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the toxicity (symptoms) section of the Follow-up Form. SAEs and SARs should be notified immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

5.11.3.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' then an SAE form must be completed and notification sent within one working day.

5.11.3.2 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (eg the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (eg the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (eg because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (eg the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal	SAR

	relationship and the influence of other factors is unlikely	
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

5.11.4 Trial Team

The Trial Team will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

5.11.5 Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the Chief Investigator, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

5.11.6 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to: initiate, manage and finance the trial.

6 Ethics and Dissemination

6.1 Research Ethics Approval

Before initiation of the trial, the protocol, all informed consent/declaration forms and any material given to the prospective participant/consultee will have been approved by the relevant REC. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason will be respected. The participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

6.2 Protocol Amendments

The chief investigator is responsible for communicating any regulatory approved substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) to all principal investigators in all participating centres, trial registries, journals and regulators. Relevant parties will be informed by postal letter containing an amended version of the protocol for storing in the trial master file.

6.3 Consent or Consultation

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitably trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. There will be a minimum of 24 hours between provision of the PIS to the participant and seeking informed consent. Members of the trial team seeking consent will be fully trained in Good Clinical Practice (GCP). During the consent process, it will be made completely and unambiguously clear to participants they are free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

A number of potential participants for this feasibility study may not have the decisional capacity to give informed consent. Here they are, or are judged, as being unable to understand information given to them, or to use it to make an informed decision about participation. As we are investigating the use of a medical device in patients who either have memory problems (or dementia), these patients may well benefit from participation in the trial. In such situations, the consultation process will take place in accordance with the Mental Capacity Act (MCA) (this is a Non-CTIMP study). An appropriate person will be found to consult with, in order to make a decision about whether the potential participant should be included in the research. The consultee will not consent on behalf of the participant – they will provide advice which will be taken into account by the research team. In the first instance, a personal consultee will be sought for consultation. If a personal consultee cannot be found, an appropriate professional who is not connected to the research will be nominated to act as consultee.

The consultee will be informed about all aspects of the study and provided with a Consultee Information Sheet (CIS). The information given to a consultee will clarify

their legal obligations under the MCA. Following a discussion with a medical qualified investigator or suitably trained and authorised delegate, any questions will be satisfactorily answered. If the consultee advises that in their opinion the potential participant would have no objection to taking part in the study, they will be asked to sign the Consultee Declaration Form (CDF). There will be a minimum of 24 hours between provision of the CIS and seeking the consultee's advice.

If during the trial, the participant is judged to have regained capacity, their consent will be sought.

Consent will be re-sought if new information becomes available that affects the participants' consent in any way. These changes will be documented in a revision to the PIS/CIS and the participant/consultee asked to sign an updated consent/declaration form. Changes will be approved by the ethics committee prior to their use.
A copy of the approved consent form and declaration form is available from the trial team.

6.4 Confidentiality

All patients will be recorded on an identification log with pseudoanymised identifiers of initials and hospital number. This log, in both a paper and computer form, will be compiled by trial research staff and stored in either locked cabinets in swipe card access officers and on hospital or university password access computers in swipe card access offices. All potential participants are allocated a participant identification number (PIN) to replace their name. Personal information is collected by trial staff trained in the principals of Good Clinical Practice. Only members of the trial teams in each centre will have access to the e-database, identification and screening logs.

6.5 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

6.6 Indemnity

UEA holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UEA has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. UEA does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UEA or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UEA's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UEA, upon request.

6.7 Finance

The EAGLE study is part of an Alzheimer's Society doctoral fellowship (Grant number 324 (AS-CTF-16-001)). It is not expected that any further external funding will be sought.

6.8 Archiving

The investigators agree to archive and/or arrange for secure storage of trial materials and records for a minimum of 5 years after the close of the trial.

6.9 Access to Data

Access to the final trial dataset will be granted to the: chief investigator, trial statistician, chair persons of the TSC and any regulatory authorities. Access by any other parties will require approval from the CI and chairperson of the TSC. Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TSC.

6.10 Ancillary and Post-trial Care

Following completion of the trial, Flash Glucose Monitoring would not be prescribed to participants using research funding. This feasibility study does not have the objective of demonstrating benefit. Patients and carers will have to go through conventional funding channels if they wish to continue using the medical device.

6.11 Publication Policy

6.11.1 Trial Results

The Chief Investigator will co-ordinate the writing of abstracts and full publications and send these to all co-investigators before submission to scientific meetings and peer review journals for comments and approval. The full publication detailing the primary and secondary outcomes will be first submitted within 12 months after the last participant has completed follow-up. Following full publication, relevant papers will be sent to the appropriate patient groups, and participants who have requested this.

6.11.2 Authorship

Any trial related publications will include co-investigators, who in the opinion of the Chief Investigator, have made a significant contribution to the: design, conduct, analysis, funding application and report writing of the trial.

7 Protocol Amendments

This is the second version of the protocol.

November 2017 amendment: change to the selection criteria to exclude patients with obvious signs of cellulitis, bruising, bleeding, and skin tears to the upper arm.

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EAGLE study

Flash glucose monitoring in older patients with diabetes and memory problems

Patient Information Sheet

We would like to invite you to take part in the EAGLE research study run by the University of East Anglia. Before you decide whether you would like to take part, you need to know why the study is being done and what it is you would have to do. Please take time to read the following information carefully which you may wish to discuss with friends and relatives. Please contact us if you would like more information using the details below.

What is the purpose of this research project?

Diabetes and memory problems are common conditions that can occur together in older people. People with memory problems can have difficulty in managing and monitoring their diabetes, especially their blood sugars. Medication for diabetes can provoke excessively low blood sugars (aside-effect commonly known as 'hypos') needing recognition and treatment.

New technology (flash glucose monitoring) may help in keeping a closer eye on blood sugars. Small (coin-sized) sensors (fitted for 1-2 weeks) can constantly record sugar levels. Patients (or carers) do not need to remember, or recognize when to do finger prick testing. So far, no one has tested this technology to help patients with memory problems and

diabetes. There are some pictures of the device are attached to this leaflet.

This study will explore whether people aged 65 and older with memory problems and diabetes can tolerate wearing the flash glucose monitoring system for two weeks to help monitor blood sugar levels. We will recruit up to 20 patients for this study. Potential participants will be identified and invited whilst they are in hospital (the Norfolk and Norwich University Hospital).

Why have I been chosen?

You have been invited to take part as you have diabetes and memory problem. This study is about finding out whether people with diabetes and memory problems can tolerate wearing the flash glucose monitor system and make recordings for two weeks. This medical device is already publicly available for use in adults and children with diabetes. However, so far, no one has looked specifically at how adults with diabetes AND memory problems would tolerate and wear the device at home.

Do I have to take part?

No, it is up to you to decide. If you decide to take part and then change your mind, you can stop at any time. Whether or not you take part, you will still have access to the usual medical services. If you decide *not* to take part, it will not in any way harm or affect the medical care you receive.

What will happen if you agree to take part?

Each patient will be shown how to use the flash glucose monitoring system, which will be worn about one month AFTER discharge from hospital. This will give you enough time to recover from your last hospital admission and get back into your normal day to day routines. We would like you to wear this medical device for two weeks. A member of the research team will visit you either at your home or other convenient place, in order to give you the device and show how it is used. Prior to giving you

the device, a member of the research team will check the skin of your upper arms (this is where the device will be fitted) to make sure that there are no signs of bleeding, infection, skin tears or bruises. Should any of this be apparent, then it will not be possible for you to take part in the study. The visit should take no more than one hour.

After the two weeks of using the device, the research team will visit you either at your home or other convenient place, to pick up the device and to talk about your experiences. This visit should last no more than an hour.

What should I do if I wish to take part?

If you might be interested in taking part in the study, and would like to find out more, please call or email using the details below. We will arrange the initial meeting, to answer any questions you may have and ask you to complete a consent form. At this meeting, the researcher will give you an initial overview and hands-on demonstration of the medical device.

What will I have to do?

The research team will contact you about one month after your discharge from hospital to check if you are still willing to take part in the study. If you are, then we will arrange to visit you at home (or other preferred place) at a convenient time to give you the flash glucose system, fit the sensor, provide refresher training and answer any questions you may have.

You will wear the sensor for two weeks (the lifetime of one sensor), which will typically need to be swiped with a reader three times a day (for instance, before or after meals).

After one week, the research team will telephone you to check how you are getting on with wearing the device and whether issues/questions have arisen.

After the two weeks, the research team will contact you to arrange a convenient place and time to pick up the device and speak to you about your experiences. This meeting should last no more than one hour.

The research team will make audio recordings of the study visits and telephone follow-up to ensure that any concerns, questions and adverse events are documented.

During the time when you wear the device, the research team would like you to continue with the management of your diabetes as per normal and not to make any changes (unless advised to do so by a healthcare professional).

What are the possible disadvantages of taking part?

- The research team will visit you twice for up to an hour on each visit.
- You may feel worried about being able see blood sugar readings all the time. If you have any concerns at all, you will be able to contact the research team or your GP.
- You may experience discomfort when the sensor is fitted.
- You may experience a mild skin reaction where the sensor is fitted.

What are the possible benefits of taking part?

- You will potentially be able to get detailed information about blood sugar levels over a two-week period.
- Medical professionals will be able to analyze the information collected and make decisions on your treatment plan, if need be.
- You may be able to pick up trends of high or low sugars, that can be used to inform your doctors so that they can any adjustments to the treatment as they see fit.

What happens when the research stops?

The study will help shed light on whether people with diabetes and memory problems can tolerate wearing and making recordings with the flash glucose device. It may pave the way to bigger studies to improve management and safety in people with memory problems and diabetes. If you decide that you wish to continue using the device, it is available for purchase form the manufacturer's website at: https://www.freestylelibre.co.uk/libre/. It may also be possible to obtain it on prescription, but this will depend on the local primary care guidelines.

Involvement of your GP

If you decide to take part in the study, we will send a letter to your GP practice to let them know. After the study finishes and if we pick up any results that may require adjustment of your medications, we will write to your GP practice to update them.

What if there is a problem?

If you want to withdraw from the study, you can do so at any time without giving a reason. If you withdraw, your information collected can be removed before it is analyzed by the research team, but not if you withdraw after it has been analyzed. If you have a complaint about the study or how you have been treated, please contact the research team. You can also contact the Norfolk and Norwich University Hospital Trust's Patient Advice and Liaison Service (PALS). Their contact details are:

Complaints and Legal Services Department
Norfolk and Norwich University Hospitals
NHS Foundation Trust
Colney Lane
Norwich NR4 7UY
Tel: 01603 289684 or 01603 289686
Email: complaints-team@nnuh.nhs.uk

If you have any concerns about your blood sugar readings, you can contact the research team or your GP for further advice. If you have any concerns about the device itself, please contact the research team.

Will my taking part in the research be kept confidential?

Yes, all data by the research team will stay confidential. All data collected for the study will be stored and anonymized. Data will be stored securely on password-protected computers accessible only to the study team. With regard to the audio recording, a member of the research team will type this up, code and anonymize it. This process will be carried out on a University-owned computer. The audio recording will be stored for a period of 12 months and then erased by a member of the research team. Anonymized data will be stored for a period of 10 years, in line with current data archiving policy at the University of East Anglia. Disposal of data after this period of time will be carried out securely, by using data shredders.

Anonymized data will be used in reporting the results of the study at conferences and in academic journals. By giving consent, you agree for this information to be collected.

What will happen if I do not want to carry on with the research?

You can withdraw from the study at any point without any adverse consequences. You do not have to give any reason for withdrawing.

What will happen with the results of the study?

The results will be used to help improve the management of diabetes in people with memory problems. We will write up results for the funder (Alzheimer's Society), publications and conferences, as well as for the general public. You can request a copy of the full results, which we will send after the study has finished.

Will I receive any payment for being in this study?

There is no payment for taking part.

Who is organizing and funding the research?

The research is funded by the Alzheimer's Society.

Patient and public representatives have been involved at all stages of the development and review process. The research is sponsored by the University of East Anglia, which has appropriate insurance in place, to cover research activities.

Who has reviewed the study?

This research has been looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity (Ref: 17/EE/0388).

What to do next

The research team will contact you in the next few days to see whether you are interested in taking part in the study. Alternatively, please contact the research team using the contact details below.

Contact details

Dr Katharina Mattishent (researcher)

Tel: 07547886634

email: K.Mattishent@uea.ac.uk

Thank you for taking the time to read this information leaflet about the EAGLE study

Appendix 4 Consent Form

CONSENT FORM – EAGLE study

Study title: EAGLE study - **Fea**sibility and acceptability of monitoring ambulatory **gl**ucose profil**e** in older patients living with memory problems and diabetes

Chief Investigator: Dr Katharina Mattishent

Please initial box

1	I confirm that I have read and understand the information sheet dated ----------(Version .....) for the above study and have had the opportunity to ask questions and had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that sections of any of my medical notes may be looked at by responsible individuals from the Norfolk & Norwich Hospital, University of East Anglia, or from regulatory authorities where it is relevant. I give permission for these individuals to have access to my records held in NHS hospital/GP surgery and/or private health provider.	☐
4	I understand that a researcher will contact me to arrange home visits. I give my permission for the home visits to be audio recorded and I agree to my anonymous quotations being used for the project report and publications	☐
5	I agree to my GP being informed of my participation in the study.	☐
6	I understand that I my GP will be informed of my blood sugar readings	☐
7	I understand that, I will be invited to take part in an interview about how I have found wearing the medical device and what impact it has had on me. I give my permission for this to be audio recorded and I agree to my anonymous quotations being used for the project report and publications.	☐
8	I agree to take part in the EAGLE study.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

NHS
Health Research Authority

East of England - Cambridge Central Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

4th December 2017

Dr Katharina Mattishent
Alzheimer's Society Clinical Research Fellow in Geriatrics
University of East Anglia
Bob Champion Research and Education Building
Norwich Medical School
University of East Anglia
NR4 7TJ

Dear Dr Mattishent

Study title:	**Flash glucose monitoring in older patients with memory problems and diabetes: a feasibility study**
REC reference:	**17/EE/0388**
IRAS project ID:	**221757**

Thank you for your letter of 17th November 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this 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 hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

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

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk 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 management permissions 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 request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

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

NHS 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" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for any non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
GP/consultant information sheets or letters [Letter to GP to inform of participation version 1.0]	version 1.0	09 May 2017
Interview schedules or topic guides for participants [Indicative Topic guide version 1.0]	version 1.0	09 May 2017
IRAS Application Form [IRAS_Form_13092017]		13 September 2017
Letter from sponsor [I&I Letter]		03 May 2017
Letters of invitation to participant [Letter of invitation and reply slip version 1.0]	version 1.0	09 May 2017
Other [GP letter change in meds version 1.0]	version 1.0	09 May 2017
Other [Freestyle Ilbre Pictorial Guide version 1.0]	version 1.0	09 May 2017
Other [NNUH clerking book page 3 with Abbreviated Mental Test]	not applicable	04 September 2017
Other [Cover letter and response to REC 17 November 2017]	not applicable	17 November 2017
Other [Feasibility Study Protocol version 2.0]	version 2.0	20 November 2017
Other [Cover letter for participants who regain capacity version 1.0]	version 1.0	20 November 2017
Other [Consent form version 2.0]	version 2.0	20 November 2017
Other [Patient Information Sheet version 2.0]	version 2.0	20 November 2017

Other [NOMINATED consultee information sheet version 2.0]	version 2.0	20 November 2017
Other [NOMINATED consultee declaration form version 2.0]	version 2.0	20 November 2017
Other [PERSONAL consultee information sheet version 2.0]	version 2.0	20 November 2017
Other [PERSONAL consultee declaration form version 2.0]	version 2.0	20 November 2017
Summary CV for Chief Investigator (CI) [Katharina Mattishent CV]	1	10 May 2017
Summary CV for supervisor (student research) [YKLoke Short CV]	1	10 May 2017

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.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received 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/

HRA Training

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

17/EE/0388	**Please quote this number on all correspondence**

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

Yours sincerely

pp C Hollowell

Dr Joseph Cheriyan
Vice-Chair

Email:NRESCommittee.EastofEngland-CambridgeCentral@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Sarah Green*
Ms Laura Harper, Norfolk And Norwich University Hospital NHS Trust

Appendix 6 Indicative Topic Guide

The aim is to derive a more holistic account of the user and carers individual experience.
Some baseline descriptors will be needed in advance such as the level of awareness of the device (cognitive health), living circumstances and environment
Areas for discussion to include:

Acceptability
Tell me a bit about how you have got on with (wearing) the device?
Prompt for comfort, design & functionality issues:

- Did you notice it physically?
- In what ways, if any, did it change your day to day activities?
- Were there any particular positive / negative aspects of the device? Ease of use, wearablity, comfort, visibility, obtrusiveness, damage, inconvenience, stigma?

Exploration of expectations
What were your expectations of (wearing) the AGP device? (Contrast user and carer views)
Did it the device meet any expectations you had of using the AGP device?

Effectiveness
What was the experience of users/carers of scanning the device?
Was there any immediate or longer term consequences for the user and their diabetes health?

Consequences
Impact on wider health and wellbeing
'Thinking about other aspects of your health and wellbeing can you tell me a bit about your health in general?'
Prompt for:

- Overall impact of the device (positive and negative)
- Any specific areas mentioned e.g. did you feel the device made any difference to your symptoms/experiences of living with diabetes, dementia, co-morbidities, anxiety, & self-care etc
- Impact on more personal and social aspects of life and wellbeing
- Effect on day to day activities, social life, personal implications of wearing and managing the device?

Where any elements of the device reassuring or discouraging and if so – who to (user and / or carers)?

Overall
What would you say to others considering this device?

Appendix 7 FreeStyle Libre Pictorial Guide

FreeStyle Libre

1 Apply sensor
with applicator

- A thin flexible sterile fibre (5mm long) is inserted just below the skin. Most people reported that applying the sensor was painless*
- The 14-day sensor stays on the back of your upper arm and automatically captures glucose readings day and night.
- The sensor is water resistant and can be worn while bathing, swimming and exercising†

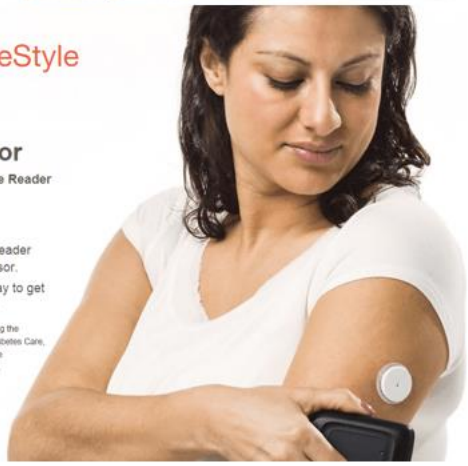
*Most people did not feel any discomfort while applying or wearing the FreeStyle Libre Sensor. In a 2013 US study conducted by Abbott Diabetes Care, 100% of patients surveyed (n=30) rated that applying the sensor was painless or almost painless, and 93.4% of patients strongly agree or agree that while wearing the sensor, they did not feel any discomfort under their skin. Data on file. † Sensor is water-resistant in up to 1 metre (3 feet) of water for a maximum of 30 minutes

How to use the FreeStyle Libre System

2 Scan sensor
using FreeStyle Libre Reader

- To get a reading, bring the FreeStyle Libre reader close to the sensor and scan it over the sensor.
- A painless*, 1 second scan offers an easy way to get your glucose reading even through clothing.

*Most people did not feel any discomfort under the skin while wearing the FreeStyle Libre sensor. In a 2013 US study conducted by Abbott Diabetes Care, 93.4% of patients surveyed (n=30) strongly agree or agree that while wearing the sensor, they did not feel any discomfort under their skin. Data on file.



How to use the FreeStyle Libre System

3 Get reading
on the reader

- Get your glucose reading anytime, anywhere
- With every painless 1 second scan you get:
  - Current glucose reading
  - Trend arrow – where your glucose is heading
  - 8 hour glucose history

IRAS Project ID 221757
Freestyle Libre Pictorial guide version 1.0
EAGLE study 9 May 2017

For further information visit:
https://www.freestylelibre.co.uk/libre/

Abbott

Norfolk and Norwich University Hospitals NHS Foundation Trust

University of East Anglia

Study Title: Hypoglycaemia and serious adverse events in older people living with diabetes and dementia – a population-based cohort study

Short title: Hypoglycaemia and serious adverse events in older people with diabetes and dementia

Date and Version No: November 2017 v3

Chief Investigator: Professor Yoon K Loke, Norwich Medical School, University of East Anglia
Email: Y.Loke@uea.ac.uk

Investigators: Dr Katharina Mattishent, Alzheimer's Society Clinical Research Fellow, Norwich Medical School, University of East Anglia; Older People's Medicine Registrar, Norfolk and Norwich University Hospital
Email: K.Mattishent@uea.ac.uk
Dr George Savva, Senior Lecturer in Applied Statistics, University of East Anglia
Email: g.savva@uea.ac.uk
Dr Kathryn Richardson, Research Fellow in Statistics, University of East Anglia
Email: Kathryn.Richardson@uea.ac.uk

Funder: Alzheimer's Society

Host organisations: University of East Anglia, Norfolk and Norwich University Hospital Foundation Trust

Signature of Chief Investigator:

Confidentiality Statement: This document contains confidential information that must not be disclosed to anyone other than the

Investigator Team, host organisation, and members of the Independent Scientific Advisory Committee, unless authorised to do so

A. Lay summary

Diabetes and dementia are common illnesses that can occur together in older people. Diabetes UK estimate that approximately 5 million people will have diabetes in the next 10 years, whereas Alzheimer's UK estimate that over 1 million people will have dementia. Currently, 1 in 5 patients with dementia also have diabetes.

Medication to control blood sugar can provoke low blood sugars (hypoglycaemia; a particularly serious side-effect that may cause serious long-term harm). Although dementia is significantly associated with hypoglycaemia, there is currently little evidence regarding long-term consequences of hypoglycaemia in patients with diabetes **and** dementia. We will analyse healthcare data from the Clinical Practice Research Datalink to determine serious complications associated with hypoglycaemia (falls or fractures, use of emergency healthcare and hospitalization, heart attacks, and death) in patients with diabetes and dementia compared to those with only diabetes.

Understanding the potentially serious consequences of hypoglycaemia is crucial in helping patients, carers and doctors make decisions on choice, intensity and monitoring of medication for diabetes and concomitant dementia.

The results will provide valuable evidence for national guidance and co-ordination of health and social care policy (e.g. provision of meals at the appropriate time) for vulnerable patients with diabetes and dementia.

B. Technical summary

Background: Treatment of diabetes in older people with dementia is challenging, as clinicians try to achieve a comfortable balance between the

pursuit of tight blood sugar control (in accordance with national targets), against pragmatism and avoidance of serious side-effects, such as hypoglycaemia. There is a paucity of evidence regarding risk of hypoglycaemia in patients with diabetes and dementia, and the relationship between hypoglycaemia and serious adverse events (falls or fractures, use of emergency healthcare and hospitalization, heart attacks, and death).

Objectives: To describe serious (medically recorded) hypoglycaemic events in older people with multimorbidity (diabetes and dementia), and to determine risk of associated serious adverse events after serious (medically recorded) hypoglycaemia (falls or fractures, use of emergency healthcare and hospitalization, heart attacks, and death). For ease of reference, all mention of hypoglycaemia is intended to mean serious (medically recorded) hypoglycaemia.

Methods Population-based cohort of patients with diabetes (± dementia) based on CPRD with linkage to Hospital episode statistics, and Office for National Statistics datasets.

Data Analysis Kaplan-Meier survival curves will be used to display the survival curve for each adverse outcome after incident exposure to a hypoglycaemic event. The association between hypoglycaemic exposure and serious subsequent adverse event, will be evaluated using Cox proportional hazard regression models with adjustment for appropriate confounders to estimate a Hazard Ratio and 95% confidence interval.

C. Objectives, Specific Aims and Rationale

Objectives

To quantify the consequences of the problem of hypoglycaemia in older people with multimorbidity (dementia and diabetes), focusing on extent of associated serious complications (falls or fractures, use of emergency healthcare and hospitalization, heart attacks, and death) during follow-up after a hypoglycaemic event.

Specific Aims

1. In older patients with dementia and diabetes, what is the risk of serious adverse events (such as falls, fractures, cardiovascular events, use of emergency services, and death) following hypoglycaemia, compared to similar patients who do not have hypoglycaemic events?
2. Does hypoglycaemia in older patients with comorbid dementia and diabetes carry any greater risk of serious adverse events, as compared to hypoglycaemia in patients with diabetes who do not have a comorbid diagnosis of dementia?

Rationale

Current NICE guidelines do not specifically address the management of patients with diabetes and dementia. There has yet to be a unified/systematic approach to the management of this vulnerable patient group, and care pathways do not take account of the special circumstances and additional burden (such as the accompanying behavioural and psychological symptoms of dementia) in such patients (1). Several governmental and international professional bodies have highlighted the urgent need for more evidence into the management of diabetes and dementia(2) .

This study will look at the occurrence of hypoglycaemic episodes in older patients with dementia and diabetes and likelihood of subsequent serious adverse events associated with hypoglycaemia. This will guide a holistic approach that takes into account shared clinician and patient decision-making on type of medication, intensity of therapy, awareness of adverse effects, additional supervision of timing and type of meal, and comprehensiveness of monitoring for dangerous sugar levels.

D. Background

Diabetes and dementia are becoming more prevalent in the ageing UK population. By 2025 there will be around 5 million people with diabetes in the UK, more than one million with dementia and around 200,000 with both dementia and diabetes (3, 4).

People living with diabetes and dementia (PLwDD) may not recognize signs and symptoms of abnormal blood sugars, or are not able to vocalize their problems, thus leading to delays in getting treatment. Decreased food intake or inability to adjust drug doses accounts for more than half of hypoglycaemia episodes in older patients (5), which means that cognitive impairment or dementia can substantially increase the risk of hypoglycaemia.

Hypoglycaemia is a growing burden with wide implications for healthcare professionals, patients, carers and healthcare service utilization. Munshi et al. detected 102 hypoglycaemic episodes over a 3-day period through continuous glucose monitoring in 40 patients (without dementia), mean age 73 years (6). East Midlands Ambulance Trust responded to 523 call outs for severe hypoglycaemia over a 3-month period (mean age 76 years for the non-insulin treated patients), with projected annual call out costs of over £235,000(7) . This is mirrored by evidence in older people elsewhere where a 10-fold increase in risk of hypoglycaemic episodes needing hospital admission has been observed over the last decade (8) (9) . This upsurge has been attributed to increased intensity of medical treatment, as well as greater co-morbidities and frailty.

The National Institute of Health Research (NIHR) has acknowledged the evidence gaps in managing this vulnerable group and commissioned a realist synthesis to identify theories, frameworks, and processes of care for PLwDD (1). The NIHR commissioning brief emphasized the high priority of this topic

whereby “Individualised diabetes care for people with dementia has been advocated that considers not only the complications of acute hypoglycaemia and hyperglycaemia but also quality of life and carer support.”

The American Geriatrics Society (AGS) has also highlighted the lack of evidence in patients with diabetes and dementia. They remarked that older people were often excluded from trials in diabetes, and so, guidelines are not based on reliable evidence in this group. The AGS has called for more research “to better understand the risks and benefits of tighter glycaemic control among older patients and those with comorbidities” because of “Increasing observational evidence … that clinicians often do not differentiate treatments for older patients who differ widely in health status” (2).

Current NICE guidelines do not specifically address the management of patients with diabetes and dementia. There has yet to be a unified/systematic approach to the management of PLwDD, and care pathways do not take account of the special circumstances and additional burden (such as the accompanying behavioural and psychological symptoms of dementia) in such patients (1).

Current research has highlighted the urgent need to investigate the understanding of the magnitude of hypoglycaemia in people with dementia and diabetes, which will inform guidance about safer management and treatment decisions.

Our database study will examine the occurrence of hypoglycaemic events in PLwDD, and the association between hypoglycaemia and subsequent serious adverse events, such as falls or fractures, use of emergency healthcare and hospitalization, heart attacks, and death. This will guide a holistic approach that takes into account shared clinician and patient

decision-making on type of medication, intensity of therapy, awareness of adverse effects, additional supervision of timing and type of meal, and comprehensiveness of monitoring for dangerous sugar levels.

E. Study Type

Descriptive and hypothesis testing

F. Study Design

Retrospective cohort study

G. Sample Size

Our power calculation is based on the within group analysis for Aim 1 (ability to detect an increased risk in fractures following hypoglycaemic episodes) - our feasibility request to CPRD has identified prevalence of 22 984 people with diabetes and dementia (1990-2013), of which about 55% (approximately 12 000 patients) may have linkage to Full HES and ONS. Patients with dementia have a baseline fracture rate of 6% per year reported by Wang et al. (10) and a relative risk increase of 2.0 for fractures identified from our systematic review to be clinically important in those with hypoglycaemia. (11) Recent published data found that proportion of patients with diabetes and dementia affected by severe hypoglycaemia is 8 in a 100, thus potentially giving 960 patients with hypoglycaemia, and 9600 without hypoglycaemia (1:10 matching). (12) Based on these estimates, our study has >99% power to detect a clinically important relative risk increase of 2.0 for fracture between groups (alpha 0.05) i.e. absolute increase in fractures from 6% in the non-hypoglycaemic group to 12% in the hypoglycaemic group.

We have also conducted a more conservative estimate, where if there was only half the number of eligible patients with hypoglycaemia, and a halving of the baseline fracture rate of 3%, then for 480 hypoglycaemic patients with diabetes and dementia, and 4800 non-hypoglycaemic controls, we have

83% power of detecting an absolute increase in fractures from 3% to 6%.

H. Data Linkage

We will define the study population using CPRD (time period April 1997-latest available dataset).

HES Admitted Patient Care and HES Accident &Emergency (from April 2006) data will be used to supplement the available CPRD GOLD data on serious adverse events (including hypoglycaemia, fall, fractures and cardiovascular events) that triggered visits to hospital. We recognize that HES linkage covers only approx. 55% of patients from April 1997 until the most current data extraction date.

ONS Death Registration Data will be used to supplement the available CPRD GOLD data to identify deaths after the exposure, and cause of death related to falls, fractures and cardiovascular events. We recognize that ONS linkage covers only approx. 55% of patients from January 1998 until the most current data extraction date. Our analysis of mortality will be based on this smaller subset of patients.

Index of Multiple Deprivation Data will also be used as one of the covariates that we are considering for addressing confounding in the data analysis.

Patients are only eligible for linkage if they (i) registered at a participating English practice prior to the transfer of identifiers to the trusted third party for matching, (ii) had a valid identifier for linkage (NHS number plus at least one other of date of birth, postcode, gender), (iii) had not opted out or dissented from CPRD or the linkage scheme.

I. Study population

Inclusion criteria: Any adult (aged over 50 years) with a new or existing diagnosis of diabetes (Type 1 or Type 2) with at least three months of registration in CPRD following the date the practice became 'up to standard'. The study entry date will be the date of first-ever prescription

(from April 1997 onwards) of any oral or injectable glucose-lowering drug (see Appendix 1). Eligible participants have to have HES linked data available.

The index date will be defined as the first recorded hypoglycaemia exposure dated on/after April 1997 following initiation of a glucose lowering agent. Only patients who are 65 years and older at the time of the index hypoglycaemia exposure will be included.
Hypoglycaemia is almost never seen in patients with diabetes who are not on glucose lowering drugs (except in the context of terminal illness). Thus, we can be fairly certain that we have constructed a cohort that is very unlikely to have a significant past history of hypoglycaemia, and any recorded hypoglycaemia on follow-up are incident exposures. It is unlikely (in this study population age >50 years) that we would enrol patients who are being initiated on metformin therapy solely for polycystic ovarian syndrome.

Follow-up: Up to five years from the index date, loss from database, death, or permanent cessation of glucose-lowering drugs, whichever is the earlier. During follow-up after hypoglycaemia exposure, participants who were originally classified as (Diabetes but No Dementia) will additionally be censored at 6 months prior to the first date of them receiving a subsequent dementia diagnosis and/or prescription of dementia drug.

Please see Appendix 2 for Read codes that have been validated in previous CPRD studies for diabetes mellitus, as well as dementia.

J. Selection of comparison group(s) or controls

From the study population (any adult aged over 50 years) with a new or existing diagnosis of diabetes in CPRD), we will extract three groups (see Appendix 1):

- Group 1: Diabetes + Dementia + no medically recorded hypoglycaemic events at the time of the index date (assigned the same index date as matched patient in Group 2)
- Group 2: Diabetes + Dementia + medically recorded hypoglycaemic event as index date. If the patient has diabetes first and then dementia, then hypoglycaemia should be assessed after dementia date; if the patient has dementia first and then develops diabetes then then hypoglycaemia should be assessed after diabetes date
- Group 3: Diabetes + no Dementia + medically recorded hypoglycaemic event as the index date

Aim 1: This will be a comparison of adverse outcomes in patients with diabetes and dementia, based on no recorded exposure (Group 1) or exposure (Group 2) to hypoglycaemia. Patients will be eligible for selection into Group 1 or Group 2 from the later of their first prescription of an oral or injectable glucose-lowering drug, and the first of (1) a first diagnosis of dementia, or (2) a first prescription of a drug used in the treatment of dementia (e.g. donepezil, galantamine, memantine, or rivastigmine) (13). Group 2 patients (hypo exposure) will be matched to each patient in Group 1 (never hypos) on ratio of up to 1:10, based on year of birth (+/- 3 years), gender, country, index of multiple deprivation quintile, availability of linked data, year of glucose-lowering drug initiation, year of meeting the dementia definition, and any diabetes complications.

Aim 2: adverse outcomes after hypoglycaemia exposure - this will be a comparison between Group 2 and Group 3 (see Appendix 1). We will match patients with diabetes and dementia (Group 2) with those who have no diagnosis of dementia (Group 3) on ratio of up to 1:10, based on year of birth (+/- 3 years), gender, country, index of multiple deprivation quintile, availability of linked data, year of glucose-lowering drug initiation, index date year, and any diabetes complications.

In a sensitivity analysis of the hazard of serious adverse events after

hypoglycaemia exposure, we will evaluate the impact in Group 3 of classifying patients into the dementia Group 2 if they fulfilled the above-mentioned dementia diagnosis criteria for up to 6 months after the hypoglycaemia exposure. This takes into account the time frame for development of dementia (which is usually a gradual process and would likely have been already present in the preceding 6 months), and the fact that dementia itself may have been a triggering factor for hypoglycaemia.

K. Exposures, outcomes and covariates

Exposure of interest: occurrence of hypoglycaemia

We will ascertain the occurrence of acute episodes of hypoglycaemia recorded on CPRD, and/or the Hospital Episode Statistics (HES) database for the study participants. We recognize that capture of hypoglycaemia is incomplete if based on CPRD alone. HES data substantially improves capture of hypoglycaemia events, because it records all hospital admissions and emergency attendances at NHS hospitals in England. The incident exposure will be considered as the first medically recorded hypoglycaemia in the period after first prescription of glucose-lowering drug.

Outcomes of interest: serious adverse events after occurrence of hypoglycaemia

The primary outcome will be falls and/or fractures. Secondary outcomes will be emergency healthcare and hospitalization, cardiovascular events (acute coronary syndrome, stroke), and overall mortality.

For the emergency healthcare and hospitalisation, we will initially use Full HES to analyse all cause hospital admission and then select out admission with one of the serious adverse events and/or hypoglycaemia recorded as the cause.

HES Admitted Patient Care data will be used in the primary analysis. ONS Death Registration Data and HES Accident & Emergency Data will form sensitivity analyses from 1998 and 2006 respectively for the subgroups of patients who have such linkage.

Co-variates

We will extract information on a wide range of patient characteristics, including duration of dementia and diabetes, medications, co-morbid conditions (hypertension, peripheral vascular disease, valvular heart disease, cardiovascular disease, chronic kidney disease, atrial fibrillation), complications (severe kidney failure, amputation, blindness), body mass index, HbA1C, hypertension, and any other risk factors that may influence adverse outcomes.

Choice of confounders will subsequently be specifically tailored to the established risk factors for the particular outcome under investigation. This will be guided by a comprehensive literature search and consensus with clinical experts within the research team. For instance, confounders for cardiovascular events will include cholesterol and blood pressure whereas evaluation of falls/fracture risk may be affected by corticosteroid use, osteoporosis, and history of excess alcohol use (this is not an exhaustive list).

L. Data/Statistical analysis

First, we will describe the patient characteristics of the groups 1, 2 and 3.

Aim 1 and 2: to estimate the association between the timing of a severe hypoglycaemic episode and serious adverse events, we will use Cox proportional hazard regression models with adjustment for appropriate confounders to generate Hazard Ratios and 95% confidence intervals for each outcome. We will also adjust for all covariates we have matched the cohorts upon to allow for differing matching ratios. We will test the proportional hazards assumption and if it is not met, we will consider

splitting the follow-up time, or apply a different modelling technique.
The first analysis will compare Groups 1 and 2. The second analysis will compare Groups 2 and 3.

For **aim 1**, we will also carry out a sensitivity analysis for multiple recorded hypoglycaemic events (e.g. those with 2 hypoglycaemic events, or ≥3 events as compared to referent group who have no hypoglycaemia). We will carry out analyses using CPRD Gold and HES Admitted Patient Care data, Read Codes alone, HES alone and, finally, HES Accident & Emergency Data alone.

Analyses will be performed with SPSS 22 (IBM) and STATA software (StataCorp LP, College Station, TX). Statistical significance will be defined as $p<0.05$.

M. Plan for addressing confounding

We will use multivariable regression models which include the confounders that have been identified (please also see Section K).

N. Plan for addressing missing data

We anticipate that there will be missing data, which will include incomplete recording of outcomes as well as confounding variables, such as HbA1C or cholesterol.
We will explore the possibility of whether data may be missing at random (by comparing the characteristics of those with and without missing data) and decide whether to impute or conduct a complete case analysis. We would prefer to impute where feasible to maintain the cohort size and reduce potential bias due to missing data.

O. Limitations of the study design, data sources and analytic methods

Hypoglycaemia events are recorded in CPRD only if the patient presents to the GP with hypoglycaemia, or the GP codes a prior hypoglycaemia event reported to them by the patient or from a secondary care source. In

practice, this is uncommon and there are relatively few events in the CPRD database with a Read code for hypoglycaemia. To resolve this issue, we will also use HES to capture data on patients admitted to hospital with recorded hypoglycaemia, which is linked with CPRD. The use of HES will retrieve hypoglycaemia exposure that are more severe or symptomatic – this is advantageous for our study because we believe that more severe hypoglycaemia has a potentially greater magnitude of association with long-term serious consequences. This approach has been successfully used in a recent CPRD-based cohort study of cardiovascular events associated with hypoglycaemic events recorded in insulin-treated patients. (14)
Missing data will be another limitation (see Section N).
Residual confounding will always be a possible limitation, for example frailty which has not been captured on CPRD or severity of dementia (we will adjust for dementia duration).

P. Patient user group involvement

The research protocol has been seen by three members of the Alzheimer's Research Network and their input and comments has been instrumental in finalizing this project. They will also be members of the Advisory Committee who will meet six-monthly and provide input in the running of the project.

Q. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

Patients and carers: Findings will be disseminated through meetings with the Alzheimer's Society, Diabetes UK and Age UK. We will extend this through webinars and materials for the websites of these charities.
Healthcare professionals: We have regular contact with medical journalists who prepare articles for the mainstream healthcare press such as Pulse (for GPs), and Pharmacy Journal. We will use these channels to

disseminate our findings to clinicians involved in patient care.

Policy makers: Findings will be submitted to three separate NICE Guideline Groups (multimorbidity, dementia, and diabetes).

Scientific community: Presentations at annual British Geriatrics Society and Alzheimer's Society conferences, and submission for publication in peer-reviewed journals.

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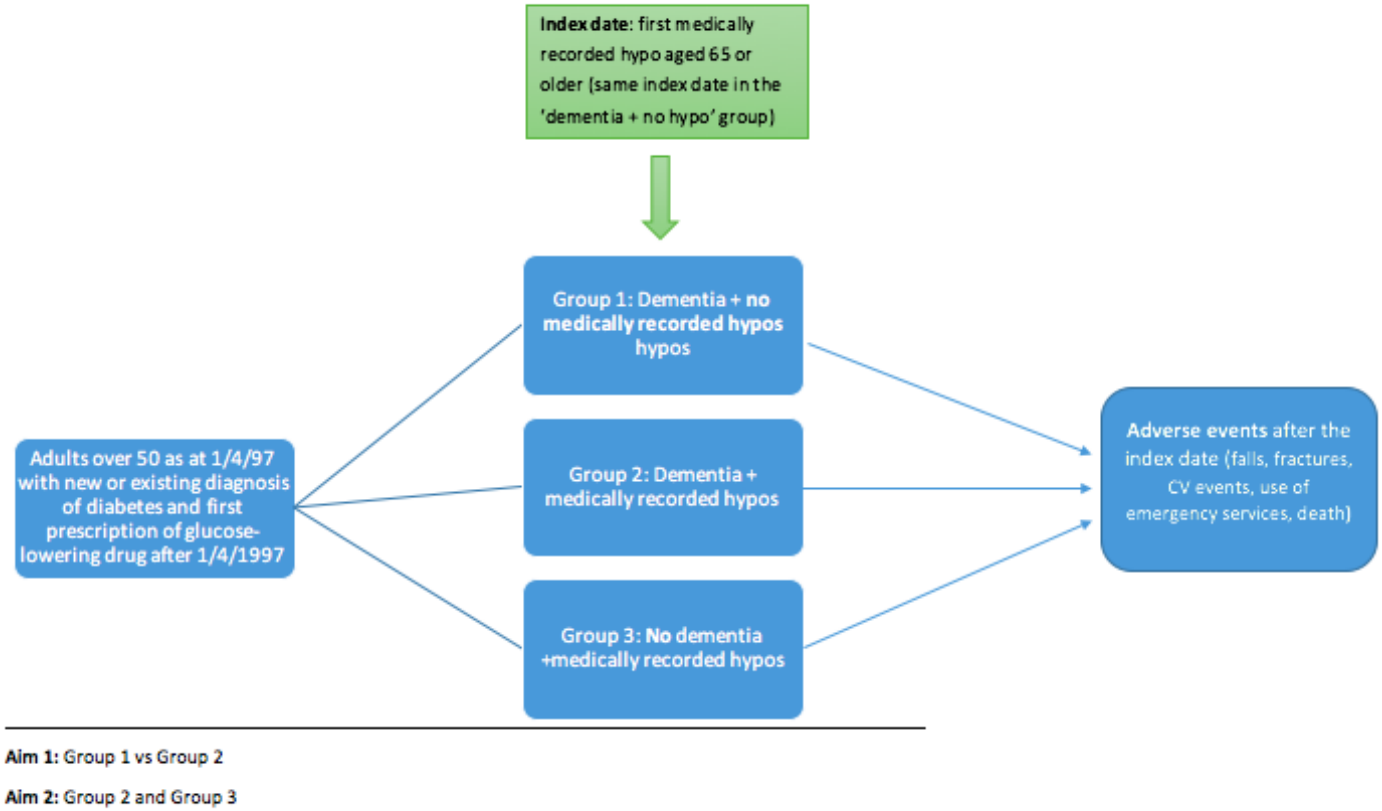
Appendix 1 – schematic representation of cohort study



Appendix 2 – READ Codes

Dementia (based on Imfeld et al.) (13)

E00, E02y1, E041, Eu00, Eu01, Eu02, Eu041, F110, F111, F112, F116, Fyu3000

Diabetes (based on Khunti et al.) (14)

C10+

Hypoglycaemia (based on Khunti et al.) (14)

C11..00, C111.00, C111000, C111100, C111z00, C112.00, C112000, C112100, C112z00, C116.00, C116000, C11y100, Cyu3000, F374500

Amendments to the Protocol, November 2017

Section I Study population

Inclusion criteria: Eligible participants have to have HES linked data available (April 1997 to March 2016)

Follow-up: Up to five years from the index date, loss from database, death, or end of available HES linkage (31 March 2016), whichever is the earlier.

We have added ICD-10 codes to Appendix 2 for dementia. Dementia diagnosis from HES, where available, will also be accepted if the patient does not have a CPRD Read code for dementia.

Section H Data linkage

HES Admitted Patient Care and HES Accident &Emergency (from April 2007) data will be used to supplement the available CPRD GOLD data on serious adverse events (including hypoglycaemia, fall, fractures and cardiovascular events) that triggered visits to hospital.

Section J Selection of comparison groups and controls

Aim 1: This will be a comparison of adverse outcomes in patients with diabetes and dementia, based on no recorded exposure (Group 1) or exposure (Group 2) to hypoglycaemia. Patients will be eligible for selection into Group 1 or Group 2 from the later of their first prescription of an oral or injectable glucose-lowering drug, and the first of (1) a first diagnosis of dementia, or (2) a first prescription of a drug used in the treatment of dementia (e.g. donepezil, galantamine, memantine, or rivastigmine).

Aim 2: adverse outcomes after hypoglycaemia exposure - this will be a comparison between Group 2 and Group 3 (see Appendix 1).

Section K Exposures, outcomes and covariates

Co-variates

We will extract information on a wide range of patient characteristics, including year of birth, gender, country, index of multiple deprivation

quintile, year of glucose-lowering drug initiation, duration of dementia and diabetes, medications, co-morbid conditions (hypertension, peripheral vascular disease, valvular heart disease, cardiovascular disease, chronic kidney disease, atrial fibrillation), complications (severe kidney failure, amputation, blindness), body mass index, HbA1C, hypertension, and any other risk factors that may influence adverse outcomes.

Appendix 2

ICD 10 codes for dementia
F00, F01, F02, F03, G30, G31.0 or G31.1

Appendix 9 Cover letter to ISAC with proposed amendments

Dear ISAC Secretariat

Protocol 16_184: "Hypoglycaemia and serious adverse events in older people living with diabetes and dementia – a population-based cohort study"
Justification for amendments to Protocol

We enclose proposed amendments to the above protocol. The amendments are listed at the end of the document in the section headed 'amendments'. No changes have been made to the already approved protocol or application form.

The justifications for the amendments are as follows:

Proposed amendment	**Justifications**
Section I Study population Inclusion criteria: Eligible participants have to have HES linked data available (April 1997 to March 2016)	We have added the HES availability dates to the inclusion criteria.
Follow-up: We would like to remove 'or permanent cessation of glucose-lowering drugs' from the follow-up period and include 'or end of available HES linkage (31 March 2016)'	On reflection, the cessation of glucose-lowering drugs after the index date is not relevant, as we are not investigating adverse events from drugs. Instead, we are interested in adverse events following hypoglycaemic event(s).
We have added ICD-10 codes to Appendix 2 for dementia. Dementia diagnosis from HES, where available, will also be accepted if the patient does not have a CPRD Read code for dementia.	Brown et al's 2016 paper showed that dementia recorded in routinely collected NHS hospital admission data (HES) has 85% diagnostic agreement with a GP survey, and is sufficiently reliable for epidemiological research. The authors looked at CPRD, GP surveys and HES records[1].
Section H Data Linkage HES Admitted Patient Care and HES Accident &Emergency (from April 2007)	We have corrected a typographical error and realise that the HES A&E data does not start until April 2007.

Section J Selection of comparison groups and controls **Aim 1**: This will be a comparison of adverse outcomes in patients with diabetes and dementia, based on no recorded exposure (Group 1) or exposure (Group 2) to hypoglycaemia. Patients will be eligible for selection into Group 1 or Group 2 from the later of their first prescription of an oral or injectable glucose-lowering drug, and the first of (1) a first diagnosis of dementia, or (2) a first prescription of a drug used in the treatment of dementia (e.g. donepezil, galantamine, memantine, or rivastigmine).	We have decided to adjust for covariates, rather than match and have removed the matching criteria previously listed in Aim 1. We assessed feasibility of matching, but this resulted in substantial loss of power. For example, cohort one included just under 10500 unmatched patient IDs, which was reduced to just under 4000 when matched 1:3 on sex and age +/- 2 years. We will instead transfer the matching criteria to the covariates (section K).
Section K. Exposures, outcomes, covariates ***Co-variates*** We will extract information on a wide range of patient characteristics, including year of birth, gender, index of multiple deprivation quintile, year of glucose-lowering drug initiation, duration of dementia and diabetes, medications, co-morbid conditions (hypertension, peripheral vascular disease, valvular heart disease, cardiovascular disease, chronic kidney disease, atrial fibrillation), complications (severe kidney failure, amputation, blindness), body mass index, HbA1C, hypertension, and any other risk factors that may influence adverse outcomes.	The items that were previously in the matching criteria are now considered to be covariates in the adjusted analysis (see above).
Appendix 2 **ICD 10 codes for dementia**	Please see justification for Section I amendment above

F00, F01, F02, F03, G30, G31.0 or G31.1	

1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5084368/ (last accessed 20 November 2017)

We would be grateful if our proposed amendments could be considered and approved.

Your sincerely

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL		*by e-mail*	
PROTOCOL NO:	16_184R		
PROTOCOL TITLE:	Hypoglycaemia and serious adverse events in older people living with diabetes and dementia – a population-based cohort study		
APPLICANT:	Professor Yoon K Loke, Professor of Medicine and Pharmacology, University of East Anglia, Norwich NR4 7TJ. Email: y.loke@uea.ac.uk		
APPROVED ☒	**APPROVED WITH COMMENTS (resubmission not required)** ☐	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:

Please include your response/s to the Reviewer's feedback below only if you are required to Revise/ Resubmit your protocol.

Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.

REVIEWER COMMENTS:

Protocol 16_184R has been approved.

DATE OF ISAC FEEDBACK:	14/03/2017
DATE OF APPLICANT FEEDBACK:	

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL	*by e-mail*
PROTOCOL NO:	16_184RA
PROTOCOL TITLE:	Hypoglycaemia and serious adverse events in older people living with diabetes and dementia – a population-based cohort study
APPLICANT:	Professor Yoon K Loke, Professor of Medicine and Pharmacology, University of East Anglia, Norwich NR4 7TJ. Email: y.loke@uea.ac.uk

APPROVED	**APPROVED WITH COMMENTS (resubmission not required)**	**REVISION/ RESUBMISSION REQUESTED**	**REJECTED**
☐	☒	☐	☐

INSTRUCTIONS:

Please include your response/s to the Reviewer's feedback below only if you are required to Revise/ Resubmit your protocol.

Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.

REVIEWER COMMENTS:

Please note that **Section H Data linkage** recorded under amended protocol section does not make mention the use of HES data to further identify dementia cases although this has been outlined (and supported) in the cover letter. Please update this section accordingly.

Suggestion only

The low yield on matching is likely due to the large number of matching variables initially proposed. Matching may be improved by simply matching on practice, year of birth and gender with the remaining variables included in the model as covariates. As matching will no longer be undertaken it is unclear what is the start of follow-up for patients without a record of hypoglycaemia. The study could perhaps be implemented as a time-dependent analysis where patients with a record of hypoglycaemia are unexposed up to the time of their hypoglycaemia diagnosis and then exposed thereafter; patients without a history of hypoglycaemia remain unexposed through the study.

DATE OF ISAC FEEDBACK:	18/12/2017

Appendix 11 Codes used to generate dataset for CPRD study

In accordance with good practice for reporting of electronic healthcare studies, the entirety of the code files will be stored on a publicly accessible site for full transparency of reporting.
https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/75/

Drugs used for dementia	**Product codes:** 9966, 62925, 7329, 36976, 60107, 56771, 11751, 68845, 5334, 53922, 11546, 10255, 38976, 5616, 68792, 61385, 63226, 20140, 60723, 61476, 65501, 24088, 58780, 11752, 68802, 68494, 11635, 68493, 48443, 56600, 53882, 9854, 55928, 65761, 59993, 37188, 2931, 39363, 6225, 66899, 63217, 39362, 11654, 56631, 63405, 65333, 61920, 62780, 48482, 39240, 59330, 66934, 55720, 37957, 63951, 57139, 61618, 60192, 11837, 29288, 62867, 11827, 35088, 61921, 37444, 62868, 10187, 58969, 65573, 53842, 11716, 60493, 58937, 18587, 65534, 36848, 56709, 67593, 59871, 2930, 35179, 7361, 56421, 18800, 4597, 61676, 5247, 5400, 58947, 62164, 57171, 63360, 14309, 48015, 18062, 57627, 58709, 9786, 20404, 37132, 64982, 18556, 48442
Dementia	**Read codes:** Eu00200, Eu00112, Eu00100, Eu00000, Eu00.00, E004.11, E004.00, E002100, E002000, E001.00, E000.00, E00..12, E00..11, 6AB..00, 66h..00, Eu00z00, Eu00z11, Eu01.00, Eu01300, Eu01z00, Eu02.00, Eu02300, Eu02500, Eu02z00, Eu02z14, F110.00, F110000, F110100, F112.00, F116.00 **ICD 9/10 codes:** 290**,** F00-F03, G30, G31.0 or G31.1, G31.83
Hypoglycemia	**Read codes:** C112100, C11y100**,** C116.00**,** C110z00**,** C112z00**,** C116000**,** C112000, C112.00**,** C110.00 **ICD9/10:** 251.0, 251.1, 251.2, E249.8 and E250.8, E10.64, E11.64, E16.0, E16.1, E16.2

Fracture codes

medcode	readterm
40643	Closed fracture of ilium, unspecified
46592	Closed fracture pelvis, multiple pubic rami - unstable
42968	Closed fracture lumbar vertebra, burst
34685	Open fracture pelvis, single pubic ramus
41698	Closed fracture pelvis, ischial tuberosity
27575	Closed fracture of fifth cervical vertebra
40587	Closed fracture pelvis, anterior inferior iliac spine
41138	Closed fracture thoracic vertebra not otherwise specified
27654	Closed fracture of sixth cervical vertebra
35260	Closed multiple fractures of thoracic spine
28234	Closed fracture pelvis, anterior superior iliac spine
56961	Fracture of rib(s), sternum, larynx and trachea
24672	Closed fracture of seventh cervical vertebra
38895	Other specified closed fracture pubis
56384	Closed fracture of three ribs
33961	Other or multiple closed fracture of pelvis
39887	Closed fracture axis, odontoid process
33967	C2 vertebra closed fracture without spinal cord lesion
36249	Flail chest
34708	Closed fracture pelvis, ischium
34403	Fracture of second cervical vertebra
16277	Closed fracture axis
32063	Fracture of spine with spinal cord lesion
29089	Closed fracture lumbar vertebra, transverse process
34166	Fracture of spine without mention of spinal cord lesion NOS
28244	Closed fracture of rib(s) NOS
28702	Closed fracture pubis NOS
27922	Fracture of ilium
40533	Closed fracture of two ribs
27818	Sternum fracture NOS
15613	Closed fracture of unspecified cervical vertebra
12406	Fracture of lumbar spine and pelvis
30058	Fracture of transverse process spine - no spinal cord lesion
19189	Multiple fractures of cervical spine
8613	Multiple fractures of lumbar spine and pelvis
27854	Closed fracture pelvis, iliac wing
16494	Closed fracture of one rib
3288	Fracture of neck
3675	Fracture of sacrum
11277	Multiple fractures of thoracic spine
10252	Fracture of neck and trunk
15877	Closed fracture sacrum
11004	Closed fracture multiple ribs
14834	Closed fracture pelvis, coccyx
1591	Closed fracture acetabulum
28524	Closed fracture thoracic vertebra, wedge
28375	Closed fracture of pelvis NOS
9072	Fracture of acetabulum
6667	Closed fracture pelvis, multiple pubic rami - stable
11969	Fracture of sternum
10990	Fracture of lumbar vertebra
11296	Closed fracture of cervical spine
835	Fracture of coccyx
8255	Fracture of spine without mention of spinal cord injury
27404	Closed fracture thoracic vertebra
4409	Fracture of vertebra without spinal cord lesion
2328	Fracture of pubis
11378	Rib fracture NOS
8266	Closed fracture lumbar vertebra, wedge
7831	Closed fracture of rib, unspecified
3983	Closed fracture sternum
5381	Fracture of thoracic vertebra
5302	Closed fracture pubis
7004	Closed fracture pelvis, single pubic ramus
3573	Closed fracture of spine, unspecified,
10696	Multiple fractures of ribs
3888	Closed fracture lumbar vertebra
738	Fracture or disruption of pelvis
9688	Fracture of rib
280	Closed fracture rib
94655	Open fracture dislocation of sacro-iliac joint
94189	Open fracture of lumbar spine with spinal cord lesion
101299	Opn spinal fracture with unspec thoracic cord lesion, T1-6
108469	Cls spinal # with incomplete thoracic cord lesion, T1-6 NOS
109377	Cls spinal fracture with complete cervcl cord lesion, C1-4
73613	Open fracture of rib, unspecified
105702	Closed fracture axis, spondylolysis
102043	Cls spinal fracture with posterior thorac cord lesion, T7-12
94844	Open fracture axis, odontoid process
62562	Other specified open fracture acetabulum
68763	Open fracture pelvis, ischial tuberosity
101956	Cls spinal # with incomplete cervical cord lesion, C5-7 NOS
101517	Closed fracture of coccyx with spinal cord lesion NOS
99516	Closed fracture thoracic vertebra, posterior arch
98267	Closed fracture acetabulum, double column unspecified
95006	Closed fracture axis, posterior arch
101318	Open fracture thoracic vertebra, posterior arch
108000	Open fracture pelvis, ischium
104598	Open complete rupture of pelvic ring
97354	Open vertical fracture of sacrum
66322	Open multiple fracture of thoracic spine
53976	Open fracture axis
94108	Open fracture of trachea
96514	Cls spinal fracture with anterior cervcl cord lesion, C5-7
100110	Cls spinal # with incomplete cervical cord lesion, C1-4 NOS
73956	Open fracture of seven ribs
104755	Opn spinal fracture with posterior thorac cord lesion, T7-12
95529	Closed spinal fracture with complete lumbar cord lesion
60382	C3 vertebra open fracture without spinal cord lesion
110732	Open fracture atlas, comminuted
94584	Open fracture of sacrum with other spinal cord injury
69763	Open complete rupture pubic symphysis
95839	Closed fracture of other parts of bony thorax
72525	Closed fracture acetabulum, anterior lip alone
44826	Open fracture of two ribs
69432	Open fracture of cervical spine with spinal cord lesion
96473	Open fracture of sacrum with spinal cord lesion
105695	Open fracture lumbar vertebra, transverse process
99376	Closed fracture of sacrum with spinal cord lesion NOS
96643	Open fracture of hyoid bone
99895	Fracture of other parts of bony thorax
96984	Open fracture of ilium, unspecified
35018	Other/multiple open fracture of pelvis NOS
96659	Closed fracture thoracic vertebra, spondylolysis
69645	Open fracture atlas
108484	Cls spinal fracture with unspec thoracic cord lesion,T1-6
105935	Open compression fracture sacrum
101560	Open fracture of rib(s) NOS
73479	Closed fracture acetabulum, anterior column
70475	Cls spinal # with incomplete thoracid cord lesion, T7-12 NOS
24671	Open fracture of fifth cervical vertebra
72617	Multiple open fractures of cervical vertebrae
73416	Closed fracture of cervical spine with cord lesion NOS
57775	Open complete rupture of sacro-iliac joint
102735	Cls spinal fracture with complete cervcl cord lesion, C5-7
73788	Closed spinal fracture with cauda equina lesion
48958	Cls spinal fracture with complete thoracic cord lesion,T1-6
99203	Other open fracture of pelvis
59996	C7 vertebra open fracture without spinal cord lesion
101574	Open fracture of unspecified cervical vertebra
52470	Closed vertical fracture of ilium
98393	Closed fracture atlas, isolated arch or articular process
95620	Closed fracture cervical vertebra, spondylolysis
57923	Closed fracture acetabulum, posterior column
72567	Open multiple disruptions of pelvis
31545	Cls spinal fracture with complete thorac cord lesion, T7-12
62719	C6 vertebra open fracture without spinal cord lesion
95842	Closed fracture lumbar vertebra, posterior arch
73601	Open fracture lumbar vertebra, burst
69974	Closed fracture atlas, comminuted
64777	Open fracture acetabulum NOS
71734	Closed complete rupture sacro-iliac joint
94127	Other specified open fracture of pubis
58190	Closed fracture of bony thorax part unspecified
54855	Closed fracture of trachea
71452	Open fracture multiple ribs
99151	C5 vertebra open fracture without spinal cord lesion
70674	Open fracture of pubis NOS
57981	Fracture of ill-defined bone of trunk NOS
94649	Closed fracture acetabulum, posterior lip alone
95513	Closed fracture cervical vertebra, posterior arch
97120	C2 vertebra open fracture without spinal cord lesion
67973	Closed fracture cervical vertebra, burst
51018	Closed fracture of coccyx with spinal cord lesion
60615	Open fracture of thoracic spine with spinal cord lesion
62337	Cls spinal fracture with unspec cervical cord lesion, C1-4
90494	Closed fracture of seven ribs
43448	Open fracture pelvis, anterior superior iliac spine
60608	Closed fracture of ill-defined bone of trunk
69098	C1 vertebra open fracture without spinal cord lesion
65302	Open fracture lumbar vertebra, wedge
49567	Closed spinal fracture with unspecified lumbar cord lesion
73611	Closed fracture of thoracic spine with cord lesion NOS
72711	Cls spinal fracture with unspec cervical cord lesion, C5-7
72324	Fracture of transverse process of spine + spinal cord lesion
66434	Open fracture sacrum
95585	Closed fracture lumbar vertebra, tricolumnar
65300	Open fracture of sixth cervical vertebra
69418	Closed fracture acetabulum, floor
59904	Other specified closed fracture acetabulum
65084	Other or multiple open fracture of pelvis
66164	Open fracture of spine, unspecified,
72600	Closed vertical fracture of sacrum
65151	Closed flail chest
71567	Closed fracture larynx and trachea
55280	Open fracture pelvis, coccyx
101447	Open fracture pelvis, multiple pubic rami - unstable
55195	Fracture of spine with spinal cord lesion NOS
43091	Cls spinal fracture with unspec thoracic cord lesion, T7-12
61150	Closed fracture lumbar vertebra, spondylolysis
42149	Closed fracture axis, spinous process
63242	Fracture of ill-defined bones of trunk
63982	Open fracture sternum
65484	Closed fracture of six ribs
67669	Open fracture pelvis, iliac wing
94292	Closed fracture axis, transverse process
62047	Open fracture thoracic vertebra, wedge
64461	Closed multiple disruptions of pelvis
63253	Open fracture thoracic vertebra

64297	Closed fracture cervical vertebra, transverse process
64872	Closed fracture thoracic vertebra, spinous process
55627	Open fracture of cervical spine
68652	Closed fracture of eight or more ribs
53566	Open fracture acetabulum
40394	Closed fracture larynx
52699	C3 vertebra closed fracture without spinal cord lesion
32638	Closed fracture of thyroid cartilage
30999	Closed complete rupture of pelvic ring
18180	Closed complete rupture pubic symphysis
35096	Closed fracture lumbar vertebra, spinous process
48886	Closed fracture thoracic vertebra, transverse process
72404	Closed compression fracture sacrum
55424	Closed fracture of five ribs
40078	Closed fracture of hyoid bone
54353	Fracture of bony thorax, part unspecified
55346	Multiple closed fractures of cervical vertebrae
57444	Closed fracture of sacrum with spinal cord lesion
24732	Traumatic rupture of symphysis pubis
67358	C4 vertebra closed fracture without spinal cord lesion
39816	Closed fracture thoracic vertebra, burst
50749	Open fracture of pubis
60593	Closed fracture of third cervical vertebra
64139	Open fracture of pelvis NOS
44059	Closed fracture of lumbar spine with spinal cord lesion
43786	Fracture of vertebra with spinal cord lesion
41548	Closed fracture of fourth cervical vertebra
34873	C5 vertebra closed fracture without spinal cord lesion
53337	Closed fracture cervical vertebra, wedge
30956	Closed fracture of spine with spinal cord lesion unspecified
34197	Closed fracture of four ribs
54299	Closed fracture cervical vertebra, spinous process
45527	Closed fracture acetabulum NOS
42780	Open fracture lumbar vertebra
11770	Other specified closed fracture thoracic vertebra
42561	C1 vertebra closed fracture - no spinal cord lesion
33503	C6 vertebra closed fracture without spinal cord lesion
51038	Open fracture pelvis, multiple pubic rami - stable

48224	Open fracture rib
34195	**Closed fracture dislocation of sacro-iliac joint**
41930	Closed fracture of cervical spine not otherwise specified
52300	Closed fracture of cervical spine with cord lesion
35849	Closed fracture of thoracic spine with spinal cord lesion
11639	Other or multiple closed fracture of pelvis NOS
5445	Closed fracture atlas
28133	Fracture of first cervical vertebra
38053	C7 vertebra closed fracture without spinal cord lesion

icd10	clinical diagnosis
S32.0	Fracture of lumbar vertebra
S32.1	Fracture of sacrum
S32.2	Fracture of coccyx
S32.3	Fracture of ilium
S32.4	Fracture of acetabulum
S32.5	Fracture of pubis
S32.7	**Multiple fractures of lumbar spine and pelvis**
S32.8	Fracture of unspecified parts of lumbosacral spine and pelvis
S22.0	Fracture of thoracic vertebra
S22.1	**Multiple fractures of thoracic spine**
S22.2	Fracture of sternum
S22.3	Fracture of rib
S22.4	Multiple fractures of ribs
S22.5	Flail chest
S22.8	**Fracture of other parts of bony thorax**
S22.9	Fracture of bony thorax, part unspecified
S12.0	Fracture of first cervical vertebra
S12.1	Fracture of second cervical vertebra
S12.2	Fracture of third cervical vertebra
S12.7	**Multiple fractures of cervical spine**
S12.8	Fracture of other parts of neck
S12.9	Fracture of neck, unspecified

medcode	readterm
17956	Open fracture clavicle, shaft
38398	Open fracture radius and ulna, distal
33933	Closed fracture of proximal forearm, unspecified part
42957	Closed fracture of proximal forearm not otherwise specified
3748	Open fracture of radius and ulna, shaft
33489	Closed fracture of proximal humerus, anatomical neck
34907	Closed fracture scapula, coracoid
44711	Closed fracture clavicle, medial end
38353	Closed fracture of proximal humerus not otherwise specified
34367	Open fracture of radius (alone), unspecified
9420	Open fracture of the proximal humerus
33540	Closed fracture of distal humerus, not otherwise specified
44538	Closed fracture radius and ulna, proximal
34172	Open fracture of the distal humerus
6380	Open fracture radial styloid
34737	Open fracture radial neck
34426	Closed fracture of the proximal ulna
19403	Closed fracture scaphoid, waist, transverse
33882	Fracture of upper limb, level unspecified
34286	Closed # radius neck
33870	Fracture of scapula NOS
19058	Closed fracture distal radius, extra-articular, other type
8410	Open fracture olecranon, intra-articular
33808	Closed fracture of radius and ulna, shaft, NOS
27590	Open fracture of radius and ulna, lower end
27620	Closed fracture of scapula
29097	Multiple # both upper limbs & upper limb with rib + sternum
35031	Closed fracture radius and ulna, middle
40367	Closed fracture distal humerus, medial condyle
44924	Open fracture of the distal radius, unspecified
36464	Closed fracture of humerus, shaft or unspecified part
50654	Closed fracture of forearm, unspecified
28393	Closed fracture distal humerus, capitellum
31760	Open fracture distal humerus, supracondylar
50223	Open fracture of proximal forearm, unspecified
53698	Open fracture distal radius, extra-articular other type
52614	Open fracture of ulna, coronoid
53689	Closed volar Barton's fracture-dislocation
53688	Open fracture of proximal humerus, unspecified part
69312	Open fracture distal humerus, medial condyle
47839	Open fracture of distal humerus, not otherwise specified
63948	Open fracture of the proximal radius
70864	Open fracture of clavicle, unspecified part
53677	Closed fracture distal humerus, bicondylar (T-Y fracture)
55687	Open fracture scapula, acromion
62833	Closed fracture of distal humerus, multiple
34371	Closed fracture of proximal ulna, comminuted
61374	Open fracture of the proximal ulna
60108	Open fracture scapula, glenoid
66774	Open fracture of forearm, lower end, NOS
37875	Open fracture radius and ulna, proximal
70987	Multiple #upper limbs & upper limb with rib + sternum NOS
63588	Open fracture distal radius, intra-articular other type
65674	Closed multiple #upper limbs & upper limb with rib + sternum
48239	Open fracture proximal humerus, greater tuberosity
53622	Open fracture proximal humerus, neck
60630	Open fracture of forearm, lower end, unspecified
18301	Open Barton's fracture
48245	Open fracture radius and ulna, middle
60518	Open fracture of radius, shaft, unspecified
70590	Open fracture of forearm, unspecified
40358	Open fracture of humerus, shaft
30418	Open Galeazzi fracture
33680	Open fracture of humerus, shaft or unspecified part
66233	Open fracture of the radial shaft
49796	Open fracture distal ulna - other
61812	Open fracture of clavicle
65301	Open fracture of radius and ulna, NOS

28293	Closed fracture distal radius, intra-articular, other type
51364	Closed fracture of radius, shaft, unspecified
10622	Shoulder fracture - open
36328	Closed fracture of radius and ulna, NOS
28739	Closed fracture proximal humerus, head
44721	Closed fracture of proximal humerus, unspecified part
18389	Closed fracture of forearm, lower end, unspecified
44790	Closed fracture of the ulnar shaft
7636	Open fracture radial head
44715	Closed fracture of clavicle, unspecified part
5344	Closed fracture scapula, blade
29899	Closed fracture clavicle, lateral end
33883	Closed fracture of the proximal radius
10149	Fracture of shafts of both ulna and radius
8915	Multiple fractures of forearm
27886	Closed fracture of humerus, shaft
42864	Closed fracture of the radial shaft
28179	Closed fracture of clavicle NOS
19186	Closed fracture of humerus NOS
15764	Closed fracture of radius and ulna, unspecified part
4029	Closed fracture scapula, glenoid
16389	Closed fracture scapula, acromion
18394	Closed fracture distal humerus, lateral condyle
7754	Elbow fracture - open
30659	Fracture of shaft of humerus
16944	Multiple fractures of clavicle, scapula and humerus
8661	Closed fracture distal humerus, lateral epicondyle
43570	Closed fracture of proximal radius and ulna
11044	Closed fracture proximal humerus, greater tuberosity
33720	Closed fracture of elbow, unspecified part
28724	Closed fracture distal humerus, medial epicondyle
10735	Shoulder blade fracture
26324	Closed fracture of radius and ulna, shaft
17107	Multiple rib fractures
27784	Open fracture of radius and ulna, shaft, NOS
32646	Open fracture distal humerus, capitellum
48859	Closed fracture scapula, spine
27605	Fractures involving multiple regions of both upper limbs
61675	Open volar Barton's fracture
50053	Closd dorsal Barton's fracture
61378	Closed fracture of humerus, shaft or unspecified part NOS
44844	Closed fracture distal radius, intra-articular, die-punch
70503	Open fracture of the ulnar shaft
48217	Open fracture distal humerus, lateral epicondyle
34370	Closed fracture proximal radius, comminuted
45695	Open fracture of proximal radius and ulna
44142	Open fracture of elbow, unspecified part
60163	Open fracture distal humerus, lateral condyle
48961	Open fracture of humerus NOS
52083	Closed fracture of distal humerus, trochlea
28741	Open fracture of ulna (alone), unspecified
36332	Closed fracture scapula, neck
42076	Closed fracture of ulna, lower epiphysis
8704	Open fracture of the radius and ulna
52406	Closed fracture of humerus, upper epiphysis
16866	Open fracture distal humerus, medial epicondyle
57592	Closed fracture of scapula NOS
38028	Closed fracture of scapula, unspecified part
11262	Open fracture of ulna, styloid process
29137	Closed fracture proximal humerus, four part
31708	Multiple fractures of arm
40976	Closed multiple fractures of clavicle, scapula and humerus
32348	Closed fracture of distal humerus, condyle(s) unspecified
54780	Open fracture of radius and ulna, unspecified part
52389	Smith's fracture - closed
40330	Closed fracture proximal humerus, three part
34730	Open Smith's fracture

12063	Closed fracture olecranon, intra-articular
27591	Closed fracture of forearm, lower end, NOS
6213	Fracture of lower end of both ulna and radius
10022	Wrist fracture - open
28307	Closed fracture clavicle, shaft
28708	Closed fracture radius and ulna, distal
7660	Closed fracture radius, neck
24621	Closed fracture of ulna (alone), unspecified
4211	Collar bone fracture
8382	Fracture of shaft of ulna
28066	Fracture of clavicle NOS
33749	Closed fracture of clavicle
11313	Closed fracture proximal humerus, neck
15376	Closed fracture of the distal humerus
2101	Fracture of upper end of humerus
1548	Fracture of lower end of humerus
10640	Forearm fracture
10382	Fracture of humerus NOS
6915	Closed fracture radial styloid
9538	Closed fracture olecranon, extra-articular
7988	Fracture of shaft of radius
1177	Fracture of scapula
11222	Closed fracture of the proximal humerus
18299	Closed fracture of radius and ulna, lower end
2303	Fracture of upper end of radius
4359	Closed fracture of the radius and ulna
6893	Closed fracture distal humerus, supracondylar
7009	Closed fracture radius, head
1073	Fracture of ulna NOS
17952	Closed fracture of radius (alone), unspecified
1250	Elbow fracture - closed
199	Fracture of lower end of radius
6195	Fracture of upper limb
6825	Fracture of radius and ulna

517	Fracture of humerus
483	Fracture of clavicle
137	Fracture of radius NOS
107741	Closed dorsal Barton fracture-subluxation
73768	Open fracture of scapula, unspecified part
72408	Open fracture proximal radius, comminuted
111584	Open multiple #upper limbs & upper limb with rib + sternum
70653	Open fracture proximal humerus, four part
99325	Open fracture of distal humerus, multiple
59943	Open fracture of humerus, upper epiphysis
97820	Open fracture distal humerus, bicondylar (T-Y fracture)
105278	Dupuytren's fracture, radius - open
73109	Open fracture scapula, blade
94435	Open fracture of scapula NOS
66237	Open multiple fractures of clavicle, scapula and humerus
96691	Open fracture of ulna, lower epiphysis
100040	Open fracture clavicle, medial end
64021	Open fracture scapula, coracoid
104070	Open fracture distal radius, intra-articular, die-punch
63899	Open fracture of distal humerus, trochlea
86803	Open fracture of distal humerus, condyle(s) unspecified
98681	Smith's fracture - open
57736	Closed dorsal Barton's fracture-dislocation
70604	Open fracture proximal humerus, three part
73426	Open fracture of humerus, shaft or unspecified part NOS
68556	Open fracture clavicle, lateral end
71207	Open fracture of proximal humerus, anatomical neck
70486	Open fracture proximal humerus, head
68899	Multiple fractures of sternum
35386	Open fracture of scapula
45275	Open fracture of proximal humerus not otherwise specified
55201	Open fracture of forearm, upper end, NOS
65636	Closed volar Barton fracture-subluxation
94460	Open fracture of clavicle NOS

icd10	clinical diagnosis
S42.0	Fracture clavicle
S42.1	Fracture scapula
S42.2	Fracture of upper end of humerus
S42.3	Fracture of shaft of humerus
S42.4	Fracture of lower end of humerus
S42.7	**Multiple fractures of clavicle, scapula and humerus**
S42.9	Fracture of shoulder girdle, part unspecified
S52.0	Fracture of upper end of ulna
S52.1	Fracture of upper end of radius
S52.2	Fracture of shaft of ulna
S52.3	Fracture of shaft of radius
S52.4	**Fracture of shafts of both ulna and radius**
S52.5	Fracture of lower end of radius
S52.6	**Fracture of lower end of both ulna and radius**
S52.8	**Fracture of othe parts of forearm**

medcode	readterm
8891	Fracture of lower limb
33656	Closed fracture proximal fibula
37662	Closed fracture of femur, unspecified part
38355	Closed fracture distal femur, lateral condyle
21922	Closed fracture of femur, lower epiphysis
36391	Closed fracture head of femur
38489	Closed fracture proximal femur, transcervical
5301	Closed fracture of proximal femur, pertrochanteric
6839	Closed fracture of distal fibula
8646	Fracture of shaft of femur
22761	Closed fracture of tibial tuberosity
8040	Other fracture of femur
35011	Fracture of patella, NOS
28118	Open fracture shaft of tibia
1093	#Knee-cap
28550	Closed fracture of the proximal tibia
44830	Closed fracture of tibia and fibula, proximal
17019	Cls # prox femur, subcapital, Garden grade unspec.
2225	Fracture of neck of femur
33520	Closed fracture of tibia and fibula, shaft
2470	Fracture of unspecified bones
52499	Closed fracture fibula, head
520	Fracture of femur, NOS
12791	Thigh fracture NOS
34151	Closed fracture distal tibia, extra-articular
45562	Closed fracture distal femur, medial condyle
10007	Fracture of lower end of tibia
2630	Fracture of tibia and fibula
28426	Closed fracture shaft of fibula
235	Fracture of patella
40368	Closed fracture of lower limb, level unspecified
52322	Closed fracture fibula, neck
8243	Subtrochanteric fracture
20678	Open fracture of tibia and fibula, shaft
29109	Closed fracture of tibia and fibula, unspecified part, NOS
28068	Open fracture of tibia/fibula, shaft
806	Fracture of fibula alone
100202	Closed fracture of distal tibia and fibula
24276	Closed fracture of unspecified proximal femur
34021	Closed fracture shaft of tibia
18840	Closed fracture proximal tibia, medial condyle (plateau)
22370	Closed fracture proximal tibia, lateral condyle (plateau)

medcode	readterm
9348	Multiple fractures of lower leg
8589	Fracture of lower end of femur
28954	Closed fracture distal femur
6320	Closed fracture of femoral condyle, unspecified
14826	Dupuytren's fracture, fibula
971	Closed fracture of tibia, unspecified part, NOS
39984	Cls # prox femur, intracapsular section, unspecified
28233	Open fracture of tibia and fibula, unspecified part, NOS
38733	Closed fracture tubercle, tibia
53279	Closed fracture of distal femur, unspecified
19387	Closed fracture of femur, greater trochanter
25485	Fracture of tibia and fibula, NOS
4304	Closed fracture of fibula, unspecified part, NOS
953	Open fracture of bones, unspecified
18273	Closed fracture of neck of femur NOS
29121	Closed fracture of tibia/fibula, shaft
27719	Closed fracture distal tibia
6917	Fracture of upper end of tibia
22329	Closed fracture of femur, distal end
11275	Fracture of lower leg, part unspecified
37310	Closed fracture of bones, unspecified
33393	Closed fracture of the patella
21773	Multiple fractures of femur
78444	Fracture of tibia
101031	Fracture tibial plateau
8648	Closed fracture of femur, intertrochanteric
29164	Open fracture of tibia, unspecified part, NOS
10095	Open fracture shaft of femur
24674	Closed fracture shaft of femur
2603	Leg fracture
33903	Fracture of lower limb, level unspecified
6868	Closed fracture of femur, shaft or unspecified part
5332	Closed fracture distal femur, supracondylar
41971	Closed fracture of tibia and fibula, unspecified part, NOS
4572	Closed fracture of tibia and fibula, unspecified part
10570	Hip fracture NOS
19117	Cls # proximal femur, trochanteric section, unspecified
28965	Pertrochanteric fracture
27992	Open fracture distal tibia
7723	Fracture of shaft of tibia
1994	Hip fracture
100771	Open fracture base of neck of femur

medcode	readterm
23803	Open fracture proximal femur,subcapital, Garden grade III
73981	Open fracture proximal femur, transcervical
105819	Open fracture ankle, trimalleolar, high fibular fracture
97971	Open fracture proximal femur, intertrochanteric, comminuted
73234	Open fracture of femur, subcapital
105816	Open fracture ankle, bimalleolar, high fibular fracture
72138	Open fracture proximal femur, transepiphyseal
33475	Open fracture patella, distal pole
47828	Open fracture ankle, trimalleolar, low fibular fracture
101567	Open fracture proximal femur, intertrochanteric, two part
100159	Open fracture patella, proximal pole
99027	Open fracture fibula, head
68668	Open fracture proximal femur, other transcervical
96518	Open fracture of femur, upper epiphysis
96644	Open fracture of femur, greater trochanter
60885	Open fracture proximal femur,subcapital, Garden grade I
51999	Open fracture proximal femur,subcapital, Garden grade IV
99161	Open fracture fibula, neck
73208	Open fracture distal femur, comminuted/intra-articular
105691	Multiple closed #both legs, leg + arm, leg + rib + sternum
54242	Closed fracture distal femur, bicondylar (T-Y fracture)
70479	Open fracture of proximal femur, pertrochanteric, NOS
88737	Open fracture of distal femur not otherwise specified
73700	Multiple #both legs, leg + arm, leg + rib + sternum NOS
73210	Open fracture head, femur
69919	Closed fracture proximal femur, transepiphyseal
67394	Open fracture proximal femur,subcapital, Garden grade II
71282	Open fracture proximal femur, subtrochanteric
49798	Open fracture tubercle, tibia
65690	Closed fracture proximal femur, midcervical section
73105	Open fracture ankle, lateral malleolus, high
66808	Open fracture ankle, bimalleolar, low fibular fracture
63633	Open fracture spine, tibia
50227	Open fracture patella, transverse
57439	Open fracture of tibia and fibula, proximal NOS
93029	Open fracture of tibial condyles
94360	Open fracture of femur, shaft or unspecified part, NOS
52346	Closed fracture ankle, trimalleolar, high fibular fracture
43566	Open fracture ankle, lateral malleolus, low
50727	Opn # proximal femur, intracapsular section, unspecified
34738	Open fracture distal femur, lateral condyle

medcode	readterm
67633	Open # of proximal femur, trochanteric section, unspecified
52371	Closed fracture ankle, bimalleolar, high fibular fracture
67294	Open fracture distal femur, medial condyle
58642	Open fracture of unspecified proximal femur
54145	Open fracture of tibia and fibula, proximal
33457	Open fracture proximal fibula
45529	Open fracture distal femur, unspecified
65228	Open fracture distal tibia, intra-articular
55327	Closed fracture distal femur, comminuted/intra-articular
44245	Open fracture of lower limb, level unspecified
62966	Closed fracture proximal femur, transcervical, NOS
27721	Open fracture distal tibia, extra-articular
38878	Open fracture proximal femur,subcapital, Garden grade unsp
48142	Open fracture of femur, lower epiphysis
50254	Open fracture patella, comminuted (stellate)
61733	Open fracture of proximal femur, pertrochanteric
50549	Closed fracture patella, proximal pole
51938	Open fracture shaft of fibula
33957	Closed fracture proximal femur, subcapital, Garden grade II
51216	Cls # proximal femur, intertrochanteric, comminuted
44735	Cls # of proximal femur, pertrochanteric section, NOS
54660	Closed fracture patella, vertical
28198	Open fracture of tibia and fibula, shaft, NOS
49801	Open fracture of tibial tuberosity
36599	Closed fracture proximal femur, subcapital, Garden grade III
49209	Closed fracture proximal femur, other transcervical
28352	Open fracture of fibula, unspecified part, NOS
40164	Closed fracture proximal tibia, bicondylar
42978	Closed fracture of tibia and fibula, proximal NOS
48337	Closed fracture of femur, lesser trochanter
68229	Closed fracture of femur, subcapital
44276	Open fracture proximal tibia, medial condyle (plateau)
56525	Closed fracture ankle, trimalleolar, low fibular fracture
34106	Open fracture of femur, unspecified part
45517	Other, multiple and ill-defined fractures of lower limb
34078	Closed fracture proximal femur, subcapital, Garden grade IV
52194	Closed fracture proximal femur, basicervical
61802	Closed fracture of distal femur not otherwise specified
35620	Closed fracture ankle, lateral malleolus, high
45141	Closed fracture proximal femur, intertrochanteric, two part
45779	Closed fracture of femur, upper epiphysis

medcode	readterm
62787	Open fracture of tibia and fibula, unspecified part, NOS
20893	Upper leg fracture NOS
44786	Open fracture proximal tibia, lateral condyle (plateau)
39396	Open fracture of femur, intertrochanteric
38054	Open fracture of neck of femur NOS
101840	Open fracture tibial plateau
34351	Closed fracture proximal femur, subcapital, Garden grade I
51170	Open fracture distal femur
54280	Closed fracture of tibia and fibula, proximal
32866	Open fracture of femur, distal end
40069	Open fracture of tibia and fibula, proximal
42972	Open fracture of femur, shaft or unspecified part
41287	Closed fracture patella, comminuted (stellate)
29145	Closed fracture proximal femur, subtrochanteric
8465	Closed fracture distal tibia, intra-articular
55464	Closed fracture of tibia and fibula, shaft, NOS
33706	Open fracture of the proximal tibia
51861	Closed fracture, base of neck of femur
42805	Open fracture distal femur, supracondylar
100640	Open fracture of distal tibia and fibula
29084	Open fracture of tibia and fibula, unspecified part
56299	Multiple #both legs, leg + arm ,leg + rib + sternum
12369	Open fracture of distal fibula
49526	Closed fracture patella, transverse
44329	Closed fracture patella, distal pole
14826	Dupuytren's fracture, fibula
42969	Closed fracture ankle, bimalleolar, low fibular fracture
28273	Open fracture of the patella

	icd10	clinical diagnosis
	S72.0	Fracture of head and neck of femur
	S72.1	Pertrochanteric fracture
	S72.2	Subtrochanteric fracture of femur
	S72.3	Fracture of shaft of femur
	S72.4	Fracture of lower end of femur
	S72.7	**Multiple fractures of femur**
	S72.8	Other fracture of femur
	S72.9	Unspecified fracture of femur
	S82.0	Fracture of patella
	S82.1	Fracture of upper end of tibia
	S82.2	Fracture of shaft of tibia
	S82.3	Fracture of lower end of tibia
	S82.4	Fracture of shaft of fibula
	S82.5	Fracture of medial malleolus
	S82.6	Fracture of lateral malleolus
	S82.8	Other fractures of lower leg

medcode	readterm
57328	Skull fracture NOS
23780	Depressed skull fracture NOS
31153	Fracture of orbit NOS, open
28913	Closed fracture of mandible, ramus, unspecified
33459	Open orbital blow-out fracture
71583	Closed fracture of mandible, symphysis of body
32011	Open fracture maxilla
36448	Fracture of upper jaw, closed
48636	Fracture of malar or maxillary bones, open
37904	Closed fracture of mandible, multiple sites
59006	Closed fracture of mandible, body, other and unspecified
44949	Le Fort II fracture maxilla
41730	Closed fracture of mandible, subcondylar
44343	Le Fort I fracture maxilla
37192	Open fracture nasal bone
29119	Closed fracture other facial bone
26408	Fracture of other facial bones, closed, NOS
49644	Fracture of malar or maxillary bones, closed, NOS
27287	Fracture of alveolus, closed
41707	Closed fracture of mandible, angle of jaw
29091	Closed fracture mandible (site unspecified)
30203	Fracture of skull and facial bones
12179	Closed fracture of mandible, condylar process
12462	Open fracture zygoma
38050	Fracture of mandible, open
16890	Fracture of lower jaw, closed
36268	Fracture of mandible, closed, NOS
30028	Fracture of malar and maxillary bones
24790	Closed orbital blow-out fracture
25631	Fracture of facial bone NOS

medcode	readterm
3408	Open fracture nose
20515	Fracture of orbital floor
4225	Closed fracture maxilla
17455	Jaw fracture NOS
4978	Fracture of orbit NOS, closed
14878	Fracture of malar or maxillary bones, closed
9103	Fracture of face bones
9771	Closed fracture nasal bone
11161	Fracture of mandible
5280	Fracture of nasal bones
2251	Closed fracture zygoma
2642	Fracture of mandible, closed
417	Closed fracture nose
31797	Multiple face fractures
39859	Multiple skull fractures
46142	Multiple fractures involving skull or face with other bones
33515	Multiple fractures involving skull and facial bones
30028	Fracture of malar and maxillary bones
60239	Fracture of mandible, open, NOS
99549	Open fracture of mandible, subcondylar
106283	Open fracture of mandible, alveolar border of body
29119	Closed fracture other facial bone
59233	Open fracture other facial bone
9103	Fracture of face bones
55531	Fracture of palate, closed
35312	Fracture of other facial bones,open, NOS
29091	Closed fracture mandible (site unspecified)
14878	Fracture of malar or maxillary bones, closed
32011	Open fracture maxilla

medcode	readterm
104738	Fracture of palate, open
60260	Open fracture of mandible, body, other and unspecified
25631	Fracture of facial bone NOS
12462	Open fracture zygoma
68940	Fracture of malar or maxillary bones, open, NOS
26408	Fracture of other facial bones, closed, NOS
11161	Fracture of mandible
57190	Closed fracture of mandible, alveolar border of body
36268	Fracture of mandible, closed, NOS
2251	Closed fracture zygoma
68660	Open fracture of mandible, ramus, unspecified
49840	Fracture of alveolus, open
17455	Jaw fracture NOS
20515	Fracture of orbital floor
71583	Closed fracture of mandible, symphysis of body
49644	Fracture of malar or maxillary bones, closed, NOS
59341	Closed fracture of mandible, coronoid process
4225	Closed fracture maxilla
59006	Closed fracture of mandible, body, other and unspecified
55955	Open fracture of mandible, angle of jaw
54553	Open fracture of mandible, multiple sites
70673	Open fracture mandible (site unspecified)
24790	Closed orbital blow-out fracture
417	Closed fracture nose
31153	Fracture of orbit NOS, open
37192	Open fracture nasal bone
36772	Fracture of lower jaw, open
70282	Fracture of upper jaw, open
41707	Closed fracture of mandible, angle of jaw

medcode	readterm
2642	Fracture of mandible, closed
37904	Closed fracture of mandible, multiple sites
41730	Closed fracture of mandible, subcondylar
44949	Le Fort II fracture maxilla
5280	Fracture of nasal bones
4978	Fracture of orbit NOS, closed
104931	Open fracture of mandible, symphysis of body
60633	Open fracture of mandible, condylar process
36448	Fracture of upper jaw, closed
9771	Closed fracture nasal bone
28913	Closed fracture of mandible, ramus, unspecified
30203	Fracture of skull and facial bones
3408	Open fracture nose
38050	Fracture of mandible, open
48636	Fracture of malar or maxillary bones, open
33459	Open orbital blow-out fracture
12179	Closed fracture of mandible, condylar process
44343	Le Fort I fracture maxilla
68981	Le Fort III fracture maxilla
27287	Fracture of alveolus, closed
62716	Fracture of inferior maxilla, closed
16890	Fracture of lower jaw, closed

icd10	clinical diagnosis
S02.0	Fracture of vault of skull
S02.1	Fracture of base of skull
S02.2	Fracture of nasal bones
S02.3	Fracture of orbital floor
S02.4	Fracture of malar, maxillary and zygoma bones
S02.6	Fracture of mandible
SO2.7	**Multiple fractures involving skull and facial bones**
S02.8	Fractures of other specified skull and facial bones

Cardiovascular codes

medcode	readterm		icd 10	diagnosis
19280	Anterior cerebral artery syndrome		G45.0	vertebro-basilar artery syndrome
24446	Cerebral infarction due to embolism of precerebral arteries		G45.1	carotid artery syndrome
45781	Precerebral arterial occlusion		G45.2	multiple and bilateral precerebral artery syndroems
40758	Cereb infarct due unsp occlus/stenos precerebr arteries		G45.3	amaurosis fugax
15252	Brainstem infarction NOS		G45.8	other transient cerebral ischemic attacks and related syndromes
19260	Posterior cerebral artery syndrome		G45.9	transient cerebral ischemic attack, unspecified
6228	Sequelae of stroke,not specfd as h'morrhage or infarction			
33499	Pure motor lacunar syndrome			
18689	Middle cerebral artery syndrome			
25615	Brainstem infarction			
36717	Cerebral infarction due to thrombosis of cerebral arteries			
21118	Vertebro-basilar artery syndrome			
23942	Basilar artery syndrome			
26424	Infarction of basal ganglia			
8443	Brain stem stroke syndrome			
15019	Cerebral embolism			
23671	Cerebral infarct due to thrombosis of precerebral arteries			
17322	Cerebellar stroke syndrome			
6489	Transient global amnesia			
10504	Right sided cerebral infarction			
10794	Vertebrobasilar insufficiency			
9985	Left sided cerebral infarction			
33543	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs			
4240	Carotid artery occlusion			
1895	Transient cerebral ischaemia NOS			
16517	Cerebral thrombosis			
569	Infarction - cerebral			
12833	Right sided CVA			
6155	Stroke due to cerebral arterial occlusion			
5268	Insufficiency - basilar artery			
7780	Left sided CVA			
6253	Stroke unspecified			
15788	Transient cerebral ischaemia NOS			
5602	Cerebellar infarction			
2417	Vertebro-basilar insufficiency			
6116	CVA - Cerebrovascular accident unspecified			
8837	Cerebral arterial occlusion			
5363	CVA - cerebral artery occlusion			
3149	Cerebral infarction NOS			
504	Transient cerebral ischaemia			
1433	Transient ischaemic attack			
1298	CVA unspecified			
1469	Stroke and cerebrovascular accident unspecified			
57527	Occlusion and stenosis of anterior cerebral artery			
105738	Carotid territory transient ischaemic attack			
55602	Occlusion and stenosis of cerebellar arteries			
34758	Cerebral embolus			
51759	Occlusion and stenosis of middle cerebral artery			

medcode	readterm	icd10	clinical diagnosis
9413	Other acute and subacute ischaemic heart disease	I20.0	unstable angina
40429	Acute anteroapical infarction	I21.0	STEMI myocardial infarction of anterior wall
27951	Other acute and subacute ischaemic heart disease	I21.1	STEMI myocardial infarction of inferior wall
41221	Acute septal infarction	I21.2	STEMI myocardial infarction of other sites
29758	Acute transmural myocardial infarction of unspecif site	I21.3	STEMI myocardial infarction of unspecified sites
34803	Other acute myocardial infarction	I21.4	NSTEMI
21844	Transient myocardial ischaemia	I21.9	Acute MI, unspecified
18842	Subsequent myocardial infarction	I21.A	other type of MI
46017	Other acute myocardial infarction NOS	I22.0	subsequent STEMI ant wall
13566	Attack - heart	I22.1	subsequent STEMI inf wall
13571	Thrombosis - coronary	I22.2	subsequent NSTEMI
17689	Silent myocardial infarction	I22.8	subsequent STEMI of other sites
29643	Acute inferoposterior infarction	I22.9	subsequent STEMI of unspecified site
14898	Lateral myocardial infarction NOS	I24.0	Acute coronary thrombosis not resulting in MI
17133	Mural thrombosis	I24.9	acute ischemic heart disease, unspecified
29421	Silent myocardial ischaemia		
23892	Posterior myocardial infarction NOS		
9507	Acute non-Q wave infarction		
17872	Acute anteroseptal infarction		
8935	Acute inferolateral infarction		
12139	Acute anterolateral infarction		
5387	Other specified anterior myocardial infarction		
9276	Acute coronary insufficiency		
14897	Anterior myocardial infarction NOS		
3704	Acute subendocardial infarction		
2491	Coronary thrombosis		
1204	Heart attack		
1678	Inferior myocardial infarction NOS		
12229	Acute ST segment elevation myocardial infarction		
7347	Unstable angina		
11983	Acute coronary syndrome		
1431	Unstable angina		
10562	Acute non-ST segment elevation myocardial infarction		
14658	Acute myocardial infarction NOS		
1677	MI - acute myocardial infarction		
241	Acute myocardial infarction		
62626	Acute papillary muscle infarction		
63467	True posterior myocardial infarction		
32854	Acute posterolateral myocardial infarction		
28736	Acute atrial infarction		
30330	Acute Q-wave infarct		

Falls

medcode	readterm	icd10	clinical diagnosis
44119	Falls caused by medication		
6008	Falls		
8694	Recurrent falls	W01	Fall on same level from slipping, tripping and stumbling
46559	Number of falls in last year	W06	Fall from bed
4859	[D] Geriatric fall	W07	Fall from chair
6815	Accidental falls	W08	Fall from other furniture
384	Fall - accidental	W10	Fall on and from stairs and steps
11307	Fall on or from stairs or steps	W11	Fall on and from ladder
17167	Fall on or from stairs	W18	Other fall on same level
17728	Fall on stairs	W19	Unspecified fall
21081	Fall from stairs		
41909	Fall on or from stairs NOS		
44626	Fall on or from steps		
43092	Fall on steps		
53082	Fall from steps		
35468	Fall on or from ladders or scaffolding		
18034	Fall from ladder		
34923	Fall from scaffolding		
18761	Fall from or out of building or other structure		
25172	Fall from window		
43571	Fall into hole or other opening in surface		
33887	Other fall from one level to another		
38818	Fall from chair		
26432	Fall from bed		
21306	Fall from one level to another NOS		
15112	Fall on same level from slipping, tripping or stumbling		
18007	Fall on same level from slipping		
11709	Fall on same level from tripping		
7948	Fall on same level from stumbling		
33529	Fall on same level from slipping, tripping or stumbling NOS		
8730	Other falls		
11308	Other accidental fall NOS		
6835	Accidental falls NOS		
7970	[X]Falls		
29821	[X]Fall on same level from slipping, tripping and stumbling		
24776	[X]Unspecified fall		

Appendix 12 Steps used when cleaning CPRD data and assumptions made when categories needed to be allocated

Generating covariates

Covariate	**What is the problem with data as extracted, such that we can't use it directly in Cox Regression?**	**What should the correct formatted data look like?**
HbA1C	Extracted values date back from index date to years before, and may not reflect recent ones	Only HbA1C in 18-months prior to index date should be keyed into analysis.
BMI	Extracted values date back from index date to years before, and may not reflect recent ones	Only BMI in 18-months prior to index date should be keyed into analysis.
Smoking	Extracted values provide dates available for non-smoker, ex-smoker, current smoker	Need to generate variables representing smoking status (yes/no)
ETOH	Extracted values provide dates available for ETOH user and non-user	Need to generate variables representing ETOH status (yes/no)
Diabetes duration	Extracted values include participants with index date PRIOR to date of first diabetes drug	Only participants with index date AFTER commencing drug therapy should be keyed into analysis
History of MI	Hx of MI is a confounder for future cardiovascular events	Need to generate variable representing history of MI prior to index_date
Ethnicity	Ethnicity is coded as a string variable	Need to convert to a numerical variable

Generating outcomes

Outcome	**What is the problem with data as extracted, such that we can't use it directly in Cox Regression?**	**What should the correct formatted data look like?**
MI	Some MI recorded on CPRD/HES after date of death on ONS.	If MI is coded in both CPRD and ONS then we re-allocate first-MI date to match ONS date of death.
Stroke	Some Stroke recorded on CPRD/HES after date of death on ONS.	If Stroke is coded in both CPRD and ONS, then we re-allocate first stroke date to match ONS date of death.
CV data	Need to construct composite of MI or stroke	Date of first MI or stroke, whichever is earlier
Death date before 1998	ONS linkage only starts from 1 Jan 1998	Patients with index date before Jan 1998 need to have their CPRD death status checked, and the date entered into date of death

Appendix 13 Reporting of hypoglycaemia incidence

Study ID	Reporting of hypoglycaemia incidence
Bedenis 2014[140]	Total 1066; at least one episode of severe hypoglycaemia n=87
Bonds 2010[137]	Total n=10194; patients with at least one hypoglycaemic event requiring assistance n=703
Cha 2016[141]	Total n=1260; severe hypoglycaemia n=85
Chiba 2015[142]	Total n=211; hypoglycaemia in patients with falls 22/62 (35%)
Chin 2016[143]	Total n=1957; participants with hypoglycaemia n=118; no hypoglycaemia n=1839
Cukierman-Yaffe 2019[144]	Severe hypoglycaemia n=427; no severe hypoglycaemia n=11068
Davis 2019[145]	Rate of severe hypoglycemia in the intensive treatment group was 10.3 per 100 patient-years compared with 3.7 per 100 patient-years in the standard treatment group; at least one severe hypoglcyaemic event n=268
Duckworth 2011[146]	9 episodes per 100 patient years in intensive arm
Escalada 2016[147]	Total n=31035; hypoglycaemia group n=3066
Freemantle 2016[148]	Total of 175 (6.6%) participants reported at least one severe hypoglycaemic event, and 1508 (53.7%) reported at least one symptomatic hypoglycaemic event
Goto 2016[149]	58223 with T2DM; 128 (0.2%) patients experienced severe hypoglycemia
Haroon 2015[150]	Total cohort 225045; secondary analysis hospitalizations or ED visits for hypoglycaemia during follow-up as a risk factor for dementia – total number of hypoglycaemic episodes not reported.

Heller 2017[151]	5380 patients with type 2 diabetes; any reported hypoglycaemia n=354
Hsu 2013[152]	1,844 hypoglycemic events among 77,611 new type 2 diabetic patients from 1998 to 2009. The incidence of hypoglycemia was 2.38% (1,844/77,611).
Hung 2017[72]	Total cohort n=5173; 2588 patients with severe hypoglcyaemia
Johnston 2011[154]	Total n=860845; 27,065 (3.1%) had hypoglycaemic events during the evaluation period
Johnston 2012[153]	361 210 included patients; 16 936 had hypoglycaemic events during the evaluation period
Kacharoo 2015[155]	21,613 hypoglycemia patients were matched with 21,613 non-hypoglycemic patients
Khunti 2015[122]	3,260 patients with type 1 diabetes and 10,422 patients with type 2 diabetes included; during follow-up, 573 patients (18%) with type 1 diabetes and 1,463 patients (14%) with type 2 diabetes experienced hypoglycemia.
Kong 2014 (CKD) [156]	Cohort of 8,767 type 2 diabetic patients; on enrolment, 209 patients had severe hypoglycaemia and 194 developed severe hypoglycaemia during follow-up.
Lee 2018 (CV mortality) [71]	1,209 participants with diagnosed diabetes; 195 participants with at least one severe hypoglycemic episode
Lee 2018 (dementia) [68]	2001 participants with diabetes; 63 had history of severe hypoglcyaemia (3.1%)
Leong 2016[157]	Three percent of patients (n = 285) had previous hypoglycemia
Lin 2013[70]	15 404 diabetic subjects; 2% (n = 289) of participants had at least one episode of hypoglycaemia in a 3-year period
Lu 2015[158]	Diabetes with hypoglycaemia group n=31049; Diabetes without hypoglycaemia group n=31049

Majumdar 2013[159]	Cohort included 85,810 patients; 440 patients (0.5%) had severe hypoglycemia associated with hospitalization
Mattishent 2019[160]	1679 participants had a medically recorded hypoglycaemic episode
McCoy 2012[161]	625 (61.7%) reported any hypoglycaemia, and 76 (7.5%) reported severe hypoglycaemia.
Mehta 2017 [162]	5.7% (n = 3,018) had at least one hypoglycaemia episode during the follow-up period; 0.8% (n = 503) had two episodes; and 0.5% (n = 314) had more than two episodes
Mellbin 2013[164]	3518 participants had at least one episode of hypoglycaemia. Of these 2614 (74.3%) occurred in the glargine group and 904 (25.7%) in the standard group. Of the 472 participants with at least one episode of severe hypoglycaemia, 76.1% (359) occurred in the glargine group and 23.9% (113) in the standard group with an estimated annual incidence of 0.9 and 0.3%, respectively.
Ntouva 2019[163]	14147 patients in the exposed cohort (patients with a documented hypoglycaemic event at index date)
Pieber 2018[165]	Severe hypoglycaemia prior to all-cause mortality n=38; 7.32 events per 100 patient-years
Rajpathak 2015[166]	Documented hypoglycaemia during follow-up period n=1056; no documented hypoglycaemia n=25334
Rathmann 2013[167]	Hypoglycaemic episodes (≥1) were documented in 0.18% patients with DPP-4 and in 1.00% with SU
Signorovitch 2013[168]	A total of N=5582 people with claims for hypoglycaemia and N=27 910 with no such claims were included.
Standl 2018[169]	Severe hypoglycaemic episodes were uncommon and unassociated with sitagliptin therapy (N = 160 [2.2%],0.78/100 patient-years vs. N = 143 [1.9%], 0.70/100 patient-years for placebo
Whitmer 2009[69]	At least 1 episode of hypoglycaemia was diagnosed in 1465 patients (8.8%)
Yaffe 2013[170]	During the 12-year follow-up period, 61 participants (7.8%) had a reported hypoglycemic event,
Zhao 2012[171]	The analytical population consisted of 44,261 patients, including 761 patients in the hypoglycemia group and 43,500 in the control group. The incidence rate of hypoglycemia events was calculated as 3.57/100 patient-years

Zhao 2015[172]	A total of 4215 patients with hypoglycaemia were identified and 4215 non-hypoglycaemia patients were match to the hypoglycaemia patients
Zinman 2018[173]	4.3% (n=180) participants who used insulin at baseline had had severe hypoglycaemia
Zoungas 2010[174]	During a median follow-up period of 5 years, 231 patients (2.1%) had at least one severe hypoglycemic episode; 150 had been assigned to intensive glucose control (2.7% of the 5571 patients in that group), and 81 had been assigned to standard glucose control (1.5% of the 5569 patients in that group).

Appendix 14 Pooled Odds Ratios for different associations using fixed and random effects methods

	Pooled Odds Ratios – fixed effect	**Pooled Odds Ratios – random effect**	**I^2**
Association between hypoglycaemia and mortality	1.86 (95% CI 1.78 to 1.94)	2.02 (95% CI 1.75 to 2.32)	86%
Association between hypoglycaemia and dementia	1.62 (95% CI 1.54 to 1.71)	1.55 (95% CI 1.33 to 1.79)	70%
Association between hypoglycaemia and falls	1.54 (95% CI 1.45 to 1.63)	1.78 (95% CI 1.44 to 2.21)	87%
Association between hypoglycaemia and fractures	1.51 (95% CI 1.43 to 1.58)	1.68 (95% CI 1.37 to 2.07)	91%
Association between hypoglycaemia and macrovascular events	1.80 (95% CI 1.71 to 1.91)	1.81 (95% CI 1.69 to 1.95)	10%
Association between hypoglycaemia and microvascular events	1.77 (95% CI 1.49 to 2.10)	1.77 (95% CI 1.49 to 2.10)	0%