The effects of hypoglycemia and dementia on cardiovascular events, falls and fractures and all-cause mortality in older people – a retrospective cohort study

Running title: Hypoglycemia and dementia –adverse events

Katharina Mattishent MRCP; University of East Anglia, Norwich Medical School

Kathryn Richardson PhD; University of East Anglia, School of Health Sciences

Ketan Dhatariya PhD; Norfolk and Norwich University Hospital NHS Foundation Trust

George M Savva PhD; Quadram Institute Bioscience, Norwich Research Park

Chris Fox MD; University of East Anglia, Norwich Medical School

Yoon K Loke MD; University of East Anglia, Norwich Medical School

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Corresponding author:

Katharina Mattishent

Alzheimer's Society Clinical Research Fellow

Floor 2, Bob Champion Research and Educational Building,

James Watson Road,

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University of East Anglia,

Norwich Research Park, Norwich, NR4 7UQ

Email: k.mattishent@uea.ac.uk

Abstract

Aims

Older people with diabetes are susceptible to harm from hypoglycemia, however the consequences of hypoglycemia in older people with dementia are not known. We aimed to test association between hypoglycemia and serious adverse events in older patients with diabetes and dementia, and whether the consequences of hypoglycemia were affected by presence of dementia.

Materials and Methods

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

We used Cox proportional hazard regression to estimate adjusted hazard ratios (aHR) for falls, fractures, cardiovascular events and mortality.

Results

In target trial 1, hypoglycemia was associated with an increased risk during 12 months follow-up of falls and fractures - 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 hypoglycemia (12 months follow-up): falls & factures - 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).

Conclusions and Relevance

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

Introduction

Worldwide, there are 425 million people living with diabetes and this is expected to rise to 629 million by 2045 (1). It is also estimated that around 50 million people across the world are living with dementia, which is expected to rise to 125 million by 2050 (2). These projections indicate that comorbid diabetes and dementia is likely to pose a major healthcare burden, given 13-20% of people with dementia also have diabetes (3).

Self-management of diabetes is particularly challenging for older patients because they have limited recall of the dangers of hypoglycemia and what remedial action to take (4), and because they are more prone to hypoglycemia from their medication (5) (6). The burden of hypoglycemia in older patients has steadily mounted (7) (8) (9), with one study reporting a 267% increase in hypoglycemia hospitalizations for patients aged 75 years or older in England and Wales (2000-2014), and a 10-fold higher admission rate compared to patients in the 15-59 years age group (7). A worldwide study of 109 countries found a 60% increase in hypoglycemia-related deaths between 2000-2010, with these deaths occurring mainly in individuals over the age of 50 years (10).

Other studies involving older people with diabetes have identified potentially serious consequences (e.g. cardiovascular events, falls, fractures and death) that extend beyond the acute event of hypoglycemia alone(6). However, most of the studies have not specifically focused on these hypoglycemia-related complications in older

people with dementia, although there is evidence from a recent meta-analysis that patients with diabetes and dementia may be even more prone to hypoglycemia and subsequent cognitive complications (11).

Hypoglycemic events are known to have serious consequences including falls and fractures and are associated with earlier mortality (6). However, the specific risks associated with hypoglycemia among older people with dementia are not well understood. A more comprehensive understanding of the consequences of hypoglycaemia in this vulnerable and complex group will help optimise the clinical management.

Our overall aim was to test the effect of hypglycemia in older people with dementia and diabetes on serious adverse events, specifically cardiovascular events (myocardial infarction, ischemic stroke), falls and fractures, and all-cause mortality. We also examined whether dementia modified the effect of hypoglycemia.

Materials and Methods

Study design

We performed a retrospective cohort study using data from the Clinical Practice Research Datalink (CPRD) database. We designed two hypothetical target trials within a cohort of older patients with diabetes. The first target trial aimed to test the effect of hypoglycemia among people with dementia and diabetes, with respect to subsequent serious adverse events. We also conducted a second target trial to

evaluate whether the effect of hypoglycemia was affected by the presence or absence of dementia. We selected participants, intervention (exposure) and follow-up to mirror the two hypothetical target randomised controlled trials (12) (see Figure 1).

Study data and Setting

CPRD holds anonymised primary care records from general practitioners (GPs), encompassing over 11 million patients from 674 practices in the United Kingdom (UK) and is broadly representative of the UK general population in terms of age, sex and ethnicity (13). A subset of primary care datasets is also linked with Hospital Episode Statistics (HES), which covers emergency department (ED) attendance and hospitalization, the Office for National Statistics (ONS), which covers mortality data, and the Index of Multiple Deprivation and Townsend scores (deprivation scores) (13).

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) – protocol number 16_184R.

We followed the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) guidelines (14).

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. We 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 and Related Health Problems (ICD) code (Supplemental Table S5). Read Codes have been used by the National Health Service (NHS) since the 1980s and are a thesaurus of clinical terms.

Exposure and Outcomes

The exposure was defined as the first hypoglycemic episode recorded on the primary (CPRD) or secondary (HES) healthcare database from April 1997 onwards following initiation of a glucose-lowering agent. Data on hypoglycemic episodes were obtained from CPRD using Read codes and HES with ICD codes (Supplemental Table S5). Combined use of CPRD and HES broadens the capture of hypoglycemia 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 hypoglycemia and cardiovascular events in insulin users (15).

For target trial 1, the exposed group's (dementia, hypoglycemia) first coded hypoglycemic episode occurred a median (IQR) of 13 (2-34) months after meeting the study eligibility criteria. For the control group (dementia, no hypoglycemia), we added a random lag to the date of first meeting study criteria to define their point of exposure (or index date for start of follow-up for adverse events) by randomly sampling the delay between first meeting the study eligibility criteria and the first hypoglycemic episode in the exposed group (16).

The outcomes were falls, fractures, cardiovascular events (myocardial infarction, ischemic stroke) and all-cause mortality. In addition, we assessed the rate of Emergency Department 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 hypoglycemic 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.

Covariates

We 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), glycated hemoglobin (HbA1c) (17) (18).

Covariates were measured at the point of exposure. We 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.

Statistical analysis

To estimate the association between the timing of hypoglycemic episodes and defined outcomes, we used Cox proportional hazard regression models with adjustment for appropriate confounders to generate Hazard Ratios (HRs) and 95% Confidence Intervals (95% CI) for each outcome. We visually inspected log-log plots of survival to assess the proportional hazards assumption. If the proportional hazard assumption was not met, we estimated the hazards at shorter and longer follow-up periods.

We used complete-case analysis for both hypothetical target trials, because we could not be certain that data were missing at random or not. We carried out

sensitivity analyses using different methods (multiple imputation, use of a missing data category, and exclusion of lifestyle covariates).

We 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.

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

Results

Our cohort consisted of a total of 19,993 patients with diabetes (Figure 2). Patient demographics are set out in Table 1. 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 hypoglycemia compared to those with dementia and no hypoglycemia (48% versus 13%).

The proportional hazards assumption for the majority of the outcomes was not met in the statistical analysis, hence we stratified the analysis according to less than or more than 12 months of follow-up (Tables 2 and 3).

The number of events is reported in Tables 2 and 3 and the median time to event is reported in Supplemental Table S3.

Target trial 1 – the effect of hypoglycemia on outcomes in patients with dementia (Table 2)

During the first 12 months, adverse events occurred at about twice the rate among those with hypoglycemia 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]).

Hypoglycemia was associated with an increase in subsequent myocardial infarction (MI) (aHR 2.24 [95% CI 1.59 to 3.15]) and ischemic 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 hypoglycemia (Table 3)

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 hypoglcyemia.

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 ischemic 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]).

Sensitivity analyses (Supplemental Tables S1 and S2)

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

Emergency department attendances (Supplemental Table S4)

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

Discussion

We have shown that older people with dementia and diabetes who have had a hypoglycemic event have substantially higher risk of death, cardiovascular events, falls, fractures and emergency department attendances, than those who have not. The hazard ratios of complications were found to be greatest within the first 12 months of follow-up. The magnitude of risk diminished with longer follow-up time, which indicates that our findings are probably not related to unmeasured confounders. Persistent residual confounding would more likely be associated with constantly elevated hazard ratios across the entire duration.

The results underscore the importance of management strategies tailored towards avoidance of hypoglycemic episodes rather than just chasing tight glycemic targets in this vulnerable group. This is of particular significance in the light of recent findings that asymptomatic hypoglycemic episodes are often missed in older people with diabetes (19), as this study may only be looking at the tip of the iceberg regarding the impact of hypoglycemia.

Furthermore, the higher risk in the first 12 months would be clinically consistent with the potential impact of an acute episode of hypoglycemia, especially if the underlying harm stems from cardiac damage. For example, Pistrosch et al's study of continuous glucose monitoring (CGM) and ambulatory cardiac monitoring found a link between hypoglycemia and the occurrence of ventricular arrhythmias (20). A recently published meta-analysis confirmed that hypoglycemia can result in ECG

changes associated with cardiac arrhythmias that are markers of increased risk of mortality and cardiovascular events (21). Cardiac arrhythmias may be an underlying factor to explain our findings of increased risk of myocardial infarction, stroke, falls and death following hypoglycemia. Nevertheless, the effects of hypoglycemia on the cardiovascular physiology of frail, multi-morbid older patients with diabetes remains unclear.

More recent studies estimated the link between hypoglycemia and accelerated cognitive decline. Hypoglycemia in older people is linked to an increased risk in cognitive decline (11) and one recent study found that hypoglycemia was associated with smaller total brain volume on MRI (22). Cognitive decline may in turn pre-dispose older frail people to falls, fractures and death following hypoglycemia. This ties in with our findings that dementia contributes to greater hazards in terms of mortality, falls and fractures in older patients with hypoglycemia.

However, the effect of co-existing dementia on subsequent risk of myocardial infarction in older people with hypoglycemia is unclear and diagnostic difficulty or misclassification may be a source of bias here. Older people with myocardial infarction can present with vague symptoms such as shortness of breath, nausea, sweating or collapse, which may result in them 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 (23) (24). 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 (25) (26).

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 we used to address confounding. We were aware that differences in patient characteristics and medication could be potentially important contributors to risk of adverse outcomes. Hence, our 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 we are presenting the results of an observational study, we are not able to prove a causal link, however, this study does demonstrate that hypoglycemia is a marker of risk for subsequent adverse events.

We evaluated validity of our study against the domains listed in the ROBINS-I tool (27). The three areas which carry a moderate risk of bias are: confounding, missing data and classification of intervention. We are 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, we

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

Our findings are principally applicable to severe hypoglycemic 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 hypoglycemia and its complications, and our approach is therefore compatible with current research practice (28) (29) . We recognize that risk of subsequent complications may be of greater magnitude due to the severity of the hypoglycemia and we cannot determine whether self-managed or asymptomatic hypoglycemia 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 hypoglycemic episodes for research purposes. Hypoglycemic episodes documented in primary and secondary care healthcare records are currently the only available source.

In addition, we are not able to accurately ascertain from the database the precise timing of the hypoglycemic episode and what the blood glucose concentrations were, although, by virtue of the fact that these hypoglycemic 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, we have not attempted to analyse the effects of recurrent hypoglycemia because

very few patients experienced recurrent events in previous studies using the same database (30) (31).

Similarly, we are not able to accurately determine dementia severity or duration from onset due to the insidious onset and substantial variation in clinical presentation.

A combination of less rigorous management regimes, but greater intensity of monitoring should be considered to reduce hypoglycemia in this vulnerable population. Simply changing or loosening HbA1c targets for the older frail population may not help in reducing hypoglycemic events. The risk of hypoglycemia 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 hypoglycemia (30). Future research has to focus on a randomized controlled trial (in older people with diabetes and dementia), where the treatment strategy would be aimed at minimizing (or even eradicating) hypoglycemic episodes. An essential component of the trial would be the use of CGM, in order capture hypoglycemic episodes that may otherwise go unrecorded and guide the hypoglycemia 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, hypoglycemia 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 hypoglycemia.

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Contributors: KM and YKL conceived and developed the initial study. KR and GS helped design the study. 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. YKL is the guarantor.

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Ethical approval: The study was approved by the Independent Scientific Advisory Committee for Clinical Practice Research Datalink (CPRD) research (Protocol No 16_184). No further ethical approval was required for the analysis of the data. CPRD has obtained ethical approval from a multicentre research ethics committee for all purely observational research using CPRD data.
https://www.cprd.com/isac/Protocol_16_184R.asp

Data sharing: Data from the Clinical Practice Research Datalink (CPRD) is available directly from CPRD. Full code lists are available from the corresponding author at k.mattishent@uea.ac.uk.

Transparency: The lead author (KM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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Figure legends

Figure 1. Schematic presentation of study

Figure 2. Patient flowchart

Table 1. Baseline characteristics

	Dementia, no hypoglycemia (n=6134)	Dementia, hypoglycemia (n=1679)	Hypoglycemia, 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)
Hemoglobin A1c (mmol/L), mean (SD)	56.71 (17.10)	62.46 (20.89)	60.51 (17.74)
Hemoglobin 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	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)
Parkinsons 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)
Sulphonylureas	2511 (40.94)	786 (46.81)	5662 (46.49)
Insulin	794 (12.94)	801 (47.71)	5974 (49.05)
Other oral hypoglycemics	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

Table 2. Target trial 1 – effect of hypoglycemia in patients with diabetes and dementia

	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 hypoglycemia (n=6134)	Dementia, hypoglycemia (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)

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, sulphonylureas, other oral hypoglycemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i), 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, 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, sulphonylureas, other oral hypoglycemics, 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, sulphonylureas, other oral hypoglycemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i), dementia drugs

MI=myocardial infarction, ACE-i= angiotensin-converting-enzyme inhibitor, COPD=chronic obstructive pulmonary disease
HR=Hazard Ratio, 95% CI=95% Confidence Interval

Table 3. Target trial 2 – dementia as an effect modifier

	Number of events, n		Adjusted HR (95% CI) Up to one-year follow-up	Adjusted HR (95% CI) 12-60 months follow-up
	Dementia, hypoglycemia (n=1679)	Hypoglycemia, no dementia (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)

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, sulphonylureas, other oral hypoglycemics, 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, sulphonylureas, other oral hypoglycemics, 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, sulphonylureas, other oral hypoglycemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i)

MI=myocardial infarction, ACE-i= angiotensin-converting-enzyme inhibitor, COPD=chronic obstructive pulmonary disease
HR=Hazard Ratio, 95% CI=95% Confidence Interval

Figure 1. Schematic presentation of study

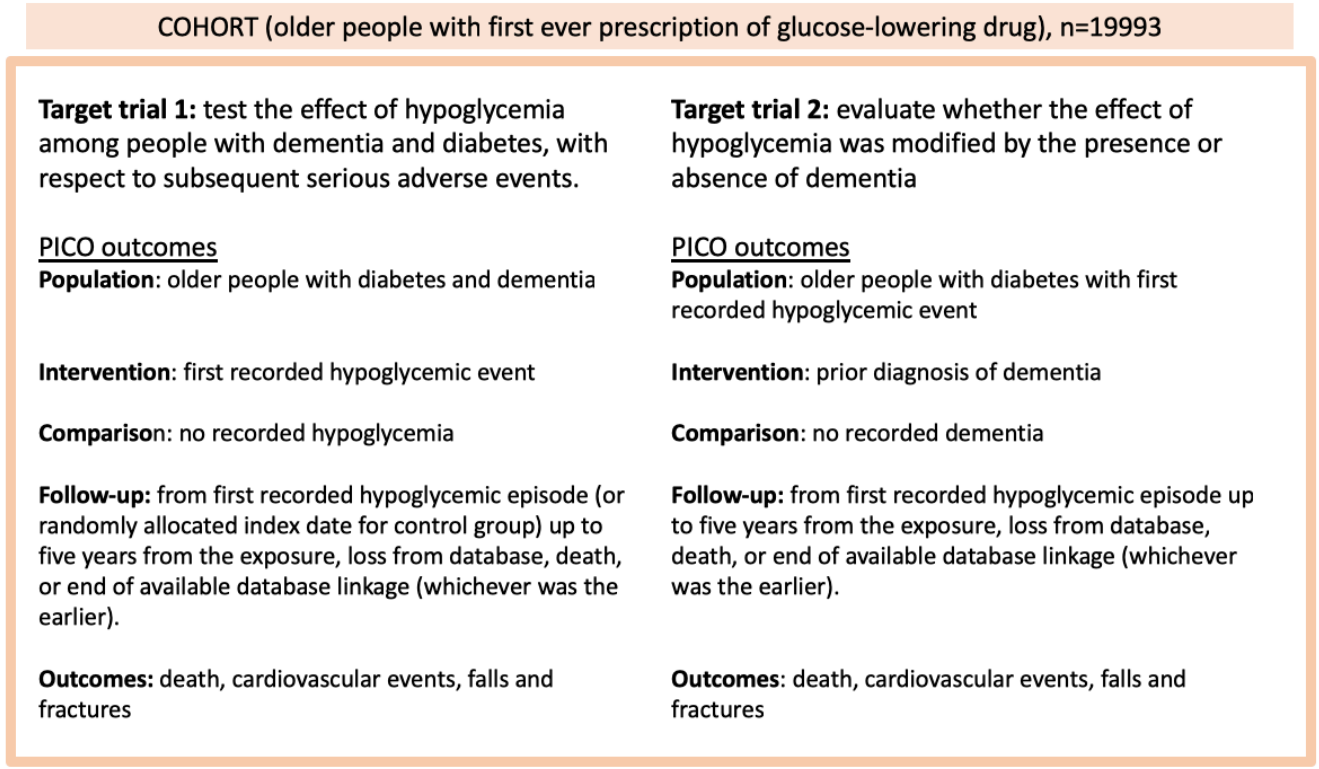
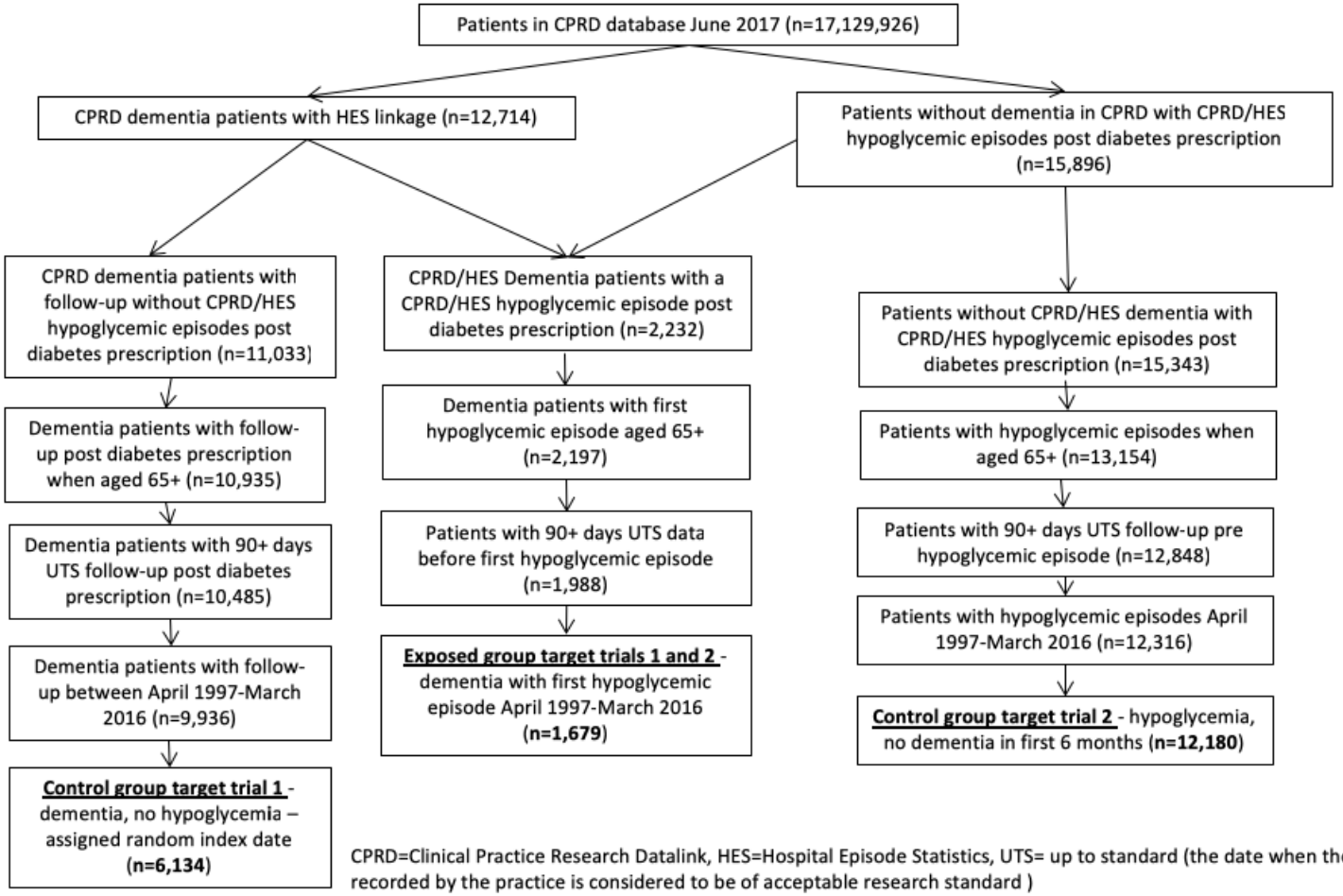


Figure 2. Patient flowchart



CPRD=Clinical Practice Research Datalink, HES=Hospital Episode Statistics, UTS= up to standard (the date when the data recorded by the practice is considered to be of acceptable research standard)