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The effects of hypoglycaemia and dementia on cardiovascular events, falls and fractures and all-cause mortality in older individuals: A retrospective cohort study

Katharina Mattishent MRCP[1] | Kathryn Richardson PhD[2] | Ketan Dhatariya PhD[3] | George M. Savva PhD[4] | Chris Fox MD[1] | Yoon K. Loke MD[1]

[1]Norwich Medical School, University of East Anglia, Norwich, UK

[2]School of Health Sciences, University of East Anglia, Norwich, UK

[3]Department of Diabetes and Endocrinology, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK

[4]Quadram Institute Bioscience, Norwich Research Park, Norwich, UK

Correspondence
Katharina Mattishent, MRCP Alzheimer's Society Clinical Research Fellow, Floor 2, Bob Champion Research and Educational Building, James Watson Road, University of East Anglia, Norwich Research Park, Norwich, NR4 7UQ, UK.
Email: k.mattishent@uea.ac.uk

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Abstract

Aims: Older individuals with diabetes are susceptible to harm as the result of hypoglycaemia; however, the consequences of hypoglycaemia in older individuals with dementia are not known. We 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.

Materials and methods: This was a cohort study using the Clinical Practice Research Datalink in England (1997-2016). We selected participants, intervention (exposure) and follow-up to mirror two hypothetical target randomized controlled trials. The exposure of target trial 1 was hypoglycaemia in patients with dementia. Target trial 2 examined adverse effects of hypoglycaemia 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, hypoglycaemia was associated with increased risk during a 12-month follow-up period for falls and fractures (aHR, 1.94 [95% CI, 1.67-2.24]), for cardiovascular events (aHR, 2.00 [95% CI, 1.61-2.48]) and for mortality (aHR, 2.36 [95% CI, 2.09-2.67]). In target trial 2, the presence of dementia was associated with increased risk of adverse events, following hypoglycaemia, during a 12-month follow-up period for falls and factures (aHR, 1.72 [95% CI, 1.51-1.96]) and for mortality (aHR, 1.27 [95% CI, 1.15-1.41]), but dementia had no effect on cardiovascular events (aHR, 1.14 [95% CI, 0.95 to 1.36]).

Conclusions: Hypoglycaemia is associated with early increased risk of serious adverse events in older individuals with diabetes and dementia.

KEYWORDS

cohort study, diabetes complications, hypoglycaemia, observational study, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Worldwide, 425 million individuals are living with diabetes and this figure is expected to rise to 629 million by 2045.[1] It is also estimated that approximately 50 million individuals 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 that 13% to 20% of individuals 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 hypoglycaemia and what remedial action to take,[4] and because they are more prone to hypoglycaemia because of their medication.[5,6] The burden of hypoglycaemia in older patients has mounted steadily,[7-9] with one study reporting a 267% increase in hospitalizations for hypoglycaemia in 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 of age group.[7] A worldwide study of 109 countries revealed a 60% increase in hypoglycaemia-related deaths between 2000 and 2010, with these deaths occurring mainly in individuals over the age of 50 years.[10]

Other studies involving older individuals with diabetes have identified potentially serious consequences (eg, cardiovascular events, falls, fractures and death) that extend beyond the acute event of hypoglycaemia.[6] However, most of the studies have not specifically focused on these hypoglycaemia-related complications in older individuals with dementia, although there is evidence from a recent meta-analysis that patients with diabetes and dementia may be even more prone to hypoglycaemia and subsequent cognitive complications.[11]

Hypoglycaemic events are known to have serious consequences, including falls and fractures, and are associated with earlier mortality.[6] However, the specific risks associated with hypoglycaemia among older individuals with dementia are not well understood. A more comprehensive understanding of the consequences of hypoglycaemia in this vulnerable and complex group will help optimize clinical management. Our overall aim was to test the effect of hypglycaemia in older individuals with dementia and diabetes on serious adverse events, specifically cardiovascular events (myocardial infarction, ischaemic stroke), falls and fractures and all-cause mortality. We also examined whether dementia modified the effect of hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | 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 hypoglycaemia among individuals with dementia and diabetes, with respect to subsequent serious adverse events. We also conducted a second target trial to evaluate whether the effect of hypoglycaemia was influenced by the presence or absence of dementia. We selected participants, intervention (exposure) and follow-up to mirror the two hypothetical target randomized controlled trials[12] (Figure 1).

2.2 | Study data and setting

CPRD holds anonymized primary care records from general practitioners (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.[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

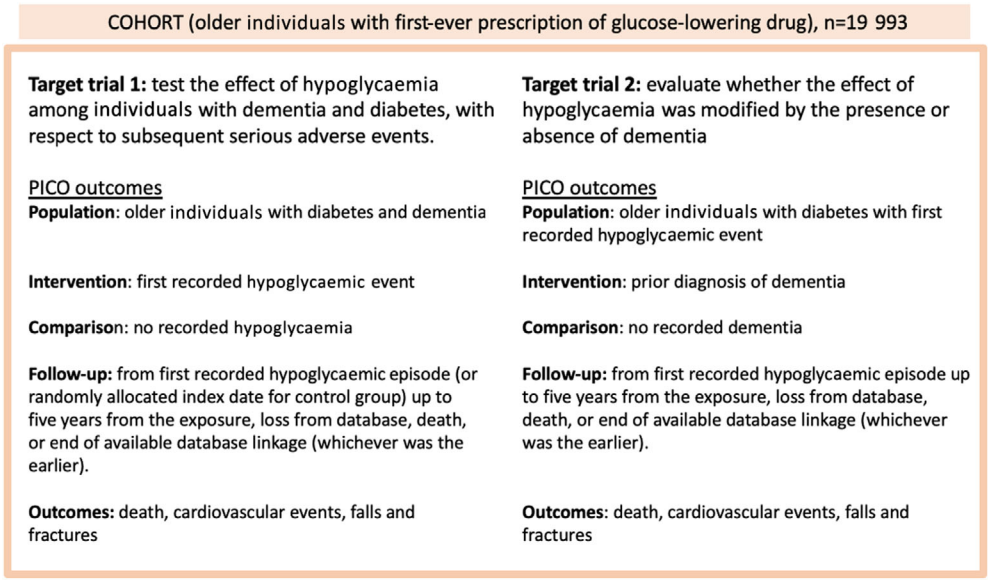

FIGURE 1 Schematic presentation of study

the Independent Scientific Advisory Committee for the CPRD, protocol number 16_184R. No further ethical approval was required for data analysis as CPRD has obtained ethical approval from a multicentre research ethics committee for all purely observational research using CPRD data (available at https://www.cprd.com/isac/Protocol_16_184R.asp). We followed Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) guidelines.[14]

2.3 | Participants

The cohort consisted of patients aged 65 years 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 (eg, polycystic ovary syndrome) for such drugs in this age group.

Participants were eligible only if HES-linked data were available. Dementia status was ascertained based on the presence of a CPRD Read Code or HES International Classification of Diseases and Related Health Problems (ICD) code (Table S5). Read Codes have been used by the National Health Service (NHS) since the 1980s and comprise a thesaurus of clinical terms.

2.4 | Exposure and outcomes

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. Data concerning episodes of hypoglycaemia were obtained from CPRD using Read codes and HES with ICD codes (Table S5). Combined use of CPRD and HES broadens the capture of hypoglycaemia to include events recorded by medical personnel in both primary and secondary care settings; a similar approach has been used in previous research concerning the association between hypoglycaemia and cardiovascular events in insulin users.[15]

For target trial 1, the exposed (dementia, hypoglycaemia) group's first coded hypoglycaemic episode occurred a median (IQR) of 13 (2-34) months after meeting study eligibility criteria. For the control (dementia, without hypoglycaemia) group, we added a random lag to the date of first meeting study criteria to define the point of exposure, or index date for beginning of follow-up for adverse events, by randomly sampling the delay between first meeting study eligibility criteria and first hypoglycaemic episode in the exposed group.[16]

The outcomes were falls and fractures, cardiovascular events (myocardial infarction, ischaemic stroke) and all-cause mortality. In addition, we assessed the rate of ED attendances for patients with a point of exposure after April 1, 2007 (HES accident and emergency data are available only for the time period 1 April 2007 to 31 March 2016). The beginning of follow-up was the first episode of hypoglycaemia, or the randomly allocated exposure date, for the control group in target trial 1. Follow-up continued for up to 5 years from exposure, loss from database, death or the end of available database linkage (HES, 31 March 2016 and ONS, 17 April 2017), whichever took place first.

2.5 | 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) and glycated haemoglobin (HbA1c).[17,18] Covariates were measured at the point of exposure. We took into account medication history for the past 90 days, most recent BMI within the last 3 years and most recent HbA1c within the last 18 months.

2.6 | Statistical analysis

To estimate the association between the timing of episodes of hypoglycaemia 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% CIs) for each outcome. We visually inspected log-log plots of survival to assess the proportional hazard 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 whether data were missing at random or not. We carried out sensitivity analyses using multiple imputation, a missing data category and exclusion of lifestyle covariates. We used negative binomial regression to estimate adjusted rate ratios of ED attendances for patients with a point of exposure after 1 April 2007. Analyses were performed using STATA version 14.2 software (StataCorp LP, College Station, Texas).

3 | RESULTS

The study cohort comprised a total of 19 993 patients with diabetes (Figure 2). Patient demographics are set out in Table 1. The mean age in the dementia group was 82 years and in the non-dementia group it was 77 years. Insulin use was higher in those with dementia and hypoglycaemia compared to those with dementia without hypoglycaemia (48% vs 13%). The proportional hazard assumption for the majority of 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 Table S3.

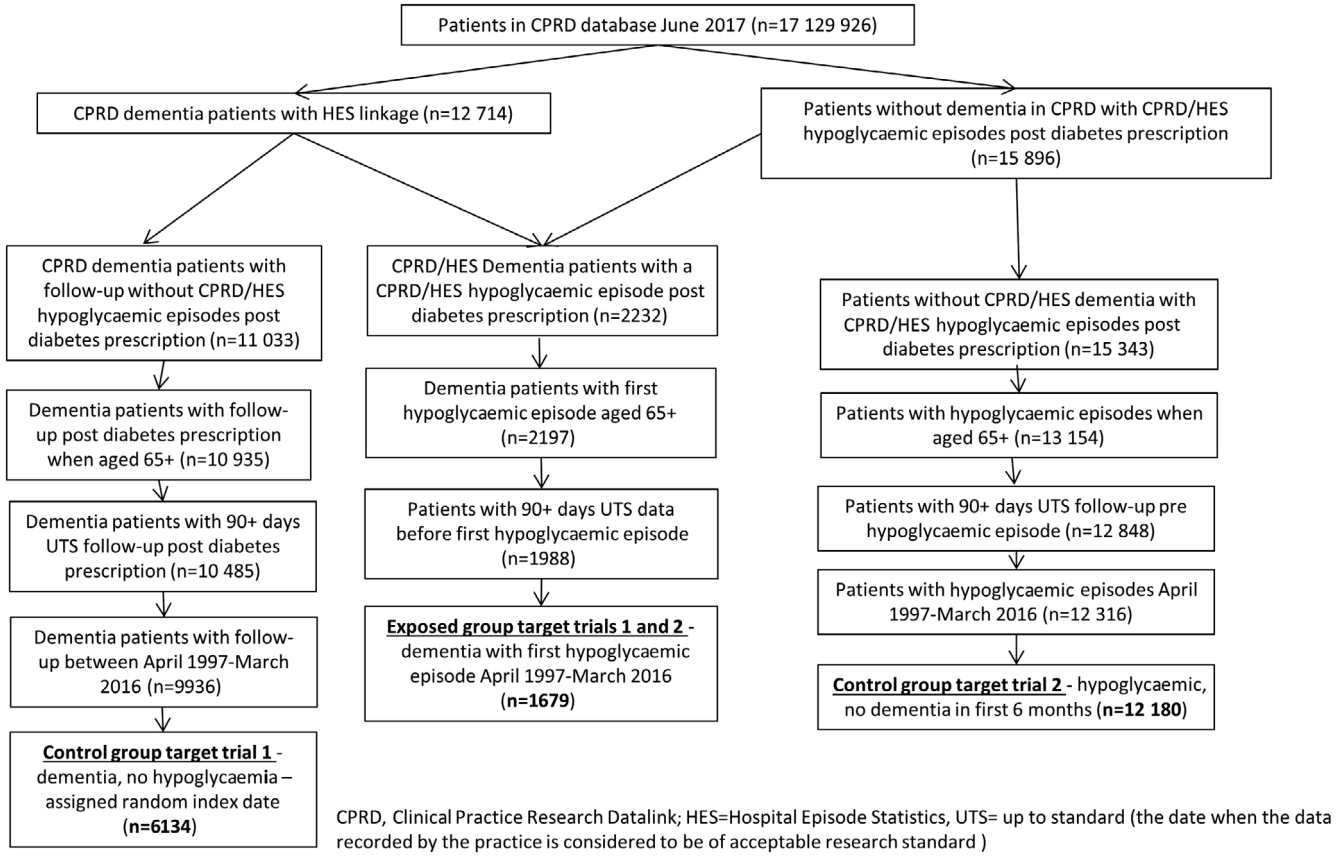

FIGURE 2 Patient flowchart

3.1 | Target trial 1: Effect of hypoglycaemia on outcomes in patients with dementia (Table 2)

During the first 12 months, adverse events occurred at approximately twice the rate among individuals with hypoglycaemia compared to those without: all-cause mortality (aHR, 2.36 [95% CI, 2.09-2.67]), cardiovascular events (aHR, 2.00 [95% CI, 1.61-2.48)] 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, 1.59-3.15]) and ischaemic stroke (aHR, 1.80 [95% CI, 1.37-2.36]) among individuals with dementia. Risks of falls and fracture, individually, were both increased (aHR, 1.96 [95% CI, 1.69-2.29] and aHR, 1.62 [95% CI, 1.25-2.08]). However, the associations diminished with longer follow-up. During the 12-60-month follow-up, there remained an association with mortality (aHR, 1.33 [95% CI, 1.19-1.48]), but not with other outcomes.

3.2 | Target trial 2: Effect of co-morbid dementia on outcomes in patients with hypoglycaemia

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, 1.15-1.41]) in older individuals with hypoglycaemia. The risk of mortality increased to more than double during the 12-60-month follow-up period (aHR, 2.15 [95% CI, 1.94 to 2.37]). Dementia was not statistically significantly associated with cardiovascular events (aHR, 1.14 [95% CI, 0.95-1.36]). It was associated with a significant increase in risk of ischaemic stroke (aHR, 1.41 [95% CI, 1.12-1.78]), but not of myocardial infarction (aHR, 0.84 [95% CI, 0.64-1.10]).

3.3 | Sensitivity analyses

Certain lifestyle variables such as BMI, alcohol use, smoking status and HbA1c were not regularly measured or were not necessarily measured close to exposure (Tables S1 and S2). Our findings did not substantially change when using different methods to account for missing data.

3.4 | Emergency department attendance

The rate of ED attendance in patients with dementia and hypoglycaemia was 113 per 100 patient-years; the rate in those with dementia but without hypoglycaemia was 64 per 100 patient-years (aRR, 1.43 [95% CI, 1.30-1.57]) (Table S4).

4 | DISCUSSION

We have shown that older individuals with both dementia and diabetes who have experienced a hypoglycaemic event have a substantially higher risk of death, cardiovascular events, falls and fractures and ED

TABLE 1 Baseline characteristics

	Dementia without hypoglycaemia (n = 6134)	Dementia with hypoglycaemia (n = 1679)	Hypoglycaemia without dementia (n = 12 180)
Characteristics			
Age (y), 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)	10 787 (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 (y), mean (SD)	5.22 (5.53)	8.55 (6.66)	8.62 (5.77)
Dementia duration (y), 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)
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)

TABLE 1 (Continued)

	Dementia without hypoglycaemia (n = 6134)	Dementia with hypoglycaemia (n = 1679)	Hypoglycaemia without dementia (n = 12 180)
Previous fractures	1143 (18.63)	397 (23.65)	1753 (14.39)
Cancer metastasizing 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 d, 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 hypoglycaemics	3512 (57.25)	678 (40.38)	5528 (45.39)
Dementia drugs	1027 (16.74)	180 (10.72)	Not applicable

Bisphosphonates, Calcitonin, Calcium and Vitamin D supplements.

attendances than those who have not. Hazard ratios of complications were found to be greatest within the first 12 months of follow-up. The magnitude of risk diminished with a longer period of follow-up, indicating that our findings are probably not related to unmeasured confounders. Persistent residual confounding would more probably be associated with constantly elevated hazard ratios across the entire duration.

The present results underscore the importance of management strategies that are tailored for avoidance of hypoglycaemic episodes rather than simply pursuing tight glycaemic targets in this vulnerable group. This is of particular significance in light of recent findings that asymptomatic hypoglyceamic episodes are often missed in older individuals with diabetes,[19] as this study may be looking at only the tip of the iceberg regarding the impact of hypoglycaemia.

The higher risk during the first 12 months is clinically consistent with the potential impact of an acute episode of hypoglycaemia, especially if the underlying harm stems from cardiac damage. For example, the study of Pistrosch et al. of continuous glucose monitoring (CGM) and ambulatory cardiac monitoring found a link between hypoglycaemia and the occurrence of ventricular arrhythmias.[20] 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.[21] Cardiac arrhythmias may be an underlying factor that explains our findings of increased risk of myocardial infarction, stroke, falls and fractures, 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 individuals is linked to increased risk of cognitive decline[11] and one recent study found, using MRI, that hypoglycaemia was associated with smaller total brain volume.[22] Cognitive decline may, in turn, predispose older frail patients to falls, fractures and death following hypoglycaemia. This ties in with our findings that dementia contributes to greater hazards in terms of falls and fractures as well as mortality in older patients with hypoglycaemia.

The effect of co-existing dementia on subsequent risk of myocardial infarction in older individuals with hypoglycaemia is unclear, however, and diagnostic difficulty or misclassification may be a source of bias here. Older individuals with myocardial infarction can present with vague symptoms such as shortness of breath, nausea, sweating

TABLE 2 Target trial 1: Effect of hypoglycaemia in patients with diabetes and dementia

	Number of events, n		Adjusted HR (95% CI) Up to 1-y follow-up	
	Dementia without hypoglycaemia (n = 6134)	Dementia with hypoglycaemia (n = 1679)	Complete case analysis (n = 5607)	Adjusted HR (95% CI) 12-60 months follow-up
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 and 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)

Note. 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 hypoglycaemics, 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 metastasizes to the bone), medications (bone protection medications, insulin, sulphonylureas, 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 metastasizes to the bone), medications (insulin, sulphonylureas, other oral hypoglycaemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i, dementia drugs).
Abbreviations: ACE-i, angiotensin-converting-enzyme inhibitor; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MI, myocardial infarction; 95% CI, 95% confidence interval.

or collapse, which may result in failure to recognize them. Alexander et al. found that only 40% of individuals over 85 year of age 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 upon initial presentation. Bronchopneumonia is reported to be the most common cause of death in older individuals with dementia.[25,26]

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 hypoglycaemia is a marker of risk for subsequent adverse events.

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

TABLE 3 Target trial 2: Dementia as an effect modifier

	Number of events, n		Adjusted HR (95% CI) Up to 1-y follow-up	Adjusted HR (95% CI) 12-60 months follow-up
	Dementia with hypoglyacemia (n = 1679)	Hypoglycaemia without dementia (n = 12 180)	Complete case analysis (n = 11 683)	
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 and 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)

Note. 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 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 metastasizes to the bone), medications (bone protection medications, insulin, sulphonylureas, 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 metastasizes to the bone), medications (insulin, sulphonylureas, other oral hypoglycaemics, beta blockers, calcium channel blockers, loop diuretics, thiazide diuretics, anticoagulants, antiplatelets, cholesterol-lowering medications, ACE-i).
Abbreviations: ACE-i, angiotensin-converting-enzyme inhibitor; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MI, myocardial infarction; 95% CI, 95% confidence interval.

We are aware that, in some patients, covariates such as BMI, HbA1c, smoking status and alcohol use may not have been regularly documented in the period preceding exposure. However, we used three different methods to address this issue in sensitivity analyses, all of which yielded similar results.

Our findings are principally applicable to severe hypoglycaemic events that require medical assistance and, hence, result in an entry on the patient's medical record. Large trials have used the same methodology in assessing severe hypoglycaemia and its complications; our approach is therefore consistent with current research practice.[28,29] We recognize that risk of subsequent complications may be of greater magnitude in association with the severity of the hypoglycaemia and we cannot determine whether self-managed or asymptomatic hypoglycaemia is associated with a similar or lower risk of serious consequences. However, in the absence of large CGM trials in older individuals 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.

We are unable to accurately ascertain from the database the precise timing of the episode of hypoglycaemia and the concentrations of blood glucose; however, by virtue of the fact that these episodes of

hypoglycaemia have been recorded in a medical database, one would assume that they were of a severity that warranted the attention of the patient's healthcare team. Moreover, we have not attempted to analyse the effects of recurrent hypoglycaemia because very few patients experienced recurrent events in previous studies using the same database.[30,31]

Similarly, we are unable to accurately determine dementia severity or duration from onset because of the insidious onset and substantial variation in clinical presentation.

A combination of less rigourous management regimes, but greater intensity of monitoring should be considered to reduce hypoglycaemia in this vulnerable population. Simply changing or relaxing HbA1c targets for the older frail population may not be sufficient in reducing hypoglycaemic events. The risk of hypoglycaemia may also have some relationship with 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 for hypoglycaemia.[30]

Future research should focus on a randomized controlled trial in older individuals with diabetes and dementia, in which the treatment strategy would be aimed at minimizing, or even eradicating, episodes of hypoglycaemia. An essential component of the trial would be the use of CGM, to capture episodes of hypoglycaemia that may otherwise go unrecorded and to guide the hypoglycaemia minimization strategy by analysing the ambulatory glucose profiles obtained with CGM. Additionally, CGM is a useful tool that supports caregivers in their day-to-day management of this vulnerable group of older individuals.

To sum up, hypoglycaemia is associated with greater risk of subsequent complications such as falls and fractures as well as greater risk of death in patients with dementia. Future work should focus on personalized management of diabetes and on monitoring strategies for patients with co-morbid dementia, aiming for an optimal treatment effect while minimizing the risk of hypoglycaemia.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

K. M. and Y. K. L. conceived of and developed the initial study. K. R. and G. S. contributed to the design of the study. K. M., Y. K. L. and K. R. developed the code lists. Y. K. L., K. M. and K. R. conducted the statistical analysis. All authors contributed to the study protocol development and revision, the interpretation of findings, and revision of the manuscript. Y. K. L. is the guarantor. The lead author (K. M.) 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.

Data from the Clinical Practice Research Datalink (CPRD) are available directly from CPRD. Full code lists are available from the corresponding author.

ORCID

Katharina Mattishent https://orcid.org/0000-0002-7577-0689
Yoon K. Loke https://orcid.org/0000-0001-9109-2307

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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