Bi-directional Interaction Between Hypoglycaemia And Cognitive Impairment In Elderly Patients Treated with Glucose Lowering Agents: Systematic Review and Meta-analysis

Running title: Hypoglycaemia and dementia in older patients

Katharina Mattishent MBBS, Yoon K Loke MD

Norwich Medical School, University of East Anglia, Norwich NR4 7TJ

Katharina Mattishent

Norwich Medical School

University of East Anglia

Norwich Research Park

Norwich

NR4 7TJ, UK

e-mail: k.mattishent@uea.ac.uk

Telephone number: 01603456161

Fax number: 01603593752

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Abstract

Aims: Recent research suggests the possibility of a bi-directional relationship whereby hypoglycaemia is a risk factor for dementia, and also where dementia increases risk of hypoglycaemia. We aimed to examine this relationship in older patients with diabetes mellitus treated with glucose lowering agents.

Materials and Methods: We searched MEDLINE and EMBASE over a ten year span 2005 to 2015 (with automated PubMed updates to August 2015) for observational studies of the association between hypoglycaemia and cognitive impairment or dementia in participants aged >55 years. Assessment of study validity was based on ascertainment of hypoglycaemia, dementia and risk of confounding. We conducted random effects inverse variance meta-analyses, and assessed heterogeneity using the I^2 statistic.

Results: We screened 1177 citations, and selected twelve studies, with nine suitable for meta-analysis. There were a total of 1,439,818 participants, mean age 75 years. Meta-analysis of five studies demonstrated a significantly increased risk of dementia in patients who had hypoglycaemic episodes, pooled odds ratio of 1.68 (95% Confidence Interval 1.45, 1.95). We also found a significantly increased risk of hypoglycaemia in patients with dementia, pooled odds ratio from five studies 1.61 (95% Confidence Interval 1.25, 2.06). Limitations are heterogeneity in the meta-analysis, and uncertain ascertainment of dementia and hypoglycaemic outcomes and temporal relationships. Publication bias may favour reporting of more significant findings.

Conclusions*:* Our meta-analysis demonstrates a bi-directional relationship between cognitive impairment and hypoglycaemia in older patients. Glucose

lowering therapy should be carefully tailored and monitored in older patients

who are susceptible to cognitive decline.

Introduction

Diabetes and dementia are two major chronic diseases, affecting millions of people worldwide. In the UK, 5% of people aged over 80 with Type 2 diabetes mellitus also have co-existing cognitive impairment/dementia[1]. Managing this group of people can be challenging, as clinicians try to balance the need for good blood sugar control against the avoidance of side-effects of drug therapy, such as hypoglycaemia.[2, 3]

Previous research has indicated that patients with diabetes mellitus have an increased risk of cognitive decline over time[4]. Concerns have also recently been raised regarding the possibility of a bi-directional relationship between hypoglycaemia in older patients with Type 2 diabetes mellitus and cognitive impairment/dementia[5]. This bi-directional relationship potentially creates the possibility of a vicious circle whereby cognitive impairment occurs as a result of recurrent hypoglycaemic events, and the subsequent deterioration in cognitive function causes patients to be at even greater risk for further hypoglycaemia. Hence, strategies should be developed for the individualized management of patients with these co-morbid conditions, aimed at minimizing the risk and serious consequences of hypoglycaemia.

In a previous systematic review dating back to 2005, Cuikerman et al argued that there is little evidence to say that hypoglycaemia leads to chronic cognitive impairment. In contrast, a more recent review article by Bordier et al concludes, based on emergent new evidence, that hypoglycaemia can affect long-term cognitive function in older patients [4, 6]. Bordier et al. also point to the growing

accumulation of research evidence suggesting that patients with cognitive impairment are at increased risk of hypoglycaemia. Conversely, a systematic review by Bloomfield et al in 2012 reported that whilst severe hypoglycaemia might contribute to increased long-term mortality, lower quality of life and higher anxiety, there was no robust evidence to support the association between hypoglycaemia and other important adverse events in older people such as dementia, falls, and cardiovascular events.[7]

In light of the contrasting views, we aimed to systematically review and analyze the recent evidence on the relationship between hypoglycaemia and cognitive impairment/dementia in older patients treated with glucose lowering drugs.

Material and Methods

Data sources and searches

Full details of the search strings are listed in the Supplementary Appendix. We searched MEDLINE and EMBASE for the last 10 years up to March 2015 with English language restriction, and we also checked the bibliographies of included studies for any potentially suitable studies. In addition, we signed up for the PubMed automated update email notifications of any newly published articles on hypoglycaemia in older patients (most recent update August 2015). We chose only the last 10 years, as we wanted the most up to date studies based on contemporary practice and populations. Moreover, studies before 2005 have been reviewed in Cuikerman et al's systematic review.

Study selection

We selected prospective and retrospective cohort studies reporting on the association between hypoglycaemia and cognitive impairment or dementia in older participants aged >55 years who were treated with glucose lowering agents. We excluded studies that reported on the association between diabetes and cognitive decline, but which did not explicitly assess hypoglycaemic events. Reviews and abstracts were also excluded.

Data extraction and quality assessment

YKL and KM performed study screening and data extraction. Both independently scanned all titles and abstracts for potentially relevant articles, before proceeding to obtain full text versions for further checking. Any uncertainties and discrepancies were resolved through discussion. We used a standardized form for data collection, which included details of the study design, setting, date of the study, country of origin, selection criteria, participant characteristics and outcome measures. We extracted odds or hazard ratios as a measure of the association between hypoglycaemia and dementia (and vice versa).

For the assessment of study validity, both reviewers independently checked the methods used for recording hypoglycaemic episodes and determining cognitive decline, as well as adjustment for confounding factors.

Data synthesis and analysis

We conducted a random effects meta-analysis of odds ratios using inverse variance method (Revman 5.3, Nordic Cochrane Centre, Kobenhavn). We assessed heterogeneity using the I^2 statistic and visual inspection of the forest

plots. As both dementia and hypoglycaemic episodes are uncommon events, we considered odds ratios and hazard ratios suitable for pooling together in the meta-analysis.

We aimed to construct a Funnel plot if we had more than 10 studies in the meta-analysis, with no evidence of statistical heterogeneity.

We did not submit a protocol to a registry of systematic reviews.

Results

After screening 1177 citations, we included 12 studies.   The flow chart of the study selection is also shown in Supplementary Appendix Figure). Characteristics and results of the included studies are shown in Supplementary Appendix Table, while assessment of study validity is reported in Table 1.

The included studies had a total of 1,439,818 participants (sample size from 60 to 893,115) with mean age 75. 53% of the participants were male (from the studies that reported gender distribution). Geographical locations were diverse and included North America, Canada, Europe and Asia. All the studies evaluated patients with Type 2 Diabetes Mellitus, who were receiving insulin and/or oral agents.

Measurement of hypoglycaemic events

Five studies used hospital records[8-12], four studies relied on self-reported hypoglycaemic episodes [13-16], one relied on symptoms without apparent cause or blood glucose levels <2.8mmol/L (collected as part of adverse events

reports in a trial)[17] , one relied on insurance database records[18], and one did not state the method of ascertaining hypoglycaemic events[18, 19].

We considered self-reporting to be potentially unreliable, because a patient may experience non-specific symptoms suggestive of hypoglycaemia, without the blood sugars being documented at a level when treatment is necessary (<4mmol/L).

Measurement of cognitive impairment

We found that a diverse variety of tests were used for ascertaining cognitive impairment, which reflects the reality of there not being one single 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.

Confounding factors

All studies used multivariable regression models to adjust for confounding.

Five studies excluded patients with either established dementia or cognitive impairment [11, 12, 14, 16, 20].

Meta-analysis

Nine studies were included in meta-analysis. One study had data for both hypoglycaemia being a predictor for dementia and vice versa (dementia being a predictor for hypoglycaemia)[11].

Hypoglycaemia as a predictor for dementia

We identified five relevant studies that evaluated the relationship of hypoglycaemia as a predictor of dementia [11, 12, 18-20]. *(Figure 1a)* The meta-analysis shows an increased risk of dementia in patients known to suffer from hypoglycaemic episodes, with a pooled odds ratio of 1.68 (95% Confidence Interval 1.45, 1.95). We detected some degree of heterogeneity with $I^2 = 64\%$.

Dementia as a predictor for hypoglycaemia

We identified five relevant studies that evaluated the relationship of dementia as a predictor of increased risk of hypoglycaemia[14] [8, 11, 17, 21]. *(Figure 1b)* The meta-analysis shows an increased risk of hypoglycaemia in patients known to have dementia, with a pooled odds ratio of 1.61 (95% Confidence Interval 1.25, 2.06). We identified substantial heterogeneity in this meta-analysis ($I^2=84\%$).

Sensitivity analysis focused on results of studies at lower risk of bias is reported in Supplementary Results.

Narrative synthesis of studies not included in meta-analysis

There were three studies that did not provide odds ratios for the relationship between diabetes and dementia. [13, 15, 16] The three studies were methodologically similar in that they carried out a diverse battery of cognitive tests in patients who had self-reported hypoglycaemia.

Aung et al. conducted cognitive testing in 1066 participants in the Edinburgh Type 2 Diabetes Study, and found that self-reported history of severe hypoglycaemia was associated with reduced late-life general cognitive ability.[13] Feinkohl et al subsequently reported on a subset of participants (n=831) from Aung's study who had four years follow-up with repeat cognitive testing. [22] Only four participants were classified as having dementia after four years, thus making it impossible to evaluate the association between dementia and incident hypoglycaemia. Nevertheless, poorer cognitive function at baseline was noted in those who developed incident hypoglycaemia. Incident hypoglycaemia was also associated with subsequently greater decline in global cognitive ability measured at the four year follow-up.

Gao et al. demonstrated in a Chinese study that self-reported history of hypoglycaemic events was associated with mild cognitive impairment.[15] In contrast, Munshi reported that patients who were found to have cognitive impairment reported a higher (not statistically significant) incidence of hypoglycaemic events.[16] Although Gao and Munshi both took steps to exclude patients with known dementia, the major limitation is the uncertain temporal relationship, where it is unclear if the cognitive impairment or the hypoglycaemia events came first.

Publication bias and selective outcome reporting

Although we did not construct a funnel plot because we did not have more than ten studies in the meta-analyses, we were able to identify the possibility of reporting bias. For instance, Bruce et al. stated in their study that hypoglycaemia did not increase the likelihood of cognitive impairment[14].

However, these data were not available for our meta-analysis (odds ratios were not given) because the authors selective chose to omit non-statistically significant findings whilst reporting significant ones. Similarly, Munshi et al. did not report the non-statistically significant adjusted odds ratio for the risk of hypoglycaemia in those with cognitive impairment[16]. The incomplete reporting of null results means that our meta-analyses may potentially over-estimate the strength of the association between hypoglycaemia and cognitive impairment.

Discussion

Our meta-analyses present quantitative evidence of a bi-directional relationship between cognitive impairment and hypoglycaemia in older patients. There is reasonable data from five studies identifying the increased likelihood of cognitive decline or dementia in those with a history of hypoglycaemic events. Similarly, evidence from the meta-analysis of five studies also reveals an identifiable relationship the other way around, where patients with cognitive impairment have greater risk of developing hypoglycaemic events. These findings remained apparent even in a sensitivity analysis focused on three studies of higher quality.

Our meta-analysis is clinically important because patients with co-morbid diabetes and cognitive impairment may find themselves in an awkward spiral descent resulting in ever-worsening cognitive decline and more frequent hypoglycaemic episodes at the same time. In such patients, there is an argument that the possibility of a vicious circle could be broken by abandoning

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the almost relentless pursuit of normoglycaemia, and instead focusing on a more balanced strategy towards reducing the risk of hypoglycaemic events.

Hypoglycaemic adverse events are a particular problem in older patients because of impaired hypoglycaemia awareness. This was highlighted by Bremer et al, who found an age-related (over 65) impairment of hypoglycaemia that did not depend on altered neuroendocrine counter-regulation[23]. 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[24]. Recent evidence from Taiwan and Korea shows a worrying sharp rise in emergency admissions for hypoglycaemia in older patients, which lends further weight to the importance of our meta-analysis.[25, 26] In addition, studies that used rigorous methods for ascertaining hypoglycaemia have found that the burden of hypoglycaemic events may be higher than envisaged [27] [28]

A number of mechanistic reasons have been identified to explain why hypoglycaemic events can lead to cognitive impairment (e.g. neuroglycopaenia). Bordier et al report that in animal models acute hypoglycaemia exacerbates neuronal damage, however, the impact of repeated hypoglycaemic episodes was less clear.[6] Experimental studies in rats found that severe hypoglycaemia caused damage to neurons in the cortex and hippocampal regions, and that diabetes was associated with greater susceptibility to such damage. [29]

Adults with diabetes have been found to have structural changes to their brain, including atrophy and leukariosis, but it is not clear what the relative impact of hypo/hyperglycaemia is on these changes[30]. Imaging and spectroscopy studies in diabetes have demonstrated significant reductions in the gray matter content of N-acetylaspartate and glutamate, which is associated with neuronal loss or dysfunction [30]. Magnetic resonance imagining in patients with Type 1 diabetes with hypoglycaemia unawareness showed a significantly reduced thalamic response during a hypoglycaemic episode compared to control participants. It remains unclear though how recurrent hypoglycaemia might alter thalamic response.

A recent paper suggests that Type 2 diabetes appears to also be associated with tau-phosphorylation leading to neurodegeneration, but the mechanism is unclear. Other research suggests that reduced glucose uptake into the brain worsens neurodegenerative process associated with Alzheimer's disease [31, 32]. However, on the other hand, Mayeda et al highlighted that the individual complex disease processes of Type 2 diabetes and the development of dementia make it difficult to identify the mechanism linking the two[33].

We recognize important limitations in our meta-analyses, principally stemming from observational datasets that reveal associations but cannot prove causality. Moreover, there is some heterogeneity, the temporal relationships are not always clear and our 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. Conversely, patients with dementia may have been more closely monitored with frequent healthcare visits, thus resulting in bias towards detecting higher frequency of hypoglycaemic events as compared to those without dementia. Finally, we are conscious of 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.

Nevertheless, we believe that our results have important implications, particularly in light of the substantial proportion of patients at risk of hypoglycaemia[34]. Clinicians should look at the whole patient and their associated comorbidities rather than over-emphasize a single target (for which there is little robust evidence of benefit in the elderly). Equally, variability in blood glucose (swings of too high and too low) have not been explored in this group, and further research using continuous glucose monitoring would be valuable in determining the true pattern over periods of weeks.

Clinicians are faced with the challenge of trying to balance the need for tight blood sugar control in accordance with national targets, against pragmatism and the avoidance of adverse drug reactions, in particular hypoglycaemia. There is an urgent need to further evaluate the burden of hypoglycaemia and to optimize the benefit: harm profile of glucose-lowering drugs in older people with co-morbid diabetes and dementia. Further mechanistic research is also needed to better understand how diabetes interacts with the ageing process[30] particularly with regards to recurrent hypoglycaemia and long-term cognitive decline.

Supplementary Figure. PRISMA flow diagram (see Supplementary Appendix)

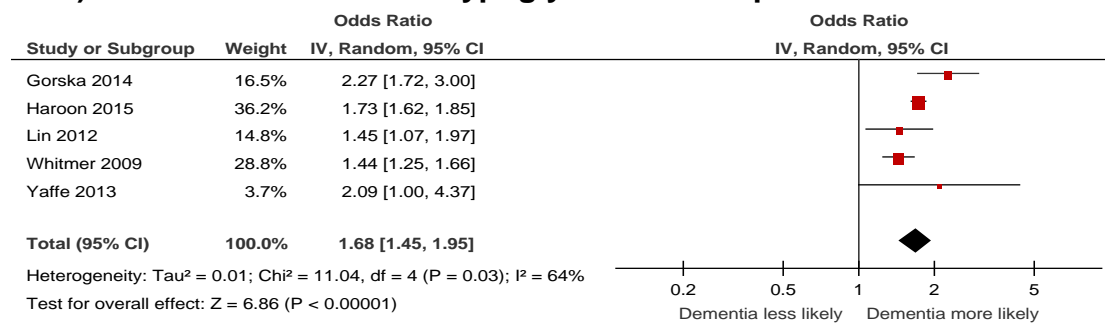**Figure 1 Meta-Analysis of Relationship between hypoglycaemia and dementia**

    a) **Pooled Odds Ratio of hypoglycaemia as a predictor for dementia**

    b) **Pooled Odds Ratio for Dementia as predictor for hypoglycaemia**

Figure 2

Meta-Analysis of Relationship between hypoglycaemia and dementia

c) Pooled Odds Ratio of hypoglycaemia as a predictor for dementia

Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
Gorska 2014	16.5%	2.27 [1.72, 3.00]
Haroon 2015	36.2%	1.73 [1.62, 1.85]
Lin 2012	14.8%	1.45 [1.07, 1.97]
Whitmer 2009	28.8%	1.44 [1.25, 1.66]
Yaffe 2013	3.7%	2.09 [1.00, 4.37]
Total (95% CI)	100.0%	1.68 [1.45, 1.95]

Heterogeneity: Tau² = 0.01; Chi² = 11.04, df = 4 (P = 0.03); I² = 64%

Test for overall effect: Z = 6.86 (P < 0.00001)

Odds Ratio IV, Random, 95% CI

0.2 0.5 1 2 5

Dementia less likely   Dementia more likely

d) Pooled Odds Ratio for dementia as predictor for hypoglycaemia

Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
Bruce 2009	5.0%	3.02 [1.07, 8.52]
de Galan 2009	11.7%	2.10 [1.14, 3.87]
Feil 2011	39.1%	1.57 [1.53, 1.61]
Punthakee 2012	35.7%	1.18 [1.04, 1.34]
Yaffe 2013	8.5%	3.10 [1.46, 6.58]
Total (95% CI)	100.0%	1.61 [1.25, 2.06]

Heterogeneity: Tau² = 0.04; Chi² = 24.62, df = 4 (P < 0.0001); I² = 84%

Test for overall effect: Z = 3.73 (P = 0.0002)

Odds Ratio IV, Random, 95% CI

0.5 0.7 1 1.5 2
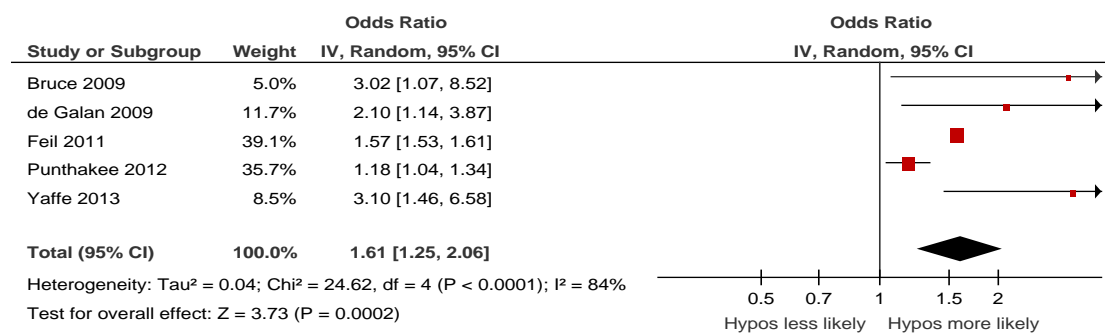
Hypos less likely   Hypos more likely

Table 1: Study outcomes, results and risk of bias

Study ID	Method of diagnosing cognitive impairment	Method of diagnosing or determining that patients had hypoglycaemia	Statistical adjustments for confounding factors	Results (relationship between hypoglycaemia and cognitive impairment and vice versa)
Aung 2011 [13] [22]	Faces and Family Pictures subtest, Logical Memory from Wechsler Memory Scale III, Verbal Fluency test, Trail-Marking Test, Mill Hill Vocabulary Scale Score	Self-reported requiring extra help (severe hypo) – no verification by plasma glucose Reports of milder hypos not collected	Multivariable models adjusted for age/sex/estimated prior cognitive ability, anxiety, depression, duration of diabetes, insulin use, alcohol, vascular disease	Severe hypos associated with reduced general cognitive ability. For those with 4 year follow up, cognitive decline greater in incident hypoglycaemia group than those without hypos (p=0.03).
Bruce 2009 [14]	MMSE, IQCODE, question on subjective memory. If MMSE <28 or IQCODE >3.31, or subjective memory loss, detailed cognitive assessment and clinical review to diagnose dementia (DSM-IV)	Self-reporting, investigator-assessed based signs, symptoms and availability of glucose measures, health service use for hypoglycaemia.	Multiple logistic regression adjusted for: age, sex, education, CVD for cognitive impairment without dementia; PAD and duration of diabetes for dementia; CVD, PAD and duration of diabetes for all cognitive impairment.	Dementia increases hypos: HR 3.02 (1.07, 8.52), but hypoglycaemia does not cause cognitive impairment (authors state no significant difference, but figures not given)
De Galan 2009 [17]	MMSE at baseline entry to trial	Symptoms without apparent cause or blood glucose <2.8mmol/L, adverse events reports in a trial.	Cox models	Severe cognitive dysfunction increased risk of severe hypos: HR 2.10 (1.14, 3.87)

Feil 2011 [9]	ICD9-CM, NCQA dementia code schema	ICD9-CM codes combined from OP visits, emergency department, and inpatient encounters with an admission diagnosis of hypoglycaemia	Multiple regression analysis in total sample, stratified analysis in subsamples. Adjustments for diabetes drugs and disease burden, demographics, nursing home stay	Dementia and cognitive impairment independently associated with greater risk of hypos: OR 1.57 (1.53, 3.87) based on fully adjusted Model 3
Gao 2015 [15]	Peterson's diagnostic standard on MCI MMSE, Wechsler Adult Intelligence Scale (WAIS)-III Block Design, WAIS III Digit Span, Trail Making Test A & B, Weschler Memory Scale (WMS)-III Word List Learning, WMS-III Logical Memory, Verbal Fluency	Self-reported	Multiple logistic regression analysis used to examine association between diabetic factors and MMSE, Trails B, digit span, and block design	Impaired performance in T2DM-MCI in MMSE, Trails B, digit span, and block design tests Self-reported history of severe hypoglycaemia was associated with T2DM-MCI independent of diabetes duration and vascular disease. OR not estimable
Gorska 2014 [19]	MoCA, GDS-30, BADL, IADL	Not stated – appears to rely on 'history of hypoglycaemia'	Stepwise multivariable logistic regression including gender, age, education, marital status, smoking, physical activity, diabetes duration, body mass index, HbA1c, lipids, treatment of T2DM, vascular complications, hypertension history and drugs, co-morbidities	Hypoglycaemia is a predictor for depressive symptoms/mild cognitive impairment: OR 2.27 (1.72, 2.98)

Haroon 2015 [12]	New cases of dementia defined based on ≥1 hospitalisation record or two outpatient billing claims (within six months) ICD-9 code. Algorithm validated against cognitive testing, with 73 and 94% positive and negative predictive values respectively.	Healthcare administrative database records of hospitalisation or emergency department visits for hypoglycaemia	Cox proportional hazard modelling with sensitivity analyses examining whether detection bias could explain elevated risk of dementia Adjusted for baseline income and co-morbidities, including hypertension, chronic kidney disease and vascular diseases of varying aetiologies.	Hospitalisation and emergency department visits for hypoglycaemia were significant predictors of dementia aHR 1.73 (1.62, 1.84) based on comparison of one or more episodes versus none.
Lin 2012 [18]	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: HR 1.45 (1.07, 1.97). Hypoglycaemia, age, female gender and insulin use independently predicted dementia
Munshi 2006 [16]	MMSE, clock drawing test, Clock-in-a box test, GDS, questionnaires (ADLs, IADLs)	Self-reporting	Linear regression Multivariable analyses, controlling for age, sex, living status, BMI, duration of diabetes, depression, MMSE, education, co-morbidities	Higher incidence of hypos in patients with cognitive dysfunction – but not statistically significant OR not estimable
Punthakee 2012 [8]	Digit Symbol Substitution Test (subset of Wechsler Adult Intelligence Scale)	Hypoglycaemia requiring medical assistance. Severe hypoglycaemia documented with plasma	Multivariable Cox models adjusted for age, education, language of test administration, depression	Five point decrease in DSST associated with increased hypoglycaemia requiring medical

	Rey Auditory Verbal Learning Test, Stroop Test, MMSE	glucose <2.8 or symptoms that promptly resolved with therapy		assistance: OR 1.18 (1.04, 1.33)
Whitmer 2009 [20]	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, mean HbA1c, diabetes duration and treatment,	History of severe hypoglycaemic episodes was associated with a greater risk of dementia: HR 1.44 (1.25, 1.66)
Yaffe 2013 [11]	Hospital records of admission associated with dementia or 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	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: HR 2.09 (1.00, 4.35) Subsequent Dementia is associated with hypoglycaemia events: HR 3.10 (1.46, 6.58)

OR= Odds ratio, HR=Hazard ratio, 95% CI= 95% Confidence Interval, T2DM=Type 2 diabetes mellitus, MMSE=mini mental state examination, ICD9-CM= International classification of diseases 9th revision clinical modification, GDS= Geriatric Depression Scale, ADL=Activities of daily living, IADL= Instrumental activities of daily living, BADL= Basic Activities of daily living, NCQA=National Committee for Quality Assurance, MoCA=Montreal Cognitive Assessment, MCI=mild cognitive impairment, DSM=Diagnostic and statistical manual of mental disorders

References

[1]   Hamada S, Gulliford MC. Antidiabetic and cardiovascular drug utilisation in patients diagnosed with type 2 diabetes mellitus over the age of 80 years: a population-based cohort study. Age Ageing. 2015; **44**: 566-573

[2]   Sleath JD. In pursuit of normoglycaemia: the overtreatment of type 2 diabetes in general practice. Br J Gen Pract. 2015; **65**: 334-335

[3]   Dhatariya K. Pharmacotherapy for type 2 diabetes in very elderly patients: practicing nihilism or pragmatism? Age Ageing. 2015; **44**: 540-542

[4]   Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. Diabetologia. 2005; **48**: 2460-2469

[5]   Biessels GJ. Hypoglycemia and cognitive decline in older people with type 2 diabetes: A bidirectional relationship. Diabetic Hypoglycemia. 2014; **6**: 11-14

[6]   Bordier L, Doucet J, Boudet J, Bauduceau B. Update on cognitive decline and dementia in elderly patients with diabetes. Diabetes Metab. 2014; **40**: 331-337

[7]   Bloomfield HE, Greer N, Newman D*, et al.* Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes - A Systematic Review of the Evidence. Washington DC, 2012.

[8]   Punthakee Z, Miller ME, Launer LJ*, et al.* Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care. 2012; **35**: 787-793

[9]   Feil DG, Rajan M, Soroka O, Tseng CL, Miller DR, Pogach LM. Risk of hypoglycemia in older veterans with dementia and cognitive impairment: implications for practice and policy. J Am Geriatr Soc. 2011; **59**: 2263-2272

[10]   Whitmer RA, Karter AJ, Yaffe K, Quesenberry Jr CP, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA - Journal of the American Medical Association. 2009; **301**: 1565-1572

[11]   Yaffe K, Falvey CM, Hamilton N*, et al.* Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Intern Med. 2013; **173**: 1300-1306

[12]   Haroon NN, Austin PC, Shah BR, Wu J, Gill SS, Booth GL. Risk of Dementia in Seniors With Newly Diagnosed Diabetes: A Population-Based Study. Diabetes Care. 2015:

[13]   Aung PP, Strachan MW, Frier BM*, et al.* Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabet Med. 2012; **29**: 328-336

[14]   Bruce DG, Davis WA, Casey GP*, et al.* Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. Diabetologia. 2009; **52**: 1808-1815

[15]   Gao Y, Xiao Y, Miao R*, et al.* The characteristic of cognitive function in Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2015:

[16]   Munshi M, Grande L, Hayes M*, et al.* Cognitive dysfunction is associated with poor diabetes control in older adults. Diabetes Care. 2006; **29**: 1794-1799

[17]   de Galan BE, Zoungas S, Chalmers J*, et al.* Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia. 2009; **52**: 2328-2336

[18]   Lin CH, Sheu WH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. J Intern Med. 2013; **273**: 102-110

[19]   Gorska-Ciebiada M, Saryusz-Wolska M, Ciebiada M, Loba J. Mild cognitive impairment and depressive symptoms in elderly patients with diabetes: Prevalence, risk factors, and comorbidity. Journal of Diabetes Research. 2014; **2014**:

[20]   Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr., Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009; **301**: 1565-1572

[21]   Feil D, Rajan M, Soroka O, Miller DR, Pogach L. Increased risk of hypoglycemia in older patients with dementia and cognitive impairment: Is more intensive glycemic control at the expense of safety? American Journal of Geriatric Psychiatry. 2011; **1**): S114

[22]   Feinkohl I, Aung PP, Keller M*, et al.* Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. Diabetes Care. 2014; **37**: 507-515

[23]   Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. Diabetes Care. 2009; **32**: 1513-1517

[24]   Bunn F, Reece Jones R, Goodman C*, et al.* Managing diabetes in people with demenita (DIaMonD): a realist review 2015 [17 July 2015]. Available from: http://www.nets.nihr.ac.uk/projects/hta/1313803.

[25]   Kim JT, Oh TJ, Lee YA*, et al.* Increasing trend in the number of severe hypoglycemia patients in Korea. Diabetes Metab J. 2011; **35**: 166-172

[26]   Chen YJ, Yang CC, Huang LC, Chen L, Hwu CM. Increasing trend in emergency department visits for hypoglycemia from patients with type 2 diabetes mellitus in Taiwan. Prim Care Diabetes. 2015:

[27]   Peene B, D'Hooge D, Vandebrouck T, Mathieu C. Patient-reported frequency, awareness and patient-physician communication of hypoglycaemia in Belgium. Acta Clin Belg. 2014; **69**: 439-445

[28]   Cariou B, Fontaine P, Eschwege E*, et al.* Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: results from the DIALOG study. Diabetes Metab. 2015; **41**: 116-125

[29]   Bree AJ, Puente EC, Daphna-Iken D, Fisher SJ. Diabetes increases brain damage caused by severe hypoglycemia. Am J Physiol Endocrinol Metab. 2009; **297**: E194-201

[30]   Seaquist ER. The Impact of Diabetes on Cerebral Structure and Function. Psychosom Med. 2015; **77**: 616-621

[31]   Winkler EA, Nishida Y, Sagare AP*, et al.* GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration. Nat Neurosci. 2015; **18**: 521-530

[32]   Moran C, Beare R, Phan TG*, et al.* Type 2 diabetes mellitus and biomarkers of neurodegeneration. Neurology. 2015:

[33]   Mayeda ER, Whitmer RA, Yaffe K. Diabetes and cognition. Clin Geriatr Med. 2015; **31**: 101-115, ix

[34]   Tseng CL, Soroka O, Maney M, Aron DC, Pogach LM. Assessing potential glycemic overtreatment in persons at hypoglycemic risk. JAMA Intern Med. 2014; **174**: 259-268