

# Impact of pharmacological treatment of diabetes mellitus on dementia risk: systematic review and meta-analysis

Jacqueline M McMillan,<sup>1,2</sup> Bria S Mele,<sup>2</sup> David B Hogan,<sup>1</sup> Alexander A Leung<sup>1,2</sup>

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<sup>1</sup>Department of Medicine, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada

<sup>2</sup>Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

**Correspondence to**  
Jacqueline M McMillan;  
mcmilljm@ucalgary.ca

## ABSTRACT

**Background** The association between diabetes mellitus (DM) treatment and dementia is not well understood.

**Objective** To investigate the association between treatment of diabetes, hypoglycemia, and dementia risk.

**Research design and methods** We performed a systematic review and meta-analysis of pharmacological treatment of diabetes and incident or progressive cognitive impairment. We searched Ovid MEDLINE, Embase, Cochrane Central Registry of Controlled Trials, and PsychINFO from inception to 18 October 2017. We included cross-sectional, case-control, cohort, and randomized controlled studies. The study was registered with PROSPERO (ID CRD42017077953).

**Results** We included 37 studies into our systematic review and 13 into our meta-analysis. Ten studies investigated any antidiabetic treatment compared with no treatment or as add-on therapy to prior care. Treatment with an antidiabetic agent, in general, was not associated with incident dementia (risk ratio (RR) 1.01; 95% CI 0.93 to 1.10). However, we found differential effects across drug classes, with a signal of harm associated with insulin therapy (RR 1.21; 95% CI 1.06 to 1.39), but potentially protective effects with thiazolidinedione exposure (RR 0.71; 95% CI 0.55 to 0.93). Severe hypoglycemic episodes were associated with a nearly twofold increased likelihood of incident dementia (RR 1.77; 95% CI 1.35 to 2.33). Most studies did not account for DM duration or severity.

**Conclusions and limitations** The association between treatment for diabetes and dementia is differential according to drug class, which is potentially mediated by hypoglycemic risk. Not accounting for DM duration and/or severity is a major limitation in the available evidence base.

## INTRODUCTION

Approximately 10% of people with dementia have diabetes mellitus (DM).<sup>1</sup> Diabetes is a risk factor for developing vascular dementia (VaD),<sup>2 3</sup> mixed dementia, Alzheimer's disease (AD), and mild cognitive impairment (MCI).<sup>4 5</sup> Dementia in patients with DM occurs at a younger age and is more frequently vascular in etiology compared with individuals without DM.<sup>6</sup>

Studies suggest that cognitive decline in older individuals with DM is associated with poor glycaemic control and more frequent

## Significance of this study

### What is already known about this subject?

- Diabetes is a risk factor for developing dementia, yet the impact of diabetes management on cognitive decline remains uncertain.

### What are the new findings?

- We found that antidiabetic treatment effects on cognitive outcomes may differ by drug class.
- We also found that severe hypoglycemia is associated with nearly a twofold increased risk of incident dementia.

### How might these results change the focus of research or clinical practice?

- Past studies have poorly accounted for duration and severity of diabetes, which introduces confounding in the association between specific antidiabetic treatments and incident cognitive impairment. This is an area that may be addressed by future studies.

episodes of severe hypoglycemia.<sup>7</sup> However, the impact of diabetes management on the rate of cognitive decline in individuals with established cognitive deficits including dementia remains uncertain.<sup>7</sup> The association between treatment of DM and cognitive outcomes has been variably reported across studies with significant differences in the type of diabetic treatment and its intensity, size of the studies, follow-up duration, and handling of potential confounding. Addressing this, we conducted a systematic review and meta-analysis to investigate the association between pharmacological treatment of DM and cognitive outcomes in adults.

## METHODS

Our primary objective was to determine whether specific pharmacological treatments for DM (compared with placebo or an alternative agent) were associated with cognitive outcomes in adults (≥18 years of age) with diabetes. As a secondary objective, we examined the association between the frequency

of severe hypoglycemia and adverse cognitive outcomes.<sup>7</sup> The study was registered with PROSPERO (ID number CRD42017077953) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>8</sup>

### Search strategy and literature sources

We performed literature searches of Ovid MEDLINE, Embase, Cochrane Central Registry of Controlled Trials, and PsychINFO electronic databases from inception to 18 October 2017. Two authors (JMM and BSM) reviewed reference lists of included articles for additional relevant studies and contacted study authors of included studies if further information was required.

The main search concepts were type 2 DM, dementia or mild cognitive impairment, and pharmacological agents used to treat DM (online supplementary appendix). We developed a comprehensive list of pharmacological agents in use for the treatment of DM based on numerous international clinical practice guidelines including the Canadian Diabetes Association, the American Diabetes Association, Diabetes Australia, and the National Institute for Health and Care Excellence. We sought the expertise of a content expert in the management of DM to assist in creating the list of pharmacological treatments. The search strategy was developed in consultation with two medical librarians at the University of Calgary. Within each search cluster, the keywords Medical Subject Headings, Emtree, PsychINFO, and Cochrane terms were combined using “or”. Each cluster was then combined using “and” (online supplementary appendix).

### Study screening and selection

Two independent reviewers (BSM and JMM) screened titles and abstracts in duplicate. The primary inclusion criterion was pharmacological treatment of DM in adults. In the initial screening phase, titles and abstracts were included if the study enrolled participants with DM and any form of cognitive outcome. In the full-text screening phase, articles were reviewed in duplicate (BSM and JMM) and included if the study investigated the pharmacological treatment of DM in adults with both DM and cognitive outcome measures. Studies were excluded if they did not enroll patients with both DM and dementia, investigate one or more pharmacological treatments for DM, report cognitive outcomes, present primary data, or if they were duplicate reports or reported findings of another study. Discrepancies were resolved by consensus.

### Data extraction, synthesis, and analysis

A kappa statistic was calculated to quantify agreement on the selection of papers for full-text review. This was done using inter-rater agreement and possibility of agreement due to chance, calculated in Stata V.14.2.426. Data from studies selected for full-text review were extracted in duplicate for quality assessment and analysis. Data collection included (if available) author; year of publication; country of origin; study design; population demographics

(mean or median age, percentage female); method of diagnosis for DM, dementia, and/or MCI; intervention/exposure and control group; study duration; number of participants enrolled in study; number of participants completing study; duration of DM; glycated hemoglobin A1c (A1c) values; hypoglycemic episodes; and cognitive outcomes. Only studies using validated instruments to assess cognition (eg, Mini-Mental State Examination (MMSE), Alzheimer’s Disease Assessment Scale–Cognitive Subscale) were eligible for inclusion.

The primary composite outcome of interest was the risk of incident dementia or progression of cognitive impairment associated with pharmacological treatment of DM. We additionally examined cognitive outcomes (either incident dementia, or progression of dementia or MCI) associated with the frequency of severe hypoglycemic episodes.

### Quality and risk of bias assessment

Quality and risk of bias assessments were performed in duplicate. We used the Newcastle Ottawa Quality Assessment Scale for non-randomized studies (cohort, cross-sectional, and case–control studies).<sup>9</sup> For randomized controlled trials, the Cochrane Collaboration’s tool for assessing risk of bias in randomized studies was used.<sup>10</sup>

### Meta-analysis of relative risk

We used risk ratios (RRs) as the common measure of association across studies. HRs were considered to be interchangeable with RRs as per methods described in previous meta-analysis by Chen *et al.*<sup>11</sup> ORs were converted to RRs using the formula:  $RR = OR / [(1 - P_0) + (P_0 \times OR)]$ , where  $P_0$  is the incidence of the outcome of interest in the non-exposed (control) group. When there were insufficient data, study authors were contacted to request additional information if possible. A random-effects model was used to pool estimates across studies to account for both between-study and within-study variance. This was based on our assumption that there would be no one true estimate, but rather a distribution of estimates that would vary across studies. Where adequate data were available, we performed stratified analysis by mean age (<65 years vs  $\geq 65$  years), study size ( $\geq 10\,000$  participants versus <10 000), design (randomized controlled trials vs observational studies), study duration ( $\geq 3$  years vs <3 years), and class of pharmacological agent(s). We divided sample sizes into <10 000 versus  $\geq 10\,000$  individuals to ensure roughly equal numbers of studies were present in each stratified group. We categorized studies that investigated  $\geq 1$  antidiabetic medication compared with either no treatment or add-on to usual care as intensive treatment. We also evaluated the association between severe hypoglycemic episodes and the risk of adverse cognitive outcomes.

We assessed for between-study heterogeneity using the  $I^2$  test statistic. Low, moderate, and high heterogeneity were defined as <25%, 25%–50%, and >50%, respectively.<sup>12</sup> Stratified analyses were performed to explore for

potential sources of heterogeneity when present. We used STATA V.14.2 (College Station, Texas, USA) to perform statistical analysis.

### Assessment of publication bias

Conventional methods to assess for publication bias, such as funnel plots, are challenging to interpret for meta-analyses of observational studies where small study effects may be present. The presence of asymmetry may not necessarily represent publication bias, but rather clinical heterogeneity or bias inherent to the included studies (eg, residual confounding). As such, we did not assess for publication bias because the majority of included studies were observational in design.

## RESULTS

The electronic database search produced 5088 unique citations (online supplementary figure). After screening titles and abstracts, 370 articles were identified for full-text review. Of these, 37 studies were included in our systematic review and 13 of these were incorporated into our quantitative (meta) analysis. There was overall excellent agreement between the reviewers on articles selected for full-text review ( $\kappa=0.81$ ; 95% CI 0.71 to 0.91).

Of the 37 included studies, most were from Asia ( $n=14$ ), Europe ( $n=10$ ), and North America ( $n=10$ ) and published between 1996 and 2017 (75% were published within the last 5 years; table 1). Study size ranged from 634 to 145 928 participants (72% were >1000 participants). Nearly one-third (27%) of studies did not report mean or median participant ages. When provided, 70% of studies reported a mean age >65. Duration of follow-up was reported in 81% of studies. This ranged from 6 months to 14.7 years (77% >3 years). Metformin and insulin were the two most common interventions. For most studies, the comparator was either placebo or standard care. Duration of DM, its severity and level of control, and frequency and severity of hypoglycemia were not consistently reported. All studies commented on the presence of dementia, but only a quarter (24%) provided data on MCI or dementia subtype (such as AD and VaD).

### Quality assessment of included studies

Thirty-three studies were observational (ie, cohort, cross-section, case-control studies) and four were randomized controlled trials (RCTs) (online supplementary tables 1 and 2).

Most observational studies (82%) enrolled exposed cases who were truly or somewhat representative of the population of interest. Nearly all studies (97%) enrolled non-exposed controls drawn from the same population as cases. When reported, the majority of studies (85%) had follow-up of  $\geq 3$  years. However, many studies did not provide information on the completeness of follow-up (eg, loss to follow-up was not reported in 64% of studies), how cognitive outcomes were assessed (39%), or whether the outcome of interest (eg, dementia) was present at enrolment (27%).

The study quality of the four RCTs was generally weak. Two did not provide sufficient detail to determine random sequence generation, allocation concealment, blinding of participants/personnel, or blinding of outcome assessment. Two were at risk of selective or incomplete outcome reporting. Two of the studies were potentially subject to industry bias.

### Risk of incident dementia in DM

Thirteen studies were included in our meta-analysis. Ten investigated intensive therapy including any antidiabetic agent compared with no DM treatment, insulin added to prior therapy, metformin compared with no treatment, sulfonylurea compared with no treatment or as add-on therapy, and thiazolidinedione compared with no treatment or as add-on therapy. Intensive therapy (defined as add-on treatment) compared with prior care was not associated with incident dementia (RR 1.01; 95% CI 0.93 to 1.10). However, there was significant between-study heterogeneity ( $I^2$  92.4%,  $p=0.0001$ ) (figure 1).

Meta-regression was performed to explore heterogeneity, evaluating the effect of intervention type, age, sample size, proportion loss to follow-up, and duration of study on cognitive outcomes (online supplementary table 3). Only stratification by age (<65 and  $\geq 65$ ) had a notable effect on the RR estimates. Younger compared with older individuals were at greater risk for adverse cognitive outcomes during treatment (1.66, 95% CI 1.05 to 2.61 ( $n=2$ ) for <65; and 1.00, 95% CI 0.94 to 1.07 ( $n=7$ ) for  $\geq 65$ ;  $p=0.046$ ). The meta-regression analyses may have been underpowered to detect significant differences for the other variables assessed due to a limited number of studies within categories.

### Risk estimates of dementia and other adverse cognitive outcomes by pharmacological agent

#### Any oral antidiabetic agent

Heterogeneity remained high even after stratification by drug class (figure 2). Seven studies reported on the effect of any oral antidiabetic agent on cognitive outcomes.<sup>13–19</sup> In our pooled analysis of unadjusted relative risks, when compared with usual care the use of an oral antidiabetic agent was not associated with a statistically significant difference in dementia incidence (RR 0.95; 95% CI 0.88 to 1.03).<sup>13–15</sup>

Of the four studies not included in the meta-analysis, two reported ORs for incident dementia, but there were insufficient data to convert these into RRs.<sup>16 17</sup> One reported a 23% reduced odds of cognitive decline with oral antidiabetic agents compared with no treatment that was not statistically significant (95% CI 0.54 to 1.08).<sup>17</sup> The other reported no difference (OR 1.0; 95% CI 0.6 to 1.8).<sup>16</sup>

#### Insulin

Six studies were included in our meta-analysis.<sup>13–15 18 20 21</sup> Treatment with insulin was associated with a 21% increased risk of incident dementia

**Table 1\*** Characteristics of included studies

Author, year	Study design	Study duration	Number of participants enrolled	Mean age (years)	Cognitive outcome	Cognitive diagnosis	Diabetes diagnosis	Intervention group	Control group
Biemans <i>et al.</i> , <sup>27</sup> 2015	Cohort	NR	550	61.6	Alzheimer's disease (AD) and multi-infarct dementia	ICPC	ICPC	Metformin B <sub>12</sub> deficient	Metformin B <sub>12</sub> replete
Bruce <i>et al.</i> , <sup>23</sup> 2014	Cohort	14.7 years	335	57.5	Cognitive impairment (CI) and dementia	MMSE and CDR	Chart records	Insulin	NR
Cheng <i>et al.</i> , <sup>29*</sup> 2014	Cohort	3.1 years	5420	73.6	Dementia	ICD-9	ICD-9	Metformin, sulfonylurea, thiazolidinedione	NR
Chin <i>et al.</i> , <sup>41*</sup> 2016	Cohort	3.4 years	1957	67.5	Dementia	HIRAS claim database	HIRAS claim database	No hypoglycemic event, hypoglycemic event, two or more hypoglycemic events	NR
Chou <i>et al.</i> , <sup>36*</sup> 2017	Case-control	5 years	19 203	NR	Dementia	ICD-9	ICD-9	Pioglitazone (high cumulative dose, long-term use, high daily dose)	No pioglitazone
Cukierman <i>et al.</i> , 2014	RCT	6.2 years	11 685	63.4	CI	NR	NR	Insulin glargine targeting FBG <5.3	Standard care
Fei <i>et al.</i> , <sup>18*</sup> 2013	Cross-sectional	NR	1 109	NR	All-cause dementia, AD, vascular dementia (VaD)	DSM-IV	WHO and ADA	Insulin	NR
Feinkohl <i>et al.</i> , <sup>45</sup> 2014	Cohort	4 years	831	67.7	NR	MMSE	NR	Hypoglycemic event	No hypoglycemia
Ha <i>et al.</i> , 2017	Cohort	10.5 years	67 458	NR	NR	NR	NR	Hypoglycemic event	NR
Heneka <i>et al.</i> , <sup>20*</sup> 2015	Cohort	6 years	145 928	NR	NR	NR	NR	Pioglitazones (≥8 calendar quarters and <8 calendar quarters), rosiglitazone, metformin, insulin	No pioglitazone, no pioglitazone, no rosiglitazone, no metformin, no insulin

Continued

Table 1 Continued

Author, year	Study design	Study duration	Number of participants enrolled	Mean age (years)	Cognitive outcome	Cognitive diagnosis	Diabetes diagnosis	Intervention group	Control group
Hsiao <i>et al.</i> , <sup>33</sup> 2014	Cohort	NR	65 620	NR	NR	NR	NR	Any metformin use, past metformin use, recent metformin use, current metformin use, cumulative use less than 2 years, cumulative use greater than 4 years	NR
Hsu <i>et al.</i> , <sup>30*</sup> 2011	Cohort	7 years	25 393	NR	Dementia	ICD-9	NR	Sulfonylurea, metformin, sulfonylurea and metformin	NR
Huang <i>et al.</i> , <sup>24</sup> 2014	Cohort	10 years	71 433	58.7	AD	ICD-9	ICD-9	Metformin, sulfonylurea, thiazolidinedione, alpha glucosidase inhibitor, insulin	NR
Isik <i>et al.</i> , <sup>37</sup> 2016	Cohort	6 months	253	75.4	AD	NIINDs criteria	Serum glucose	Sitagliptin	No sitagliptin, regular DM meds
Kuan <i>et al.</i> , <sup>31*</sup> 2017	Cohort	12 years	9302	64.7	Dementia, AD, VaD	ICD-9	ICD-9	Metformin	No metformin
Kuo <i>et al.</i> , <sup>21*</sup> 2015	Cohort	11 years	33 709	62.3	Dementia	ICD-9	ICD-9	Insulin use	No insulin use
Launer <i>et al.</i> , 2011	RCT	3.33 years	2977	62.3	NR	NR	NR	Intensive diabetic control target A1c <6%, standard glycemic control A1c target 7% to 7.9%	NR
Logroscino <i>et al.</i> , <sup>17</sup> 2004	Cohort	2 years	1394	74.2	Cognitive decline	Non-specified cognitive tests	Self-report	Oral antidiabetic agents, insulin, no antidiabetic treatment	NR
Ma <i>et al.</i> ,* 2015	Cohort	4 years	8213	75.3	Mild cognitive impairment, dementia, VaD, other cause dementia	Petersen's classification, NINCDS-ADRDA, DSM-III	Self-report, physician diagnosis of diabetes complication, medical records	Insulin, oral antidiabetic agent	No treatment
Mehta <i>et al.</i> , <sup>43</sup> 2017	Cohort	3.8 years	53 055	75.5	NR	NR	NR	NR	NR
Moore <i>et al.</i> , <sup>28</sup> 2013	Cross-sectional	NR	104	73.8	NR	NR	NR	Metformin	No metformin
Murray <i>et al.</i> , 2017	Cohort	7 years	1328	62.1	NR	NR	NR	Intensive therapy (A1c<6%), standard therapy A1c 7-7.9%	NR

Continued

**Table 1** Continued

Author, year	Study design	Study duration	Number of participants enrolled	Mean age (years)	Cognitive outcome	Cognitive diagnosis	Diabetes diagnosis	Intervention group	Control group
Naharci <i>et al.</i> , <sup>34</sup> 2016	Cohort	NR	1221	75.6	Dementia	NR	NR	Metformin	No metformin
Ng <i>et al.</i> , <sup>35</sup> 2014	Cohort	4 years	365	67	NR	NR	NR	Metformin use <6 years, metformin use >6 years	NR
Orkaby <i>et al.</i> , <sup>32</sup> 2017	Cohort	5 years	42 651	73.5	Dementia, AD, VaD	ICD-9	NR	Metformin, metformin, and sulfonylurea	Sulfonylurea
Ott <i>et al.</i> , <sup>15*</sup> 1999	Cohort	2.1 years	6370	80.6	Dementia, VaD	DSM, NINCDS	NR	No drug, oral medication, insulin	NR
Ott <i>et al.</i> , <sup>16</sup> 1996	Cross-sectional	NR	6330	69.3	AD and VaD	DSM and ADNI criteria Screen with MMSE or Geriatric Mental State Schedule followed by physician interview and brain imaging	Use of antidiabetic medication or blood glucose >11	No drug, oral medication, insulin	NR
Parikh <i>et al.</i> , <sup>13*</sup> 2011	Cohort	2 years	377 838	75.5	Dementia	ICD-9-CM	ICD-9-CM	Insulin, oral antidiabetic agent	NR
Plastino <i>et al.</i> , <sup>22</sup> 2010	Cohort	1 year	104	76.2	AD	DSM-IV	Use of antidiabetic medication or blood glucose >11	Oral agents only, insulin plus oral agents	NR
Rhee <i>et al.</i> , 2014	Cohort	3.4 years	1957	NR	NR	NR	NR	Hypoglycemic event	NR
Sato <i>et al.</i> , 2011	RCT	6 months	42	77.4	NR	NINCDS, CDR score 0.5 or 1	DM drug Rx or elevated FBG	Pioglitazone in addition to use antidiabetic medications	No pioglitazone only regular antidiabetic medications
Trento <i>et al.</i> , 2015	Cohort	8 years	498	66.8	NR	NR	NR	Insulin	No insulin
Whitmer <i>et al.</i> , <sup>25</sup> 2013	Cohort	5 years	14 891	NR	NR	NR	NR	Metformin, sulfonylurea, thiazolidinedione, insulin	SU acted as reference

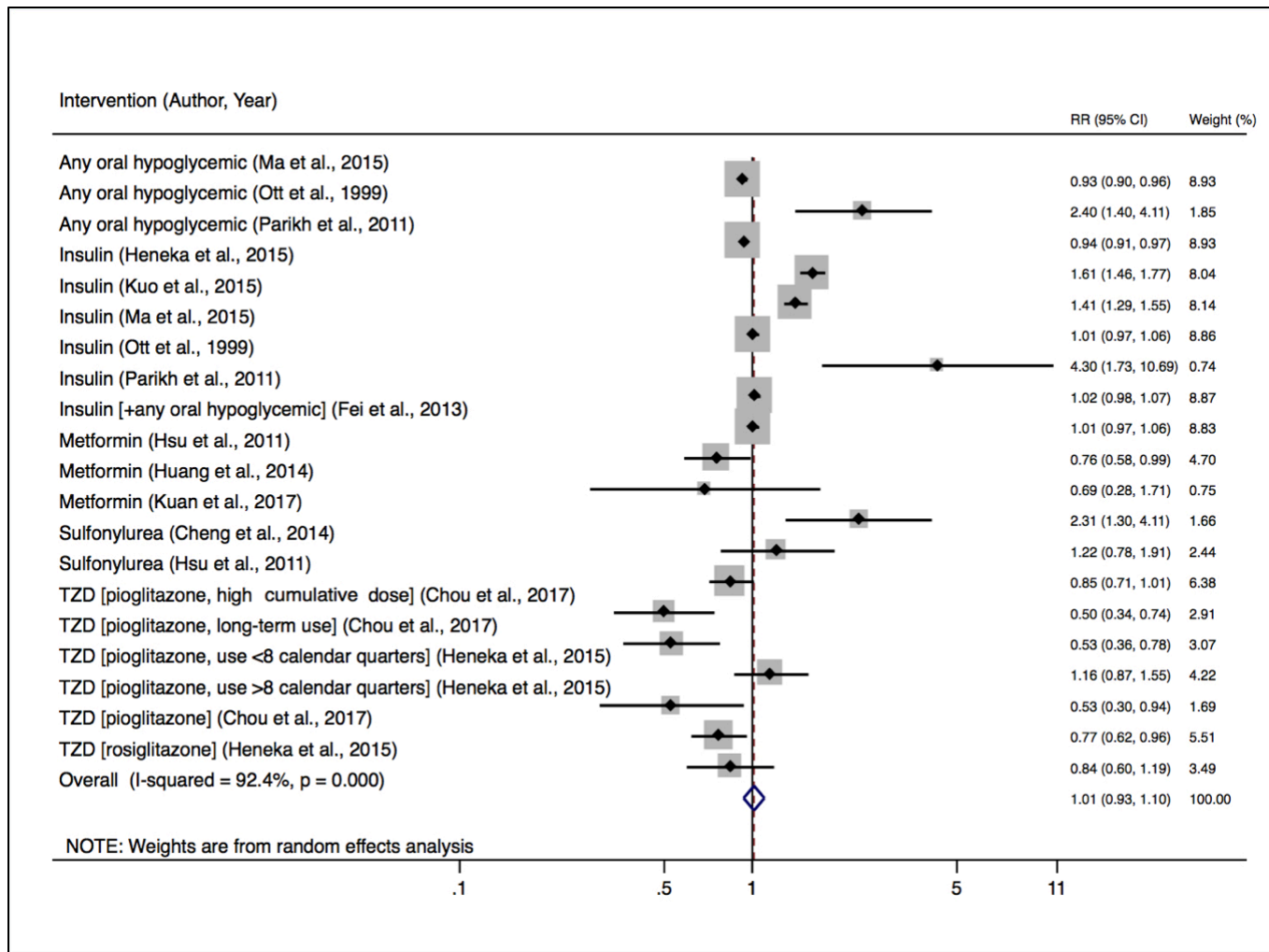
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**Table 1** Continued

Author, year	Study design	Study duration	Number of participants enrolled	Mean age (years)	Cognitive outcome	Cognitive diagnosis	Diabetes diagnosis	Intervention group	Control group
Whitmer <i>et al.</i> , <sup>40*</sup> 2009	Cohort	3.8 years	16 667	66.3	Dementia, AD, VaD	ICD-9	Medical records, pharmacy Rx	One, two, or three episodes of severe hypoglycemia requiring hospital	NR
Yaffee <i>et al.</i> , <sup>*</sup> 2013	Cohort	12 years	783	74.6	NR	ICD-9	Self-report, anti-diabetic medication, elevated FBG according to ADA criteria	Hypoglycemic event	No hypoglycemic event
Yuan <i>et al.</i> , 2015	Cohort	2 years	NR	NR	NR	Self-report, diagnosis codes in Medicare claims, dementia drug use	NR	Metformin, thiazolidinedione, insulin	NR
Zullo <i>et al.</i> , <sup>38</sup> 2017	Cohort	NR	2016	NR	NR	1-point increase in MDS Cognitive Performance Scale score	NR	DPP-4 inhibitor	SU

indicates the study was included within meta-analysis.

ADA, Alzheimer's Disease Association; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR, Clinical Dementia Rating; DPP-4, dipeptidyl peptidase-4; DSM, Diagnostic and Statistical Manual; FBG, fasting blood glucose; HIRAS, Health Insurance Review and Assessment Service; ICD, Internal Classification of Diseases; ICPC, International Classification of Primary Care; MDS, minimum data set; MMSE, Mini-Mental State Examination; NINCDS-ADRD, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINDS, National Institute of Neurological Disorders and Stroke; NR, not reported; RCT, randomized controlled trial; SU, sulfonylurea.



**Figure 1** Relative risk of developing dementia with intensive versus non-intensive antidiabetic treatment. RR, risk ratio; TZD, thiazolidinedione.

compared with other therapies or placebo (RR 1.21; 95% CI 1.06 to 1.39). In the eight studies that could not be included in our meta-analysis,<sup>16 17 19 22–26</sup> there was a general pattern of adverse cognitive outcomes associated with insulin therapy, but there were important differences between the studies in patient characteristics, study duration, and whether (and how) DM duration and/or severity were adjusted for.

### Metformin

Thirteen studies evaluated the association of metformin treatment on dementia in patients with DM<sup>20 24–35</sup> with three included in our meta-analysis.<sup>24 30 31</sup> A pooled estimate showed no significant difference in risk for developing dementia (RR 1.08; 95% CI 0.49 to 2.36). DM duration and severity could not be accounted for in the analysis.

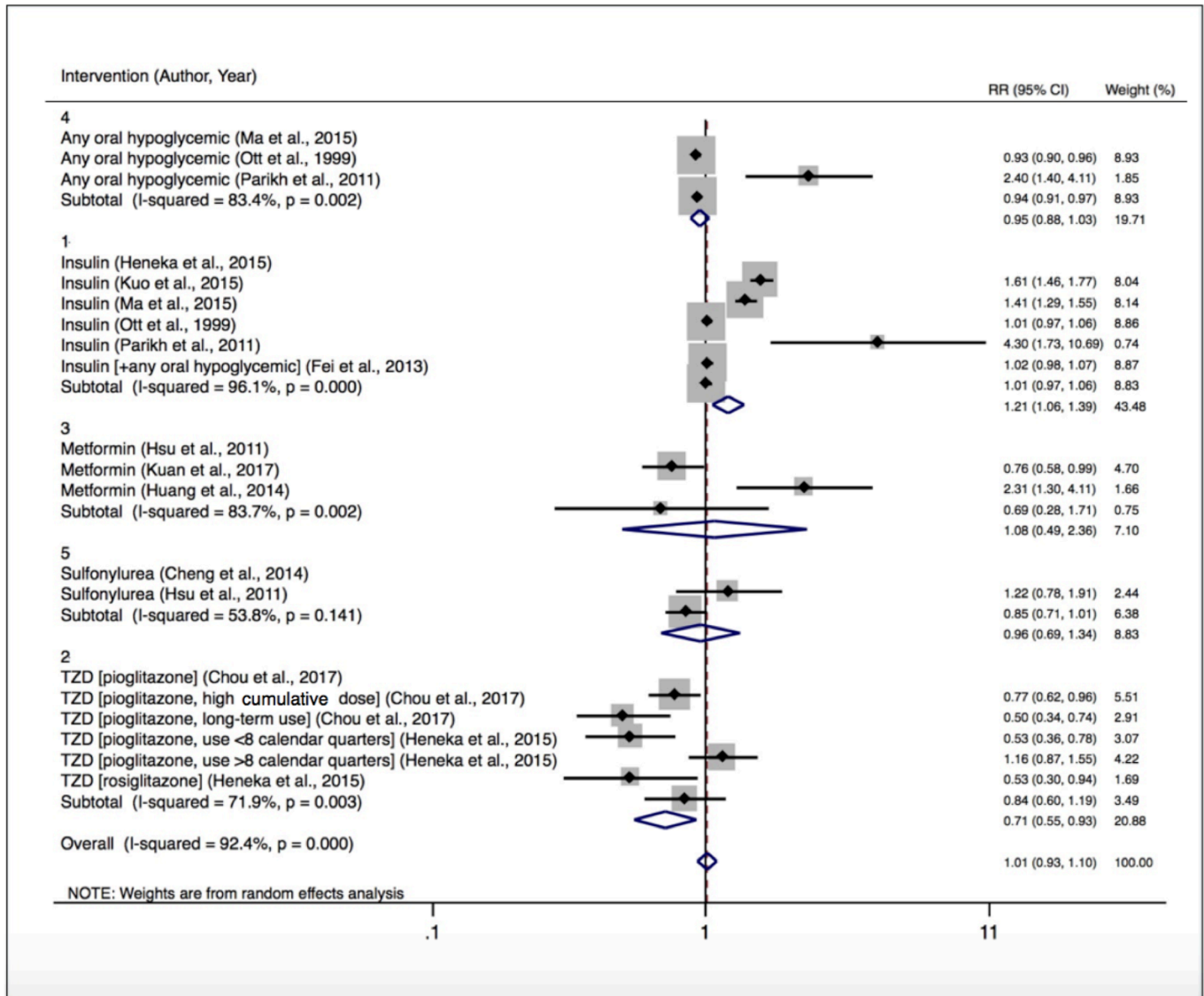
In the studies not included in the meta-analysis, the effect of metformin was inconclusive. In a study that adjusted for DM duration, the odds of cognitive impairment among metformin users was reduced compared with non-users (OR 0.49; 95% CI 0.25 to 0.95). Long-term use (>6 years) was associated with the greatest

cognitive benefit (OR 0.27; 95% CI 0.12 to 0.60).<sup>35</sup> The variable results between studies were potentially related to inconsistent adjustment for DM duration and severity. Two studies reported on the association of vitamin B<sub>12</sub> levels on cognitive outcomes for those treated with metformin.<sup>27 28</sup> In one, the apparent adverse cognitive performance associated with metformin use ceased to be statistically significant after adjustment for vitamin B<sub>12</sub> levels.<sup>28</sup> In the other, vitamin B<sub>12</sub> deficiency was independently associated with lower cognitive performance in metformin users.<sup>27</sup>

### Sulfonylureas

Four studies investigated the effects of sulfonylurea treatment with two included in the meta-analysis.<sup>29 30</sup> The pooled RR for incident dementia for patients treated with sulfonylurea was 0.96 (95% CI 0.69 to 1.34). Two studies could not be incorporated because the comparisons were not against placebo. In one, the use of a sulfonylurea was associated with increased risk of dementia compared with metformin (HR 1.24; 95% CI 1.10 to 1.40).<sup>25</sup> The other found a





**Figure 2** Relative risk of developing dementia by treatment type. RR, risk ratio; TZD, thiazolidinedione.

trend toward reduced risk of dementia with sulfonylurea use (HR 0.75; 95% CI 0.50 to 1.13).<sup>24</sup>

### Thiazolidinediones

Seven studies evaluated the use of thiazolidinediones (TZDs) with two included in the meta-analysis that allowed six comparisons based on differing dose and duration of use.<sup>20, 36</sup> Pooled results showed a 29% decreased risk of dementia with TZDs compared with placebo (RR 0.71; 95% CI 0.55 to 0.93). One study reported that, compared with non-exposed individuals, pioglitazone users had a 33% reduced risk of dementia (HR 0.77; 95% CI 0.62 to 0.96) with the greatest risk reduction at both the highest cumulative doses (HR 0.50; 95% CI 0.34 to 0.75) and longest durations of use (HR 0.53; 95% CI 0.36 to 0.77; for >536 days vs no use).<sup>36</sup>

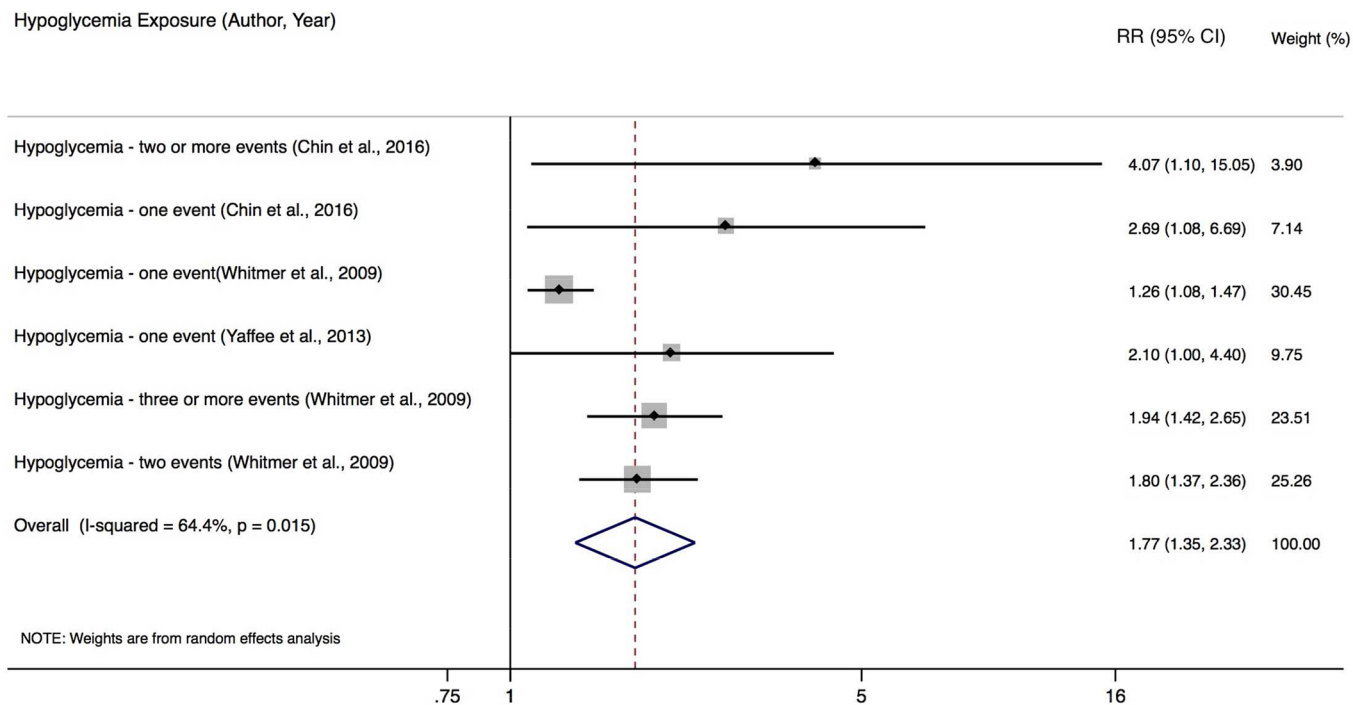
### Dipeptidyl peptidase-4 inhibitor

Two studies assessed the association of dipeptidyl peptidase-4 (DPP-4) inhibitors on cognitive function,<sup>37, 38</sup>

but neither could be included in our meta-analysis. In patients with DM, with and without dementia at baseline, MMSE scores improved with sitagliptin.<sup>37</sup> Among nursing home residents with DM, there were fewer hospitalizations for cognitive issues among residents prescribed DPP-4 inhibitors compared with sulfonylureas.<sup>38</sup>

### Hypoglycemia

Seven studies investigated the association between one or more hypoglycemic episodes and cognitive function. Three of these reported on severe hypoglycemia (ie, requiring immediate medical assistance) and were included in the meta-analysis.<sup>39–41</sup> The risk of developing dementia was nearly double with the occurrence of severe hypoglycemia (RR 1.77; 95% CI 1.35 to 2.33) (figure 3). There was an increased risk of harm seen across all studies. Four studies were not included in meta-analysis because RRs could not be calculated.<sup>42–45</sup> In general, hypoglycemia was associated with cognitive decline.



**Figure 3** Relative risk of developing dementia based on to the occurrence of one or more hypoglycemic events. RR, risk ratio.

## DISCUSSION

While the association between DM and dementia is well established, the potential impact of DM treatment on the risk of incident dementia or progression of pre-existing cognitive impairment is less clear. In our systematic review and meta-analysis, we found differential effects across drug classes with a signal of harm associated with insulin therapy, but a potential protective effect with TZD exposure. Potentially related, the occurrence of severe hypoglycemia (a risk of insulin and sulfonylurea therapy, but not metformin or TZDs) increased the likelihood of incident dementia nearly twofold. Online supplementary table 4<sup>46 47</sup> provides proposed mechanisms to explain potential relationships between the treatment of DM and dementia that might explain differential effects between therapies.<sup>46 47</sup>

The risk of cognitive impairment increases with the duration and severity of DM.<sup>17 48</sup> These factors, which should be considered when assessing the association between DM treatment and cognitive outcomes, were not accounted for in many studies. Whether insulin directly increases the risk of incident dementia and other adverse cognitive outcomes remains uncertain. The apparent association may be driven, at least in part, by DM duration and severity, though severe hypoglycemia related to insulin treatment is another plausible mechanism.

The association between metformin and dementia is complex. In one clinical trial, the use of metformin in newly treated patients with DM reduced the risk of MCI.<sup>49</sup> Our systematic review found highly variable results across studies. The meta-analysis did not demonstrate any significant association between metformin use and adverse cognitive outcomes, though significant between-study

heterogeneity was seen. Vitamin B<sub>12</sub> deficiency, which is associated with metformin use,<sup>49</sup> may be a potential factor that may adversely affect cognition. Other potential reasons for study heterogeneity may relate to unreported differences in DM severity, co-intervention, and comorbidity.

Two studies reported a protective association with pioglitazone on the risk of dementia with this benefit directly related to higher dosage and longer duration of exposure.<sup>36</sup> This observation warrants further study. There are two ongoing phase III trials examining the potential impact of pioglitazone on the course of AD.<sup>50</sup>

A complex, possibly bidirectional relationship exists between severe hypoglycemia and cognitive deficits. Severe hypoglycemia may cause neurological impairment, and impaired cognition may increase the risk of hypoglycemia. Studies have consistently shown that diabetic patients with cognitive dysfunction are more likely to experience hypoglycemia.<sup>51–54</sup> Accordingly, clinical practice guidelines from the American College of Physicians recommend that in diabetic patients with dementia, treatment should focus on avoidance of symptomatic hyperglycemia, rather than achieving a strict A1c target in order to mitigate the risk of hypoglycemia.<sup>55</sup>

## Future research directions

Pilot studies have reported benefit with intranasal insulin in individuals with AD.<sup>56</sup> Further clinical trials are ongoing.<sup>57</sup> In contrast to subcutaneous injections, intranasal insulin crosses the blood–brain barrier and poses a lower risk of hypoglycemia.<sup>58</sup> A systematic review reported improvements in verbal memory and

functional status with intranasal insulin, compared with placebo, but no apparent effect on other cognitive domains.<sup>58</sup>

### Limitations

Our findings should be interpreted in the context of the study design. The major limitation of our study was the inability to account for the duration or severity of diabetes because of inconsistent reporting in the primary studies. The majority of included studies were observational in nature. Inherent to all observational studies, residual confounding cannot be excluded. Among the four RCTs that were included, study quality was generally poor, which may have impacted our estimates. Furthermore, we quantified a large amount of heterogeneity, likely arising from true clinical differences between studies. Statistically combining heterogeneous data may be problematic. Although we were able to account for some of the observed heterogeneity in our stratified and meta-regression analyses, the results from these subgroups should be interpreted to be hypothesis-generating. Although heterogeneity was also seen in our estimates of harm associated with severe hypoglycemia, the direction of association was consistently reported in every study, thus strengthening the likelihood of a true association.

### Conclusions

The various antidiabetic therapies may have differential effects on cognitive outcomes, potentially mediated by risk of severe hypoglycemia. Future studies should consider DM duration and severity, and frequency and severity of hypoglycemia in assessing the complex association between DM and cognitive impairment.

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