Received: 15 December 2021 | Revised: 4 October 2022 | Accepted: 22 November 2022

DOI: 10.1002/dmrr.3610

WILEY

REVIEW ARTICLE

Association between severe hypoglycaemia and risk of dementia in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

María Dolores Gómez-Guijarro[1] | Celia Álvarez-Bueno[1,2] | Alicia Saz-Lara[1] | Irene Sequí-Domínguez[1] | Maribel Lucerón-Lucas-Torres[1] | Iván Cavero-Redondo[1,3]

[1]Health and Social Research Center, Universidad de Castilla – La Mancha, Cuenca, Spain

[2]Universidad Politécnica y artística del Paraguay, Asunción, Paraguay

[3]Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, Chile

Correspondence
Alicia Saz-Lara, Centro de Estudios Socio-Sanitarios, Universidad de Castilla-La Mancha, Edificio Melchor Cano, Santa Teresa Jornet s/n, Cuenca 16071, Spain.
Email: alicia.delsaz@uclm.es

Funding information
University of Castilla-La Mancha, Grant/Award Number: 2019-PREDUCLM-10708; Science, innovation and universities, Grant/Award Number: FPU19/00109; ERDF funds

Abstract

The aim of this systematic review was to analyse whether there is an association between severe hypoglycaemia and the incidence of dementia in patients with type 2 diabetes mellitus. We systematically searched the MEDLINE, Scopus, and Cochrane databases from their inception until September 2022 for observational studies on the association between hypoglycaemia and the risk of dementia. The DerSimonian and Laird method was used to compute a pooled estimate of the risk for such association. Risk ratio (RR) and its respective 95% confidence interval (95% CI). Two analyses were performed to estimate the risk of dementia: (i) any hypoglycaemia versus no hypoglycaemia and (ii) a dose–response analysis for one, two, or more than three hypoglycemic events versus no hypoglycaemia. PROSPERO registration number CRD42020219200. Seven studies were included. The pooled RR for the association of severe hypoglycaemia and risk of dementia was 1.47 (95% CI: 1.24–1.74). When the dose–response trend was analysed, the pooled RR for the risk of dementia was increased according to the hypoglycaemia events as follows: 1.29 (95% CI: 1.15–1.44) for one hypoglycemic event; 1.68 (95% CI: 1.38–2.04) for two hypoglycemic events; and 1.99 (95% CI: 1.48–2.68) for three or more hypoglycemic events. Our study demonstrates a 54% higher risk of dementia among people who suffer a hypoglycaemia event compared to non-hypoglycaemia. Considering our results and the prevalence of people suffering from diabetes mellitus, health education for both newly diagnosed and already diagnosed people could be a useful tool for glycaemic control, thus avoiding hypoglycaemic events.

KEYWORDS
cognitive impairment, dementia, diabetes mellitus, dose–response effect, hypoglycemia

1 | INTRODUCTION

Based on previous evidence, it is estimated that approximately 44 million people worldwide suffer from dementia, mainly affecting people over 65 years, most of whom live in low- and middle-income countries. Additionally, the current cost of dementia is estimated to be 720 billion euros per year, representing a large health and social cost.[1–3] Dementia is a clinical syndrome characterised by acquired cognitive impairment affecting higher cognitive functions such as memory, thinking, understanding, and judgement. However, as mentioned above, dementia is not a single disease; the syndrome can be developed by nonmodifiable risk factors such as age and genetics and by modifiable factors, including low education, hypertension, obesity, and diabetes mellitus.[1–5]

Among the predictors of dementia, type 2 diabetes mellitus (T2DM) is associated with a 1.5- to 2.5-fold risk of dementia and cognitive dysfunction. Although the aetiology of dementia in people with T2DM is probably multifactorial, poor glycaemic control, and the resulting hypoglycaemia, with or without other associated risk factors, have been shown to promote the development of cognitive impairment, increasing the risk of dementia in the elderly.[6–10] The interaction between hypoglycaemia and cognitive impairment has been previously analysed, showing a two-way relationship.[11]

Additionally, when examining the relationship between hypoglycaemia and the risk of dementia, certain factors may be considered. Some population and study characteristics, including age, sex, and length of follow-up, could influence this relationship. Furthermore, there is a lack of evidence on the dose–response effect between the number of hypoglycemic events and the development of cognitive impairment. Therefore, the aims of this systematic review and meta-analysis were (i) to analyse the dose–response effect on the incidence of dementia according to the number of hypoglycemic events in patients with T2DM and (ii) to analyse whether there is an association between severe hypoglycaemia and the incidence of dementia in patients with T2DM.

2 | METHODS

Before conducting this systematic review and meta-analysis, we registered it in the PROSPERO database (registration number ID: CRD42020219200). We followed the Cochrane Handbook for Systematic Reviews of Interventions[12] to conduct it and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13] to report it.

2.1 | Search strategy

We systematically searched the PubMed, Scopus, Web of Science, and Cochrane Library databases from their inception until September 2022, searching for articles reporting the association between hypoglycaemia and the risk of dementia using the following key terms: 'diabetes mellitus', 'type 2 diabetes mellitus', 'T2DM', 'hypoglycemia', 'hypoglycemia', 'severe hypoglycemia', 'severe hypoglycemia', 'dementia', 'cognitive impairment', and 'mild cognitive impairment'. The literature search was complemented by reviewing the references of the articles considered for inclusion in this systematic review and meta-analysis.

2.2 | Study selection

The included studies met the following inclusion criteria: (i) participants with T2DM, (ii) studies searching for the association between severe hypoglycaemia and the risk of dementia and cognitive decline, (iii) studies providing data comparing the association between diabetes mellitus and the risk of dementia, and (iv) observational studies providing risk (risk ratio [RR], odds ratio or hazard ratio) of dementia or including the number of subjects with dementia.

The criteria for excluding studies were as follows: (i) non-English or Spanish language reports, (ii) studies without longitudinal design, (iii) types of publications not suitable as review articles, (iv) duplicate reports of the same studies, and (v) patients with gestational diabetes.

When more than one study provided data for the same sample, those presenting the results in more detail or providing data with a larger sample size were considered. However, data regarding sample characteristics could be extracted from multiple reports to obtain the most complex information.

The literature search was conducted independently by two reviewers (CA-B and MDG-G), and inconsistencies were resolved by consensus and involving a third researcher (IC-R).

2.3 | Data extraction and risk of bias assessment

The following data were extracted from the original reports: (1) reference (author and year of publication), (2) country, (3) study design, (4) length of follow-up, (5) population characteristics (mean age, type of population, sample size), (6) hypoglycaemia characteristics (measured as number of hypoglycemic events), and (7) dementia characteristics.

The validated Newcastle–Ottawa scale was used to assess the risk of bias of the included cohort studies. In this scale, four points are assigned for the selection domain, two points for the comparability domain, and three points for the outcome and the adequacy of the follow-up domain, with a maximum of nine points. Each study was rated as 'good', 'fair', or 'poor' quality depending on whether the study scored more than six, five or less than five points, respectively.[14]

Data extraction and risk of bias assessment were conducted independently by two researchers (CA-B and MDG-G), and inconsistencies were resolved by consensus with the participation of a third researcher (IC-R).

2.4 | Statistical analysis and data synthesis

The DerSimonian and Laird method[15] for random effects was used to compute a pooled estimate of the RR with the respective 95% confidence interval (95% CI). Two analyses were performed to estimate the risk of dementia: (i) any hypoglycaemia versus no hypoglycaemia and (ii) a dose–response analysis for one, two, or more than three hypoglycemic episodes versus no hypoglycemic episodes. The heterogeneity of the results across studies was assessed using the I^2 statistic. I^2 values were interpreted as follows: might not be important (0%–30%); may represent moderate heterogeneity (30%–50%); substantial heterogeneity (50%–75%); or considerable heterogeneity (75%–100%). The corresponding p values were also considered.[16]

Sensitivity analyses were performed to evaluate the robustness of the summary estimates and to detect whether any particular study accounted for a large proportion of the heterogeneity. Random-effects meta-regressions were used to investigate whether the results were associated with the age of participants, the length of follow-up, or the percentage of women included in the sample. Publication bias was evaluated using Egger's regression asymmetry test[17] and through visual inspection of funnel plots.

Statistical analyses were performed using STATA SE software version 15 (StataCorp).

3 | RESULTS

3.1 | Systematic review

After searching the databases, a total of 995 studies were selected, of which 114 studies were eliminated due to duplicates. After selecting 881 studies based on title and abstract, a total of

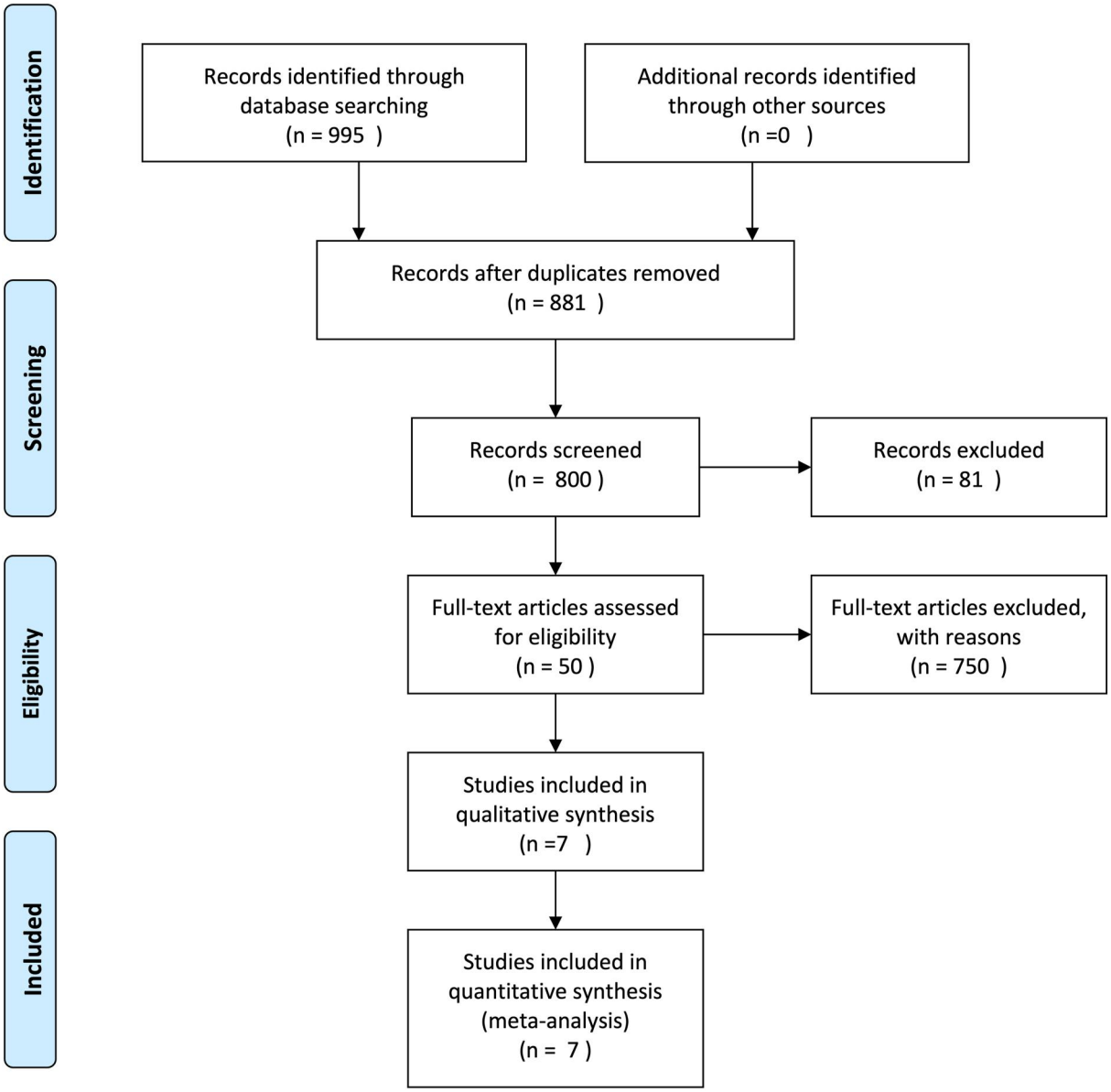

FIGURE 1 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the systematic literature.

750 studies were selected for full-text reading. Fifty studies were excluded for the following reasons: noneligible publication types, no people with dementia only, no control group, not including main outcomes studied, and no intervention. Finally, seven studies were included in the systematic review and meta-analysis,[9,10,18–22] which analysed the association between severe hypoglycaemia and the risk of dementia as well as the association between the number of hypoglycemic events and the risk of dementia (Figure 1). These studies were conducted in five countries: two in the United Kingdom,[10,21] two in the United States,[18,19] one in Korea,[22] one in Canada,[20] and one in Taiwan.[9] The included studies were published between 2013 and 2017 and their follow-up ranged between 1 and 27 years. The sample size of the included studies ranged from 279 to 893,115 subjects (including a total of 981,812 subjects, of which 50.3% were women) aged between 45 and 75 years. All studies included subjects with T2DM except two that did not specify the type of diabetes mellitus (Table 1).

Hypoglycaemia was quantified through hospital records,[18–20] clinical diagnosis,[9,10,22] and questionnaires.[21] Furthermore, the incidence of dementia varied between 8.51% and 72.34% and was established according to the ICM-9-CM diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification),[19] cognition tests[21] or based on hospital records.[18,20] Finally, the studies adjusted the association between hypoglycaemia events and the risk of dementia, including different variables, with the most common being age, sex, cardiovascular diseases, comorbidity, dementia, and hypertension (Table S2).

3.2 | Risk of bias

The risk of bias assessed by the Newcastle–Ottawa scale showed that 25% of the studies were rated as 'good', showing a low risk of bias, and 75% were rated as 'moderate' showing an unclear risk of bias.

3.3 | Meta-analysis

The pooled RR for the association of severe hypoglycaemia and risk of dementia was 1.54 (95% CI: 1.36–1.74). Heterogeneity between studies was substantial (I-squared = 60.8%, p = 0.001) (Figure 2).

TABLE 1 Characteristics of the included studies

			Population characteristics			Hypoglycemia characteristics		Dementia characteristics	
Reference	Country	Length of follow-up (years)	Mean age (years)	Type of poblation	Sample size (n)	Measurement	No. of hypoglycemias	Measurement	People with dementia (%)
Chin et al. (2016)	Korea	8	67.5 ± 5.5	DMT2	1957	Diagnosis code	1	NA	Diagnosis code
							2		
Feinkohl et al. (2014)	Scocia	4	67.7 ± 4.16	DMT2	831	Questionnaire	ND	BVFT, TMT-B, DSC, LNS, MR, MHVS	NA
Haroon et al. (2015)	Canada	12	73 (69–78)	DM	893115	Hospital records	ND	NA	NA
Lin y Sheu (2013)	Taiwan	7	64.2 ± 9.9	DMT2	15404	ICD9-CM	1	NA	72.34
							2		19.14
							3 or +		8.51
Mehta et al. (2017)	United Kingdom	9	75.25 ± 6.55	DMT2	53055	NA	1	NA	NA
							2		
Yaffe et al. (2013)	United States	12	>74 ± 2.75	DM	783	Hospital records	NA	Hospital records	NA
Whitmer et al. (2009)	United States	27	65 ± 3.25	DMT2	16667	ICD-9-CM	1	ICD-9-CM	60
							2		28.8
							3 or +		17.2

Note: Data are shown as mean ± standard deviation (SD) or interquartile range (IR).

Abbreviations: BVFT, Borkowski's verbal fluency test; DSC: Symbols of digits: codification; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LNS, Sequencing of letters and numbers; MHVS, Escala de vocabularios de Mill Hill junior y senior; MR, Matrix Reasoning; NA, not available; TMT-B, Test of creation of B paths.

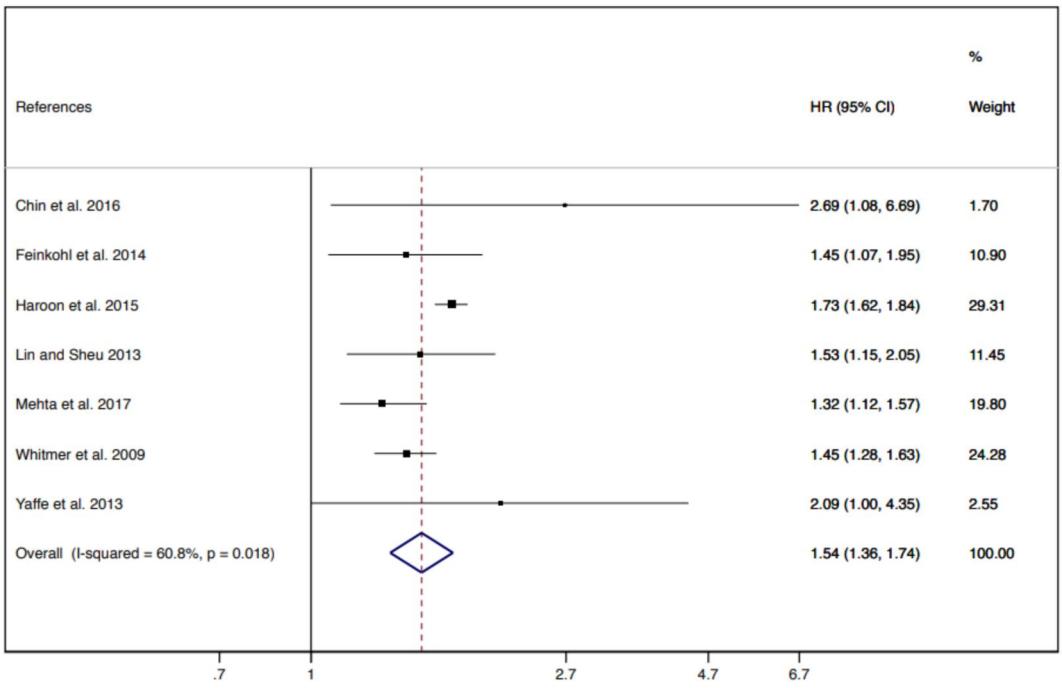

FIGURE 2 Forest plot of pooled hazard ratio estimates of hypoglycemia and dementia.

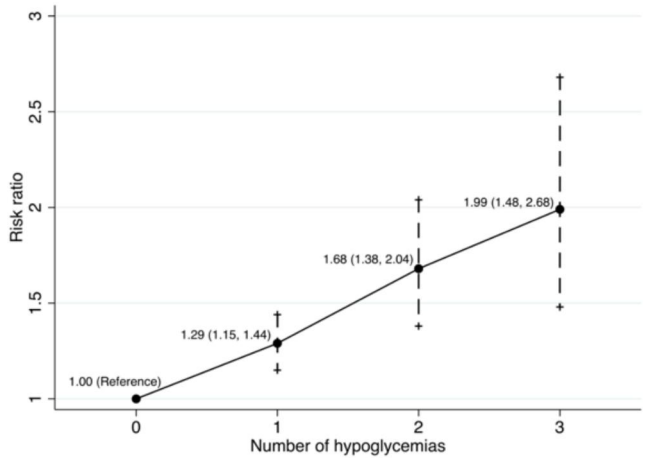

FIGURE 3 Trend for the increased risk of dementia according to the number of hypoglycemias.

Furthermore, when the dose–response was analysed, the pooled RR for the risk of dementia was increased according to the number of hypoglycemic events as follows: (i) 1.29 (95% CI: 1.15–1.44) for one hypoglycemic event; (ii) 1.68 (95% CI: 1.38–2.04) for two hypoglycemic events; and (iii) 1.99 (95% CI: 1.48–2.68) for three or more hypoglycemic events. Heterogeneity for each number of hypoglycemic events was not important (I^2 = 0.0%) (Figure 3).

3.4 | Sensitivity analysis and meta-regressions

The pooled RR was slightly reduced when the data from the Haroon et al.[20] study were removed from the analyses one at a time.

Additionally, random-effects meta-regression models for the association between hypoglycaemia events and the risk of dementia showed that age (p = 0.650), percentage of women (p = 0.450), and length of follow-up (p = 0.911) were not related to the heterogeneity across studies (Figures S1, S2 and S3).

3.5 | Publication bias

Publication bias, as assessed by Egger's test and funnel plot asymmetry, was not found for the association between hypoglycaemia events and the risk of dementia (p = 0.696) (Figure S4).

4 | DISCUSSION

This systematic review and meta-analysis provides an overview of the association between hypoglycaemia events and the risk of dementia in patients with T2DM. Our findings showed a 54% increased risk of dementia when suffering from hypoglycaemia compared to no hypoglycaemia. Furthermore, each increment in the number of hypoglycemic events increases the risk of dementia by approximately 30%. Finally, age, percentage of women and length of follow-up did not seem to influence the association between severe hypoglycaemia and risk of dementia.

A previous systematic review and meta-analysis analysed the two-way interaction between hypoglycaemia and cognitive impairment in elderly individuals. In addition to our findings, this previous systematic review showed that hypoglycemic events were associated with a higher risk of dementia. Similarly,

this study showed that cognitive decline, in turn, could jeopardise the management of diabetes mellitus and lead to hypoglycaemia.[11]

The mechanism for the onset of this chronic process may be that when blood glucose drops to low levels, cognitive functions deteriorate, and severe hypoglycaemia can cause damage to neurons in the brain.[23] Hypoglycemia commonly occurs in patients with T2DM and can negatively influence cognitive performance.[18] Furthermore, this association was maintained even after adjusting for age, sex, and length of follow-up.

Moreover, our findings demonstrate a dose–response relationship for the risk of dementia by increasing approximately 30% for each hypoglycaemia. However, in this study, the association between severe hypoglycaemia and dementia observed in each study was consistently confirmed in the results with all studies combined, although there was substantial heterogeneity (60.8%). Recent evidence has shown that recurrent hypoglycaemia makes the brain and in particular the hippocampus, more vulnerable to oxidative damage and neuronal death induced by a subsequent episode of hypoglycaemia, ultimately leading to cognitive dysfunction.[24]

Given the magnitude of diabetes mellitus incidence and prevalence of those suffering from a hypoglycaemia episode, health education for patients with diabetes mellitus is essential.[25] Diabetes education can offer patients options to reduce fear and discourage decisions that justify poor glycaemic control.[26] In addition, the health costs associated with the admission of people with severe hypoglycaemia and the long-term treatment of people who have developed dementia as a result of one or more episodes of hypoglycaemia could be reduced.[27] Some of the factors that may be associated with severe hypoglycaemia and dementia could be functional dependency, depression, malnutrition, comorbidities, polypharmacy and social problems,[28,29] factors that are not reflected in most studies and therefore could not be analysed in this systematic review and meta-analysis.

Our systematic review and meta-analysis has some limitations that should be acknowledged. First, there was a scarcity of studies comparing the number of hypoglycemic events to estimate the dose–response relationship. Second, the included studies differed in the tools used to measure hypoglycaemia and dementia; however, all examined the association of hypoglycaemia and the risk of dementia, regardless of how they were reported. Third, there were differences in the variables used for adjustment in each study, although most studies included age, education, duration of diabetes, body mass, race/ethnicity, baseline HbA1c, hypertension, cardiovascular disease, and insulin dose. Fourth, most of the studies showed a moderate risk of bias; therefore, our results should be interpreted with caution. Fifth, the included articles did not establish an association between cognitive dysfunction and nonsevere hypoglycaemia, as they only focussed on severe hypoglycaemia. Sixth, significant heterogeneity was found, perhaps due to different population settings, centres, etc. Seventh, a causal relationship between hypoglycaemia and dementia cannot be established. Eighth, the included studies only reported cases of severe hypoglycaemia, disregarding mild or moderate hypoglycaemia. Finally, it should be noted that the effect was often assessed by very few studies, so the evidence is low.

5 | CONCLUSIONS

In summary, our study demonstrates a 54% higher risk of dementia among people who suffer a hypoglycaemia event compared to non-hypoglycaemia. Furthermore, each increase in the number of hypoglycemic episodes increases the risk of dementia by approximately 30%. Considering our results and the prevalence of T2DM, health education for both newly diagnosed and already diagnosed people could be a useful tool for blood glucose control and avoiding hypoglycemic events. In addition, it would be essential that well-designed studies be conducted in the future to strengthen the evidence which remains weak.

AUTHOR CONTRIBUTIONS

Conceptualization: María Dolores Gómez-Guijarro, Iván Cavero-Redondo, and Alicia Saz-Lara. *Data curation*: María Dolores Gómez-Guijarro and Alicia Saz-Lara. *Formal Analysis*: María Dolores Gómez-Guijarro, Iván Cavero-Redondo and Alicia Saz-Lara. *Research*: María Dolores Gómez-Guijarro, Alicia Saz-Lara, Maribel Lucerón-Lucas-Torres, Irene Sequí-Domínguez and Celia Álvarez-Bueno. *Methodology*: Iván Cavero-Redondo and Alicia Saz-Lara. *Supervision*: Iván Cavero-Redondo and Alicia Saz-Lara. *Visualization*: María Dolores Gómez-Guijarro and Maribel Lucerón-Lucas-Torres. *Drafting – original draft*: María Dolores Gómez-Guijarro and Iván Cavero-Redondo; *Writing – proofreading and editing*: All authors. The corresponding author attests that all listed authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

ACKNOWLEDGEMENTS

The study was funded by ERDF funds. ASL is supported by a grant from the University of Castilla-La Mancha (2019-PREDUCLM-10708). ISD is supported by a grant (FPU19/00109) from the Science, innovation and universities.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors, AS-L, upon reasonable request.

ETHICS STATEMENT

The lead authors and manuscript's guarantor affirm 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 have been explained.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/dmrr.3610.

REFERENCES

1. Dening T, Sandilyan MB. Dementia: definitions and types. *Nurs Stand*. 2014;39(37):37-42. https://doi.org/10.7748/ns.29.37.37.e9405
2. Asociación Americana de Psiquiatría. *Manual diagnóstico y estadístico de los trastornos mentales (DSM-5®)*. 5a Ed. Asociación Americana de Psiquiatría; 2014.
3. Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev*. 2008;29(4):494-511. https://doi.org/10.1210/er.2007-0034
4. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366(9503):2112-2117. https://doi.org/10.1016/s0140-6736(05)67889-0
5. Sacuiu SF. Dementias. *Handb Clin Neurol*. 2016;138:123-151.
6. Gale SA, Acar D, Daffner KR. Dementia. *Am J Med*. 2018;131(10):1161-1169. https://doi.org/10.1016/j.amjmed.2018.01.022
7. Meneilly GS, Tessier DM. Diabetes, dementia and hypoglycemia. *Can J Diabetes*. 2016;40(1):73-76. https://doi.org/10.1016/j.jcjd.2015.09.006
8. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006;5(1):64-74. https://doi.org/10.1016/s1474-4422(05)70284-2
9. Lin CH, Sheu WH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. *J Intern Med*. 2013;273(1):102-110. https://doi.org/10.1111/joim.12000
10. Mehta HB, Mehta V, Goodwin JS. Association of hypoglycemia with subsequent dementia in older patients with type 2 diabetes mellitus. *J Gerontol*. 2017;72(8):1110-1116.
11. Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2016;18(2):135-141. https://doi.org/10.1111/dom.12587
12. Higgins JPT, Green S. Selecting studies and collecting data. In: *Cochrane Handbook of Systematic Reviews of Interventions, Version 5.1.0: Cochrane Collaboration*; 2011. Accessed March 2011. www.cochranehandbook.org
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012. https://doi.org/10.1016/j.jclinepi.2009.06.005
14. Wells G, Shea B, O'Connell D, et al. The Newcastle-Otawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2022. Accessed 15 October 2022. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
15. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28(2):105-114. https://doi.org/10.1016/j.cct.2006.04.004
16. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. https://doi.org/10.1002/sim.1186
17. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-aanalysis. *BMJ*. 2001;323(7304):101-105. https://doi.org/10.1136/bmj.323.7304.101
18. 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(14):1300-1306. https://doi.org/10.1001/jamainternmed.2013.6176
19. Whitmer RA, Karter AJ, Yaffe K, et al. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *J Am Med Assoc*. 2009;301(15):1565-1572. https://doi.org/10.1001/jama.2009.460
20. 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;38(10):1868-1875. https://doi.org/10.2337/dc15-0491
21. 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(2):507-515. https://doi.org/10.2337/dc13-1384
22. Chin SO, Rhee SY, Chon S, et al. Hypoglycemia is associated with dementia in elderly patients with type 2 diabetes mellitus: an analysis based on the Korea National Diabetes Program Cohort. *Diabetes Res Clin Pract*. 2016;122:54-61. https://doi.org/10.1016/j.diabres.2016.09.027
23. Languren G, Montiel T, Julio-Amilpas A, Massieu L. Neuronal damage and cognitive impairment associated with hypoglycemia: an integrated view. *Neurochem Int*. 2013;63(4):331-343. https://doi.org/10.1016/j.neuint.2013.06.018
24. Languren G, Montiel T, Ramírez-Lugo L, et al. Recurrent moderate hypoglycemia exacerbates oxidative damage and neuronal death leading to cognitive dysfunction after the hypoglycemic coma. *J Cereb Blood Flow Metab*. 2019;39(5):808-821. https://doi.org/10.1177/0271678x17733640
25. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies. *PLoS One*. 2015;10(6):e0126427. https://doi.org/10.1371/journal.pone.0126427
26. Perlmuter LC, Flanagan BP, Shah PH, Singh SP. Glycemic control and hypoglycemia: is the loser the winner? *Diabetes Care*. 2008;31(10):2072-2076. https://doi.org/10.2337/dc08-1441
27. 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(12):2263-2272. https://doi.org/10.1111/j.1532-5415.2011.03726.x
28. Chen NC, Chen CL, Shen FC. The risk factors of severe hypoglycemia in older patients with dementia and type 2 diabetes mellitus. *J Pers Med*. 2022;12(1):67. https://doi.org/10.3390/jpm12010067
29. Araki A, Ito H. Diabetes mellitus and geriatric syndromes. *Geriatr Gerontol Int*. 2009;9(2):105-114. https://doi.org/10.1111/j.1447-0594.2008.00495.x

SUPPORTING INFORMATION

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

How to cite this article: Gómez-Guijarro MD, Álvarez-Bueno C, Saz-Lara A, Sequí-Domínguez I, Lucerón-Lucas-Torres M, Cavero-Redondo I. Association between severe hypoglycaemia and risk of dementia in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2023;39(3):e3610. https://doi.org/10.1002/dmrr.3610