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RESEARCH

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The role of diabetes mellitus on delirium onset: a systematic review and meta-analysis

Klara Komici[1*], Carlo Fantini[2], Gaetano Santulli[3,4], Leonardo Bencivenga[5], Grazia Daniela Femminella[5], Germano Guerra[1], Pasquale Mone[1,6] and Giuseppe Rengo[5,7]

Abstract

Background Delirium may develop in association with an underlying cardiovascular or cerebrovascular disease and complicates one out of three medical admissions representing a significant economic burden for healthcare systems. However, a clear relationship between delirium onset and diabetes mellitus has not been clarified. The purpose of this study was to explore the association between DM and delirium with the following aims: (a) to assess the incidence of delirium among DM patients (b) to assess the risk of delirium onset in patients with DM (c) to assess the role of anti-diabetic drugs on delirium onset.

Methods MEDLINE, Scopus, and Web of Science and ClinicalTrials.gov were searched from inception up to 30th of December 2024. Studies reporting the incidence of delirium in diabetic patients, delirium events in diabetic patients compared to non- diabetic patients, and the role of antidiabetic drugs on delirium development were considered.

Results The pooled incidence of delirium resulted 29% (95% CI 26.0%- 33.0% I2 = 99.6%). The OR for developing delirium resulted: 1.78 (95% CI 1.59–1.99 i2 = 88.3%) Intranasal insulin administration compared to placebo groups was characterized by a RR = 0.34 (95% CI 0.23–0.52). Metformin use compared to non-metformin use in diabetic patients was characterized by lower RR for delirium: pooled RR = 0.71 (95% CI 0.59–0.85, I2 = 84.8%).

Conclusions The incidence of delirium in patients with diabetes is about 29% and patients with diabetes have higher odds of delirium. Chronic use of metformin, and intranasal insulin administration before surgery may offer benefits in the prevention of delirium. These findings are characterized by significant heterogeneity which hampers their interpretation. Future research for developing diabetes-specific delirium screening protocols, and evidence-based preventive interventions is needed.

Keywords Diabetes mellitus, Delirium, Elderly, Metformin, Insulin

*Correspondence:
Klara Komici
klara.komici@unimol.it
[1]Department of Medicine and Health Sciences, University of Molise, Via F de Sanctis, Campobasso 86100, Italy
[2]Department of Mental Health, ASREM, "Antonio Cardarelli Hospital", Campobasso, Italy
[3]Department of Advanced Biomedical Sciences, Academic Research Unit, International Translational Research and Medical Education (ITME) Consortium, 'Federico II' University, Naples, Italy
[4]Departments of Medicine, Division of Cardiology) and Molecular Pharmacology, Einstein-Mount Sinai Diabetes Research Center (ES-DRC), Einstein Institute for Neuroimmunology and In ammation, Fleischer Institute for Diabetes and Metabolism (FIDAM), Wilf Family Cardiovascular Research Institute, Albert Einstein College of Medicine, New York, NY, USA
[5]Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy
[6]Casa di Cura Montevergine, GVM Care and Research, Mercogliano, Italy
[7]Istituti Clinici Scientifici Maugeri IRCCS-Scientific Intitute of Telese Terme, Telese Terme, BN, Italy

Research awareness

What is currently known about this topic?

- Delirium may develop in association with an underlying cardiovascular or cerebrovascular disease. However, the relationship between delirium onset and diabetes is not clear.

What is the key research question?

- We sought to describe the incidence, the risk of delirium among patients with diabetes mellitus, and the role of anti-diabetic drugs on delirium onset.

What is new?

- The incidence of delirium was about 29%. The OR for developing delirium in patients with diabetes resulted: 1.78. Intranasal insulin administration and metformin use presented a lower relative risk for developing delirium. However, the heterogeneity of these findings was high.

How might this study influence clinical practice?

- Clinicians dealing with diabetes should be strongly motivated to regularly monitor for onset of delirium in this population. Chronic use of metformin may reduce the risk of delirium onset and intranasal insulin administration appears promising in the reduction of post-operative delirium.Future research should develop diabetes-specific delirium screening protocols, and establish evidence-based preventive interventions.

Introduction

Delirium is a neurocognitive disorder characterized by acute alterations in attention, awareness, sleep-wake cycle, cognition, and behavior [1]. Delirium develops in association with underlying systemic or cerebral disease, opioid withdrawal, drug abuse, or exposure to toxins of multiple etiologies [2, 3]. Patients with delirium have an increased risk of disability, longer hospitalization length, institutionalization, and higher mortality rate [4, 5]. Furthermore, it has been reported that delirium complicates one out of three medical admissions in patients aged ≥ 75 years, representing a significant economic burden for healthcare system [6, 7]. Advanced age, dementia, multiple long term conditions defined as the coexistence of two or more chronic conditions in the same individual, malnutrition, and drugs have been described as potential predisposing risk factors for the development of delirium [8–10]. In addition, a wide range of precipitating risk factors are: sepsis, surgery, trauma, dehydration, metabolic disorders which trigger the onset of delirium [5, 11]. Although inflammation, neurotransmitter imbalance, and cerebral metabolic insufficiency have been proposed as pathways involved in delirium development, the fundamental mechanisms still aren't well understood [10]. Impairment of glucose metabolism can result in dysfunction of neural networks essential for cognition and attention. Worldwide the prevalence of Diabetes Mellitus (DM) has increased and almost one in eleven adults is affected by type 2 DM [12]. Increased longevity and population aging influence the prevalence of DM, 90% of whom have Type 2 DM. Different studies have suggested that diabetic patients undergoing surgery have an increased risk for the development of post-operative delirium [13, 14]. However other studies failed to find an association [15, 16]. Furthermore, there are no systematic reviews on the incidence of delirium among diabetic patients.

Over the past decades research has underlined that cognitive impairment is a common complication of DM [17]. Diabetes increased the risk of cognitive impairment and dementia by 1.25–1.91 times compared to individuals without diabetes [18]. Moreover, research suggests a connection between insulin resistance and disruption of the circadian timing clock, which has subsequently been linked to delirium [19, 20]. Diabetic patients were found to have a 41% higher risk of developing anxiety disorders, and anxiety was found to increase the risk of delirium [21, 22].

In experimental model of sepsis, which is considered a precipitating factor for delirium, FDG-PET imaging has revealed substantial modification in glucose uptake [23], while in humans FDG-PET imaging has demonstrated impaired glucose metabolism during delirium episodes [24]. Notably, several interventions targeting glucose metabolism show promising results: intranasal insulin has been reported to ameliorate post-operative cognition, metformin use reduced the occurrence of delirium [25, 26] and liraglutide has ameliorated delirium-like behavior in an experimental model of cardiac-reperfusion ischemia [27].

Given these connections between diabetes, glucose metabolism, and cognitive dysfunction,

the purpose of this systematic review and meta-analysis study was to explore the association between DM and delirium with the following aims: (a) to assess the incidence of delirium among DM patients (b) to assess the risk of delirium onset in patients with DM (c) to assess the role of anti-diabetic drugs on delirium onset.

Materials and methods

This systematic review and meta-analysis study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

[28] criteria and the recommendations in the Preferred Reporting Items for Statistic Reviews and Meta-Analyses (PRISMA) statement [29]. The research question for aim (a) was developed based on Condition, Context, Population (CoCoPop) framework, for aim (b) Population Exposure Outcome (PEO) and aim (c): Population, Intervention, Comparator and Outcome (PICO) format [30–32]. (Supplementary Material Study Appendix).

This protocol was registered in Research Registry - Registry of Systematic Reviews/Meta- Analyses, a specific to Systematic Reviews registration site [33], identification number: reviewregistry1956 (https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/67aa58055643630313e932ac/).

Search strategy and selection criteria

Search strategy was developed by two authors (K.K and C.F) and peer reviewed by a third author (G.R) following the Peer Review of Electronic Search Strategies for systematic review guideline statement [34]. Studies were identified and evaluated independently by two authors (K.K and C.F) in different databases including: PubMed/MEDLINE, Scopus, Web of Science ClinicalTrials.gov and citation searching. Disagreement were discussed with a third author (G.R) and a consensus was reached. The timeline of the publication of studies which were screened in our search strategy was up to 30th of December 2024, without any start day. The following MeSH terms and or free text terms according to the requirements of each database were used for the search strategy: “Delirium”, “Diabetes”, “Insulin”, “Metformin”, “Sulfonylurea”, “Sodium-glucose co-transporter-2 inhibitors”, “Glucagon-like peptide-1 receptor agonists”. Details regarding the keywords and terms used for each database and the respective query are reported in Supplementary Study Protocol. Additional eligible studies were identified by screening the reference lists of included studies. Only articles published in English language were considered. We applied the same inclusion and exclusion criteria in all databases following the specific aims of the study.

Studies were considered eligible if the following criteria were fulfilled: (a) they reported the incidence of delirium in patients with diabetes; (b) they reported the number of delirium events in diabetic patients compared to non-diabetic patients; (c) they reported delirium events in population receiving antidiabetic drugs; (d) randomized controlled trials, quasi-experimental studies, cross-sectional, case-control, and cohort design were considered. In the case where studies did not clearly state the presence of incidence or the prevalence data, delirium events at admission or within 24 h from admission were defined as prevalence data. Delirium developed during admission, was analyzed as incidence. Studies where delirium diagnosis was based on DSM criteria, ICD criteria, evaluations such as Confusion Assessment methods (CAM) and medical records data were considered for inclusion. Studies in hospital medical, surgery, post-operative setting, emergency departments, and community living adults were included. Studies performed in hospice setting, nursing home residents and studies including population < 18 years of age were not considered. Pre-prints, conference papers, conference abstracts, dissertations, thesis, book chapters case-series, case reports, and non-human studies were excluded.

Based on the explicit inclusion and exclusion criteria in a random sample of 80 abstracts inter-rater agreement was tested using the kappa statistics. The level of agreement between the authors was 89.9% agreement, kappa = 0.79, indicating substantial agreement.

Data extraction

Two authors (K.K and C.F), independently using a standardized form, completed data extraction. The results of data extraction were discussed with a third author (G.R) and a final excel database was completed. Any disagreement was resolved by consensus and by the opinion of the third reviewer (G.R) if necessary. For each study the following data if available were recorded: first author’ name and year, study design, diagnosis criteria for delirium and diabetes, clinical setting of the study, sample size, data regarding number of delirium cases, mean age of the study subjects, percentage of male population, other comorbidities, therapy related to diabetes, type of intervention and comparator, number of events in intervention and comparators. The detailed form is reported in supplementary material study protocol appendix.

Study quality and publication bias

According to the study design the following critical appraisal tools were used to assess the quality of the included studies: Joanna Briggs Institute (JBI) critical appraisal checklist for cohort studies [35], randomized studies [36], cross-sectional [35], case-control [35] and prevalence studies [30]. Assessment of the quality was performed by C.F and checked by K.K. Disagreement was resolved by consensus of a third reviewer (G.R). Presence of publication bias was explored visually performing the test for asymmetry of the funnel plot by Egger test [37].

Data analysis

The crude incidence of delirium in patients with diabetes was summarized using descriptive statistics. Pooled incidence rates accounting for inter-study variation were analyzed using a non-linear random effects model. Data were expressed in 95% Confidence Intervals (CI). To estimate the risk of delirium onset in patients with diabetes, the effect size was represented by Odds Ratio (OR) with 95% Confidence Intervals (CI) and calculated by 2 × 2 table. The choice to use OR was driven by the studies' design which was in majority retrospective, subjects' population, outcome measure and quality [38]. Relative Risk (RR) estimates together with CI were calculated from each study and a pooled overall average effect size was calculated using random effect models. Heterogeneity was assessed using I2 statistic that accounts of between-study (or inter-study) variability as opposed to within-study (or intra-study) variability. Because of latent clinical heterogeneity, random effects model was used to synthesize data. Heterogeneity has been considered substantial if I2 value was greater than 25%. To verify the consistency of our results and to investigate the influence of individual studies on the summary effect estimate, we undertook one study-removed sensitivity analysis by omitting one study in each turn and recalculating the pooled estimates on remaining studies. Meta-regression analysis with random effect models was performed to explore the influence of potential effect modifiers on endpoints. The regression coefficient (β) achieved from meta-regression analysis describes how the outcome variable changes with a unit increase in the explanatory variable. Exponentiated regression coefficients (e^{β}) were also calculated. Age, sex, clinical setting (surgical vs. non-surgical setting) were tested. Subgroup analyses were performed for studies applying CAM and DSM criteria for delirium diagnosis, retrospective and prospective cohort design and for studies which explored the role of intranasal insulin on delirium incidence. All reported test results were two- tailed and a p value ≤ 0.05 was considered significant. Data analyses were performed with STATA version 16.

Results

A total of 4123 articles were identified by the initial search (Fig. 1). One hundred twelve manuscripts have been retrieved for more detailed evaluation and the studies finally included in the systematic review were fifty-two. Forty six studies [15, 39–83] for the assessment of the incidence of delirium in diabetic patients (Supplementary Table 1); forty seven studies [15, 39–74, 76–85] for the evaluation of the impact of diabetes on delirium onset (Supplementary Table 2); eight studies [25, 26, 41, 52, 86–89] for the role of antidiabetic drugs on delirium development (Table 1).

Incidence of delirium in patients with diabetes

A total number of 124291 diabetic patients was identified with a mean age of 72 0.1 years, male sex ranging from 20.6 to 91.2%. The pooled incidence of delirium resulted 29% (95% CI 26.0.

%- 33.0%), with a wide range from 1 to 74% (supplementary material Fig. 1). The heterogeneity of the

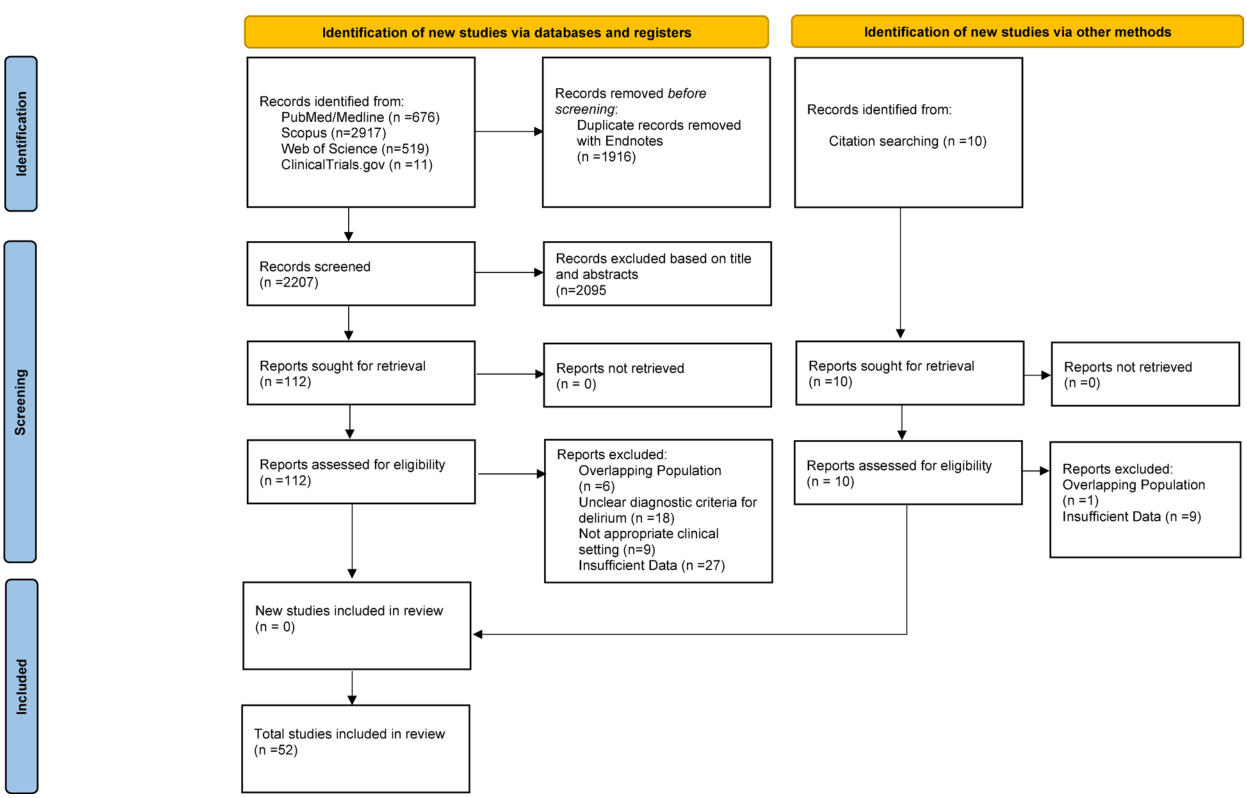

Fig. 1 Study selection flowchart based on PRISMA 2020 flow-diagram [29]

Table 1 Characteristics of the included studies for aim c: anti-diabetic drugs and delirium onset

First author and year	Study design	Aim of study	Clinical setting	Diagnosis of delirium	Inclusion criteria	Intervention	Population (*n*)	Main results
Bowman et al. 2020	Case-control	Identification of risk factors for delirium	Primary Care	Medical Records	(a) Diagnosis of delirium in primary- care or during emergency admission to hospital b) Age ≥ 60 years	NA	First Stage: 17,286 patients with delirium 85,607 controls; Second Stage: 429,548 patients (calibration and validation)	Identification of 55 risk factors for delirium; Predictive model for incident delirium (AUC = 0.867, 95% CI 0.852–0.881) Metformin use OR = 1.15 95% CI 1.05–1.26 Insulin use OR = 1.52 95% CI 1.34–1.73
Yamanashi et al. 2022	Retrospective cohort study	Investigation of metformin use on delirium risk and long-term mortality.	In-patients.	Medical Records	(a) Age ≥ 18 years b) Hospitalized patients c)patients admitted at Emergency units	NA	242 subjects with T2DM without-metformin 264 subjects with DM-with-metformin	The occurrence of delirium in non-metformin group:37.5% vs. 25.8% in metformin group Metformin use: OR = 0.5 95% CI 0.32–0.79 Insulin use: OR = 2.85 95% CI 1.71–4.74
Ishibashi et al. 2024	Retrospective Cohort Study	Effects of antidiabetic medications on delirium	NA (adverse events reporting data)	Medical Records	Age ≥ 20 years Reporting delirium	NA	Metformin users: 12,603 Sulfonyluria users: 17,504 α G-i users: 12,030 DPP-4i: 26,106 SGLT-2i: 6987 GLP1 ago- nists: 2170 Thiazolidine users: 5968 Insulin: 16,285	Metformin: ROR 0.95 95% CI 0.79–1.13 Sulfonyluria: ROR 1.75 95% CI 1.74–2.0 α G-i: ROR 0.84 95% CI 0.7–1.1 DPP4i: ROR 0.86 95% CI 0.76–0.97 SGLT2-i adROR 0.24 95% CI 0.16–0.36; GLP-1 ROR 0.41 95% CI 0.24–0.73 Thiazolidines ROR: 0.49 95% CI 0.36–0.67 Insulin ROR 1.35 95% CI 1.20–1.54
Paredes et al. 2024	Retrospective Cohort Study	to explore if chronic metformin use in adults with type2DM is associated with less delirium	Major non cardiac surgery	CAM-ICU	Adults with type 2 diabetes who did or did not routinely use metformin daily and had noncardiac surgery.	NA	Metformin users: 4744 Non-metformin users 5918	Metformin users: 260 of 4744 cases Non-Metformin Users 502 of 5918 cases

Table 1 (continued)

First author and year	Study design	Aim of study	Clinical setting	Diagnosis of delirium	Inclusion criteria	Intervention	Population (*n*)	Main results
Huang et al. 2023	Randomized Controlled Trail	To explore the effects of preoperative intranasal insulin administration on preoperative sleep quality and post-operative delirium	valve replacement for rheumathic disease	CAM-ICU	Patients aged 18–65 years who underwent heart valve replacement surgery under cardiopulmonary bypass Non diabetic patients	Starting two days pre-operatively 0.5 mL of intranasal saline (0.5 mL) or insulin (20 U), respectively, twice daily	Intranasal Insulin Users:35 Control Group: 36	Post-operative delirium 8 cases among Intranasal Insulin users vs. 18 cases in control group.
Huang et al. 2024	Randomized, placebo-controlled, double-blind, parallel-group study.	the effect of repeated intranasal administration of different insulin doses before surgery on postoperative delirium	Patients undergoing thoracoscopy and laporoscopy for radical resection for esophagal cancer	CAM-ICU	age ≥ 65 years, American Society of Anesthesiologists (ASA) physical status I to III, body mass index (BMI) ≤ 28 kg/m Non diabetic patients	Controls: 0.5 mL of intranasal saline, Insulin 20 U (0.5 mL) insulin, and Insulin 30 U (0.75 mL) insulin, starting 2 days preoperatively, twice daily	intranasal Insulin Group 20 UI: 30 intranasal Insulin Group 30 UI: 30 Control Group:30	Post- operative delirium 19 cases in Control Group; 9 Cases in Insulin 20 UI group; 1 case in Insulin 40 UI.
Sun et al. 2024	Randomized, placebo-controlled, double-blind, parallel-group study.	The effect of repeated intranasal administration of different insulin doses before surgery on postoperative delirium	Orthopedic surgery or pancreatic surgery with general anaesthesia	NR*	NR*	Intranasal administration of 400 µL of normal saline or 40 IU/400 µL of insulin, respectively, once daily from 5 min before anaesthesia induction until 3 days postoperatively	Intranasal Insulin Group: 64 Control Group: 64	Post-operative delirium 7 cases in Insulin group 17 cases in controls.
Sun et al. 2024	Cohort Study	The effects of metformin against delirium in older adults with T2D	Data from Taiwan Health Insurances Program	Medical Records	Age ≥ 65 years with T2D between 1 January 2008 and 31 December 2019, with follow-up extending until 31 December 2021	NA	Metformin users: 66,568 Non-Metformin users (other than metformin antidiabetic drugs): 66,568	1452 cases of delirium in metformin users; 2396 cases in non-metformin users

NA: not applicable; 95% CI: 95% confidence interval; OR: odds ratio; T2DM: type 2 diabetes mellitus; α G-i: alpha glucosidase inhibitors; DPP4i: dipeptidyl peptidase-4 inhibitors; SGLT2i: sodium-glucose co-transporter-2 inhibitors; GLP1R- agonists: glucagon-like peptide-1 receptor agonists; NR*: data not reported in the Article but referred to clinical trial registration

included studies was high: I2 = 99.6%. Sensitivity analysis showed that the estimate remained close to 29–30% regardless of omitted studies (supplementary material Table 3). Age, male sex, clinical setting considering cardiovascular surgery, orthopedics surgery, intensive care unit (ICU) were not significant modifiers of the results: Coef. β= -0.06 e^{β} =0.94 $p = 0.22$; Coef. β = -0.01 e^{β}=0.99 $p = 0.23$; Coef. β = 0.03 e^{β} =1.03 $p = 0.56$; Coef. β =-0.03 e^{β} =0.97 $p = 0.56$; Coef. β = 0.07 e^{β} =1.07 $p = 0.23$.

The incidence of delirium in studies with prospective cohort design resulted: 31% (95% CI 24.0%- 39.0%, I2 = 94.4). Retrospective studies were characterized by an overall incidence of 26% (95% CI 22%-31%, I2 = 99.7%). Application of CAM criteria was characterized by an overall incidence of 32% (95% CI 26%-38%, I2 = 96.8%), while DSM criteria 29% (95% CI 22–35% I2 = 87.6%).

Prevalence of delirium in patients with diabetes

Two studies provided both prevalence and incidence data, however estimation of prevalence among diabetic patients could not be performed [45, 55]. Jang et al. [85] Yamanashi et al. [88] and Bucerius et al. [84] reported a prevalence rate of delirium among diabetic patients of 23%, 32% and 8.4% respectively.

Risk of developing delirium in diabetic patients

In this analysis a total of 874,990 patients were included: 127,828 diabetic and 747,162 non diabetic patients. The difference of 3537 patients compared to the population of incidence data was related to the inclusion of the study [75] only in incidence analysis and the studies [84, 85] only in risk analysis. Mean age was 72.8 years, male sex ranged from 20.6 up to 82%. In most of the cohort diagnosis of delirium was based on CAM scale. DSM-IV and DSM-5, ICD-9 ICD-10 were also applied. The OR for developing delirium resulted: 1.78 (95% CI 1.59–1.99) (Fig. 2). Heterogeneity was high I2 = 88.3%. However, sensitivity analysis showed a combined OR = 1.50 (95% CI 1.38–1.63), lowest estimate 1.46 after the study by Chu et al. [43] was omitted and highest estimate 1.53 after the study by Ahn et al. [39] was omitted. Meta regression analysis did not reveal significant modifiers of the results. Age Coef. β=-0.02, e^{β} =0.98 $p = 0.12$, male sex Coef. β=-0.006 e^{β} =0.94 $p = 0.21$, cardiovascular surgery Coef. β = 0.05 e^{β} =1.05 $p = 0.78$, orthopedic surgery Coef. β = 0.09 e^{β} =1.09 $p = 0.64$, intensive care unit β = 0.18 e^{β} =1.19 $p = 0.49$. Subgroup analysis based on the study design showed that in prospective cohort studies the OR for delirium onset was: 2.16 (95% CI 1.68–2.78, I2 = 80.4%); retrospective cohort studies: OR = 1.63 (95% CI 1.41–1.90 I2 = 89.1%); studies which applied DSM criteria: OR = 1.60 (95% CI 1.20–2.13, I2 = 66.1%); studies which applied CAM criteria: OR = 2.09 (95% CI 1.65–2.66, I2 = 82.6%).

Antidiabetic drugs and delirium

A total of eight articles were included (Table 1). Three randomized studies reported the effects of intranasal insulin administration in non-diabetic population undergoing surgery procedures under general anesthesia. The protocols were based on 20 UI of intranasal insulin used twice daily, 30 UI of intranasal insulin twice daily and 40 UI once daily. Meta-analysis of these data revealed that intranasal insulin administration compared to placebo groups was characterized by a RR = 0.34 (95% CI 0.23–0.52). The heterogeneity was low I2: 0% $p = 0.514$. 514 (Fig. 3). Subgroup analysis of randomized studies which administrated an overall dose of 40 UI of intranasal insulin demonstrated a RR = 0.44 (95% CI 0.29–0.66). Data for insulin use were reported in three studies. Two studies reported adjusted OR. The adjusted OR for delirium resulted significant in insulin users compared to non-insulin users: OR = 1.98 (95% CI 1.07–3.63). Heterogeneity was high I2 = 81.8%. Four studies reported data on the chronic use of metformin and delirium risk. Overall, there were 84,157 metformin users and 723,028 metformin non-user. Metformin use compared to non-metformin use in diabetic patients was characterized by lower RR for delirium: pooled RR = 0.71 (95% CI 0.59–0.85, I2 = 84.8%) (Fig. 4). Sensitivity analysis showed that when the study by Sun et al. was omitted RR: 0.76 (95% CI: 0.62–0.93). Ishibashi and colleagues reported that dipeptidyl peptidase-4 inhibitors (DPP4i) reporting OR (ROR) = 0.86 95% CI 0.76–0.97; sodium-glucose co-transporter-2 inhibitors (SGLT2-i) ROR = 0.24 (95% CI 0.16–0.36); glucagon-like peptide-1 receptor agonists (GLP1R -agonists) ROR = 0.41 (95% CI 0.24–0.73), were associated with reduced odds for delirium onset, while sulfonylurea with increased odds: ROR = 1.75 (95% CI 1.54-2.00).

Study quality

The quality of the included studies, evaluated by JBI checklist for cohort, case-control cross-sectional, prevalence and randomized studies indicated and overall good appraisal. The included studies reported validated measures for the assessment of delirium and diabetes diagnosis was based on the medical records and confounding factors were evaluated. It should be mentioned that most of the studies did not report clear data regarding follow-up duration. Results of the quality assessment reported in Supplementary Tables 4 and 5.

Publication bias

Asymmetry was assessed by the visual inspection of all funnel plots.(Supplementary material, Fig. 2). Egger's regression resulted significant for aim 1 $p < 0.01$, aim 2 $p = 0.01$, indicating publication bias. Regarding the role of antidiabetic drugs on delirium onset, Egger's test did not indicate publication bias for intranasal insulin use and metformin use: $p = 0.49$; $p = 0.89$ (subgroup analysis) and $p = 0.11$ respectively.

Discussion

In this systematic review and meta-analysis study we analyzed the incidence of delirium in patients with diabetes and found and overall estimate of 29%. A history of diabetes is associated with 1.78 higher odds of developing delirium compared to patients without diabetes. However, the heterogeneity is high. Chronic use of metformin suggested a protective role regarding delirium development. Furthermore, intranasal insulin administration before surgery procedures was associated with lower risk of delirium onset.

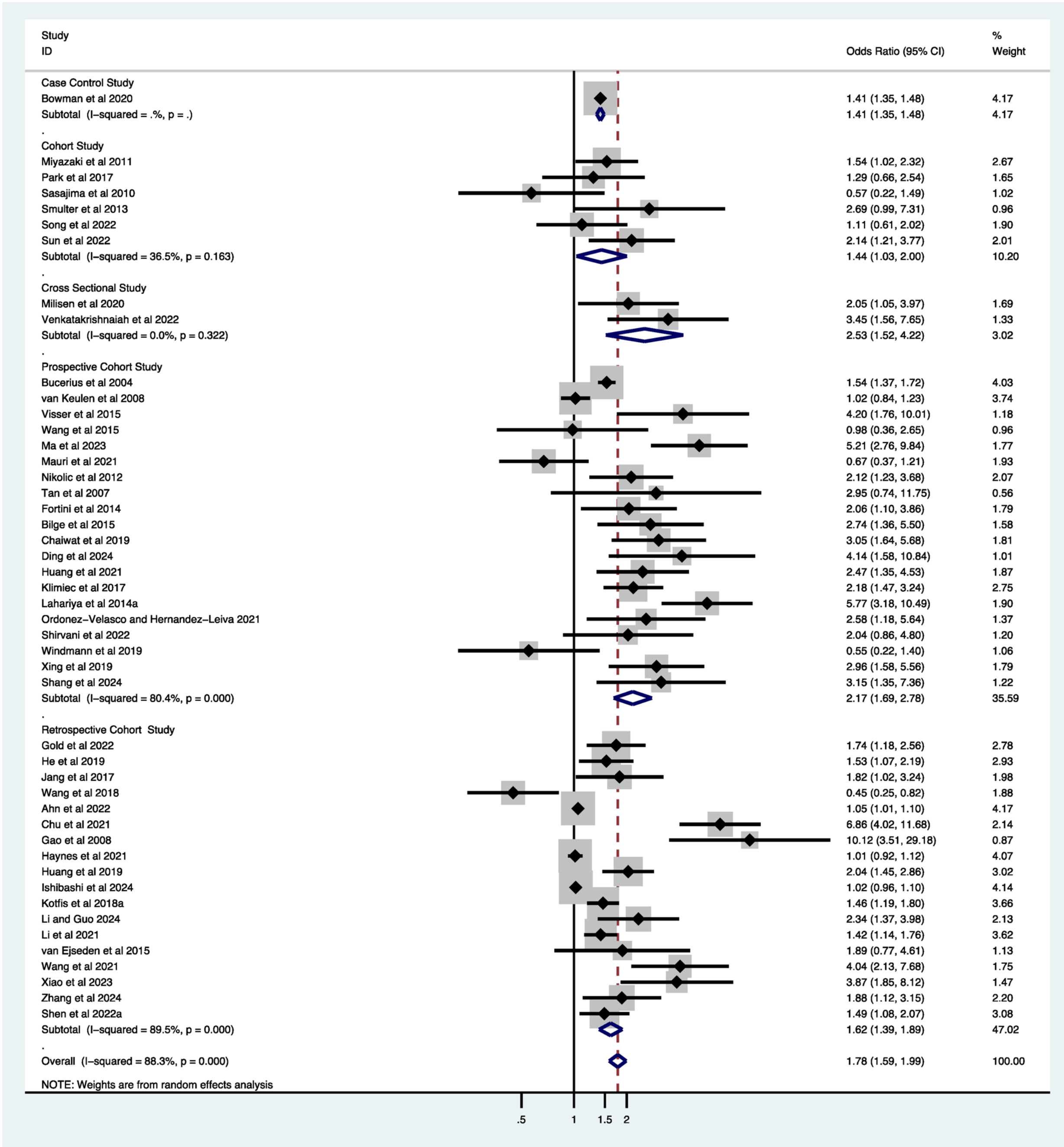

Fig. 2 Risk of delirium onset in patients with diabetes mellitus

It has been reported that the incidence of delirium in diabetic patients undergoing cardiac surgery is about 15.8% [90] and the prevalence up to 37.8% [91]. Previous meta-analysis assessed the incidence of delirium in adults with cancers, in elderly receiving chemotherapy, and older patients undergoing surgical procedures, reporting a range from 10 to about 36% [92–95]. In addition, the incidence of new delirium per admission ranged between 3 and 29% [96]. Our findings regarding the incidence of delirium in diabetic patients are comparable with the other studies mentioned above, but we provide a more robust evidence of how frequent delirium may be among diabetic patients. In addition, we estimated the risk of delirium onset based on pooled adjusted OR for confounders.

Significant heterogeneity was found in incidence measures and risk estimation, which was not explained by subgroup analysis considering study design and diagnostic criteria for delirium.

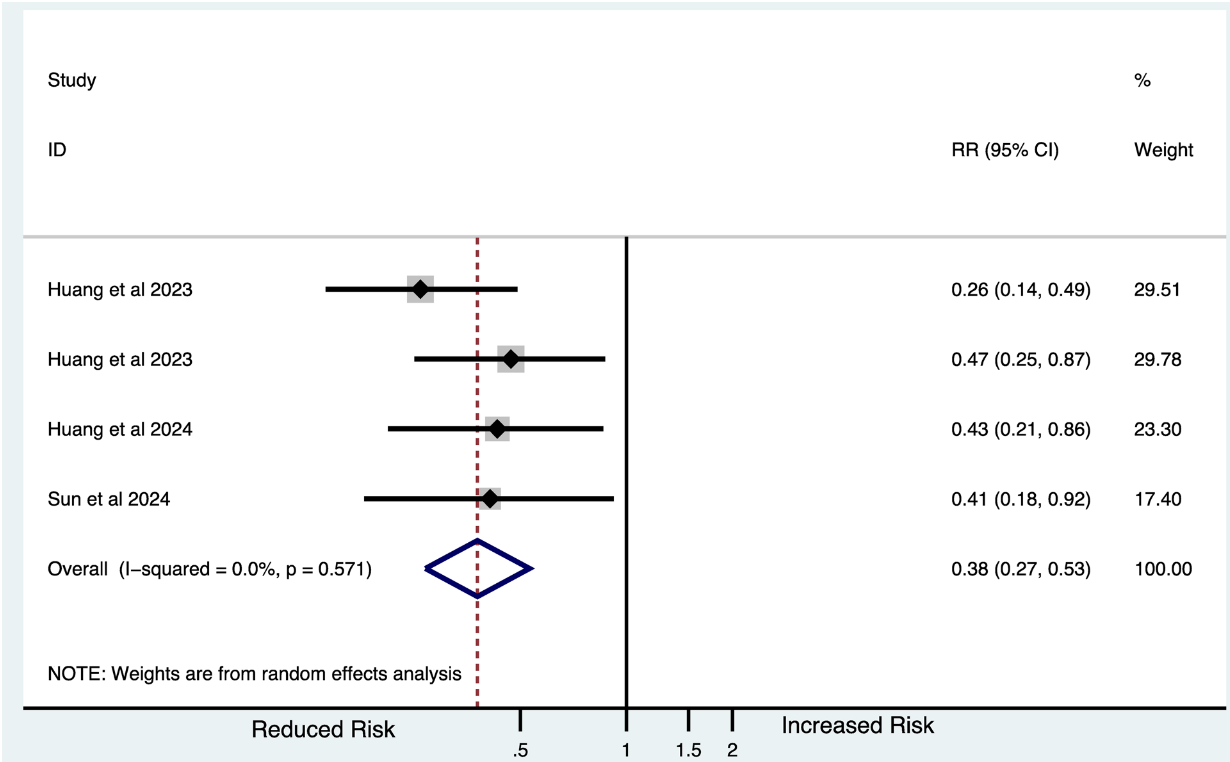

Fig. 3 Intranasal insulin and delirium risk

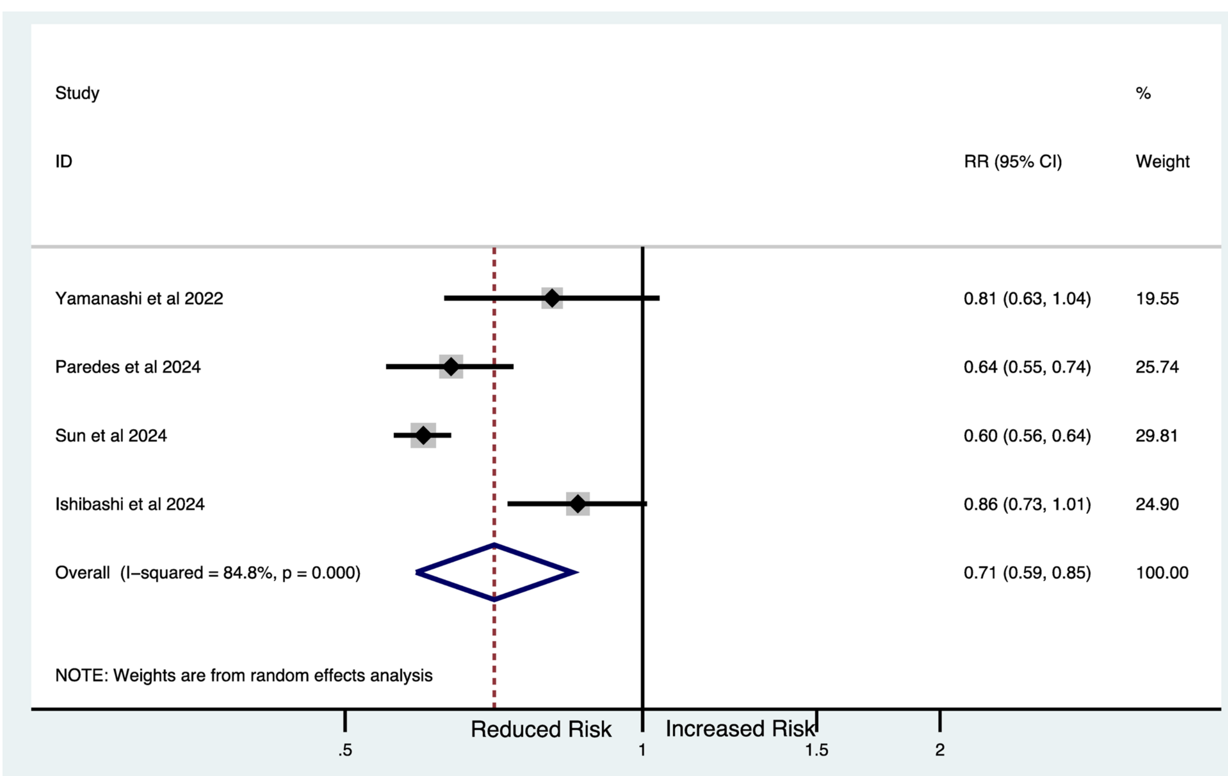

Fig. 4 Metformin use and delirium risk

The clinical presentation of delirium is heterogenous but on the basis of psychomotor behavior is classified in hypoactive, hyperactive and mixed presentation. Hypoactive delirium most frequently occurs in elderly patients but is often misdiagnosed with dementia or depression and this may clearly underestimate delirium incidence [10]. In addition, diagnostic criteria and screening tools have a suboptimal performance in delirium superimposed on dementia, which is often underrecognized [97]. The methods applied for delirium screening include a variety validated screening tools. CAM is the most frequent screening tools applied in research studies. Despite CAM is characterized by a high diagnostic accuracy, its sensitivity in the clinical practice appears lower when used without the cognitive test and interview [98]. Other important source of heterogeneity may be the wide diversity of sample sizes across the studies in the present review. Anyhow sensitivity analysis showed that when individual studies were excluded from the analysis the pooled estimate remained stable. Furthermore, from our analysis delirium in patients with diabetes was not a function of surgical, medical setting, or age. Probably, the interrelationship between diabetes and delirium goes beyond the relationship with pre-disposing risk factors such as age and comorbidities and precipitating acute conditions related to medical or surgical events. Genome-wide association studies did not support the hypothesis between type 2 DM or glycemic traits on delirium risk [99]. However, a recent study found that geriatric patients with delirium presented higher HOMA-IR levels and lower cerebral-fluid (CBF) insulin levels [100]. The association between delirium severity and insulin resistance was also suggested by another study [101]. Insulin signaling is a potential regulator of brain amyloid beta (Aβ) protein metabolism, and a recent meta-analysis study underlined a negative correlation between CBF Aβ42 protein levels and delirium [102]. Abnormal extracellular Aβ protein deposition stimulates the phosphorylation of intracellular tau protein with detrimental consequences on synaptic function leading to memory and cognition impairment [103]. Indeed, modification of plasma tau protein expression was associated with the incidence and severity of delirium [104]. Moreover, changes in tau protein correlated with the release of inflammatory biomarkers IL-8 and IL-10, which suggests a connection with neuroinflammatory pathways [104].

Of interest, different experimental models of post-operative cognitive disorders have suggested a relationship between nucleotide oligomerization domain (NOD)-, leucine-rich repeat (LRR)- and pyrin domain-containing protein 3 (NLRP3) inflammasomes pathways and delirium. Inhibition of inflammasome and caspase-1 reduced the expression of inflammatory biomarkers and attenuated peri-operative cognitive disorders [105, 106]. It should be mentioned that inflammasome pathways are closely related to diabetes mellitus and insulin resistance [107]. In addition, the relationship between inflammation, neurohormonal axis and stress hyperglycemia may in part intermediate the connection between diabetes and delirium. Both higher and lower stress hyperglycemia ratio resulted associated with delirium [69, 108]. It should be mentioned that all the above- mentioned mechanisms are closely related to neurodegenerative disorders and in particular dementia [109]. From the other side the relationship between cognitive decline and diabetes are widely studied [110]. However regardless the co-presence of dementia, the relationship between insulin resistance and delirium resulted significant [100].

Aligned to the pathophysiological rationale, pooled chronic use of metformin was associated with lower risk of delirium 0.71 (95% CI 0.59–0.85). It should be mentioned that the heterogeneity was high and the width of CIs of the included studies indicated that the effect size could range from a reduction of 45% to an increased risk of 4%. Therefore, our results should be interpreted with caution and more research is needed. Nevertheless, in a cohort of 17,200 participants metformin use was associated to a 24% reduction in dementia risk [111], metformin improves insulin sensitivity, activates AMPK signaling which in turn reduces accumulation of Aβ and ameliorates synaptic functioning and neuron plasticity [112].

The pooled results of intranasal insulin administration resulted positively associated with post-operative delirium. Despite, all the included studies described a significant risk reduction the variation of CIs was from 8 to 70% reduction. Intranasal insulin administration has not been associated with clinical important adverse events in patients with Alzheimer's Disease [113] and insulin facilitates glucose uptake, improves neuronal glucose metabolism and strength brain blood barrier [114, 115]. In contrast, subgroup analysis of diabetic patients with insulin therapy showed an increased risk for delirium development. This finding may be explained in part by the complication of both diabetes itself and insulin treatment [52]. It should be mentioned that the association between insulin therapy and delirium was not confirmed when patients with hypoglycemic encephalopathy were excluded from the analysis, suggesting that in patients treated with insulin delirium may be related to the hypoglycemic risk [52]. Intranasal insulin administration results in a rapid accumulation of insulin in cerebrospinal fluid, modulates sleep neurophysiology, neuroendocrine axes [116]. Experimental models have shown that intranasal insulin prevented anesthesia-induced spatial memory deficits and tau protein hyperphosphorylation [117]. Importantly, intranasal insulin administration has not been associated with hypoglycemia [118].

Ishibashi et al. [52] suggested that SGLT2-i, GLP1R -agonists and DPP4-i may have a protective effect on delirium onset. Experimental models also suggest that liraglutide inhibits NLRP3 inflammasome activation and microglial dysfunction and counteracts surgery-induced synaptic loss and impairment of synaptic plasticity [27]. SGLT2-i improves blood-brain barrier, astrocytes, microglia, and oligodendrocytes functioning contributing to amelioration of cognitive performance [119]. Future studies should explore the role of this drugs on delirium onset.

Our study provides the first summary of the literature on the incidence of delirium in patients with diabetes and identifies diabetes as a risk factor for the development of delirium. Based on the important incidence of delirium, clinicians dealing with diabetes should be strongly motivated to regularly monitor for onset of delirium in this population. Validated screening tools may be considered such as CAM, however future studies should explore the diagnostic accuracy and the clinical utility of specific tools for the diabetic population. Our study suggests a possible beneficial role of metformin on delirium onset, but is limited by the high heterogeneity. Anyhow, this information may be of value on the comprehensive care of patients with type 2 diabetes mellitus and other risk factors for delirium development such as cognitive decline. Further research on the neuroprotective role and cognitive health of antidiabetic drugs is necessary. Finally, intranasal insulin administration appears promising in the reduction of post-operative delirium. Future research on the specific mechanism by which intranasal insulin interacts with neuronal network and neurotransmitters should be prioritized. Larger multicenter studies focused on the safety and efficacy of intranasal insulin administration are necessary and application beyond the surgical setting may be considered.

Study limitation

Our study has some limitations that should be mentioned. The majority of studies did not clearly state in the methods if the population presented type 1 and or type 2 DM, type. However, considering the use of oral antidiabetic drugs and that the mean age of the population about 73 years old, type 2 DM is expected to be more prevalent. Secondly, the diagnosis of diabetes was mostly based on medical records and medical history. Thirdly, and utmost, we observed high heterogeneity in all analyses conducted for aim a and b and risk of publication bias. Meta- analysis of observational studies are characterized by an expected heterogeneity, nevertheless they are necessary to address question for which randomized evidence may be unable [120]. English language restriction and not including other databases may present a limitation of our study, anyhow our search focused on four databases produced a considerable number of articles.

Conclusions

The incidence of delirium in patients with diabetes is about 29% and patients with diabetes are characterized by higher odds of delirium compared to patients without diabetes. Chronic use of metformin, and intranasal insulin administration before surgery may offer benefits in the prevention of delirium. These findings are characterized by significant heterogeneity which hampers their interpretation. Future research should focus on elucidating the pathophysiological mechanisms linking diabetes to delirium, developing diabetes-specific delirium screening protocols, and establishing evidence-based preventive interventions.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
K.K and C.F contributed to conceptualization, researched data, and wrote the first draft. P.M, G.D.F, G.S and L.B contributes to data analysis and reviewed the edited manuscript. G.G and G.R supervised the data, wrote the discussion and reviewed the manuscript. K.K is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability
The data will be shared on reasonable request to the corresponding author.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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