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Letter to the Editor

Whether Metformin Actually has an Anti-Delirium Effect Compared to Dipeptidyl Peptidase-4 Inhibitors must be Proven in Appropriate Studies

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Letter to the Editor

We were interested to read the article by Sun *et al*. on a multinational cohort study that analyzed the primary endpoint of delirium in 860,388 patients with type 2 diabetes (T2DM) using the TriNetX network [1]. Metformin use was associated with a lower risk of delirium and death than dipeptidyl peptidase-4 inhibitor (DPP-4i) use [1]. The study is noteworthy, but several points should be discussed.

The first point is that the study design was retrospective [1]. Retrospective designs have the disadvantage of limited control over population sampling and limited control over the type and quality of predictor variables. In addition, the relevant predictors may not have been recorded in the medical record, and it may be difficult or impossible to detect confounding variables and causality. In addition, some information may inevitably be missing, as the data are based on the review of medical records that were not originally intended for the collection of data for research purposes. Selection and recall errors also affect the results, which can lead to bias [2].

The second point is that the development of delirium is not solely dependent on the use of a single drug, such as DPP-4i, but is usually multifactorial. Factors that can trigger delirium include physical illness, medication, infection, alcohol or drug use and withdrawal, psychological stress and lack of sleep. Age, previous illnesses, sensory deficits and the environment can also play a role. Triggering factors include, in particular, the use of ≥3 new medications, dehydration, shock, hypoxia, anemia, immobility, malnutrition, use of urinary catheters, hospitalization, pain, sleep deprivation and emotional stress [3].

The third point refers to the co-mediations in each of the included patients. Since some medications, such as anticholinergics, tri- and tetracyclic antidepressants, antihistamines, benzodiazepines, opioids, and certain cardiotropic drugs (e.g. digoxin, beta-blockers, captopril, diuretics), can induce delirium [4]. and since some medications, such as benzodiazepines, haloperidol, phenobarbital, propofol or dexmetetomidine can prevent delirium [5]. it is conceivable that those who were on metformin were less likely to have delirium because they were taking fewer or no delirium-inducing drugs or were taking drugs that prevent delirium.

Fourthly, we should know how it was ensured that the same criteria were used for the diagnosis of delirium in all 142 participating healthcare facilities worldwide.

Before concluding that metformin prevents delirium, prospective double-blind placebo controlled cross-over studies are needed to confirm or dismiss such an assumption.

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References
1. Sun M, Wang X, Lu Z, Yang Y, Lv S, Miao M, Chen WM, *et al*. Metformin vs. second-line therapy for delirium prevention in type 2 diabetes: A multinational study. Diabetes Res Clin Pract, May 20, 2025, 112270. Doi: 10.1016/j.diabres.2025.112270
2. Talari K, Goyal M. Retrospective studies - utility and caveats. J R Coll Physicians Edinb, Dec 2020; 50(4):398-402. Doi: 10.4997/JRCPE.2020.409
3. Ramírez Echeverría MDL, Schoo C, Paul M. Delirium. [Updated 2022 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, Jan 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470399/
4. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: A systematic review. Age Ageing, Jan 2011; 40(1):23-29. Doi: 10.1093/ageing/afq140
5. Page VJ, Ely EW. How to prevent delirium? In: Delirium in Critical Care. Core Critical Care. Cambridge University Press, 2015, 140-156.