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Intranasal insulin for postoperative delirium prevention and treatment of established delirium: a retrospective systematic review and meta-analysis protocol

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Retrospective registration material — Not yet submitted.

Conflicts of interest - The corresponding author reports no conflicts beyond the disclosed co-guest-editor roles of Congli Zeng, Si Cao and Weidong Liang in the target collection.

INPLASY registration number: INPLASY2026100089

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 October 2026 and was last updated on 20 October 2026.

INTRODUCTION

Review question / Objective In adults, does intranasal insulin compared with placebo or saline reduce incident postoperative delirium? Trials treating established delirium are examined separately for duration and severity.

Rationale Existing reviews have addressed prevention. This review incorporates reports identified through 20 October 2026, separates prevention from treatment, examines assessment windows and perioperative regimens, and documents denominator and biomarker discrepancies. It is not the first review of this question. Its incremental value must be judged against recent reviews, including DOI 10.3389/fmed.2025.1670982 and 10.1177/17504589261421004. An ongoing prevention-and-treatment review, CRD420261416154, also substantially overlaps. The incremental contribution is an updated search

and explicit data-discrepancy and missing-outcome analyses, not a claim to the first prevention/treatment synthesis.

Condition being studied Postoperative delirium in adult surgical patients, and established delirium in adults in a separate treatment synthesis. Cognitive dysfunction without a delirium outcome does not satisfy the efficacy criteria.

METHODS

Search strategy Actual searches through 20 October 2026. PubMed: (insulin[Title/Abstract] AND (intranasal[Title/Abstract] OR transnasal[Title/Abstract] OR nasal[Title/Abstract])) AND (delirium[Title/Abstract] OR postoperative[Title/Abstract] OR perioperative[Title/Abstract])) AND ("1900/01/01"[Date - Publication] : "2026/10/20"[Date - Publication]) Europe PMC: TITLE_ABS:(insulin AND (intranasal OR transnasal OR "intra-nasal") AND (delirium OR postoperative

OR perioperative)) AND FIRST_PDATE:[1900-01-01 TO 2026-10-20] Publisher and reference searches supplemented these searches. No language filter was applied.

Participant or population Adults aged 18 years or older undergoing surgery for the prevention question, or adults with established delirium for the separate treatment question.

Intervention Intranasal or transnasal insulin, including short-acting and long-acting formulations, at any dose or perioperative schedule. Insulin combined with an additional active cointervention is excluded from the insulin-only comparison unless that cointervention is balanced between groups.

Comparator Placebo or saline with otherwise comparable care.

Study designs to be included Randomized controlled trials. Companion reports and preprints are linked to the same trial rather than counted as independent studies.

Eligibility criteria Trials must report delirium incidence, severity or duration. Animal studies, observational studies, protocols without results, correspondence and duplicate trial reports are excluded from efficacy pooling. Reports of postoperative cognitive dysfunction without a delirium outcome are not included in this efficacy synthesis.

Information sources PubMed and Europe PMC; publisher pages and reference lists. Crossref was used for bibliographic verification. Embase, CENTRAL, Web of Science, CNKI and Wanfang have not been comprehensively searched. Any additional searches will be dated and documented as amendments.

Main outcome(s) Cumulative occurrence of at least one postoperative delirium episode within the reported three- or five-day window, assessed by a validated delirium instrument. Effect measure: risk ratio with 95% confidence interval. Daily assessments are not summed as independent events.

Additional outcome(s) Delirium severity and duration; cognition; hospital length of stay; hypoglycaemia; inflammatory biomarkers, including IL-6; blood glucose; insulin resistance, including HOMA-IR; sleep; and pain. Different constructs, biological compartments and incompatible time windows are kept separate.

Established-delirium treatment is not pooled with prevention.

Data management Record-level screening decisions, trial extraction, source links and analysis scripts are retained locally in versioned files. Duplicate PMIDs are removed. Full-text and abstract-derived values are distinguished. Multiarm insulin-only groups are combined against one shared control. Independent duplicate screening and extraction have not yet been completed; no claim of dual review is made.

Quality assessment / Risk of bias analysis

Outcome-specific RoB 2 domains are assessed with supporting reasons. Current judgments are provisional, from one assessment workflow, and await independent verification and protocol checks. Missing full texts prevent complete judgments for four reports. GRADE domains are considered; final certainty grading remains pending.

Strategy of data synthesis For delirium incidence, random-effects risk ratios use REML between-study variance and a modified Hartung–Knapp interval with variance multiplier bounded below at one. Q , Q -based I^2 , REML τ^2 and a 95% prediction interval are reported. Secondary pooling requires at least three independent comparable trials with sufficient variance information: mean differences for common scales and standardized mean differences only for compatible constructs measured on different scales. This rule was adopted during the review, after study findings were available, and is not prospectively specified. Double-zero adverse-event trials are summarized by counts. A funnel plot is descriptive; asymmetry tests are not applied with fewer than ten trials. Python scripts reproduce the analyses.

Subgroup analysis Assessment windows of three versus five days and cardiac versus noncardiac surgery are examined descriptively. Dose, formulation and first-dose timing are summarized at trial level; sparse and confounded regimen comparisons do not establish an optimal dose or interaction.

Sensitivity analysis Leave-one-out analyses; restriction to retrieved full-text prevention trials; selected trial exclusions; alternative Sun denominators; DerSimonian–Laird pooling; and extreme missing-outcome assumptions for Yang Mi and Wang. Li 2025 is excluded from the primary analysis because of a denominator discrepancy; a separate explicitly assumed-count analysis does not resolve that discrepancy. These analyses were

performed before registration and must be reported as retrospective decisions.

Language restriction No language filter was applied. Access to Chinese full texts remains incomplete.

Country(ies) involved United States of America and China.

Other relevant information RETROSPECTIVE REGISTRATION DRAFT, 20 October 2026. Searches, initial extraction and primary/sensitivity analyses have already been performed, and study results were known when analysis decisions were documented. Four full texts, independent duplicate verification and final certainty assessment remain outstanding. Proposed stage: Data analysis; current status: Ongoing. Registration was initiated during preparation for JIMR after its registration requirement was identified. No registration identifier has been assigned. Related published reviews have been identified. A direct INPLASY search for intranasal insulin on 20 October 2026 returned INPLASY202280054, an ongoing review of cognition in mild cognitive impairment or dementia rather than delirium. Published delirium reviews report PROSPERO records CRD42024614995 and CRD42025643975; those identifiers belong to other reviews and are not this project's registration. The registry search is not evidence that no overlapping protocol exists elsewhere. Later registration cannot make earlier decisions prospective. Direct PROSPERO searching on 20 October 2026 returned 63 records for intranasal insulin and 20 for intranasal insulin AND delirium. All 20 displayed records were examined at title/status level. CRD420261416154 was inspected in detail: registered 17 June 2026 by Sonya Jung and colleagues, it also covers adult prevention and treatment and remains listed as ongoing. Its planned search cutoff is 8 June 2026. Thus prevention/treatment separation is not unique to the present review. The present project uses an updated search through 20 October 2026 and explicitly audits denominator discrepancies, missing outcomes and regimen interpretation; these differences do not eliminate overlap.

Keywords intranasal insulin; postoperative delirium; randomized controlled trial; perioperative care; systematic review; meta-analysis.

Dissemination plans Submission to a peer-reviewed journal, currently Journal of International Medical Research, with the aggregate extraction data and analysis scripts. Registration acceptance does not establish journal acceptance.

Contributions of each author

The corresponding author confirmed these contributions and all six authors' agreement to public registration on 20 October 2026. Independent duplicate review remains incomplete; author confirmation of contributions does not establish completion of independent review.

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