Impact of Nasal Insulin Administration on Postoperative Delirium in Adults: A Meta-Analysis

Lu WEI, Guiping WEI, Jingya TU

Jingshan Traditional Chinese Medicine Hospital, Jingmen 431899, China

Abstract [**Objectives**] To evaluate the impact of nasal insulin administration on postoperative delirium (POD) through meta-analysis. [**Methods**] The Cochrane Library, PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Database, and China Science and Technology Journal Database (CSTJ) were systematically searched for relevant literature published prior to February 27, 2025. Literature screening and data extraction were conducted by two independent researchers in accordance with predetermined inclusion and exclusion criteria. The primary observation indicator was the incidence of POD across various treatment populations. The risk ratio for the primary outcome was calculated using the Mantel-Haenszel method. The secondary outcomes included the adverse effects associated with insulin treatment, which encompassed the glycemic variability indices, the incidence of nasal irritation symptoms following administration, hypoglycemic reactions, and insulin allergic reactions. The study protocol was registered on PROSPERO (CRD420250607492) before data extraction. [**Results**] A total of five randomized controlled trials involving 357 patients were included in the analysis. In the adult population undergoing surgical procedures, the administration of insulin via nasal delivery was found to significantly reduce the incidence of POD [$RR = 0.35$, 95% CI (0.23 - 0.53), $P < 0.001$]. The results of the subgroup analysis indicated that there were notable differences in the effectiveness of various doses of insulin administered nasally in preventing POD. Specifically, both the 20 U dose group [$RR = 0.45$, 95% CI: (0.29, 0.70), $P < 0.001$] and the 30 U dose group [$RR = 0.01$, 95% CI: (0.03, 0.42), $P < 0.001$] showed a significantly lower incidence of POD compared to the control group, with statistically significant conclusions. Conversely, the 40 U dose group [$RR = 0.47$, 95% CI: (0.17, 1.34), $P = 0.16$] yielded no statistically significant difference. Furthermore, the efficacy in preventing POD was found to be greater in the 30 U dose group compared to the 20 U dose group. Additionally, two cases of hypoglycemic reactions and increased nasal irritation symptom scores were reported in the 40 U dose group across the entire study population ($P < 0.05$), suggesting potential adverse risks associated with this dosage. [**Conclusions**] The nasal administration of insulin significantly decreases the incidence of POD at a specific dosage, with optimal efficacy and high safety observed at a dosage of 30 U.

Key words Postoperative delirium (POD), Intranasal insulin (INI), Meta

1 Introduction

Postoperative delirium (POD) is characterized as an acute decline in cerebral function following surgical procedures, often manifesting as persistent cognitive impairment and confusion. This condition has been well-documented as a prevalent neurological complication in elderly patients post-surgery. POD significantly hampers postoperative recovery, with reported 30 d mortality rates ranging from 7% to 10%[1-3]. POD is frequently observed in patients undergoing cardiac surgery and significant non-cardiac surgical procedures, such as radical gastric and intestinal tumor resections and hip fracture procedures. The onset of POD typically occurs 2 to 5 d after surgery, with an incidence rate reaching approximately 70% among high-risk non-cardiac surgical patients[4-6]. In recent years, there has been a notable increase in both animal experiments and clinical studies concerning POD. However, the precise mechanisms underlying its occurrence and effective preventive strategies remain poorly understood. Consequently, the predominant approach to managing POD continues to be symptomatic treatment with pharmacological agents, which is associated with numerous limitations. Currently, acknowledged risk factors for POD encompass the type of surgical procedure, advanced age (greater than 65 years), dementia, *etc.*[7]. Several prominent hypotheses have been put forth to explain the mechanisms underlying the occurrence of POD[8], one of which is the central nervous system insulin hypothesis. The hypothesis posits that significant trauma or surgical intervention results in impaired or deficient utilization of insulin within the brain, leading to abnormal functioning of insulin-mediated signaling pathways and hampering the effective regulation of brain signaling networks. Therefore, intranasal insulin (INI) can be administered to the nasal cavity through nebulization and subsequently delivered to the brain via the axons of the olfactory and trigeminal nerves, utilizing both intracellular and extracellular pathways, such as the delivery of tissue fluid. This process is accomplished through receptor-mediated endocytosis, which circumvents the blood-brain barrier and delivers essential insulin to the brain, serving as an effective intervention to restore the functionality of the brain's nervous system[9-11]. A number of relevant preliminary pilot studies are currently underway to determine whether INI can prevent POD. This paper conducts a meta-analysis to explore the role of INI in an adult surgical population and assess the effect of varying doses of INI on the incidence of POD.

2 Information and methods

2.1 Search strategy and literature screening Computerized searches were conducted using PubMed, Embase, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, and China Science and Technology Journal Database (CSTJ), with the search period lim-

Received: April 10, 2025 Accepted: July 8, 2025

Lu WEI, bachelor's degree, physician-in-charge.

ited to February 27, 2025, from the inception of each database. Subject terms combined with free word search method were employed for the retrieval. The English subject terms included "delirium", "insulin", and "postoperative". The Chinese subject terms included "delirium" and "insulin". The retrieved literature was imported into EndNoteX9. Two researchers independently reviewed the titles and abstracts for initial screening, followed by a full-text review for re-screening to finalize the inclusion of the literature. When disagreements arose regarding the results of the literature screening, they were negotiated and resolved by two researchers or referred to a senior physician for adjudication. The study protocol was registered on PROSPERO (registration No.: CRD420250607492) prior to data extraction.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria. Inclusion criteria were established based on the principles of PICOS (Population, Intervention, Comparison, Outcome, Study) as follows: the study population comprised adult patients undergoing major cardiac surgery or non-cardiac surgery. The intervention involved preoperative treatment with INI for patients in the experimental group, while the control group received preoperative treatment with a placebo (equivalent normal saline). The primary outcome indicator was the incidence of POD during the postoperative observation period. The secondary outcomes included the incidence of postoperative hypoglycemic reactions, insulin allergies, and nasal irritation adverse reactions. This study was a randomized controlled trial, and the languages used were Chinese and English.

2.2.2 Exclusion criteria. Patients under 18 years of age; individuals undergoing minor minimally invasive surgeries; reports of basic research, including animal and cellular experiments; guidelines or consensus statements; conference papers; reviews; commentaries; editorials; letters; meta-analysis; duplicates of publications; literature that has not been published in print; pathology reports; data that could not be extracted; literature with missing results; studies that were merged with unavailable full-text literature; studies that did not meet the criteria for high-quality RCTs; studies lacking a POD assessment tool; and studies involving non-intranasal routes of insulin administration.

2.3 Literature quality assessment and data extraction This study employed the Cochrane bias tool to evaluate the quality of studies[12] based on seven criteria: the method of random sequence generation, the concealment of allocation, the blinding of both participants and researchers, the blinding of outcome assessment, the completeness of outcome data, selective reporting, and the presence of other biases. In addition, for each study that met the inclusion criteria, relevant data were extracted using a standardized form, which included the number of subjects, intervention measures, and primary outcomes. Any disagreements were resolved through discussions among two researchers and senior physicians.

2.4 Statistical methods A meta-analysis was conducted using Stata 18.0. Relative risk (*RR*) was utilized as an effect indicator for dichotomous variables, while $\bar{x} \pm s$ was employed for continuous variables. Additionally, data reported as median with interquartile ranges were converted to mean ± standard deviation for data analysis[13-14]. The heterogeneity of the included studies was analyzed using the *Q*-test, and the magnitude of heterogeneity was assessed by calculating I^2. If there was no statistical heterogeneity among the results of various studies ($P > 0.1$ and $I^2 < 50\%$), a meta-analysis was conducted using a fixed-effects model. Conversely, if heterogeneity was present, as indicated by $P \leqslant 0.1$ or $I^2 \geqslant 50\%$, it necessitated an investigation into the sources of heterogeneity and a meta-analysis employing a random-effects model. The pooled relative risk (*RR*) was calculated, and a difference was deemed statistically significant at $P < 0.05$. A funnel plot was utilized to assess publication bias when the literature included more than 10 studies. Additionally, subgroup analysis of POD incidence across various insulin dose groups was conducted to identify the subgroup population that would derive the greatest benefit in the trial.

3 Results and analysis

3.1 Literature screening The initial search yielded a total of 345 records. After eliminating 65 duplicates, 280 documents remained. Following a further screening of titles and abstracts, including 10 articles for which the full text was unavailable, a total of 263 documents were removed. The remaining nine documents were screened by reading the full text, resulting in the exclusion of four documents. Ultimately, five documents were included in the study after screening[15-19]. The flowchart illustrating the screening process is shown in Fig. 1.

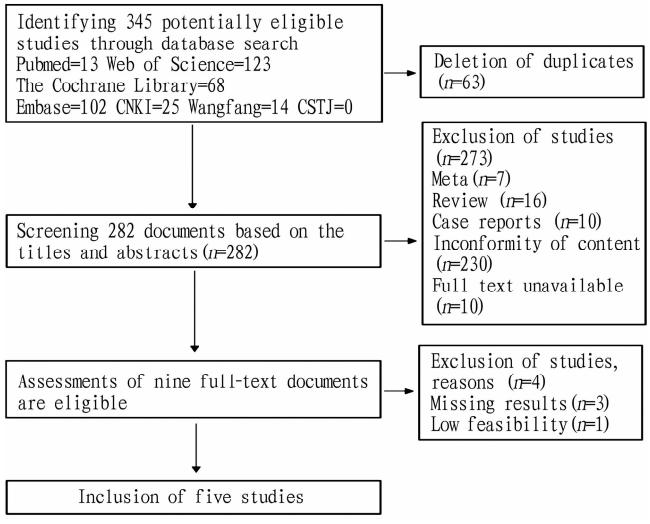

Fig. 1 Flow chart of literature screening

3.2 Characteristics of the included literature The five documents included in this review were all randomized controlled studies, encompassing a total of 357 patients. This cohort consisted of 21 patients who underwent cardiac surgery, 146 patients with radical gastrointestinal tumor resections, and 184 patients with radical

resection of esophageal cancer. Additionally, 214 patients received treatment with INI. The review included three studies published in English and two studies published in Chinese. The basic information regarding the included studies is presented in Table 1.

Table 1 Basic features of the included literature

First author	Year	Type of surgery	Test group	Control group	Number of case (T/C)	Year	Assessment method, time
Hsieh SJ	2015	Cardiac surgery	Intranasal administration of 40 U of insulin aspart once 2 h prior to the surgical procedure and then continuing for 7 d until discharge, 6 h daily	NS	11/10	73.0±11.0/ 72.0±8.0	CAM-ICU, POD7
Huang Q	2023	Radical gastrointestinal resection	Intranasal administration of insulin at a dosage of 20–30 U, administered twice daily for 2 d prior to surgery and continuing until the day of surgery, 10 min before the induction of anesthesia	NS	60/30	68.5±2.3/ 68.4±3.8	CAM-ICU, POD3
Huang Q	2021	Radical resection of esophageal cancer	Intranasal administration of insulin at a dosage of 20 U, administered twice daily for 2 d prior to surgery and continuing until the day of surgery, 10 min before the induction of anesthesia	NS	40/40	66.4±3.1/ 68.0±3.1	CAM-ICU, POD5
Shi Q	2023	Radical resection of esophageal cancer	Intranasal administration of insulin at a dosage of 20–40 U, administered twice daily for 2 d prior to surgery and continuing until the day of surgery, 10 min before the induction of anesthesia	NS	70/24	67.1±4.5/ 66.0±4.4	RASS,CAM-ICU, POD3
Huang QQ	2021	Radical gastrointestinal resection	Intranasal administration of insulin at a dosage of 20 U, administered twice daily for 2 d prior to surgery and continuing until the day of surgery, 10 min before the induction of anesthesia	NS	33/33	69.0±4.0/ 69.0±4.0	CAM-ICU, POD3

NOTE NS. Normal saline; T. Test group; C. Control group; CAM-ICU. Confusion assessment method of intensive care unit; RASS. Richmond Agitation and Sedation Scale; POD numbers: postoperative assessment of delirium days.

3.3 Literature quality assessment Five studies were evaluated using the Cochrane bias risk tool. All five studies were randomized controlled trials; four of them[15-18] employed the randomized numeric table method for allocation, while one study[19] did not specify the allocation method in the text, which was deemed "uncertain"; one[18] provided the allocation method of concealment and a detailed description of the specific blinding process, whereas the remaining four[15-17,19] lacked explicit statements regarding these aspects, leading to a judgment of "unclear"; four had complete information on participant follow-up, while one study[19] did not include any information on this matter and was classified as "high risk"; studies demonstrated complete and non-selective reporting of outcome indicators and were assessed as "low risk". No other relevant biases were identified in the included literature (Fig. 2).

3.4 Meta analysis

3.4.1 Combined statistics. A meta-analysis of the results from the five included studies revealed no statistical heterogeneity among the studies ($I^2=0\%$, $P=0.96$), while demonstrating acceptable clinical heterogeneity, utilizing a fixed-effects model. The findings indicated that the overall incidence of POD in all patients treated with INI preoperatively (12.1%) was significantly lower than that in the placebo group (46.0%). This difference was statistically significant [$RR=0.35$, 95% CI (0.23–0.53), $Z=5.09$, $P<0.001$], suggesting that INI has a substantial protective effect (Fig. 3). Additionally, a sensitivity analysis was conducted, indicating that the current conclusions were robust (Fig. 4).

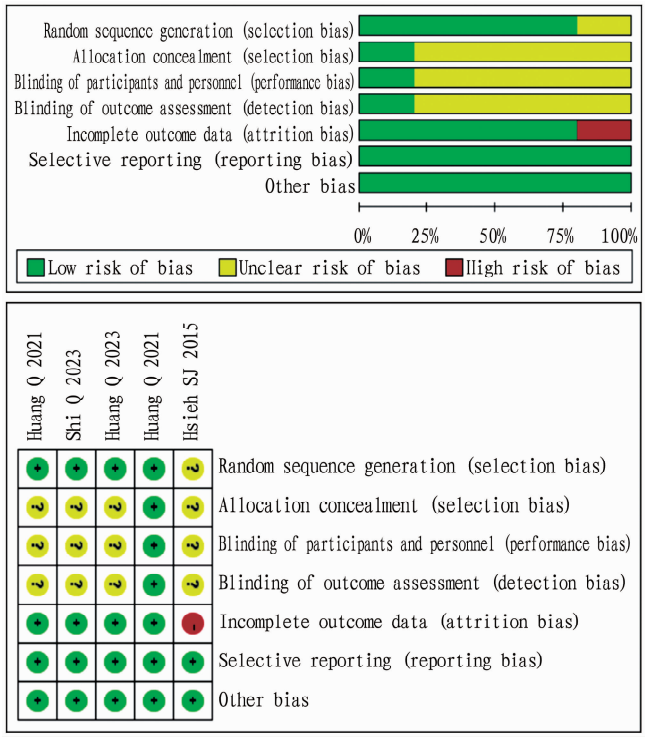

Fig. 2 Risk of bias assessment of the included literature

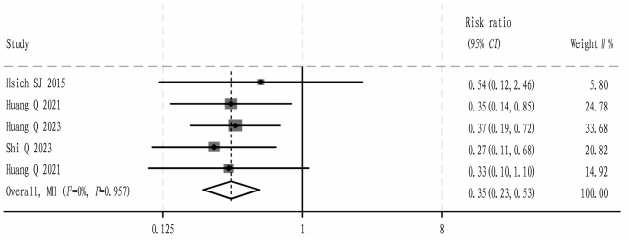

Fig. 3 Forest plot of total effective rate of repeated intranasal insulin in the prevention of postoperative delirium

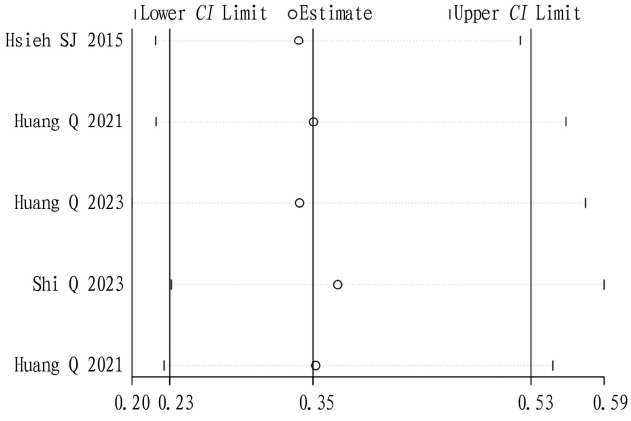

Fig. 4 Sensitivity analysis

3.4.2 Insulin dose. To further investigate the potential impact of varying doses of INI on the incidence of POD, we compared the different doses administered in the aforementioned population. The heterogeneity among the study results was substantial ($I^2 = 55\%$, $P = 0.141$), and a meta-analysis was conducted using a random-effects model. The results indicated that the incidence of POD was significantly lower in the 20 U dose group [$RR = 0.45$, 95% CI: (0.29, 0.70), $P < 0.001$] and the 30 U dose group [$RR = 0.10$, 95% CI: (0.03, 0.42), $P < 0.001$] compared to the control group. The findings were statistically significant in both groups. However, in the 40 U dose group ([$RR = 0.47$, 95% CI: (0.17, 1.34), $P = 0.16$), the results were not statistically significant (Fig. 5). In accordance with the literature, the incidence of POD in the 30 U dose group was significantly lower than that in both the control group and the 20 U dose group. This suggests that the preventive effect of administering a 30 U dose is more pronounced when using the INI method.

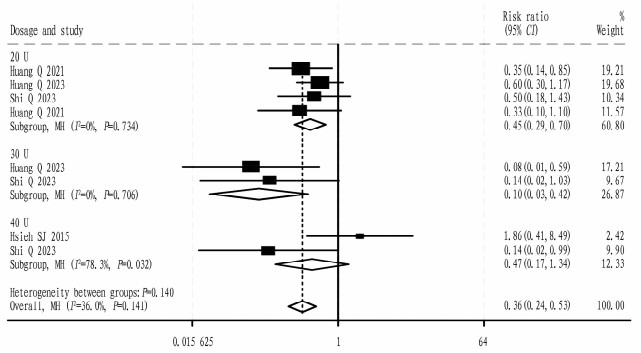

Fig. 5 Forest map of effective rate of prevention of postoperative delirium with different doses of intranasal insulin

3.4.3 Safety. Adverse reactions, including symptoms of nasal irritation following administration, hypoglycemic reactions, and allergic reactions to insulin, were reported in four of the five studies included, as shown in Table 2. In the test group that received a nasal dose of 40 U, there were two cases of hypoglycemic reactions, accompanied by a significant increase in the TNSS compared to the control group and the other groups ($P < 0.05$). However, none of the participants exhibited edema, bleeding, or ulceration in the visualized area of the nose. The text did not specifically report the distribution of population, indicating a potential risk of hypoglycemia and nasal irritation symptoms associated with the nasal administration of 40 U insulin, compared to the other trial groups.

Table 2 Overview of the primary and secondary outcomes included in the literature

First author	Year	Number of case (T/C)	Primary outcome	Secondary outcome		
			Proportion of POD occurrence (T/C)	Nasal irritation	Hypoglycemic reaction	Allergic reaction
Hsieh SJ	2015	10/11	2/11 VS 4/10	–	–	–
Huang Q	2023	60/30	10/60 VS 19/30	0	0	0
Huang Q	2021	40/40	5/40 VS 19/40	0	0	0
Shi Q	2023	70/24	6/70 VS 10/24	*	2	0
Huang Q	2021	33/33	3/33 VS 11/33	0	0	0

NOTE T. Trial group; C. Control group; –. Unreported; *. statistically different TNSS in the literature.

4 Discussion

Currently, the specific mechanisms underlying POD remain unclear. Several hypotheses have been proposed, including the "neuroinflammatory hypothesis"[6,20], the "neurotransmitter hypothesis"[21], and the "central nervous system insulin hypothesis"[22]. Additionally, treatment approaches for POD are also a subject of controversy. In clinical practice, the current treatment for POD primarily relies on psychotropic sedatives to alleviate patient symptoms. These medications include dexmedetomidine, ketamine, diazepam, and etizolam[23]. For patients with pre-existing psychiatric disorders, there are absolute contraindications to the use of these medications, as they may exacerbate the condition and increase risks if not managed appropriately. In recent years, advancements in central insulin research have revealed that insulin plays a crucial role in the growth and differentiation of neurons and glial cells, as well as in the regulation of the nervous system. Animal model studies have demonstrated that impaired central insulin signaling contributes to neurodegeneration, which not only affects

intracranial nerve conduction but also weakens the integrity of the blood-brain barrier[11]. When the body experiences significant trauma, the systemic inflammatory response can extend to the central nervous system, resulting in an imbalance in the intracranial environment and potentially triggering mental disorders. It has been demonstrated that timely supplementation with insulin or insulin activators promotes the survival of nerve cells and prevents their degeneration. Based on this finding, INI may be a viable treatment option for mild cognitive dysfunction. For patients with POD, surgery and trauma are significant triggers. Research has demonstrated that the risk of POD is closely associated with patient age, quality of life, and the duration of surgery. These various factors interact to ultimately contribute to the development of POD.

The literature included in this study reported adverse reactions associated with the use of INI. The results indicated that administering INI at the appropriate dosage was effective in preventing POD and minimizing the occurrence of adverse reactions. Nevertheless, the current evidence base is somewhat limited by the small number of high-quality, well-controlled studies, which calls for cautious interpretation of the findings and highlights the need for further robust research.. The four papers included were derived from studies involving the same subject group at different time points, which inevitably introduced some bias. Furthermore, there was inadequate control of confounding factors during the experimental process, such as the surgical team, duration of surgery, and preoperative nutritional status. These factors may influence the study's results and consequently introduce additional bias. Additionally, the limited number of cases included in the study may have contributed to inaccuracies in the results. In the subgroup analysis, the 40 U dose group did not demonstrate a statistically significant difference in the prevention of POD. The potential reasons for this lack of significance are as follows: i) the presence of sampling error, compounded by the small sample size, which hindered the ability to detect statistical differences, and ii) fluctuations in the rates of transport via pathways such as axonal transport and receptor-mediated cytophagy through the trigeminal pathway, which may diminish the preventive effect of POD when administering the 40 U dose. Among the secondary outcomes, the various adverse effects exhibited a significant difference solely in the Total Nasal Symptom Score (TNSS) within the 40 U dose group. However, the existing literature further underscores that the absence of visible symptoms, such as edema, bleeding, and ulceration, indicates that this treatment is relatively safe for use. In one study, there were only a limited number of reports regarding TNSS and two cases of hypoglycemia, and it was not feasible to obtain sufficient detailed information for a comprehensive analysis.

Furthermore, it is important to emphasize that preoperative insulin prophylaxis is not currently recommended as the preferred treatment approach according to both domestic and international guidelines for the prevention and management of POD[24]. To ensure patient safety and uphold the patient's best interests, it is essential to adhere strictly to the established contraindications[19].

References

[1] PLASCHKE K, FICHTENKAMM P, SCHRAMM C, *et al.* Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6[J]. Intensive Care Medicine, 2010, 36(12): 2081 – 2089.

[2] JIN Z, HU J, MA D. Postoperative delirium: Perioperative assessment, risk reduction, and management[J]. British Journal of Anaesthesia, 2020, 125(4): 492 – 504.

[3] KUNICKI ZJ, NGO LH, MARCANTONIO ER, *et al.* Six-year cognitive trajectory in older adults following major surgery and delirium[J]. JAMA Internal Medicine, 2023, 183(5): 442 – 450.

[4] WATNE LO, IDLAND AV, FEKES D, *et al.* Increased CSF levels of aromatic amino acids in hip fracture patients with delirium suggests higher monoaminergic activity[J]. BMC Geriatrics, 2016, 16: 149.

[5] SWARBRICK CJ, PARTRIDGE J. Evidence-based strategies to reduce the incidence of postoperative delirium: A narrative review[J]. Anaesthesia, 2022, 77(Suppl 1): 92 – 101.

[6] CHEN H, MO L, HU H, *et al.* Risk factors of postoperative delirium after cardiac surgery: A meta-analysis[J]. Journal of Cardiothoracic Surgery, 2021, 16(1): 113.

[7] EVERED LA, SILBERT BS. Postoperative cognitive dysfunction and noncardiac surgery[J]. Anesthesia & Analgesia, 2018, 127(2): 496 – 505.

[8] MIAO M, WANG Y, WANG YC, *et al.* Research progress on postoperative delirium in elderly patients[J]. Basic Medical Theory Research, 2022, 4(4): 22 – 25. (in Chinese).

[9] CROWE TP, GREENLEE M, KANTHASAMY AG, *et al.* Mechanism of intranasal drug delivery directly to the brain[J]. Life Sciences, 2018, 195: 44 – 52.

[10] PICONE P, SABATINO MA, DITTA LA, *et al.* Nose-to-brain delivery of insulin enhanced by a nanogel carrier[J]. Journal of Controlled Release, 2018, 270: 23 – 36.

[11] FAN LW, CARTER K, BHATT A, *et al.* Rapid transport of insulin to the brain following intranasal administration in rats[J]. Neural Regeneration Research, 2019, 14(6): 1046 – 1051.

[12] HIGGINS JP, ALTMAN DG, GOTZSCHE PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials[J]. BMJ, 2011, 343: d5928.

[13] WAN X, WANG W, LIU J, *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range[J]. BMC Medical Research Methodology, 2014, 14: 135.

[14] LUO D, WAN X, LIU J, *et al.* Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range[J]. Statistical Methods in Medical Research, 2018, 27(6): 1785 – 1805.

[15] SHI Q, HUANG QQ, LIN L, *et al.* Effects of different doses of insulin nasal drops on postoperative delirium in elderly patients undergoing radical esophageal cancer surgery[J]. Chongqing Medicine, 2023, 52(19): 2930 – 2934, 2939. (in Chinese).

[16] HUANG QQ, LI Q, YUAN LB, *et al.* Effect of repeated intranasal insulin on postoperative delirium in elderly patients undergoing general anesthesia[J]. Chinese Journal of Anesthesiology, 2021, 41(1): 39 – 42. (in Chinese).

[17] HUANG Q, SHI Q, YI X, *et al.* Effect of repeated intranasal administration of different doses of insulin on postoperative delirium, serum tau and Aβ protein in elderly patients undergoing radical esophageal cancer surgery[J]. Neuropsychiatric Disease and Treatment, 2023, 19: 1017 – 1026.

[18] HUANG Q, LI Q, QIN F, *et al.* Repeated preoperative intranasal administration of insulin decreases the incidence of postoperative delirium in elderly patients undergoing laparoscopic radical gastrointestinal surgery: A randomized, placebo-controlled, double-blinded clinical study[J]. American Journal of Geriatric Psychiatry, 2021, 29(12): 1202 – 1211.

(To page 70)

[34] FERNANDES AC, MCINTYRE T, COELHO R, *et al*. Impact of a brief psychological intervention on lifestyle, risk factors and disease knowledge during phase I of cardiac rehabilitation after acute coronary syndrome[J]. Revista Portuguesa de Cardiologia, 2019, 38(5): 361 – 368.
[35] HUFFMAN JC, MASTROMAURO CA, BEACH SR, *et al*. Collaborative care for depression and anxiety disorders in patients with recent cardiac events[J]. JAMA Internal Medicine, 2014, 174(6): 927 – 935.
[36] BLUMENTHAL JA, SHERWOOD A, SMITH PJ, *et al*. Enhancing cardiac rehabilitation with stress management training: A randomized, clinical efficacy trial[J]. Circulation, 2016, 133(14): 1341 – 1350.
[37] SKI CF, CASTLE DJ, GARRY T, *et al*. Brief psychological intervention in phase I of cardiac rehabilitation after acute coronary syndrome [J]. Revista Portuguesa de Cardiologia, 2017, 36(9): 641 – 649.
[38] ABREU A. Brief psychological intervention in patients admitted after acute coronary syndrome: Essential or secondary[J]. Revista Portuguesa de Cardiologia, 2017, 36(9): 651 – 654.
[39] DAO TK, YOUSSEF NA, ARMSWORTH M, *et al*. Randomized controlled trial of brief cognitive behavioral intervention for depression and anxiety symptoms preoperatively in patients undergoing coronary artery bypass graft surgery [J]. Journal of Thoracic and Cardiovascular Surgery, 2011, 142(3): e109 – e115.
[40] WHALLEY B, THOMPSON DR, TAYLOR RS. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis[J]. International Journal of Behavioral Medicine, 2014, 21 (1): 109 – 121.
[41] LESPÉRANCE F, FRASURE-SMITH N, KOSZYCKI D, *et al*. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease[J]. JAMA, 2007, 297(4): 367 – 379.
[42] KRONISH IM, RIECKMANN N, BURG MM, *et al*. The effect of enhanced depression care on adherence to risk-reducing behaviors after acute coronary syndromes: Findings from the COPES trial[J]. American Heart Journal, 2012, 164(4): 524 – 529.
[43] COSSETTE S, FRASURE-SMITH N, LESPÉRANCE F. Clinical implications of a reduction in psychological distress on cardiac prognosis in patients participating in a psychosocial intervention program[J]. Psychosomatic Medicine, 2001, 63(2): 257 – 266.
[44] COSSETTE S, FRASURE-SMITH N, LESPÉRANCE F. Nursing approaches to reducing psychological distress in men and women recovering from myocardial infarction[J]. International Journal of Nursing Studies, 2002, 39(5): 479 – 494.
[45] BURG MM, LESPÉRANCE F, RIECKMANN N, *et al*. Treating persistent depressive symptoms in post-ACS patients: The project COPES phase-I randomized controlled trial[J]. Contemporary Clinical Trials, 2007, 28(4): 468 – 481.
[46] COWAN MJ, PIKE KC, BUDZYNSKI HK. Psychosocial nursing therapy following sudden cardiac arrest: Impact on two-year survival[J]. Nursing Research, 2001, 50(2): 68 – 76.
[47] BAUMEISTER H, HUTTER N, BENGEL J. Psychological and pharmacological interventions for depression in patients with coronary artery disease [J]. Cochrane Database of Systematic Reviews, 2011 (9): CD008012.
[48] COLLINS LM, MURPHY SA, STRECHER V. The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): New methods for more potent eHealth interventions [J]. American Journal of Preventive Medicine, 2007, 32(5 Suppl): S112 – S118.
[49] TOROUS J, NICHOLAS J, LARSEN ME, *et al*. Clinical review of user engagement with mental health smartphone apps[J]. Evidence-Based Mental Health, 2018, 21(3): 116 – 119.
[50] NICHOLAS J, LARSEN ME, PROUDFOOT J, *et al*. Mobile apps for bipolar disorder: A systematic review of features and content quality[J]. Journal of Medical Internet Research, 2015, 17(8): e198.
[51] FIRTH J, TOROUS J, NICHOLAS J, *et al*. The efficacy of smartphone-based mental health interventions for depressive symptoms: A meta-analysis of randomized controlled trials[J]. World Psychiatry, 2017, 16 (3): 287 – 298.
[52] ANDERSON L, OLDRIDGE N, THOMPSON DR, *et al*. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis[J]. Journal of the American College of Cardiology, 2016, 67(1): 1 – 12.
[53] PIEPOLI MF, HOES AW, AGEWALL S, *et al*. 2016 European Guidelines on cardiovascular disease prevention in clinical practice[J]. European Heart Journal, 2016, 37(29): 2315 – 2381.
[54] PORTER ME. What is value in health care[J]. New England Journal of Medicine, 2010, 363(26): 2477 – 2481.
[55] LADAPO JA, SHAFFER JA, FANG Y, *et al*. Cost-effectiveness of enhanced depression care after acute coronary syndrome: Results from the Coronary Psychosocial Evaluation Studies randomized controlled trial [J]. Archives of Internal Medicine, 2012, 172(21): 1682 – 1684.
[56] DAVIDSON KW, BIGGER JT, BURG MM, *et al*. Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: CODIACS vanguard randomized controlled trial [J]. JAMA Internal Medicine, 2013, 173(11): 997 – 1004.

(From page 62)

[19] HSIEH SJ, FUSTER D, D'ALESSANDRO DA, *et al*. Feasibility and efficacy of intranasal insulin for post-operative delirium the CNS-elders randomized[J]. American Journal of Respiratory and Critical Care Medicine, 2015, 191: A4018.
[20] MALDONADO JR. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways[J]. American Journal of Geriatric Psychiatry, 2013, 21(12): 1190 – 1222.
[21] WANG S, SHI QK, MU XW. Research progress on postoperative delirium and α7 nicotinic acetylcholine receptor[J]. Journal of Clinical Anesthesiology, 2017, 33(12): 1225 – 1227. (in Chinese).
[22] SHPAROV AO, ZORINA II, DERKACH KV. Hot spots for the use of intranasal insulin: Cerebral ischemia, brain injury, diabetes mellitus, endocrine disorders and postoperative delirium[J]. International Journal of Molecular Sciences, 2023, 24(4): 3278.
[23] DUNING T, ILTING-REUKE K, BECKHUIS M, *et al*. Postoperative delirium-treatment and prevention[J]. Current Opinion in Anaesthesiology, 2021, 34(1): 27 – 32.
[24] Chinese Society of Geriatric Anesthesiology. Chinese expert consensus on prevention and treatment of postoperative delirium in elderly patients [J]. International Journal of Anesthesiology and Resuscitation, 2023, 44(1): 1 – 27. (in Chinese).