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Effectiveness of continuous subcutaneous insulin infusion versus multiple daily injections on glycaemic control among older adults with type 2 diabetes: protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Insulin therapy plays an irreplaceable role in glycaemic control among older adults with type 2 diabetes mellitus (T2DM) and can be administered by either multiple daily injections (MDI) of insulin or by a continuous subcutaneous insulin infusion (CSII) pump. Many clinical trials have compared the effects of CSII pumps and MDI in various diabetic populations, but there has been no systematic review and meta-analysis focusing on older adults with T2DM. This study aims to determine whether the CSII pump is associated with better glycaemic control relative to the MDI in older adults with T2DM.

Methods and analysis PubMed, Medline, Cochrane Library, Web of Science core collection, China National Knowledge Infrastructure (CNKI), Wan Fang Database, Chinese Science and Technology Journal Database (VIP) and Chinese Biomedical Literature Database (SinoMed) will be searched from inception to December 2021. Only randomised controlled trials will be included, and the language of the selected studies will be restricted to English and Chinese. Two researchers will independently screen the studies, extract data, assess the risk of bias and evaluate the quality of evidence. Any disagreement will be resolved by consensus or by a third researcher. Data analysis and synthesis will be conducted using RevMan V.5.3. Subgroup analysis, sensitivity analysis and publication bias assessment will be performed, as necessary.

Ethics and dissemination As this study will not contain personal information, ethical approval will not be required. The results of the study will be published in a peer-reviewed journal or at relevant conference.

PROSPERO registration number CRD42021283729.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Only relevant randomised controlled trials, that is, evidence of the highest quality rating, will be included in this study.
⇒ Outcomes are clearly categorised to assess as comprehensively as possible the effect of two injection methods among older adults with type 2 diabetes mellitus.
⇒ The trial sequential analysis will be applied to improve the reliability of the meta-analysis results.
⇒ Various types of insulin usage would be the potential sources of heterogeneity and challenges in analysis and interpretation.
⇒ This study will be limited to English and Chinese languages, consequently, language bias may exist.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the predominant subtype of diabetes, with 1 in 10 people diagnosed with diabetes worldwide, of which 90% are T2DM.[1] T2DM is extremely common among older adults,[2] and it is estimated that older adults with T2DM account for nearly 50% of the population with diabetes.[3] T2DM is characterised by hyperglycaemia, which is mainly attributed to progressive deterioration in the function of insulin-secreting β-cells and is usually accompanied by varying degrees of insulin resistance.[4] Poor glycaemic control in T2DM is exacerbated by ageing, which leads to a decrease in β-cell function, aggravating the lack of insulin secretion.[5] Moreover, chronic exposure to cardiometabolic risk factors, such as obesity and increased insulin resistance, indirectly led to hyperglycaemia.[6] As a result, older adults with T2DM are characterised by higher fluctuating glucose levels, more complications and a higher vulnerability to episodes of severe hypoglycaemia than younger patients.[7] Insulin therapy is recommended to older adults when glycaemic control cannot be optimally maintained with lifestyle management or antidiabetic drugs.[8] Insulin therapy can be delivered by either multiple daily injections (MDI) or by a

continuous subcutaneous insulin infusion (CSII) pump, both of which are standard practices in the National Health Service.[9] The CSII pump can administer insulin continuously to maximise the simulation of physiological insulin secretion using artificial intelligent insulin delivery devices.[10] The advantage of CSII over MDI is that the basal insulin supply can be regulated more accurately, including the possibility of temporarily reducing or suspending basal infusion in the event of hypoglycaemia or exercise.[11] Currently, adolescents and middle-aged adults with type 1 diabetes mellitus (T1DM) are the primary consumers of CSII pumps.[12] Of these, CSII pump therapy (ie, non-hybrid CSII) was shown to be more effective than MDI treatment in lowering HbA1c levels, reducing the incidence of hypoglycaemia and improving the quality of life.[13 14]

Despite the positive effects of CSII pump use in younger adults with T1DM, CSII pump effectiveness has not yet been convincingly demonstrated in T2DM.[15] Several studies have shown that similar to patients with T1DM, patients with T2DM also experienced more improvement in glycaemic control with CSII pumps than with MDI.[16 17] However, Monami and Mitra found that glycaemic control improved equally between the two delivery regimens.[18 19] To date, although CSII pumps have been increasingly used among older adults,[11] there is no systematic review and meta-analysis (SRMA) that has focused on seniors with T2DM comparing the effect of the two injection methods on glycaemic control. Considering that CSII pump therapy involves the use of advanced technology, cognitive decline, physical deterioration, dexterity and visual impairment with ageing, CSII pumps are challenging to navigate for most older adults.[20] The risk of adverse events, such as pump malfunction, catheter infection and even diabetic ketoacidosis caused by dislodgement and occlusion of insulin pumps, may be higher in older adults. Furthermore, skin complications such as inflammation or allergic contact dermatitis, attributed to the insertion or adhesive fixation of the CSII pump, can hinder CSII pump use among older adults with T2DM.[21 22] Another major concern for older patients is the cost of the pumps and supplies. CSII pumps are not reimbursed by the healthcare system for patients with T2DM in most countries, and some surveys have shown that CSII pump therapy is not cost-effective compared with MDI therapy.[23 24]

In conclusion, the effectiveness of these two insulin delivery methods for glycaemic control in patients with T2DM is controversial. Moreover, previous SRMAs in related trials have rarely reported adequate information, especially for older adults in treatment selection.[25 26] Therefore, this study aims to determine if CSII pump therapy is associated with better glycaemic control than MDI treatment among older adults with T2DM and to provide reliable evidence for related clinical applications.

METHODS AND ANALYSIS

The Cochrane Collaboration Handbook[27] will be used to guide the review methods, and the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P)[28] will serve as guidelines for reporting the present protocol and the subsequent formal study. The meta-analysis will be conducted using the Review Manager V.5.3 and the trial sequential analysis will be performed to examine the robustness and reliability of the quantitative findings.

Patient and public involvement
No patients or the public were involved.

Criteria for considering studies
Inclusion criteria
Types of studies

All published randomised controlled trials (RCTs) designed to compare the use of continuous insulin infusions with multiple daily insulin injections in older adults with diabetes will be included.

Types of participants

▶ Patients diagnosed with type 2 diabetes according to the diagnostic criteria proposed by the WHO and International Diabetes Federation.[29] Newly diagnosed type 2 diabetes will be excluded.
▶ Age≥60 years.[30]
▶ Non-perioperative patients.
▶ Participants were able to manage the insulin administration.
▶ No other physical condition that would affect insulin absorption or glucose metabolism, such as uncontrolled hypertension (blood pressure: diastolic>100 or systolic>160 mm Hg), eating disorders (bulimia nervosa) or chronic kidney disease (estimated glomerular filtration rate<45 mL/min/1.73 m^2).
▶ No other active mental health issues that prevent patients from appropriately engaging in diabetes care, such as depression.
▶ No malignant tumour.
▶ No current diabetic ketoacidosis or hyperosmolar coma.

Types of interventions

The experimental group received CSII pump therapy, which allows different basal rates to be set in advance, and automatic infusion of precise boluses can be initiated through CSII pump. In contrast, the control group received MDIs of insulin, usually administered with insulin pens or syringes, consisting of premeal short-acting insulin and long-acting insulin at bedtime. Starting insulin regimens are standardised across both groups, and then modified according to clinical need. For both groups, the total daily dose (TDD) of insulin will be calculated based on body weight: (0.5–0.8) units per kg of body weight per day. For experimental group, TDD will be divided into 50% of basal dosing and 50% of prandial dosing. Additional boluses of insulin will be given when 5 g or more

of carbohydrate are consumed. For control group, 50% of TDD as long-acting insulin will be administered once daily, and the remaining 50% will be administered as short-acting insulin in three divided doses before meals. Further boluses of short-acting insulin will be administered when 10g or more of carbohydrate consumed. Specific adjustments to prandial dosing will be made in accordance with the individual's blood glucose values and carbohydrate consumption. There was no restriction on the method of blood glucose monitoring and other antidiabetic medications, but the method should be consistent between the two groups. Additionally, studies that achieve continuous insulin infusion via a hybrid loop system will not be considered for inclusion.

Types of outcome measures
Main outcomes
1. Immediate blood glucose levels
   – Fasting plasma glucose (FPG) is defined as no caloric intake for at least 8h.[31]
   – 2-hour postprandial blood glucose (2h-PBG).
2. Long-term blood glucose levels
   – The mean value of haemoglobinA1c (HbA1c) at the end of treatment.
   – The mean value of glycosylated albumin at the end of treatment.
3. Glycaemic variability.
   – Mean amplitude of glycaemic excursion (MAGE).
   – The SD of mean glucose (SDBG).
   – Per cent time in target glycaemic range (3.9–10.0mmol/L (70–180mg/dL)).[7]
4. The incidence of adverse events
   – The incidence of hypoglycaemia episodes which is defined as blood glucose≤3.9mmol/L.[32]
   – The incidence of diabetic ketoacidosis.

Additional outcomes
► Quality of life scores.
► Treatment satisfaction.
► Adherence to the treatment regimen.
► The total daily dose of insulin.
► Incidence of adverse skin reactions, such as inflammation and allergic contact dermatitis at the infusion site.

Exclusion criteria
► Observational studies, systematic reviews, case reports, conference summaries, etc.
► Duplicate articles.
► The extracted data are unavailable after being contacted by the corresponding author.

Data sources and search strategy
Electronic searches
Online electronic databases will be searched from inception to December 2021, including PubMed, Medline, Cochrane Library, Web of Science Core Collection, China National Knowledge Infrastructure (CNKI), Wan Fang Database, Chinese Science and Technology Journal

Table 1 Search strategy for Cochrane

Number	Search terms
1	Mesh descriptor: (Diabetes Mellitus, Type 2) explode all trees
2	(diabetes mellitus, non-insulin dependent OR diabetes mellitus, ketosis resistant OR diabetes mellitus, type II OR type 2 diabetes mellitus OR diabetes, type 2 OR NIDDM): ti, ab, kw
3	#1 OR #2
4	Mesh descriptor: (Insulin Infusion System) explode all trees
5	(continuous subcutaneous insulin infusion OR insulin pump OR artificial endocrine pancreas OR artificial beta cell OR CSII): ti, ab, kw
6	#4 OR #5
7	(multiple daily injections OR MDI OR flexible multiple daily insulin OR FMDI OR multiple subcutaneous injections OR MSI OR intensive insulin therapy OR multiple injection regimens): ti, ab, kw
8	#6 AND #7
9	Mesh descriptor: (Aged) explode all trees
10	(old* OR elderly OR senile OR aging OR senior citizen OR geriatric OR seniors OR older adult): ti, ab, kw
11	#9 OR #10
12	Mesh descriptor:(Randomized Controlled Trial (Publication Type)) explode all trees
13	('randomized controlled trial'): pt
14	(randomised OR randomized OR controlled OR RCT OR randomly): ti, ab, kw
15	#12 OR #13 OR #14
16	#3 AND #8 AND #11 AND #15

Database (VIP) and Chinese Biomedical Literature Database (SinoMed). The language of the final selected research was restricted to Chinese or English. The detailed Cochrane search strategy is presented in table 1, and the search strategies for other databases are shown in online supplemental file 1.

Other resources
The National Institutes of Health clinical registry Clinical Trials, International Clinical Trials Registry Platform, Australian New Zealand Clinical Trials Registry and Chinese Clinical Registry will be searched for unpublished or ongoing trial data.

Data collection and extraction
Selection of studies
The results of the above-mentioned databases search will be exported to EndNote software V.X9 (Clarivate Analytics, Pennsylvania, USA). After removing duplicates, two reviewers, who have learnt evidence-based courses, will work independently to check the eligibility of the

studies: title, abstract section and keywords. Full articles were retrieved for further assessment if the information provided was insufficient to determine eligibility or if the information provided suggested that the study: (1) included people aged≥60 years with type 2 diabetes; (2) compared CSII and MDI (three or more insulin injections per day) and (3) assessed one or more relevant clinical outcome measure(s). If disagreement exists, divergence will be resolved by discussion until a consensus is reached or by consulting the corresponding author. The details of the research selection are displayed in the PRISMA flow diagram presented in figure 1.[33]

Data and information extraction

For studies that met the selection criteria, the data will be extracted independently and in duplicate by two reviewers
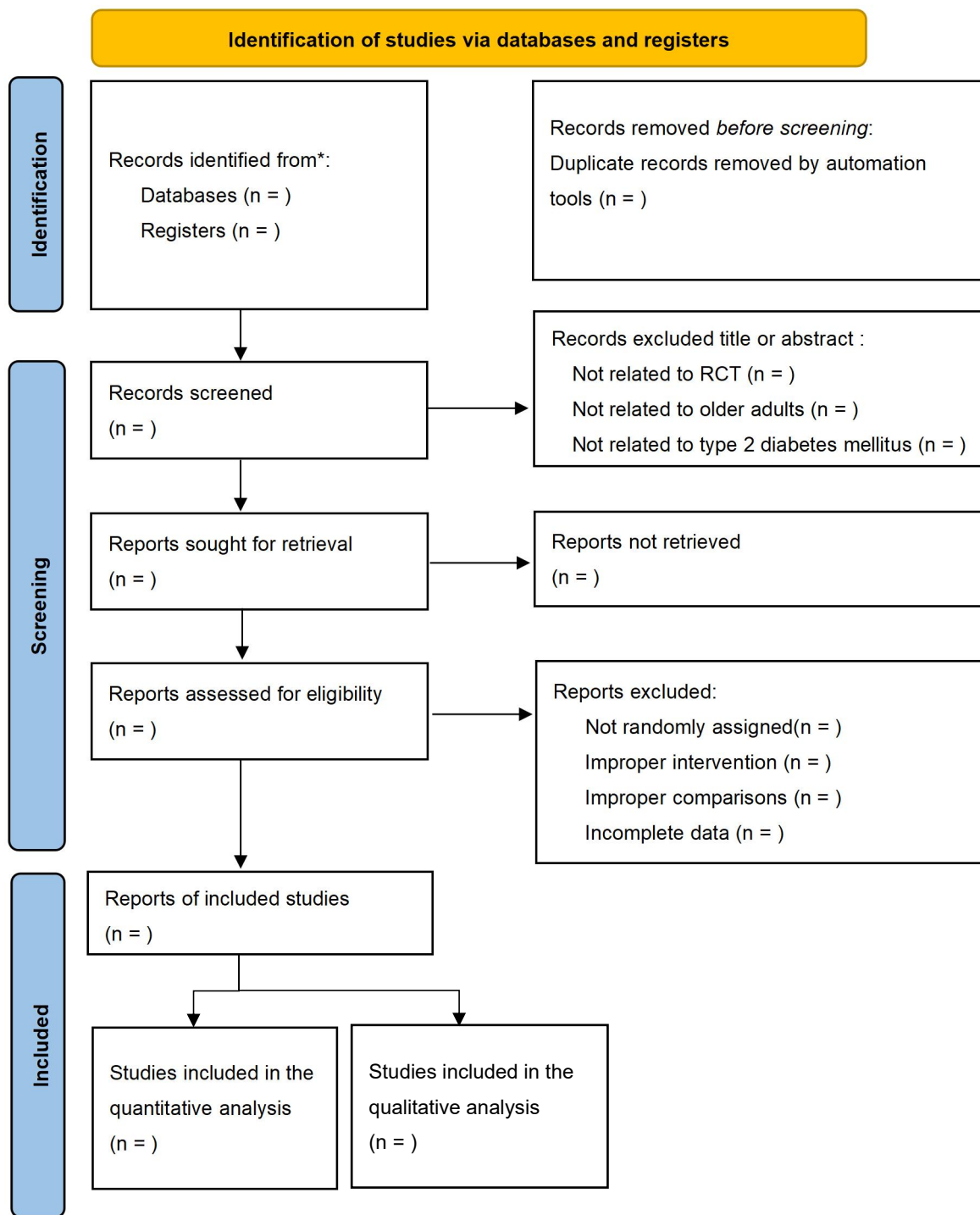

Figure1. The PRISMA flow diagram shows the details of research selection

Figure 1 The PRISMA flow diagram shows the details of research selection. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis.

Table 2 Main characteristics of the included studies

Reference	Country of origin	Sample size	Age	Interventions	Length of intervention	Outcome measures
First author, year of publication	Country or region	Number of participants received each treatment (CSII:MDI)	The mean age of participants in each treatment group	The detailed interventions of each treatment group	Duration of intervention	1. The mean value of HbA1c. 2. The mean value of glycosylated albumin. 3. Fasting plasma glucose (FPG). 4. 2-hour postprandial blood glucose (2h-PBG). 5. Mean amplitude of glycaemic excursion (MAGE). 6. The SD of mean glucose (SDBG). 7. Time in target glycaemic range (TIR). 8. The incidence of hypoglycaemia episodes. 9. Number of occurrences of diabetic ketoacidosis. 10. Number of adverse reactions of the skin at the infusion site. 11. Quality of life scores. 12. Treatment satisfaction. 13. Adherence to the treatment regimen. 14. The total daily dose of insulin. 15. The time to achieve glycaemic target.

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

with a predesigned data extraction template. The template will be piloted independently by two reviewers trained in data extraction. Both reviewers will then extract three studies independently and discuss any discrepancies to ensure accuracy and consistency with data extraction for the remaining studies. The corresponding author will be consulted if discrepancies persist. The following data will be extracted from the eligible studies, and detailed information is shown in table 2.
1. Basic information of the study (first author, publication year, and country of origin).
2. Participant characteristics (sample size average age).
3. Intervention and control (insulin therapy protocols and duration of treatment).
4. Outcome measures.

One reviewer will be responsible for transferring data into Microsoft Office Excel. Another will confirm that data are input correctly by comparing the data presented in Excel with the study reports. Inquiries will be directed to the corresponding author if data to be extracted are missing, incomplete, or ambiguous.

Evaluation of research quality
Each eligible paper will be evaluated by two independent reviewers before inclusion in the review using the Cochrane risk of bias tool for RCTs,[34] which contains the following six dimensions: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result and (6) overall biases. The risk of bias of each dimension will be assessed

according to three criteria: 'low risk of bias', 'high risk of bias' or 'some concerns'. Disagreements between the two reviewers will be resolved by consensus or by a third researcher if needed.

Measures of treatment effect
For continuous outcomes, results will be expressed as mean differences (MD) calculated from the end-of-treatment values, with 95% CI to measure the therapeutic effect when the quantitative data are measured in the same way or from a small data scale. Otherwise, the standardised mean difference (SMD) with 95% CI will be calculated. For dichotomous outcomes, data will be analysed using risk ratios (RR) with 95% CI.

Addressing missing data
Relevant missing information that needed to be extracted was sought from the corresponding author of the original study where feasible. Articles will be excluded if vital information is unavailable.

Data analysis
The χ^2 test will be used to qualitatively determine whether there is heterogeneity between the studies. If the p-value is <0.10, heterogeneity across studies will be statistically significant. The size of the heterogeneity among the eligible studies will be assessed using the I^2 statistic, whose values are classified as follows: no relevant heterogeneity (0%–25%), moderate heterogeneity (25%–50%) and substantial heterogeneity (>50%).[35] When the value of I^2 is less than or equal to 50%, the fixed-effects model will be used to analyse the data; if I^2>50%, the random-effects

model will be used. Moreover, subgroup analysis or meta-regression analysis will be performed to explore the causes of heterogeneity.

Publication bias will be assessed by applying a funnel plot if more than 10 trials are eventually included.

Data synthesis

Review Manager V.5.3 software will be used for data analysis in this review. For continuous outcomes, the MD and 95% CI will be calculated to describe the effect size if the outcomes are measured using the same method. Otherwise, SMD and 95% CI will be provided. For dichotomous results, data will be analysed using RR with 95% CI. When the I^2 value is less than 50, indicating acceptable heterogeneity, the fixed-effect model will then be used for data synthesis.[36] If I^2 values are greater than 50%, the heterogeneity is significant, and subgroup analysis or meta-regression is necessary. For clinically heterogeneous studies or studies with insufficient information for pooling, a qualitative analysis will be performed to synthesise the characteristics and findings of the included studies.

Subgroup analysis

Subgroup analysis will be conducted to explore sources of heterogeneity, if there exists significant clinical heterogeneity in the included trials. The predefined subgroups include the type of insulin used in each group, the length of follow-up and the age group of the participants.

Sensitivity analysis

Sensitivity analysis is mainly used to evaluate the reliability of the meta-analysis results. We will determine the stability of the meta-analysis results by excluding studies with small sample sizes or of low quality. The meta-analysis results can be accepted if the outcomes do not change after the sensitivity analysis. Otherwise, the results should be treated with caution and re-evaluation is needed.

Trial sequential analysis (TSA)

To enhance the reliability of the meta-analysis results, trial sequential analysis (TSA) V.0.9, developed by the CTU of the Copenhagen Clinical Trial Centre, will be used to avoid random errors caused by sparse data and repeated significance testing when accumulating data from multiple trials.[37] TSA is a methodology that calculates the required information size (RIS) for meta-analysis to clarify whether additional trial analyses are needed to achieve a reliable conclusion as early as possible. Additionally, TSA provides adjusting significance levels called trial sequential monitoring boundaries to control risks for type I and type II errors, which are formed by correction and the significant horizontal line and cumulative Z-value curve of the meta-analysis.

When the cumulative Z-value curve crossed the trial sequential monitoring boundary, or the futility boundary or reached the RIS, there was adequate evidence for the anticipated intervention effect, and no additional trials were required. If the Z-curve did not cross any of the boundaries and the RIS was not achieved, the evidence was inadequate to form a conclusion, and further trials were required to validate the results.

Quality of evidence

The strength of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation tool.[38] The evaluation items included the risk of bias, inconsistency, indirectness, imprecision and publication bias. Two researchers will independently access the quality of the evidence based on five criteria. The results will be divided into four levels: high, medium, low, and very low.

Ethics and dissemination

Ethics approval is not required since no human participants or their detailed identity information was involved in this study. The findings of this study will provide a systematical evidence of CSII for older adults with T2DM, which will benefit clinical applications and further research. Also, this study is anticipated to be published in a peer-reviewed journal or disseminated at relevant conference.

Amendments

If the protocol is revised, the important amendments will be described in the final report.

DISCUSSION

As diabetic management technology possesses the features of universality, affordability and accessibility, CSII pumps have gained wider use among older adults with T2DM.[11] However, most previous SRMAs primarily assessed the effect of CSII pump therapy in patients with type 1 diabetes, particularly in young and middle-aged patients.[39 40] This study will focus on older adults with T2DM and determine whether CSII pump therapy provides superior blood glucose control compared with MDI therapy. The effect of the two insulin regimes on glycaemic control will be evaluated in multiple dimensions: blood glucose level, glycaemic variability, incidence of adverse events and patient-reported outcomes. Compared with persistent hyperglycaemia, blood glucose fluctuations are more severe in older adults and are closely linked to the development and progression of chronic complications of diabetes.[41 42] MAGE, SDBG and TIR, which can precisely reflect the within-day magnitude of blood glucose fluctuations, were included in this study as observation indicators to provide a more comprehensive picture of the effect of glycaemic control.

In view of the meta-analysis increasing the power and precision of the estimated intervention effects, it may report spurious significant results (type 1 error) due to repeated significance testing when updating the meta-analysis with new trials. Therefore, TSA will be introduced in this study to avoid prematurely declaring the

superiority of intervention by providing the RIS and trial sequential monitoring boundaries.

It is essential to recognise the potential limitations of this review, the heterogeneous design may affect the reliability of the conclusion. Although the relevant subgroup analysis and meta-regression will be performed, the source of heterogeneity may be difficult to be completely elucidated due to insufficient data. In addition to this, due to the limitation of language ability, this review will only retrieve the write-ups written in Chinese and English, there is the risk of missing potential studies published in any other language, which indicates that more articles in different languages need to be included for future research.

This study expects that the evidence generated from this review will help older adults with T2DM to select a more appropriate insulin therapy method and achieve better glycaemic control, thus potentially improving their overall health status.

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