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Comparative efficacy and safety of stem cell-based therapies for diabetes mellitus: a systematic review and Bayesian network meta-analysis of randomized controlled trials

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Research Article

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Abstract

Background

Current glucose-lowering therapies improve glycemic control but do not directly reverse β-cell loss or dysfunction. Stem cell-based therapies may offer disease-modifying potential through immunomodulatory, paracrine, and regenerative mechanisms, but the relative efficacy and safety of different cellular strategies remain uncertain.

Methods

PubMed, Embase, Web of Science, the Cochrane Library, and ClinicalTrials.gov were searched from inception to June 10, 2026. Randomized controlled trials of stem cell-based therapies in type 1 or type 2 diabetes were included. Outcomes were glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting C-peptide, total daily insulin dose (TDD), and adverse events (AEs). Random-effects Bayesian network meta-analysis estimated mean differences (MDs) or odds ratios with 95% credible intervals (CrIs).

Results

Twenty-one reports representing 19 randomized controlled trials involving 691 participants were included. Compared with standard medical therapy (SMT), combined mesenchymal stem/stromal cell plus mononuclear cell therapy reduced HbA1c (MD, − 1.26%; 95% CrI, − 1.97 to − 0.54; moderate confidence) and FPG (MD, − 2.24 mmol/L; 95% CrI, − 3.93 to − 0.56; moderate confidence). Mesenchymal stem/stromal cell therapy also reduced HbA1c versus SMT (MD, − 0.95%; 95% CrI, − 1.70 to − 0.09; very low confidence), and mononuclear cell therapy reduced FPG versus SMT (MD, − 2.03 mmol/L; 95% CrI, − 3.75 to − 0.35; low confidence). Combined therapy showed the most favorable ranking probabilities for HbA1c, FPG, and TDD, but its effect on TDD was not statistically credible. No statistically credible differences were observed for fasting C-peptide or AEs, and meta-regression found no credible evidence of effect modification by diabetes type. Rankings should be interpreted cautiously because the evidence was sparse and confidence in many estimates was low or very low.

Conclusions

Combined mesenchymal stem/stromal cell plus mononuclear cell therapy may provide favorable glycemic effects, but evidence remains insufficient for firm conclusions or routine clinical use. Adequately powered, independently conducted multicenter randomized trials are needed.

Systematic review registration:

PROSPERO CRD420261420380

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder caused by absolute or relative insulin deficiency and impaired insulin utilization, characterized by persistent hyperglycemia. Clinically, DM is mainly categorized as type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus, and other specific types of diabetes. T1DM is primarily caused by immune-mediated destruction of pancreatic β cells, whereas T2DM is characterized by insulin resistance accompanied by progressive β-cell dysfunction. Despite their distinct pathogenic mechanisms, both conditions are associated with inadequate functional β-cell capacity and an increased risk of microvascular and macrovascular complications(1). According to the 11th edition of the International Diabetes Federation Diabetes Atlas, approximately 589 million adults aged 20–79 years were living with diabetes worldwide in 2024, and this number is projected to reach 853 million by 2050(2, 3). Although current glucose-lowering therapies improve glycemic control and reduce the risk of diabetes-related complications, they do not directly reverse the underlying β-cell loss or dysfunction and generally require long-term treatment.

Stem cell-based therapy has therefore attracted increasing attention as a potential disease-modifying and regenerative strategy for diabetes. A broad range of cellular products has been investigated, including mesenchymal stem/stromal cells (MSC), hematopoietic stem cells (HSC), mesenchymal precursor cells (MPC), mononuclear cells (MNC), umbilical cord blood-derived cells (UCB), and combined cellular regimens. MSC may exert therapeutic effects predominantly through immunomodulatory, anti-inflammatory, trophic, and paracrine mechanisms rather than through direct and durable replacement of pancreatic β cells(4). HSC transplantation may modify or reset pathogenic immune responses, particularly in T1DM, whereas MNC- and umbilical cord blood-based interventions comprise heterogeneous cell populations with potentially different regenerative and immunological properties. Treatment effects may consequently vary according to cell type and source, autologous or allogeneic origin, cell dose, route of administration, treatment frequency, and the use of combination regimens.

Previous systematic reviews and pairwise meta-analyses have suggested that stem cell-based therapies may improve glycated hemoglobin (HbA1c), insulin requirements, or C-peptide secretion in patients with diabetes, but their conclusions have not been uniform(5–8). Several reviews focused exclusively on T1DM, MSC therapy, or umbilical cord-derived products, while others combined randomized trials with nonrandomized, single-arm, or before–after studies. Even among reviews restricted to randomized controlled trials (RCTs), the available analyses generally pooled cell therapies into broad categories or compared them only with conventional treatment, thereby providing limited evidence regarding the relative performance of different cellular strategies. A recent meta-analysis of randomized trials in both T1DM and T2DM evaluated MSC-based therapy but did not compare MSC with other cell types or combination regimens(9). Thus, the comparative efficacy and safety of different stem cell-based approaches for diabetes remain uncertain.

Network meta-analysis (NMA) integrates direct and indirect evidence to compare multiple interventions simultaneously within a connected evidence network. Bayesian approaches further permit flexible hierarchical modeling, direct probabilistic interpretation of treatment effects, and estimation of treatment-ranking probabilities while explicitly characterizing uncertainty(10). However, no previous Bayesian NMA has comprehensively compared the main stem cell-based strategies evaluated in eligible RCTs across both T1DM and T2DM, including MSC, HSC, MPC, MNC, umbilical cord blood-derived cells, and combined MSC + MNC therapy. The comparative value of combined MSC + MNC therapy, which may provide complementary immunomodulatory and regenerative effects, also remains unclear. Therefore, we conducted a systematic review and Bayesian NMA to compare the efficacy and safety of stem cell-based interventions with placebo and standard medical therapy (SMT) in patients with diabetes. We further used Bayesian network meta-regression to explore whether diabetes type modified the relative treatment effects, and assessed confidence in the network estimates using the Confidence in Network Meta-Analysis (CINeMA) framework. These analyses may provide a transparent basis for interpreting the comparative evidence and informing future clinical research and trial design.

2. Methods

The protocol for this systematic review and Bayesian network meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261420380). This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and the PRISMA extension statement for network meta-analyses(11, 12). The completed PRISMA checklist is provided in Appendix 1 (Supplementary file).

2.1 Data sources and search strategy

PubMed, Embase, Web of Science, the Cochrane Library, and ClinicalTrials.gov were systematically searched from database inception to June 10, 2026. The search strategy combined controlled vocabulary, including Medical Subject Headings and Emtree terms, with free-text terms related to diabetes mellitus, stem cells and other stem cell-based therapies, and RCTs.

The search terms included, but were not limited to, “diabetes mellitus,” “type 1 diabetes,” “type 2 diabetes,” “stem cell,” “mesenchymal stem cell,” “mesenchymal stromal cell,” “hematopoietic stem cell,” “progenitor cell,” “bone marrow mononuclear cell,” and “peripheral blood mononuclear cell.” No language restrictions were applied. ClinicalTrials.gov was searched to identify additional potentially eligible trials; studies without published and extractable outcome data were not included. The reference lists of relevant studies and reviews were also manually examined to identify additional eligible reports.

All retrieved records were imported into EndNote 20 and duplicates were removed before screening. The complete search strategies for all databases are presented in Appendix 2 (Supplementary file).

2.2 Inclusion and screening process

Eligibility was determined according to the population, intervention, comparator, outcomes, and study design (PICOS) framework.

Studies were eligible if they met the following criteria: (1) Population: participants with a confirmed diagnosis of type 1 diabetes mellitus or type 2 diabetes mellitus, without restrictions on age, sex, ethnicity, disease duration, or baseline glycemic control. (2) Intervention: stem cell-based therapy administered alone or in combination with another eligible cell product. Eligible interventions included MSCs, HSCs, MPCs, MNCs, UCB, and combined MSC plus MNC therapy. (3) Comparator: placebo, SMT, or another eligible cell-based intervention. (4) Outcomes: reporting at least one of the following outcomes: HbA1c, fasting plasma glucose (FPG), fasting C-peptide, total daily insulin dose (TDD), or adverse events (AEs). (5) Study design: RCTs with a minimum follow-up duration of 12 weeks.

Studies were excluded if they were non-randomized or uncontrolled studies, observational studies, case reports, reviews, conference abstracts, animal or in vitro studies, duplicate publications, or studies without sufficient data for quantitative synthesis.

Two reviewers (SW and AT) independently screened the titles and abstracts of all identified records. Reports considered potentially eligible by either reviewer were retrieved for full-text assessment. The same reviewers independently assessed the full texts according to the prespecified eligibility criteria.

Disagreements were resolved through discussion. When consensus could not be reached, a third reviewer (AY) was consulted. When multiple reports described the same parent trial, the reports were linked, participants were counted only once, and duplicate outcome data were not entered more than once. For one RCT that reported results separately for participants with T1DM and T2DM, the two diabetes-type strata were retained as separate analysis units to preserve stratum-specific outcome data and facilitate meta-regression. However, these strata were counted as one parent RCT in all reported study totals. The study selection process was summarized using a PRISMA flow diagram.

2.3 Data extraction and outcome measures

Two reviewers (SW and AT) independently extracted data using a standardized data collection form. Extracted study characteristics included the first author, publication year, country, study phase, trial registration number, study design, follow-up duration, and number of participants in each treatment group.

Participant characteristics included diabetes type, age, body mass index (BMI), duration of diabetes, and baseline values of HbA1c, FPG, fasting C-peptide, and TDD. Intervention characteristics included cell type, tissue source, autologous or allogeneic origin, cell dose, route of administration, number and frequency of administrations.

For continuous outcomes, the mean change from baseline and the corresponding standard deviation were extracted for each treatment group. For the safety outcome, the number of participants experiencing one or more AEs and the total number of participants in each group were extracted. The 12-

month assessment was prespecified as the primary time point for data extraction. When the total follow-up duration of a trial was shorter than 12 months, data from the longest available follow-up were extracted.

When relevant outcome data were reported only in graphical form, they were extracted using WebPlotDigitizer version 4.6. If the standard deviation (SD) of the change score was not reported, it was derived from available P values or confidence intervals using established methods(13, 14). When the required SD could not be obtained from the published figures or calculated from the reported data, we contacted the corresponding authors to request the original data. If no additional data were available, the relevant outcome was excluded from the quantitative synthesis.

2.4 Risk of bias and certainty of evidence

Two reviewers (SW and AT) independently assessed the risk of bias in each included RCT using the Cochrane Risk of Bias 2 (RoB 2) tool(15). The assessment covered five domains: the randomization process, deviations from the intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. Each domain and the overall risk of bias were categorized as low risk of bias, some concerns, or high risk of bias. Disagreements were resolved through discussion or consultation with a third reviewer (AY).

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence in the NMA, classifying confidence into four levels—very low, low, moderate, and high-based on how closely the estimated effect reflects the true effect(16). The assessment was guided by the six domains of the Confidence in Network Meta-Analysis (CINeMA) tool(17, 18), which is designed to evaluate evidence in multi-arm comparisons: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. For CINeMA assessments, prespecified clinically important thresholds were used to judge imprecision and heterogeneity. Clinically important effects were defined as absolute mean differences of 0.50% for HbA1c, 0.50 mmol/L for FPG, 0.10 nmol/L for fasting C-peptide, and 0.20 U/kg/day for TDD. For AEs, odds ratios below 0.80 or above 1.25 were considered clinically important. Because established minimal clinically important differences were unavailable for several outcomes, these thresholds were prespecified based on available literature, clinical interpretability, and the scale of the outcome measures(19–21).

2.5 Statistical Analysis

The Bayesian network meta-analysis was performed in R software (version 4.3.3) using the BUGSnet package (version 1.1.0), with Bayesian model estimation implemented through Just Another Gibbs Sampler (JAGS; version 4.3.1). Network meta-regression analyses were conducted using the gemtc package (version 1.0.2).

Across all outcomes, eligible interventions were classified into eight possible network nodes according to the primary cellular product: MSC, HSC, MPC, MNC, UCB, combined MSC plus MNC therapy, placebo, and SMT. The outcome-specific networks contained subsets of the above nodes. Variations in tissue

source, autologous or allogeneic origin, cell dose, route of administration, and treatment frequency were not used to define separate nodes because the available evidence was insufficient to support a clinically interpretable and connected network at this level of granularity. MSC products derived from different tissue sources were therefore grouped into a common MSC node.

When multiple intervention arms within the same trial represented the same network node, such as different doses or administration routes of the same cellular product, these arms were combined before analysis. For continuous outcomes, sample sizes, means, and standard deviations were combined using the methods recommended in the Cochrane Handbook. For binary outcomes, the numbers of participants with events and the total sample sizes were summed across the relevant arms. When the intervention arms represented different network nodes, all arms were retained within the original multi-arm trial, and the Bayesian model accounted for the correlations between treatment effects sharing a common comparator.

Placebo and SMT were treated as separate nodes because placebo-controlled trials generally included a matched infusion or sham procedure in addition to background medical treatment, whereas SMT groups received background medical treatment without a matched placebo or sham procedure.

For continuous outcomes, including HbA1c, FPG, fasting C-peptide, and TDD, treatment effects were expressed as mean differences (MDs) with 95% credible intervals (CrIs) using a normal likelihood and identity link. For AEs, odds ratios (ORs) with 95% CrIs were estimated using a binomial likelihood and logit link. Random-effects consistency models were used for the primary analyses. SMT was used as the reference treatment for the continuous outcomes, whereas placebo was used as the reference treatment for AEs because SMT was not represented in the connected AEs network.

For each outcome, four Markov chain Monte Carlo (MCMC) chains were run with 5,000 adaptation iterations, 20,000 burn-in iterations, and 50,000 sampling iterations. Model convergence was assessed using trace and density plots and the Brooks–Gelman–Rubin diagnostic, with potential scale reduction factor values below 1.05 indicating satisfactory convergence. Model fit was evaluated using residual deviance, the deviance information criterion (DIC), and leverage plots.

Treatment effects were summarized in league tables and ranking plots. Treatment rankings were estimated using the surface under the cumulative ranking curve (SUCRA), with higher values indicating a more favorable treatment profile(22, 23). Greater reductions in HbA1c, FPG, and TDD and a lower risk of AEs were considered favorable, whereas a greater increase in fasting C-peptide was considered favorable. Network plots were generated using Stata, with node size proportional to the number of participants and edge thickness proportional to the number of direct comparisons.

Between-study heterogeneity was assessed using the posterior distributions of the between-study standard deviation (τ) and variance (τ^2). Global inconsistency was evaluated by comparing the DIC values of the consistency and inconsistency models, with a difference of less than 5 considered negligible(24). Local inconsistency was assessed using node-splitting models in the gemtc package,

with $P < 0.10$ indicating potential inconsistency(25). The transitivity assumption was assessed by visually comparing the distributions of available potential effect modifiers, including baseline age, BMI, HbA1c, FPG, and fasting C-peptide, across intervention groups.

Bayesian network meta-regression was conducted using the gemtc package to examine diabetes type as a potential effect modifier. Unrelated treatment–covariate interaction coefficients were used for continuous outcomes, whereas a shared coefficient was used for AEs because of the sparse evidence network. For the trial reporting separable outcome data for T1DM and T2DM populations, the two diabetes-type strata were entered separately in the meta-regression. Trials with mixed or unspecified diabetes populations were excluded only when diabetes-type-specific outcome data could not be separated. Two sensitivity analyses were conducted to assess the robustness of the primary findings. First, fixed-effect models were fitted and compared with the primary random-effects models. Second, a restricted analysis was performed using random-effects models after excluding trials that primarily targeted diabetes-related complications or included major non-cellular co-interventions that could independently influence metabolic outcomes. Background glucose-lowering therapy routinely provided to both treatment groups was not considered a major co-intervention.

Comparison-adjusted funnel plots were generated using the netmeta package to assess small-study effects. Funnel plot asymmetry was examined visually and using Egger's regression test when at least 10 studies contributed to the outcome, with $P < 0.05$ considered suggestive of asymmetry(26).

3. Results

3.1 Study selection and characteristics

The systematic search identified 4,207 records, including 930 from PubMed, 1,594 from Embase, 741 from Web of Science, 699 from the Cochrane Library, and 243 from ClinicalTrials.gov. After the removal of 1,263 duplicate records, 2,944 records underwent title and abstract screening, of which 2,898 were excluded. The full texts of 46 reports were assessed for eligibility, and 25 were excluded because they did not meet the prespecified PICOS criteria. Ultimately, 21 reports representing 19 independent RCTs involving 691 participants were included in the systematic review and Bayesian network meta-analysis(27–47). The study selection process is presented in Fig. 1.

The included trials were published between 2005 and 2024 and were conducted across 10 countries. Of the 19 independent trials, 10 enrolled participants with T2DM, six enrolled participants with T1DM, two included both T1DM and T2DM populations, and one did not clearly specify the diabetes type. Individual trial sample sizes ranged from 15 to 96 participants, and follow-up durations ranged from 3 to 96 months. The evaluated treatment nodes included mesenchymal stem/stromal cells, hematopoietic stem cells, mesenchymal precursor cells, mononuclear cells, umbilical cord blood-derived cells, combined mesenchymal stem/stromal cell plus mononuclear cell therapy, placebo, and SMT. Cell source, dose,

route of administration, and treatment frequency varied across trials. Detailed study, participant, and intervention characteristics are presented in Appendix 3 (Supplementary file).

3.2 Risk of bias and certainty of evidence

The outcome-specific risk-of-bias assessments are shown in Figs. 2 and 3. A high overall risk of bias was identified in 4 of 18 RCTs contributing to the HbA1c analysis, 1 of 13 RCTs contributing to the FPG analysis, and 4 of 14 RCTs contributing to the fasting C-peptide analysis. None of the 7 RCTs contributing to the TDD analysis or the 7 RCTs contributing to the AEs analysis was judged to be at high overall risk of bias. High-risk judgments were concentrated in the domains of deviations from the intended interventions and missing outcome data, with additional concerns regarding the randomization process. Measurement of the outcome and selection of the reported result were judged to be at low risk of bias across all included RCTs.

The CINeMA assessment indicated that confidence in the network estimates was predominantly low or very low, with a limited number of moderate-confidence comparisons. Of the 28 comparisons for HbA1c, 1 was rated as moderate confidence, 6 as low confidence, and 21 as very low confidence. For FPG, 1 of 21 comparisons was rated as moderate, 7 as low, and 13 as very low. For fasting C-peptide, 5 of 21 comparisons were rated as low and 16 as very low. Among the 15 TDD comparisons, 6 were rated as moderate, 7 as low, and 2 as very low. For AEs, 2 of 6 comparisons were rated as low and the remaining 4 as very low. No comparison was rated as high confidence. The principal reasons for downgrading were within-study bias, imprecision, heterogeneity, and incoherence. Full CINeMA assessments for all treatment comparisons are provided in Appendix 5 (Supplementary file).

3.3 Efficacy and safety outcomes

All five outcome networks were connected. The network structures are presented in Fig. 4. A consistency random-effects model was employed for data analysis in this study. The SUCRA rankings are presented in Fig. 5.

HbA1c

The HbA1c network comprised 18 independent RCTs reported in 20 publications and evaluated eight interventions. The pairwise comparisons are presented in eTable 6.1, while the rankogram and corresponding SUCRA values are shown in eFigure 7 (a) and eTable 7. Compared with SMT, MSC therapy and combined MSC plus MNC therapy were associated with greater reductions in HbA1c (MSC: MD, − 0.95%; 95% CrI, − 1.70 to − 0.09; MSC + MNC: MD, − 1.26%; 95% CrI, − 1.97 to − 0.54). MSC therapy was also associated with a reduction in HbA1c compared with placebo (MD, − 0.61%; 95% CrI, − 1.04 to − 0.15). No statistically credible differences were observed for the remaining comparisons.

According to the SUCRA values, combined MSC plus MNC therapy showed the highest probability of being among the most favorable interventions for HbA1c reduction in the current network (SUCRA, 88.53%), followed by MSC therapy (76.40%) and UCB-derived cell therapy (58.42%). However, this ranking

should be interpreted cautiously because confidence in most HbA1c estimates was low or very low, and local inconsistency was detected in several HbA1c comparisons.

FPG

The FPG network comprised 13 independent RCTs reported in 14 publications and evaluated seven interventions. The pairwise comparisons are presented in eTable 6.2, while the rankogram and corresponding SUCRA values are shown in eFigure 7 (b) and eTable 7. Compared with SMT, MNC therapy and combined MSC plus MNC therapy were associated with greater reductions in FPG (MNC: MD, − 2.03 mmol/L; 95% CrI, − 3.75 to − 0.35; MSC + MNC: MD, − 2.24 mmol/L; 95% CrI, − 3.93 to − 0.56). No statistically credible differences were observed for the remaining treatment comparisons. According to the SUCRA values, combined MSC plus MNC therapy showed the most favorable SUCRA-based ranking for FPG reduction in the current network (SUCRA, 82.62%), followed by MNC therapy (81.48%) and MSC therapy (54.41%). Nevertheless, confidence in most FPG estimates was low or very low, with only the MSC + MNC versus SMT comparison rated as moderate confidence.

Fasting C-peptide

The fasting C-peptide network comprised 14 independent RCTs reported in 15 publications and evaluated seven interventions. The pairwise comparisons are presented in eTable 6.3, while the rankogram and corresponding SUCRA values are shown in eFigure 7 (c) and eTable 7. None of the network comparisons reached statistical significance, with all 95% CrIs crossing the null value. Nevertheless, MNC therapy had the highest SUCRA value for improving fasting C-peptide levels (81.45%), followed by combined MSC plus MNC therapy (75.28%) and HSC therapy (58.94%). These rankings should be interpreted cautiously because the confidence in the estimates was low or very low, largely owing to within-study bias, imprecision, heterogeneity, and incoherence.

TDD

The TDD network comprised seven independent RCTs and evaluated six interventions. The pairwise comparisons are presented in eTable 6.4, while the rankogram and corresponding SUCRA values are shown in eFigure 7 (d) and eTable 7. No statistically credible differences were observed between treatments, as the 95% CrIs for all comparisons included zero. Compared with SMT, combined MSC plus MNC therapy showed a numerically greater reduction in TDD, but the estimate did not reach statistical credibility (MD, − 0.39 U/kg/day; 95% CrI, − 0.80 to 0.03). Combined MSC plus MNC therapy nevertheless achieved the highest SUCRA value (87.53%), followed by MNC therapy (71.41%) and UCB-derived cell therapy (43.81%). Given the absence of a statistically credible treatment effect and the moderate-to-low confidence for most TDD estimates, with very-low confidence for two comparisons, the ranking results should not be interpreted as definitive evidence of treatment superiority.

Adverse events

The AEs network comprised seven independent RCTs and evaluated four interventions. The pairwise comparisons are presented in eTable 6.5, while the rankogram and corresponding SUCRA values are shown in eFigure 7 (e) and eTable 7. No statistically credible differences in AEs risk were detected between any pair of treatments, as all 95% CrIs for the ORs included 1. In the ranking analysis, MSC therapy had the highest SUCRA value for a lower risk of AEs (79.06%), followed by placebo (61.26%), MPC therapy (35.11%), and combined MSC plus MNC therapy (24.57%). These rankings should be interpreted cautiously because of the sparse evidence, substantial imprecision, and low or very-low confidence in all AEs comparisons.

3.4 Model convergence, consistency, heterogeneity, and transitivity

Visual inspection of the trace and density plots showed adequate mixing of the MCMC chains, and the potential scale reduction factors approached 1.00 for all model parameters, indicating satisfactory convergence. The leverage plots did not reveal clear evidence of substantial model misfit. Detailed convergence diagnostics and model-fit assessments are provided in Appendix 13 (Supplementary file).

Global inconsistency was not considered important for the continuous outcomes because the absolute differences in DIC between the consistency and inconsistency models were below 5 for HbA1c (2.67), FPG (0.43), fasting C-peptide (1.06), and TDD (0.03). A DIC-based comparison could not be performed for AEs because the effective number of parameters was not estimable. Node-splitting analyses were feasible for HbA1c, FPG, and fasting C-peptide. Local inconsistency was identified in four HbA1c comparisons: placebo versus MNC (P = 0.017), SMT versus MNC (P = 0.030), placebo versus MSC (P = 0.051), and SMT versus MSC (P = 0.025). No statistically important local inconsistency was detected for FPG or fasting C-peptide. Because the inconsistent HbA1c comparisons involved MSC or MNC nodes against control nodes, potential sources may include within-node clinical heterogeneity, such as differences in MSC tissue source, autologous or allogeneic origin, cell dose, route of administration, follow-up duration, baseline glycemic status, and the distinction between placebo and SMT as control interventions.

The posterior median estimates of the between-study standard deviation (τ) were 0.37 for HbA1c, 0.98 for FPG, 0.13 for fasting C-peptide, 0.18 for TDD, and 0.87 on the log-odds-ratio scale for AEs. Detailed assessments of global inconsistency, local inconsistency, and heterogeneity are provided in Appendix 8 (Supplementary file).

Visual examination of the distributions of baseline age, BMI, HbA1c, FPG, and fasting C-peptide across intervention groups did not reveal a clear systematic imbalance that would seriously challenge the transitivity assumption. The corresponding box plots are presented in eFigure 9 of Appendix 9 (Supplementary file).

3.5 Meta-regression analyses

Network meta-regression was performed to explore whether diabetes type modified the relative treatment effects. For the continuous outcomes, unrelated treatment-specific regression coefficients were estimated, whereas a shared coefficient was used for AEs because of the limited amount of evidence. None of the diabetes-type coefficients showed a statistically credible association with treatment effects, as all 95% CrIs included zero. This was observed for HbA1c, FPG, fasting C-peptide, and TDD. For AEs, the shared treatment–covariate interaction coefficient was also compatible with no effect modification (β = 0.003; 95% CrI, − 1.05 to 4.69).

Covariate-specific estimates for the T1DM and T2DM populations were generally consistent in direction with the primary analysis, particularly for combined MSC plus MNC therapy. However, several estimates had wide credible intervals, especially for interventions represented by sparse data, and should therefore be interpreted cautiously. Detailed treatment-specific regression coefficients and covariate-specific estimates are presented in eTables 10.1–10.3 of Appendix 10 (Supplementary file).

3.6 Sensitivity analyses and assessment of publication bias

Fixed-effect models generally produced narrower credible intervals and identified statistically credible effects for some comparisons that were not supported by the primary random-effects models. In particular, combined MSC plus MNC therapy was associated with a reduction in TDD compared with SMT under the fixed-effect model (MD, − 0.41 U/kg/day; 95% CrI, − 0.51 to − 0.30), whereas the corresponding random-effects estimate crossed the null value.

In the restricted random-effects analysis, combined MSC plus MNC therapy remained associated with reductions in HbA1c (MD, − 1.23%; 95% CrI, − 2.10 to − 0.34) and FPG (MD, − 2.19 mmol/L; 95% CrI, − 4.09 to − 0.29) compared with SMT. However, its effect on TDD remained statistically uncertain (MD, − 0.39 U/kg/day; 95% CrI, − 0.80 to 0.03). The estimates for MSC therapy versus SMT for HbA1c (MD, − 0.91%; 95% CrI, − 1.91 to 0.20) and MNC therapy versus SMT for FPG (MD, − 1.88 mmol/L; 95% CrI, − 4.30 to 0.54) were attenuated and no longer statistically credible. These findings support cautious interpretation of treatment-specific effects. Detailed results are presented in Appendix 12 (Supplementary file).

Comparison-adjusted funnel plots for HbA1c, FPG, and fasting C-peptide showed no clear evidence of marked asymmetry, and the corresponding Egger’s tests were not statistically significant (all $P > 0.05$). Formal assessment was not performed for TDD or AEs because fewer than 10 independent studies were available.

4. Discussion

In this systematic review and Bayesian network meta-analysis of 21 reports representing 19 independent RCTs, combined MSC plus MNC therapy was associated with greater reductions in HbA1c and FPG than SMT and showed the most favorable SUCRA-based rankings for both outcomes. It also ranked highest

for reducing TDD, although the corresponding comparison with SMT did not reach statistical credibility. MSC therapy reduced HbA1c compared with SMT and placebo, while MNC therapy reduced FPG compared with SMT. No statistically credible differences were identified between treatments for fasting C-peptide or AEs. Meta-regression provided no credible evidence that diabetes type modified the relative treatment effects. Although several comparisons, particularly for TDD and selected glycemic outcomes, were rated as moderate confidence, most network estimates were low or very low confidence; therefore, the ranking results should be interpreted as exploratory rather than definitive evidence of treatment superiority.

These findings are broadly consistent with, but also extend, previous systematic reviews and conventional pairwise meta-analyses. He et al. reported that MSC therapy reduced HbA1c in patients with diabetes but found no clear improvement in FPG or fasting C-peptide and no significant difference in AEs risk compared with control treatment(48). Other meta-analyses reported favorable effects of MSC therapy on HbA1c and insulin requirements, although several included nonrandomized studies, single-arm trials, or comparisons between post-treatment and baseline values, which may have produced more optimistic estimates than randomized between-group comparisons(7, 49). A recent meta-analysis restricted to randomized trials concluded that cell therapy reduced insulin requirements in T2DM but did not consistently improve glycemic control and did not achieve insulin independence or improve quality of life in T1DM(50). Another recent RCT-based review of MSC therapy reported improved glycemic outcomes but also emphasized the small number and limited duration of available trials(9). Unlike these previous reviews, the present analysis simultaneously compared MSC, HSC, MPC, MNC, UCB-derived cells, combined MSC + MNC therapy, placebo, and SMT within a single connected network. It therefore provides comparative estimates and treatment rankings that cannot be obtained from conventional pairwise meta-analysis.

The favorable performance of combined MSC + MNC therapy may be biologically plausible, although this interpretation remains hypothetical. MSCs are thought to act predominantly through immunomodulatory, anti-inflammatory, trophic, and paracrine mechanisms. They may suppress excessive immune activation, alter macrophage and T-cell responses, improve the local tissue microenvironment, and enhance insulin sensitivity rather than directly replacing large numbers of functional β cells(4). In contrast, bone marrow-derived MNC preparations contain heterogeneous populations of hematopoietic, endothelial progenitor, and immune cells that may contribute to vascular support, tissue repair, and preservation of endogenous insulin secretion. In a randomized comparative trial, MSC transplantation was associated mainly with improved insulin sensitivity, whereas MNC transplantation was associated with an enhanced C-peptide response, suggesting that these cell populations may affect glucose metabolism through partly distinct mechanisms(38). Their combination could therefore theoretically provide complementary immunomodulatory, metabolic, and regenerative effects. Clinical trials of umbilical cord-derived MSC (UC-MSC) combined with autologous bone marrow-derived cells have reported improvements in metabolic outcomes, with follow-up data suggesting possible long-term benefits(44, 46). However, only a limited number of trials contributed evidence for the combined treatment node, and the apparent benefit should not be interpreted as proof of biological synergy.

An important finding of the present study was the divergence between the glycemic control outcomes and fasting C-peptide. Combined MSC + MNC therapy was associated with reductions in HbA1c and FPG and showed a numerically favorable, but statistically uncertain, effect on TDD, whereas no intervention significantly increased fasting C-peptide in the primary random-effects analysis. This difference may arise because HbA1c and insulin requirements reflect more than endogenous β-cell secretion. They are also influenced by insulin sensitivity, adjustment of exogenous insulin or other glucose-lowering treatments, dietary behavior, adherence, and baseline glycemic control. Consequently, an improvement in HbA1c or TDD does not necessarily indicate substantial regeneration of functional β-cell mass. C-peptide is a more direct marker of endogenous insulin secretion, but fasting C-peptide may be less sensitive than stimulated C-peptide or the area under the C-peptide curve for detecting modest preservation or recovery of β-cell function(51). In addition, the included trials differed in diabetes duration, baseline residual β-cell function, assay methods, follow-up duration, and diabetes type. These differences may have diluted a small biological effect and contributed to the uncertainty surrounding the fasting C-peptide estimates.

The absence of a statistically credible interaction with diabetes type should also be interpreted cautiously. T1DM and T2DM differ substantially in their dominant pathophysiological mechanisms. In T1DM, cell therapy may be intended primarily to suppress autoimmunity and preserve residual β-cell function, whereas in T2DM it may act through modulation of chronic inflammation, improvement of insulin sensitivity, or support of β-cell function. Therefore, similar pooled treatment effects across the two populations are not necessarily expected. In the present study, however, the meta-regression was based on study-level rather than individual-patient data, several interventions were represented predominantly in only one diabetes type, and the credible intervals for the regression coefficients were wide. Thus, the analysis indicates that no effect modification was detected, rather than demonstrating that treatment effects are equivalent in T1DM and T2DM. The inconsistent conclusions of previous reviews comparing both diabetes types further suggest that adequately powered, diabetes-specific trials remain necessary(9, 49, 50).

No statistically credible difference in the risk of AEs was detected between the evaluated treatments. This finding may be reassuring, but it should not be interpreted as confirmation of long-term safety. The AEs network included only seven RCTs, four treatment nodes, and a limited number of participants, most estimates were highly imprecise, and the corresponding CINeMA ratings were predominantly low or very low. Moreover, the safety profile of a stem cell-based intervention depends not only on the cell product but also on the route of administration, dose, manufacturing process, concomitant therapy, and use of conditioning regimens. Previous reviews of HSC transplantation in T1DM have described serious infectious and hematologic complications associated with immunosuppressive conditioning, including severe infection and treatment-related mortality(8, 52). By comparison, MSC-based interventions have generally been associated with fewer severe acute reactions, although existing trials remain too small and too short to reliably detect rare outcomes such as malignancy, ectopic tissue formation, immune sensitization, thrombotic events, or delayed infection. Long-term safety surveillance should therefore remain a central component of future trials.

The treatment rankings require particular caution. SUCRA summarizes the probability distribution of treatment ranks but does not establish that the highest-ranked treatment is significantly or clinically superior to every competing intervention. Treatment hierarchies may appear precise even when the underlying effects are uncertain, especially in sparse networks with few direct comparisons and wide credible intervals(53). In the present analysis, combined MSC + MNC therapy showed the most favorable SUCRA-based rankings for HbA1c, FPG, and TDD, whereas MNC therapy showed the most favorable ranking for fasting C-peptide and MSC therapy showed the most favorable ranking for a lower risk of AEs. However, no statistically significant treatment differences were observed for fasting C-peptide or AEs, and the confidence in most network estimates was low or very low. In addition, local inconsistency was detected in several HbA1c comparisons, and some estimates, particularly for fasting C-peptide, were sensitive to the use of fixed- rather than random-effects models. Therefore, the ranking results are more appropriately regarded as signals for prioritizing future head-to-head trials than as a basis for immediate clinical recommendations.

Several limitations should nevertheless be acknowledged. First, although 19 independent RCTs were identified, the evidence was distributed across multiple treatment nodes and outcomes, resulting in a sparse network in which several comparisons relied heavily on indirect evidence or a single trial. Importantly, the favorable findings for combined MSC + MNC therapy should be interpreted with particular caution because this evidence was derived mainly from two independent trials conducted by the same research group, with one trial in T1DM and one in T2DM. Moreover, one report represented long-term follow-up of the same parent trial rather than an additional independent RCT. Thus, the apparent benefit of combined MSC + MNC therapy may be influenced by study-specific protocols, cell preparation methods, patient selection, and center-level effects. Independent multicenter randomized trials are needed to validate whether this combined strategy provides reproducible advantages over MSC, MNC, or SMT. Second, substantial clinical heterogeneity existed in cell source, autologous or allogeneic origin, cell dose, culture and processing methods, route and frequency of administration, concomitant treatment, participant characteristics, and duration of follow-up. Pooling different tissue sources within broad nodes such as MSC may have obscured clinically relevant differences between bone marrow-derived MSC (BM-MSC), UC-MSC, Wharton's jelly-derived MSC (WJ-MSC), and other products. This within-node heterogeneity may also have contributed to the local inconsistency observed in the HbA1c network and could affect the validity and precision of network estimates involving MSC-based interventions. Third, several trials had methodological limitations, particularly concerning the randomization process, deviations from intended interventions, and missing outcome data. Fourth, local inconsistency was observed in several HbA1c comparisons, while sensitivity analyses indicated that the statistical credibility of some comparisons changed under fixed-effect assumptions. Fifth, the meta-regression relied on aggregate study-level classification and was limited by the small number of studies contributing to each outcome and treatment comparison. Several diabetes-type coefficients had wide credible intervals, indicating substantial statistical uncertainty and limited power to detect effect modification. Therefore, the absence of a statistically credible interaction should not be interpreted as evidence that treatment effects are equivalent between T1DM and T2DM. In addition, the analysis could

not account for participant-level factors such as age, disease duration, baseline C-peptide, autoantibody status, insulin resistance, or baseline HbA1c. Sixth, AEs definitions and attribution varied across trials, and safety follow-up was insufficient for rare or delayed complications. Finally, although the 12-month time point was prioritized, the longest available follow-up was used for trials shorter than 12 months, which introduced additional variation in outcome assessment.

Future research should prioritize adequately powered, multicenter, randomized head-to-head trials comparing combined MSC + MNC therapy with MSC, MNC, and SMT. T1DM and T2DM should be investigated separately or prospectively stratified, and participant selection should consider disease duration, residual β-cell function, metabolic phenotype, and inflammatory status. Cell products should be characterized using standardized criteria for tissue source, phenotype, purity, viability, culture passage, potency, dose, and manufacturing quality(54). Outcomes should be assessed at standardized time points and should include HbA1c, FPG, TDD, fasting and stimulated C-peptide, C-peptide area under the curve, hypoglycemia, quality of life, insulin independence, and consistently defined AEs. Longer follow-up and active surveillance for malignancy, infection, thrombotic complications, and immune sensitization will be essential for establishing the long-term benefit–risk profile.

5. Conclusion

Combined mesenchymal stem/stromal cell plus mononuclear cell therapy was associated with reductions in HbA1c and FPG compared with SMT and showed the most favorable SUCRA-based profile for glycemic outcomes in the current network. However, its potential benefit in reducing insulin requirements remains uncertain, and treatment rankings should be interpreted cautiously because of sparse evidence and limited confidence in many estimates. The current evidence does not support firm conclusions or routine clinical use, and adequately powered, standardized randomized trials are required.

Abbreviations

AE
adverse event
BMI
body mass index
BM-MSC
bone marrow-derived mesenchymal stem/stromal cell
CINeMA
Confidence in Network Meta-Analysis
CrI
credible interval
DIC
deviance information criterion

DM
diabetes mellitus
FPG
fasting plasma glucose
GRADE
Grading of Recommendations Assessment,Development and Evaluation
HbA1c
glycated hemoglobin
HSC
hematopoietic stem cell
JAGS
Just Another Gibbs Sampler
MD
mean difference
MNC
mononuclear cell
MPC
mesenchymal precursor cell
MSC
mesenchymal stem/stromal cell
MSC + MNC
combined mesenchymal stem/stromal cell plus mononuclear cell therapy
NMA
network meta-analysis
OR
odds ratio
PICOS
population,intervention,comparator,outcomes,and study design
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO
International Prospective Register of Systematic Reviews
RCT
randomized controlled trial
RoB 2
Risk of Bias 2
SD
standard deviation
SMT
standard medical therapy

SUCRA
surface under the cumulative ranking curve
T1DM
type 1 diabetes mellitus
T2DM
type 2 diabetes mellitus
TDD
total daily insulin dose
UC-MSC
umbilical cord-derived mesenchymal stem/stromal cell
UCB
umbilical cord blood-derived cell
WJ-MSC
Wharton's jelly-derived mesenchymal stem/stromal cell.

Declarations

Ethics approval and consent to participate: Not applicable. This systematic review and network meta-analysis used data from previously published studies and did not involve the recruitment of human participants or the collection of new human or animal data.

Consent for publication: Not applicable. This manuscript does not contain any individual person's data in any form.

Availability of data and materials: All data generated or analyzed during this study are included in this article and its supplementary files. The extracted datasets and analysis code are available from the corresponding author on reasonable request.

Competing interests: The authors declare no competing interests.

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Authors' contributions: SW and AT contributed equally to this work. SW and GM conceived the initial research idea. GM obtained funding for this study. SW, AT, and AY performed the relevant literature searches and screened the articles for inclusion. SW, AT, and AY extracted the data for analysis and conducted the quality assessment of eligible studies. SW, AT, and ZW performed Bayesian network meta-analysis and prepared the graphical and tabular results and summary results under the supervision of GM. SW and GM drafted the protocol and the manuscript. AT, ZW, AY, YZ, QY, LP, HL, XH and YW

contributed to designing the searches and contributed to the manuscript by providing review comments and edits. GM is the study guarantor. All authors read and approved the final manuscript.

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References

1. Abel ED, Gloyn AL, Evans-Molina C, Joseph JJ, Misra S, Pajvani UB, et al. Diabetes mellitus-Progress and opportunities in the evolving epidemic. Cell. 2024;187(15):3789–820.
2. International Diabetes Federation. IDF Diabetes Atlas. 11th ed. Brussels, Belgium: International Diabetes Federation; 2025.
3. Genitsaridi I, Salpea P, Salim A, Sajjadi SF, Tomic D, James S, et al. 11th edition of the IDF Diabetes Atlas: global, regional, and national diabetes prevalence estimates for 2024 and projections for 2050. Lancet Diabetes Endocrinol. 2026;14(2):149–56.
4. Wu X, Jiang J, Gu Z, Zhang J, Chen Y, Liu X. Mesenchymal stromal cell therapies: immunomodulatory properties and clinical progress. Stem Cell Res Ther. 2020;11(1):345.
5. Sun SY, Gao Y, Liu GJ, Li YK, Gao W, Ran XW. Efficacy and Safety of Stem Cell Therapy for T1DM: An Updated Systematic Review and Meta-Analysis. J Diabetes Res. 2020;2020:5740923.
6. Kassem DH, Kamal MM. Therapeutic efficacy of umbilical cord-derived stem cells for diabetes mellitus: a meta-analysis study. Stem Cell Res Ther. 2020;11(1):484.
7. Li Y, Wang F, Liang H, Tang D, Huang M, Zhao J, et al. Efficacy of mesenchymal stem cell transplantation therapy for type 1 and type 2 diabetes mellitus: a meta-analysis. Stem Cell Res Ther. 2021;12(1):273.
8. Madani S, Amanzadi M, Aghayan HR, Setudeh A, Rezaei N, Rouhifard M, et al. Investigating the safety and efficacy of hematopoietic and mesenchymal stem cell transplantation for treatment of T1DM: a systematic review and meta-analysis. Syst Reviews. 2022;11(1):82.
9. Kashbour M, Abdelmalik A, Yassin MNA, Abed M, Aldieb E, Abdullah DM, et al. Mesenchymal stem cell-based therapy for type 1 & 2 diabetes mellitus patients: a systematic review and meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2025;17(1):189.
10. Florez ID, De La Cruz-Mena JE, Veroniki AA. Network meta-analysis: a powerful tool for clinicians, decision-makers, and methodologists. J Clin Epidemiol. 2024;176:111537.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Reviews. 2021;10(1):89.
12. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777–84.

13. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol. 1992;45(7):769–73.
14. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10(10):Ed000142.
15. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
17. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med. 2020;17(4):e1003082.
18. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. Campbell Syst Rev. 2020;16(1):e1080.
19. Oh H, Nguyen HD, Yoon IM, Ahn BR, Kim MS. Antidiabetic effect of gemigliptin: a systematic review and meta-analysis of randomized controlled trials with Bayesian inference through a quality management system. Sci Rep. 2021;11(1):20938.
20. Viguiliouk E, Kendall CW, Kahleová H, Rahelić D, Salas-Salvadó J, Choo VL, et al. Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2019;38(3):1133–45.
21. Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA. 2014;312(9):923–33.
22. Bafeta A, Trinquart L, Seror R, Ravaud P. Reporting of results from network meta-analyses: methodological systematic review. BMJ. 2014;348:g1741.
23. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163–71.
24. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London: National Institute for Health and Care Excellence (NICE); 2014.
25. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synthesis Methods. 2016;7(1):80–93.
26. Sterne JAC, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. BMJ. 2001;323(7304):101–5.

27. Packham DK, Fraser IR, Kerr PG, Segal KR. Allogeneic Mesenchymal Precursor Cells (MPC) in Diabetic Nephropathy: A Randomized, Placebo-controlled, Dose Escalation Study. EBioMedicine. 2016;12:263–9.
28. Skyler JS, Fonseca VA, Segal KR, Rosenstock J. Allogeneic Mesenchymal Precursor Cells in Type 2 Diabetes: A Randomized, Placebo-Controlled, Dose-Escalation Safety and Tolerability Pilot Study. Diabetes Care. 2015;38(9):1742–9.
29. Sood V, Bhansali A, Mittal BR, Singh B, Marwaha N, Jain A, et al. Autologous bone marrow derived stem cell therapy in patients with type 2 diabetes mellitus - defining adequate administration methods. World J Diabetes. 2017;8(7):381–9.
30. Huang P, Li S, Han M, Xiao Z, Yang R, Han ZC. Autologous transplantation of granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells improves critical limb ischemia in diabetes. Diabetes Care. 2005;28(9):2155–60.
31. Haller MJ, Wasserfall CH, Hulme MA, Cintron M, Brusko TM, McGrail KM, et al. Autologous umbilical cord blood infusion followed by oral docosahexaenoic acid and vitamin D supplementation for C-peptide preservation in children with Type 1 diabetes. Biol Blood Marrow Transpl. 2013;19(7):1126–9.
32. Wu Z, Huang S, Li S, Cai J, Huang L, Wu W, et al. Bone marrow mesenchymal stem cell and mononuclear cell combination therapy in patients with type 2 diabetes mellitus: a randomized controlled study with 8-year follow-up. Stem Cell Res Ther. 2024;15(1):339.
33. Estrada EJ, Decima JL, Bortman G, Roberti J, Romero EB, Samaja G, et al. Combination treatment of autologous bone marrow stem cell transplantation and hyperbaric oxygen therapy for type 2 diabetes mellitus: A randomized controlled trial. Cell Transpl. 2019;28(12):1632–40.
34. Ghodsi M, Heshmat R, Amoli M, Keshtkar AA, Arjmand B, Aghayan H, et al. The effect of fetal liver-derived cell suspension allotransplantation on patients with diabetes: first year of follow-up. Acta Med Iran. 2012;50(8):541–6.
35. Mirzaei M, Bagherinasabsarab M, Pakmanesh H, Mohammadi R, Teimourian M, Jahani Y, et al. The Effect of Intracavernosal Injection of Stem Cell in the Treatment of Erectile Dysfunction in Diabetic Patients: A Randomized Single-blinded Clinical Trial. Urol J. 2021;18(6):675–81.
36. Bhansali A, Asokumar P, Walia R, Bhansali S, Gupta V, Jain A, et al. Efficacy and safety of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus: a randomized placebo-controlled study. Cell Transpl. 2014;23(9):1075–85.
37. Zang L, Li Y, Hao H, Liu J, Cheng Y, Li B, et al. Efficacy and safety of umbilical cord-derived mesenchymal stem cells in Chinese adults with type 2 diabetes: a single-center, double-blinded, randomized, placebo-controlled phase II trial. Stem Cell Res Ther. 2022;13(1):180.
38. Bhansali S, Dutta P, Kumar V, Yadav MK, Jain A, Mudaliar S, et al. Efficacy of Autologous Bone Marrow-Derived Mesenchymal Stem Cell and Mononuclear Cell Transplantation in Type 2 Diabetes Mellitus: A Randomized, Placebo-Controlled Comparative Study. Stem Cells Dev. 2017;26(7):471–81.

39. Nasli-Esfahani E, Ghodsi M, Amini P, Keshtkar AA, Amiri S, Mojahed-Yazdi N, et al. Evaluation of fetal cell transplantation safety in treatment of diabetes: a three-year follow-up. J Diabetes Metab Disord. 2015;14:33.
40. Hu J, Wang Y, Gong H, Yu C, Guo C, Wang F, et al. Long term effect and safety of Wharton's jelly-derived mesenchymal stem cells on type 2 diabetes. Exp Ther Med. 2016;12(3):1857–66.
41. Hu J, Yu X, Wang Z, Wang F, Wang L, Gao H, et al. Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus. Endocr J. 2013;60(3):347–57.
42. Izadi M, Sadr Hashemi Nejad A, Moazenchi M, Masoumi S, Rabbani A, Kompani F, et al. Mesenchymal stem cell transplantation in newly diagnosed type-1 diabetes patients: a phase I/II randomized placebo-controlled clinical trial. Stem Cell Res Ther. 2022;13(1):264.
43. Carlsson PO, Schwarcz E, Korsgren O, Le Blanc K. Preserved β-cell function in type 1 diabetes by mesenchymal stromal cells. Diabetes. 2015;64(2):587–92.
44. Wu Z, Xu X, Cai J, Chen J, Huang L, Wu W, et al. Prevention of chronic diabetic complications in type 1 diabetes by co-transplantation of umbilical cord mesenchymal stromal cells and autologous bone marrow: a pilot randomized controlled open-label clinical study with 8-year follow-up. Cytotherapy. 2022;24(4):421–7.
45. Perico N, Remuzzi G, Griffin MD, Cockwell P, Maxwell AP, Casiraghi F, et al. Safety and Preliminary Efficacy of Mesenchymal Stromal Cell (ORBCEL-M) Therapy in Diabetic Kidney Disease: A Randomized Clinical Trial (NEPHSTROM). J Am Soc Nephrol. 2023;34(10):1733–51.
46. Cai J, Wu Z, Xu X, Liao L, Chen J, Huang L, et al. Umbilical Cord Mesenchymal Stromal Cell With Autologous Bone Marrow Cell Transplantation in Established Type 1 Diabetes: A Pilot Randomized Controlled Open-Label Clinical Study to Assess Safety and Impact on Insulin Secretion. Diabetes Care. 2016;39(1):149–57.
47. Carlsson PO, Espes D, Sisay S, Davies LC, Smith CIE, Svahn MG. Umbilical cord-derived mesenchymal stromal cells preserve endogenous insulin production in type 1 diabetes: a Phase I/II randomised double-blind placebo-controlled trial. Diabetologia. 2023;66(8):1431–41.
48. He J, Kong D, Yang Z, Guo R, Amponsah AE, Feng B, et al. Clinical efficacy on glycemic control and safety of mesenchymal stem cells in patients with diabetes mellitus: Systematic review and meta-analysis of RCT data. PLoS ONE. 2021;16(3):e0247662.
49. Habiba UE, Khan N, Greene DL, Ahmad K, Shamim S, Umer A. Meta-analysis shows that mesenchymal stem cell therapy can be a possible treatment for diabetes. Front Endocrinol (Lausanne). 2024;15:1380443.
50. Manikandan S, Hariprasad R, Bagepally BS. Efficacy and safety of stem cell therapy in patients with Diabetes Mellitus - a systematic review and meta-analysis. Syst Reviews. 2026;15(1):75.
51. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21–22 October 2001. Diabetes. 2004;53(1):250–64.

52. Wu Q, Zheng S, Qin Y, Zheng X, Chen H, Yang T, et al. Efficacy and safety of stem cells transplantation in patients with type 1 diabetes mellitus-a systematic review and meta-analysis. Endocr J. 2020;67(8):827–40.
53. Salanti G, Nikolakopoulou A, Efthimiou O, Mavridis D, Egger M, White IR. Introducing the Treatment Hierarchy Question in Network Meta-Analysis. Am J Epidemiol. 2022;191(5):930–8.
54. Pawitan JA, Yang Z, Wu YN, Lee EH. Towards Standardized Stem Cell Therapy in Type 2 Diabetes Mellitus: A Systematic Review. Curr Stem Cell Res Ther. 2018;13(6):476–88.

Figures

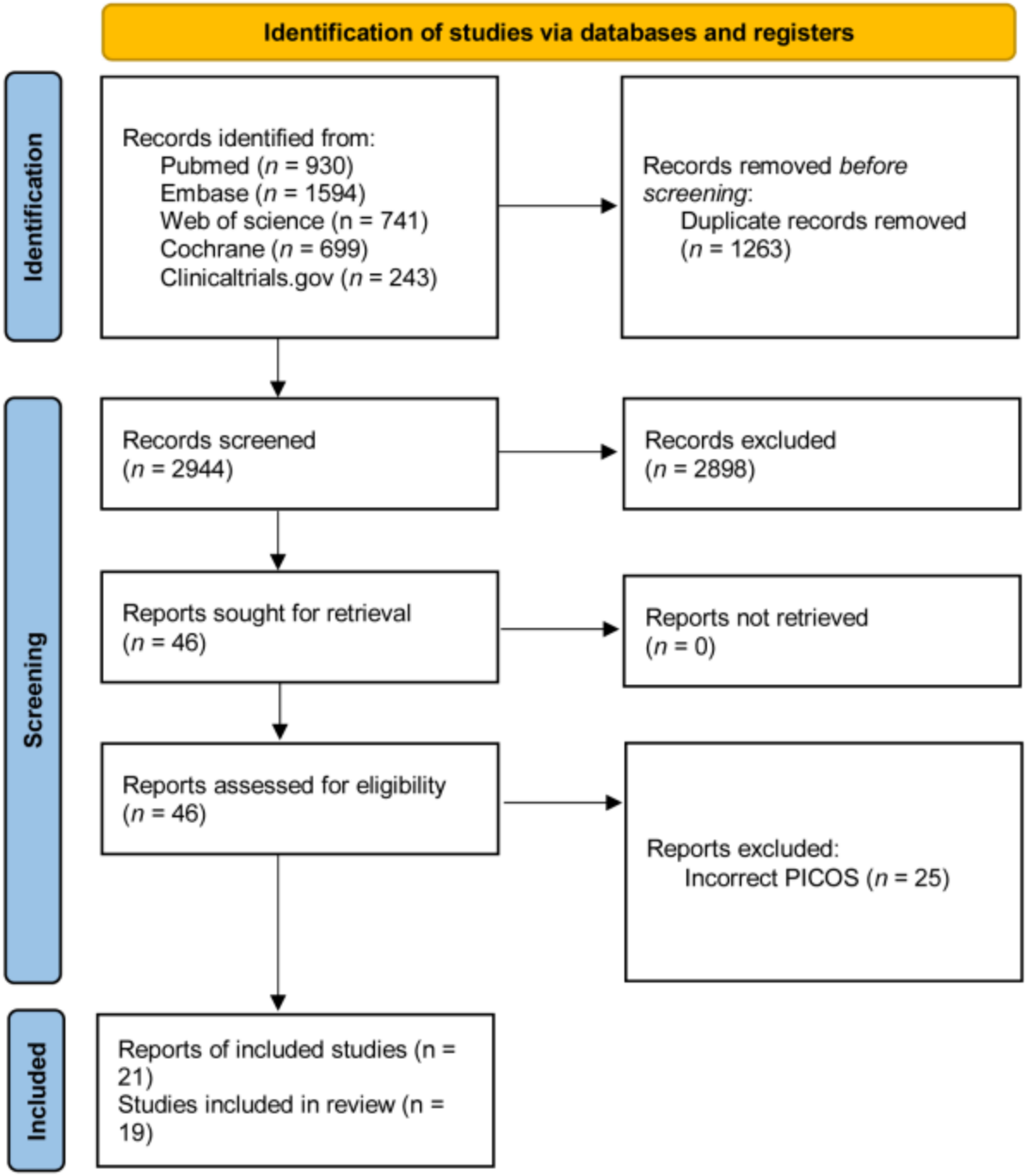


Figure 1

PRISMA 2020 flow diagram.

The report with Study ID Zhixian Wu 2022 was a follow-up report of the trial with Study ID Jinquan Cai 2016, while the report with Study ID Ensieh Nasli-Esfahani 2015 was a follow-up report of the trial with Study ID Maryam Ghodsi 2012.

Abbreviations: RCT, randomized controlled trial. PICOS, population, intervention, comparator, outcomes, and study design.

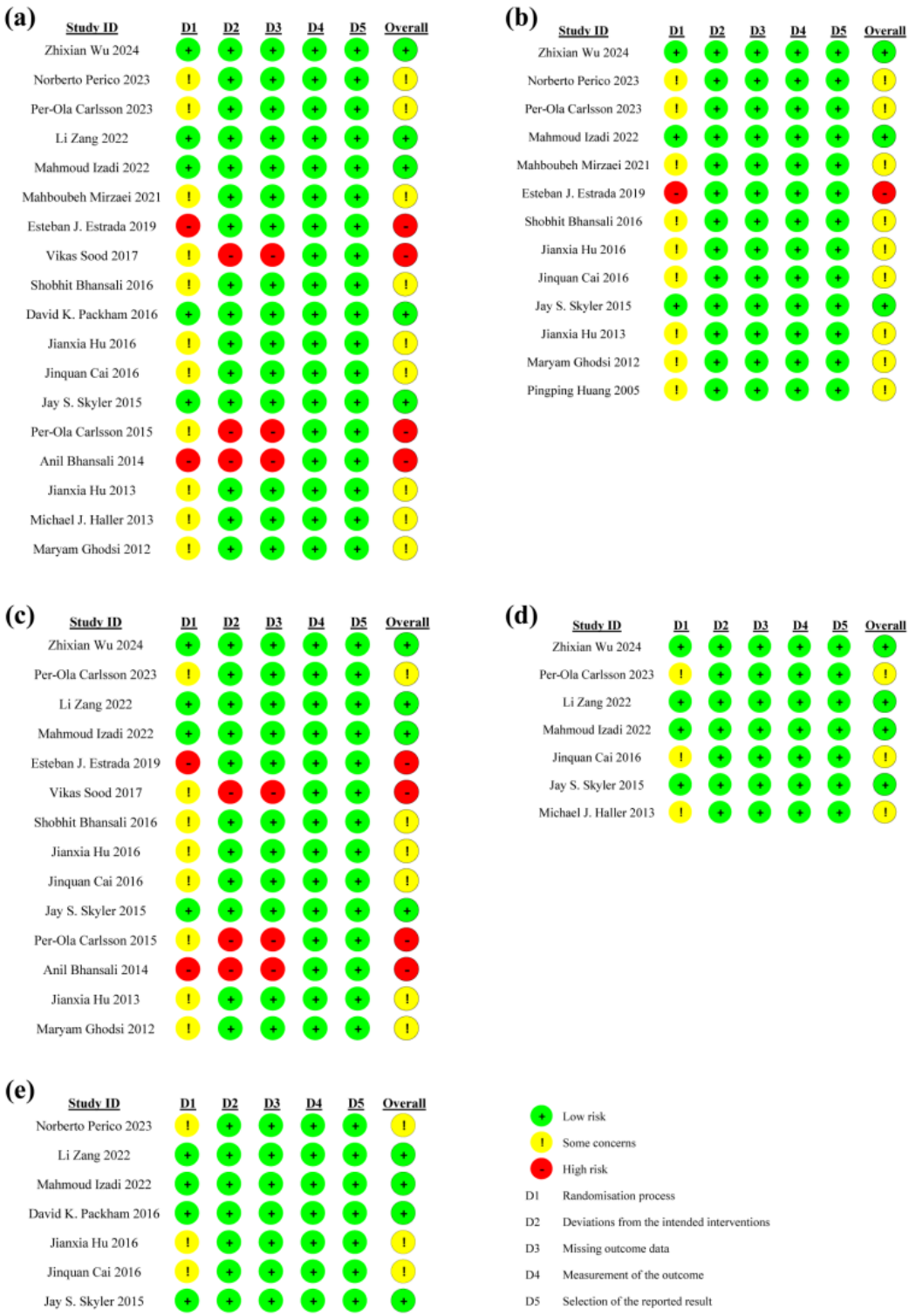


Figure 2

Study-level risk of bias assessment using the Cochrane Risk of Bias 2 (RoB 2) tool. (a) HbA1c; (b) FPG; (c) fasting C-peptide; (d) TDD; (e) AE.

Abbreviations: HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; TDD, total daily insulin dose; AE, adverse events.

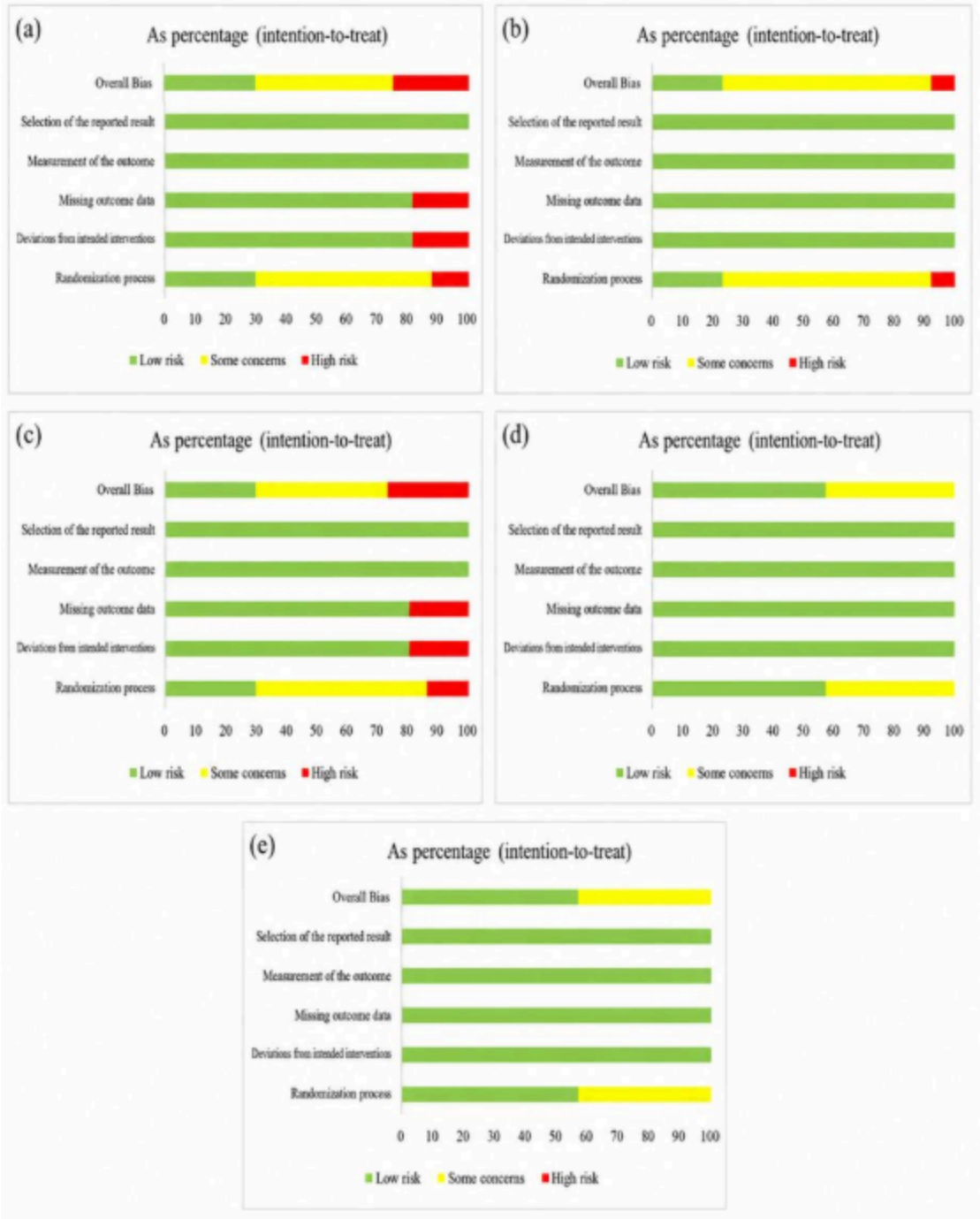


Figure 3

Summary of the risk of bias assessment using the Cochrane Risk of Bias 2 (RoB 2) tool. (a) HbA1c; (b) FPG; (c) fasting C-peptide; (d) TDD; (e) AE.

Abbreviations: HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; TDD, total daily insulin dose; AE, adverse events.

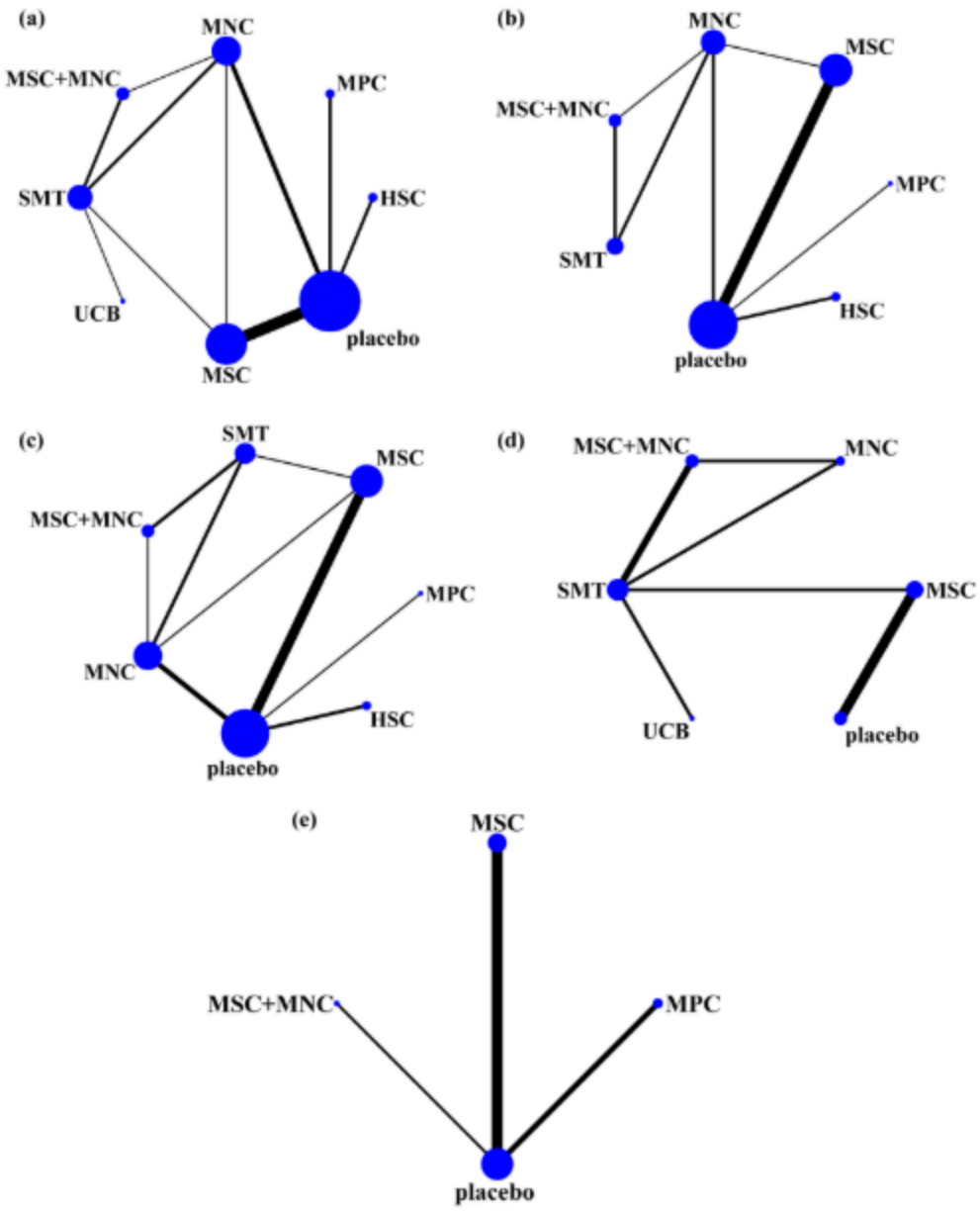


Figure 4

Network plots comparing included interventions. Each node represents an intervention, with node size proportional to the number of participants receiving that intervention. Edge width is proportional to the number of studies providing direct evidence for each comparison. (a) HbA1c; (b) FPG; (c) fasting C-peptide; (d) TDD; (e) AE.

Abbreviations: HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; TDD, total daily insulin dose; AE, adverse events.

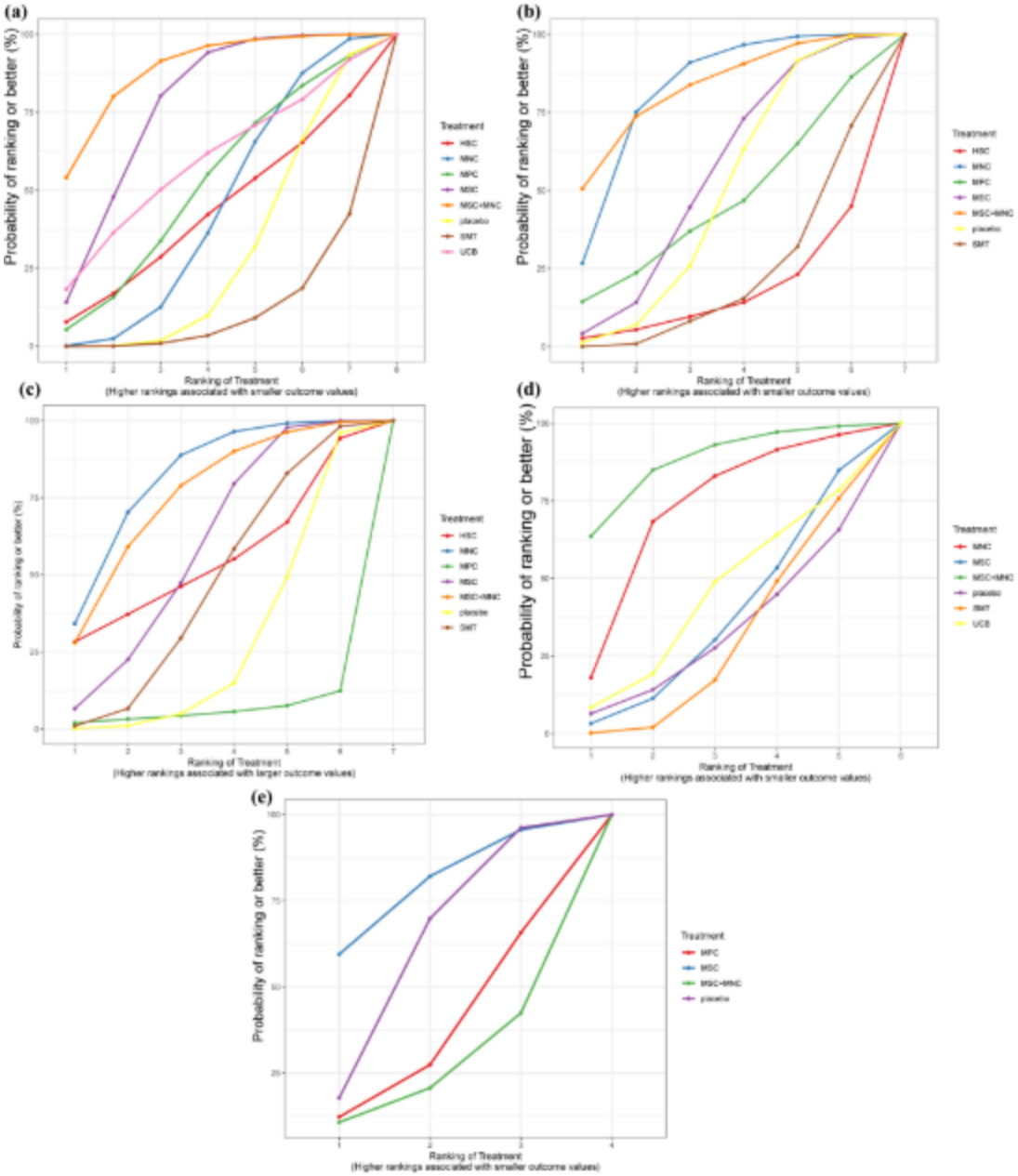


Figure 5

Plots of SUCRA. The graph shows the cumulative probability of each intervention ranking. Each curve represents an intervention. Higher SUCRA values indicate a more favorable ranking for efficacy or safety. (a) HbA1c; (b) FPG; (c) fasting C-peptide; (d) TDD; (e) AE.

Abbreviations: HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; TDD, total daily insulin dose; AE, adverse events.

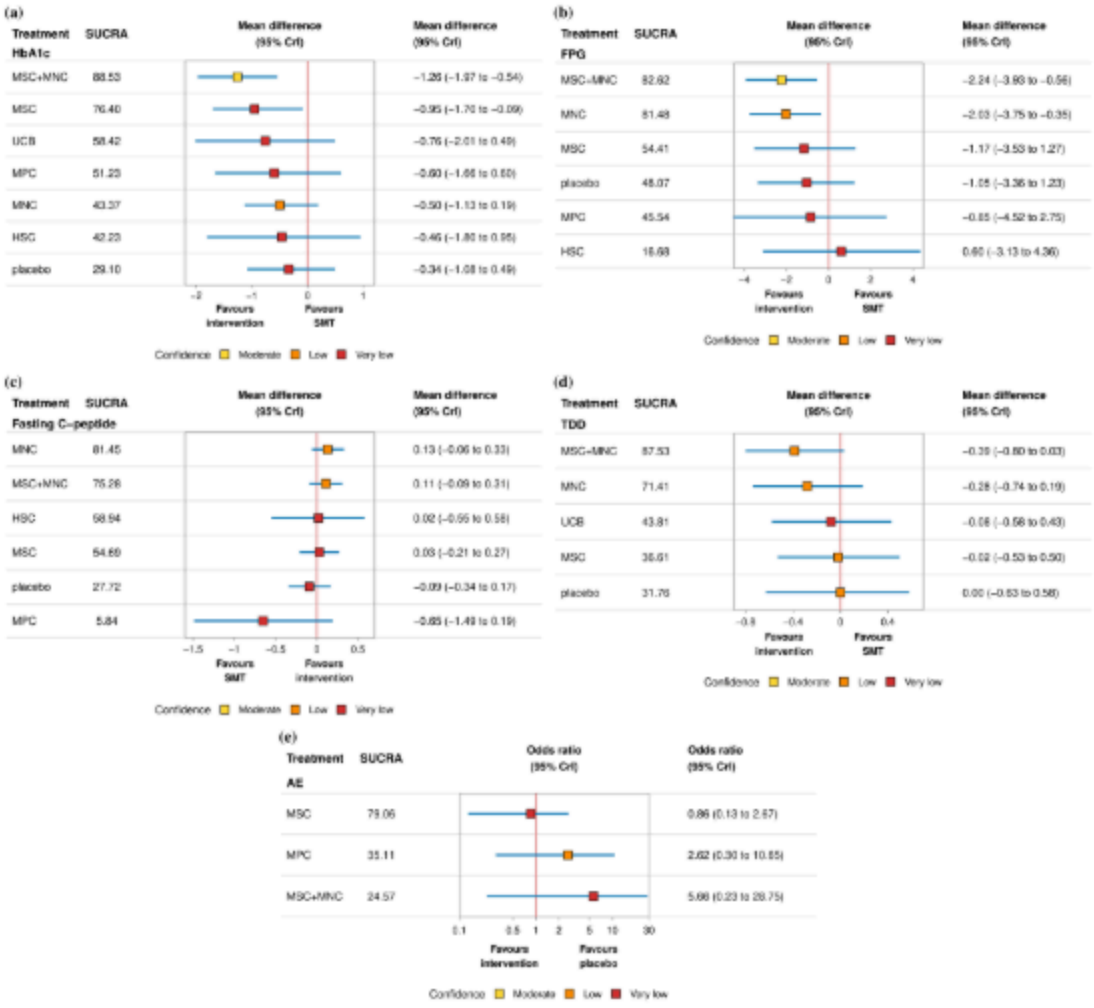


Figure 6

Forest plot of network effect sizes. (a) HbA1c; (b) FPG; (c) fasting C-peptide; (d) TDD; (e) AE.

Note: Forest plots of network estimates versus the reference intervention, with SUCRA values shown for each treatment. The color of the square indicates the CINeMA confidence rating for the corresponding network estimate.

Abbreviations: HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; TDD, total daily insulin dose; AE, adverse events.

Supplementary Files

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- SupplementMaterial.docx