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Effectiveness of five interventions used for prevention of gestational diabetes

A network meta-analysis

Qiongyao Tang, BN[a], Ying Zhong, BN[a], Chenyun Xu, BN[b,*], Wangya Li, BN[a], Haiyan Wang, BS[a], Yu Hou, MD[c]

Abstract

Background: Gestational diabetes mellitus (GDM) is associated with short- and long-term health issues for mother and child; preventing these complications is crucially important. This study aimed to perform a systematic review and network meta-analysis of the relationships among 5 interventions used to prevent GDM.

Materials and methods: A comprehensive literature search was performed to pool evidence from inception to June 30, 2020. The type of studies was confined to randomized control trials and quasi-randomized control trials published in English investigating the interventions for preventing GDM, including physical activity, dietary intervention, probiotic intervention, mixed intervention, and inositol supplementation. The data were pooled together to report the odds ratio (OR) of GDM with a corresponding 95% credible interval (CrI) and generate a network plot, the surface under the cumulative ranking curve plot, and contribution plot. In addition, loop inconsistency was examined, and a funnel plot combined with Egger test was used to measure heterogeneity.

Results: The network meta-analysis included 46 randomized control trials involving 16,545 patients. Compared with placebo, physical activity (OR: 0.64, 95% CrI: 0.46–0.88) and probiotic intervention (OR: 0.57, 95% CrI: 0.34–0.96) reduced the incidence of GDM significantly. However, dietary intervention, a combination of physical activity and diet intervention, and inositol supplementation did not significantly alter GDM risk.

Conclusions: Physical activity and probiotic intervention are more effective than placebo in reducing the risk of developing GDM. Future work should focus on the type, duration, frequency, and timing of physical activity and probiotic intervention.

Abbreviations: CrI = credible interval, GDM = gestational diabetes mellitus, OR = odds ratio, RCTs = randomized control trials, SUCRA = surface under the cumulative ranking curve.

Keywords: diabetes, diet, eating, food, gestational, meta-analysis, network, nutrition, preventive medicine

1. Introduction

Gestational diabetes mellitus (GDM) is defined as diabetes first diagnosed in the second or third trimester of pregnancy that is not pregestational diabetes by the American Diabetes Association.[1] The prevalence of GDM is increasing, with approximately 14%, and affecting nearly 18 million pregnancies worldwide.[2] However, the actual global prevalence of GDM is still currently lacking due to high-level heterogeneities existing among screening approaches and the lack of unified diagnostic criteria.[3,4] The major risk factors for GDM comprises overweight/obesity, improper eating habit, and micronutrients deficiency. Other risk factors include advanced age, familial history of insulin resistance, and hyperglycemia. While GDM usually ameliorates simultaneously after delivery, it can have long-term consequences on health, including increased risks for the development of type 2 diabetes and cardiovascular disease in the maternal side, and later obesity, cardiovascular disease, and diabetes in the child.[5] Thus, it contributes to a vicious intergenerational loop of obesity and diabetes that detriments the overall population's health. Unfortunately, there is currently no widely-accepted treatment or prevention strategy for GDM.

Preventing GDM could have economic and health benefits rather than treatment.[6] Most current studies focused on applying physical activity, diet intervention, probiotic supplementation,

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QT and YZ contributed equally to this study.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Table 1

Literature search and selection.

Data source	MEDLINE, EMBASE, PubMed, CENTRAL, and CINAHL
Search strategy	All combinations of key words in the 4 categories listed below
Search key words	Catergory 1: Gestational Diabetes Mellitus, glucose, insulin
	Catergory 2: Pregnan*, gestation*
	Catergory 3: exercise, biotics, probiotics, inositol, diet*, nutrition*, physical activit*, prenatal care, antepartum care, antenatal care, weight management, weight gain, weight control, ((lifestyle OR behavior*) AND (intervention*OR program* OR modification))
Other sources	Cross references
Last search	June 30, 2020
Method for assessing data	Structured data extraction and quality assessment were presented in Tables 2 and 3

inositol usage, or a combination of these to prevent GDM. Each interventional measure has been evaluated for its efficacy and safety issues in the previous meta-analyses. Davenport et al[7] pooled results from 23 randomized clinical trials and found that physical activity alone could reduce the incidence of GDM. The diet intervention has been appraised by Wan et al,[8] and the results also showed benefit for intervention. Probiotics and extracts from beneficial microbiota are also effective supplements for the prevention of GDM.[3,9] In addition, the 2 main forms of inositol, namely myo-inositol and D-chiro inositol, play a significant role in the prevention of GDM via the mechanism of insulin receptor sensitization and insulin-mimic properties.[10] To summarize, different interventions have demonstrated promise in the prevention of GDM. However, limited studies have been reported to clarify which strategies are most effective.

Recent studies demonstrate that the prevention of GDM could be in a dilemma since the cost of interventional measures is ever-rising. For example, 1 post hoc analysis of a large randomized clinical trial found that the incremental cost-effectiveness ratio for universal screening of GDM was $2475 per quality-adjusted life-years gained.[11] Therefore, it is crucial to sort out the most effective method for the prevention of GDM. A summary of the evidence for identifying effective preventive interventions may provide an important resource for healthcare providers caring for pregnant women, policymakers, and guideline developers and contribute to reducing the short- and long-term health risks for pregnant women and their infants. Further, an overview may highlight key areas requiring further evaluation. Therefore, the study aimed to compare the effectiveness of different interventions in preventing GDM via the methodology of network meta-analysis.

2. Materials and methods

This study was conducted using recommendations from the Cochrane Handbook for Systematic Reviews and reported following the extension statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[12] This author declares that all supporting data are available within the article and online-only supplement. No patients were involved in the development of this study; hence the approval from the local research ethics board and written informed consent were waived.

2.1. Information sources and trial search

We conducted a comprehensive search of MEDLINE, EMBASE, PubMed, CENTRAL, and CINAHL from inception until June 30, 2020. A manual search of the reference lists of relevant articles and reviews was also conducted to maximize the identification of eligible studies. In addition, details of ongoing studies were sought through a review of ClinicalTrials.gov.

2.2. Search strategy

The MEDLINE, EMBASE, PubMed, CENTRAL, and CINAHL databases were searched using the following terms: ("Gestational Diabetes Mellitus" OR "glucose" OR "insulin" OR "gestational diabetes") AND ("Pregnant" OR "gestation" OR "prevention") AND ("exercise" OR "biotics" OR "probiotics" OR "inositol" OR "diet" OR "dietary intervention" OR "nutrition" OR "physical activity" OR "prenatal care" OR "antepartum care" OR "antenatal care" OR "weight management" OR "weight gain" OR "weight control" OR (("lifestyle" OR "behavior") AND ("intervention" OR "program" OR "modification"))). A sample search strategy is available in Table 1.

2.3. Eligible criteria

The eligible criteria are detailed below, following the participants, intervention, controls, outcomes, and study design framework.[13] Participants: we included studies enrolling pregnant women. Interventions: any randomized control trials (RCTs) and quasi-randomized control trials investigating the interventions for preventing GDM, including physical activity, dietary intervention, probiotic intervention, a combination of physical activity and diet, and inositol supplementation were included. Controls: groups receiving placebo or standard care were considered. Outcomes: the outcome measure was the incidence of GDM. Studies: only RCTs and quasi-randomized control trials in English were considered. Studies were considered ineligible if they included the treatment of GDM. Nonoriginal studies, including reviews, letters, meeting abstracts, case reports, or papers that did not provide accurate and clear data, were also excluded. Studies investigating physical activities and diet intervention, either positive intervention or passive consultation, were included. No restriction on dosage, frequency, duration, route of administration, and study locations was utilized.

2.4. Study selection and data collection

Two reviewers independently screened titles, abstracts, and full-text and extracted the data from included studies using the standardized data collection form. We collected study design, enrollment criteria, baseline patients' characteristics, and details of the intervention/comparator used in each study. Baseline

patient characteristics included age, sex, background medical history, hemorrhage volume, the start time of intervention, and clinical severity. The primary outcome of interest was the incidence of GDM. Safety data and treatment dropouts were reported where possible.

2.5. Risk of bias in individual studies

Two reviewers independently assessed each study's risk of bias and tabulated the results using the Grading of Recommendations Assessment, Development, and Evaluation profiler Guideline Development Tool software . To reduce the bias in estimates of final effect, studies that scored "high risk" on a number of categories within the Cochrane risk of bias tool were excluded from our primary analysis.

2.6. Data synthesis (summary measures, synthesis of results)

We evaluated baseline characteristics of patients to ensure that exchangeability assumptions were satisfied and the sufficient similarity between the included studies to enable data pooling.[14] We adopted a network meta-analysis methodology to derive estimates of the comparative effectiveness of each intervention against a control. An indirect effect estimate was then calculated to compare the 2 interventions, utilizing the control group as a common comparator. The outcome of interest was presented in a combination of dichotomous and binary data, and findings from network meta-analysis were reported in terms of odds ratio (OR) with a corresponding 95% credible interval (CrI). The surface under the cumulative ranking curve (SUCRA) was used to estimate the ranking probabilities of the intervention effect. Adequacy of model fit was evaluated by comparing the total posterior residual deviance and the number of unconstrained data points in each analysis, and comparing models. For instance, fixed and random effects models were compared based on the deviance information criterion, with differences of 5 points or more indicating an important difference. As networks studied included multiple closed loops, examinations for the inconsistency of direct and indirect evidence were carried out. We used the I-squared (I2) statistics generated from traditional pair-wise meta-analysis to quantify the amount of heterogeneity. We performed all analyses using RevMan 5.3 (Cochrane, London, UK) and Stata MP16 (StataCorp LLC, TX).

2.7. Risk of bias across studies and additional analyses

We compared the incidence and the absolute number of GDM patients in all studies. A network plot was used to visualize network geometry and node connectivity. The SUCRA plot was used to present the overall ranking. The funnel plot with Egger test was used to evaluate publication bias and study heterogeneity. Finally, we appraised the quality of evidence for all outcomes using a framework designed explicitly by the Grading of Recommendations Assessment, Development, and Evaluation working group for randomized studies in the context of a network meta-analysis.[15]

3. Results

3.1. Study selection and characteristics

The initial search identified 2457 studies. We obtained 72 studies after reading the titles and abstracts and excluding duplicate publications. After screening the full texts manually, 26 studies were excluded for insufficient information for a meta-analysis and irrelevant outcome. Eventually, 46 studies were included in this network meta-analysis. The flowchart of the literature retrieving process is described in Figure 1. These 46 studies were RCTs and comprised a total sample size of 16,545 participants. Among them, 8478 participants were in the placebo group, 1991 participants were in the group of physical activity, 2399 participants were in the group of dietary intervention or dietary consulting, 2730 participants received a combined intervention of physical activity and diet, 609 participants received probiotics, and 471 participants received inositol supplements. These included unpublished data from 10 studies. The summary data of each included study are shown in Table 2.[16–54] The average sample size of enrolled studies was 367 and ranged from 45 to 1962. Table 3 shows the results of the quality assessment of the included studies.

3.2. Network plot

Figure 2 shows the network plot of the included studies. We included 5 interventions in the network meta-analysis: physical activity, dietary intervention, probiotic intervention, a combination of physical activity and diet intervention, inositol supplementation. Each node represents different active interventions or placebo, and the node size represents the sample size of the intervention or placebo. Lines between nodes represent the direct comparison evidence, and the thickness of the line reflects the number of trials. From 46 included studies, the majority of interventions were physical activity (n = 14), followed by a combination of physical activity and diet (n = 12) and dietary intervention (n = 10). The "star-shaped" network structure indicated a dearth of head-to-head studies directly comparing the effectiveness of interventions. Therefore, most effect estimates were derived from indirect comparisons with placebo rather than mixed treatment comparisons.

3.3. Results of network meta-analysis

The network meta-analysis showed that physical activity (OR: 0.64, 95% CrI: 0.46–0.88) and probiotic intervention (OR: 0.57, 95% CrI: 0.34–0.96) reduced the incidence of GDM significantly compared with placebo (Fig. 3). Evidence was less certain for dietary intervention (OR: 0.76, 95% CrI: 0.55–1.05), a combination of physical activity and diet (OR: 0.74, 95% CrI: 0.54–1.01) and inositol supplementation (OR: 0.82, 95% CrI: 0.43–1.56). However, no significant differences between probiotic intervention and physical activity were observed for the effectiveness in preventing GDM (OR: 0.90, 95% CrI: 0.49–1.65). In addition, patients randomized to dietary intervention (OR: 1.19, 95% CrI: 0.76–1.86), a combination of physical activity and diet (OR: 1.16, 95% CrI: 0.75–1.79) and inositol supplementation (OR: 1.29, 95% CrI: 0.63–2.61) did not have a higher risk of developing GDM than those randomized to physical activity. Similarly, there were no significant differences between the effectiveness of dietary intervention and the other interventions in preventing GDM.

A SUCRA plot showed that probiotic intervention had the highest likelihood of being ranked first, followed by physical activity, inositol supplementation, a combination of physical activity and diet, and dietary intervention; the results suggest no possibility that placebo leads to the lowest risk of developing

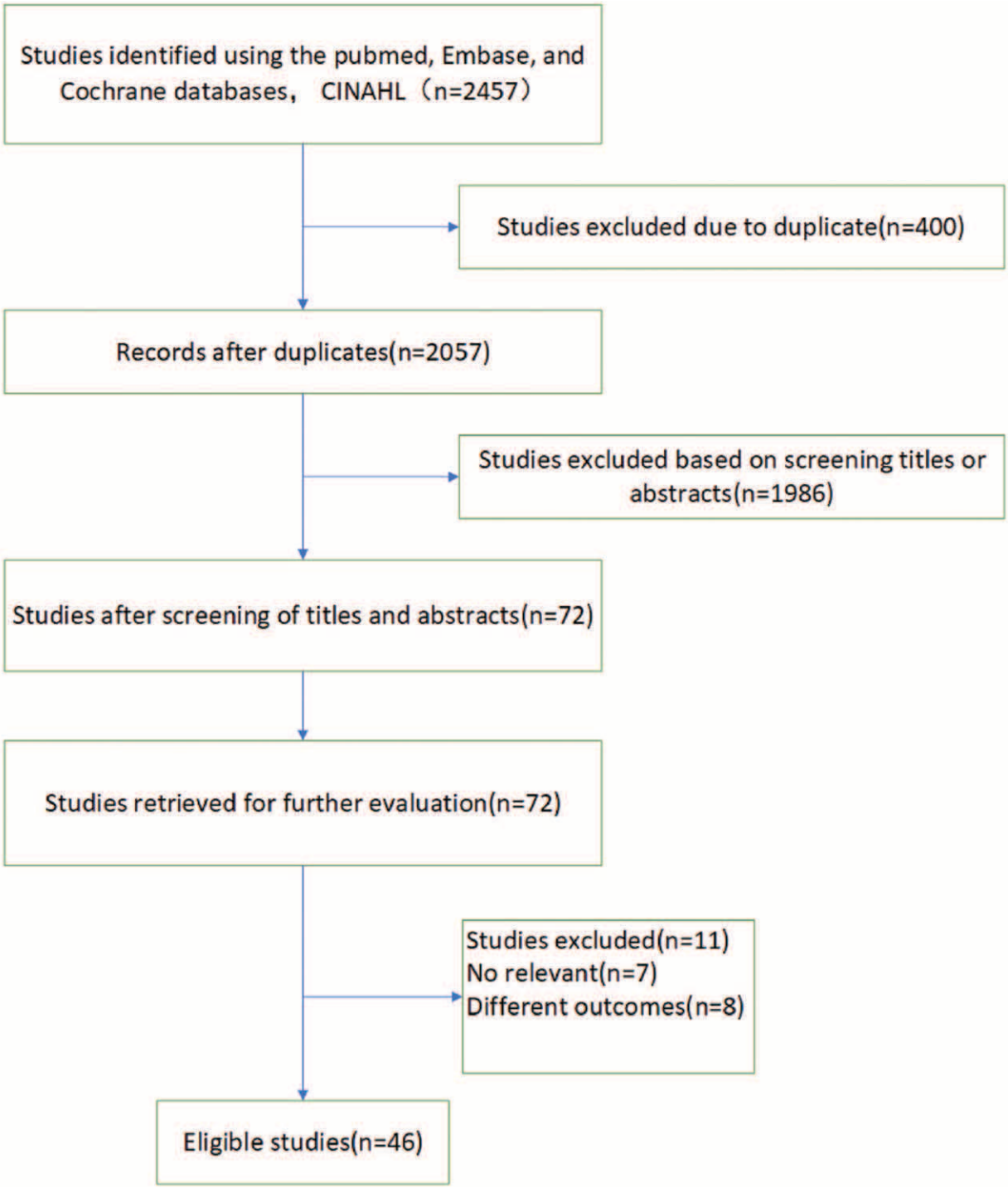

Figure 1. Flowchart of literature search and literature inclusion.

GDM (Fig. 4). The inconsistency plot revealed no significant inconsistency between direct and indirect evidence in 3 available loops within the data network (Fig. 5). Figure 6 shows a comparison-adjusted funnel plot, indicating that there were small sample effects or publication bias. For efficacy, the median heterogeneity variances were estimated at 0.49 (95% CrI 0.37–0.64), and the global I2 values were 56%. The assessment of transitivity showed that most of the comparisons had variable baseline severity, mean age, and treatment duration. The test of global incoherence showed an insignificant difference between the consistency and inconsistency models for efficacy ($P < .0001$). Tests of local incoherence showed that the percentages for inconsistent loops were within the expected ranges based on the empirical data (2 loops of 8 in total). The test of incoherence from the node-splitting model showed significant differences between some comparisons in efficacy. We also mapped out the contribution plot to illustrate each intervention's effect, and the results were consistent with the SUCRA plot (Fig. 7). Finally,

Table 2

Basic characteristics of included studies.

Author (yr, study design)	Country (municipality/province, city) [recruitment period]	Number of participants	Compliance	Outcomes of interest
Comparison: physical activity/exercise vs placebo/standard care				
Pelaez et al 2019, RCT	Spain, Santander, October, 2009—October, 2010	345	At the last visit during 34 wk of gestation	Incidence of gestational diabetes,
Barakat et al 2019, RCT	Spain, Madrid, March, 2014—April, 2018	456	Every 4–5 wks until 36–38 wks of gestation	Gestational weight gain
Wang et al 2017	China, December, 2014—July, 2016	265	Four times of follow-up includes ultrasound and cervical length measurement	Incidence of GDM
da Silva et al 2017	Brazil, January, 2015—December, 2015	639	Four times of follow-up until the end of pregnancy	Incidence of GDM
Seneviratne et al 2017	New Zealand, March, 2013—April, 2014	74	At the 36–38 wk of pregnancy	Incidence of GDM
Guelfi et al 2016	Australia June, 2011—Febuary, 2015	172	At the end of pregnancy	Incidence of GDM
Shuang et al 2016	China	272	At the end of pregnancy	Gestational weight gain
Cordero et al 2015	Spain	257	At the end of pregnancy	Incidence of gestation diabetes
Hayes et al 2014	UK, July, 2008—January, 2019	507	One month	Incidence of gestational diabetes
Stafne et al 2012	Norway, May, 2007—June, 2015	855	At 32–36 wks of gestation	Incidence of gestational diabetes
Oostdam et al 2012	Netherland, 2007–2011	121	At around 15 wks of gestation and at 24 and 32 wks of gestation	Incidence of GDM
Barakat et al 2012	Spain, 2000–2003 RCT	100	At around 15 wks of gestation and at 24 and 32 wks of gestation	Incidence of GDM
Vinter et al 2011	Denmark 2011	360	At around 20 wks of gestation wk	Incidence of GDM
Harreiter et al 2019	Austria, 2015–2017	407	At 24–28 wks of pregnancy and 35–37 wks of pregnancy	Incidence of gestational diabetes
Comparison of dietary intervention vs placebo				
Okesene-Gafa et al 2019	New Zealand, 2015–2017	230	At the end of pregnancy	Incidence of gestational diabetes
McCarthy et al 2016	Australia, April, 2011–December, 2011	382	At 28 wks of gestation	Incidence of gestational diabetes
Walsh et al 2012	Ireland, January, 2007–January, 2011	759	At 28th wk	Incidence of gestational diabetes
Wolff et al 2008	Denmark, October, 2007–August, 2008	50	At 27 and 36th wk of gestation	Incidence of gestational diabetes
Comparison of mixed intervention (diet + exercise) vs placebo				
Kunath et al 2019	Germany, September, 2013–September, 2018	1962	At 12–16,16–20, and 30–34 wks of gestation	Incidence of gestational diabetes
Rönö et al 2018	Finland, September, 2013–September, 2014	454	At 12–16,16–20, and 30–34 wks of gestation	Incidence of gestational diabetes
Chan et al 2018	China, April, 2015–April, 2017	166	At 12 and 24th wk	Incidence of gestational diabetes
Sagedal et al 2017	Norway, September, 2009–Febuary, 2013	557	At 36th wk	Incidence of gestational diabetes
Bruno et al 2017	Italy, December, 2012–December, 2015	131	At 16th, 20th, 28th, and 36th wks of gestation	Incidence of gestational diabetes
Sun and Zhao 2016	China, March, 2013–August, 2013	66	At 28th wk of gestation	Incidence of gestational diabetes
Opie et al 2016	Australia, Febuary, 2012–August, 2015	92	At the end of pregnancy	Incidence of gestational diabetes
Flynn et al 2016	UK, March, 2009–May, 2014	1023	At the end of pregnancy	Incidence of gestational diabetes
Poston et al 2015	UK, March, 2009–June, 2014	1555	At the 27–28 wks of gestation	Incidence of gestational diabetes
Vinter et al 2014	UK, October, 2007–October, 2010	304	At the 12–15, 28–30, and 34–35 wks	Incidence of gestational diabetes
Petrella et al 2014	Italy, April, 2011–October, 2011	61	at 16th, 20th, 28th, and 36th wk of gestation	Incidence of gestational diabetes
Luoto et al 2010	Finland, October, 2007–December, 2008	399	Monthly follow-up from 8th–37th wk	Incidence of gestational diabetes
Hui et al 2006	Canada, July, 2004–December, 2004	45	At the end of pregnancy	Incidence of gestational diabetes
Comparison of probiotics and placebo				
Asgharian et al 2020	Iran, June, 2016–September, 2019	128	At 16–20, 24–30, 31–34, 37–38 wks, and every wk till delivery	Incidence of gestational diabetes
Callaway et al 2019	Australia, November, 2012–November, 2015	411	At 28 wks' gestation	Incidence of gestational diabetes
Wickens et al 2017	New Zealand, Febuary, 2012–August, 2016	423	At 28 wks' gestation	Incidence of gestational diabetes Fasting glucose
Sahariah et al 2016	India, 2006–2012	1008	At 28 wks of gestation	Incidence of gestational diabetes Fasting glucose
Lindsay et al 2014	Ireland, 2012	95	At the end of study	Incidence of GDM
Comparison of inositol/myoinositol vs placebo				
Santamaria et al 2016	Italy, 2012–2015	197	At the end of pregnancy	Incidence of gestational diabetes
Farren et al 2017	Ireland, N/A	240	N/A	Incidence of gestational diabetes
D'Anna et al 2015	Italy, 2010–2013	197	At the end of pregnancy	Incidence of gestational diabetes
D'Anna et al 2015	Italy, 2012	220	At the end of pregnancy	Incidence of gestational diabetes

Table 3

Results of quality assessment.

Reference	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data aaddressed	Free of selective reporting	Free of other bias
Asgharian et al	Yes	Yes	Yes	Yes	Yes	Yes
Pelaez et al	Yes	Yes	No	Yes	Yes	Yes
Okesene-Gafa et al	Yes	Yes	Yes	Yes	Yes	Yes
Kunath et al	Yes	Yes	Yes	Yes	Yes	Yes
Callaway et al	Yes	Yes	Yes	Yes	Yes	Yes
Barakat et al	Yes	Yes	Yes	Yes	Yes	Yes
Wattat et al	Yes	Yes	No	Yes	Yes	Yes
Rönö et al	Yes	Yes	No	Yes	Yes	Yes
Chan et al	Yes	Yes	Yes	Yes	Yes	Yes
Wickens et al	Yes	Yes	Yes	Yes	Yes	Yes
Wang et al	Yes	Yes	Yes	Yes	Yes	Yes
Simmons et al	Yes	Yes	No	Yes	Yes	Yes
Farren et al	Yes	No	Yes	Yes	Yes	Yes
Da Silva et al	Yes	No	Yes	Yes	Yes	Yes
Bruno et al	Yes	Yes	No	Yes	Yes	Yes
Assaf-Balut et al	Yes	Yes	Yes	Yes	Yes	Yes
Sun et al	Yes	Yes	Yes	Yes	Yes	Yes
Seneviratne et al	Yes	Yes	Yes	Yes	Yes	Yes
Santamaria et al	Yes	Yes	No	Yes	Yes	Yes
Sahariah et al	Yes	Yes	No	Yes	Yes	Yes
Opie et al	Yes	Yes	Yes	Yes	Yes	Yes
McCarthy et al	Yes	Yes	No	Yes	Yes	Yes
Guelfi et al	Yes	Yes	No	Yes	Yes	Yes
Wang et al	Yes	Yes	Yes	Yes	Yes	Yes
Poston et al	Yes	Yes	Yes	Yes	Yes	Yes
D'Anna et al	Yes	Yes	No	Yes	Yes	Yes
Cordero et al	Yes	Yes	No	Yes	Yes	Yes
Vesco et al	Yes	Yes	Yes	Yes	Yes	Yes
Petrella et al	Yes	Yes	No	Yes	Yes	Yes
Lindsay et al	Yes	Yes	Yes	Yes	Yes	Yes
Barakat et al2	Yes	Yes	N/A	Yes	Yes	Yes
Barakat et al3	Yes	Yes	N/A	Yes	Yes	Yes
Tomic et al	Yes	Yes	Yes	Yes	Yes	Yes
Matarrelli et al	Yes	Yes	Yes	Yes	Yes	Yes
D' Anna et al	Yes	Yes	Yes	Yes	Yes	Yes
Barakat 4	Yes	Yes	No	Yes	Yes	Yes
Walsh et al	Yes	Yes	Yes	Yes	Yes	Yes
Stafne et al	Yes	Yes	Yes	Yes	Yes	Yes
Oostdam et al	Yes	Yes	Yes	Yes	Yes	Yes
Barakat et al	Yes	Yes	Yes	Yes	Yes	Yes
Vinter et al	Yes	Yes	Yes	Yes	Yes	Yes
Luoto et al	Yes	Yes	No	Yes	Yes	Yes
Thronton et al	Yes	Yes	Yes	Yes	Yes	Yes
Hui et al	Yes	Yes	No	Yes	Yes	Yes
D'Anna et al	Yes	Yes	Yes	Yes	Yes	Yes

direct comparisons between 5 interventions were illustrated with forest maps (Fig. 8). The inconsistency test showed no inconsistencies in the global analysis at P value $> .05$, indicating that the direct comparison and indirect comparison results were consistent.

4. Discussion

This updated analysis is based on 46 RCTs, which included 16,545 women with pregnancy randomly assigned to 5 active interventions or a placebo. The results indicated that physical activity and probiotic intervention were more effective than placebo in reducing the risk of developing GDM. To our knowledge, this is the first time that physical activity intervention, dietary intervention, a combination of physical activity and diet, probiotic intervention, and inositol supplementation for the prevention of gestational diabetes have been compared the effectiveness in preventing GDM. The overview may provide valuable information for healthcare providers caring for pregnant women and reduce the short- and long-term health risks for pregnant women and their infants.

According to the results of SUCRA, the probiotic intervention was the best for reducing the risk of developing GDM compared with the effects of the other interventions, and physical activity ranked second. Probiotic bacteria have been used to change the gut's microbiome and shown to alleviate insulin resistance by

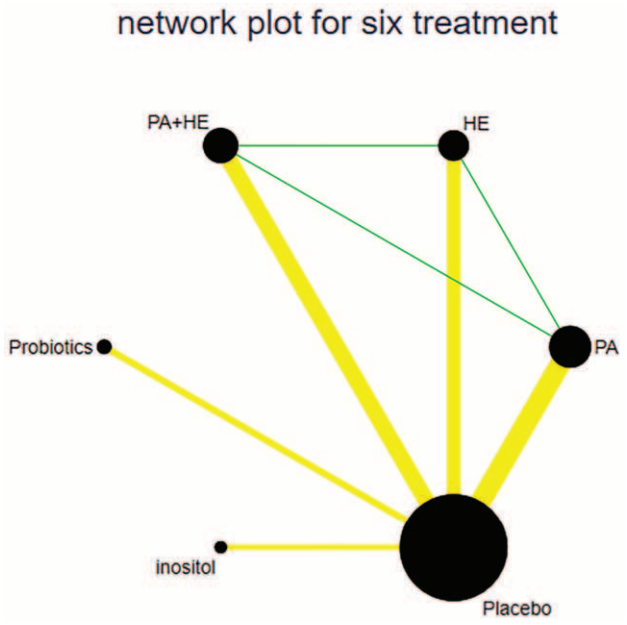

Figure 2. The network plot of 5 interventions.

reducing inflammatory signaling and upregulating genes involved in insulin sensitivity and lipid metabolism.[55–57] In concordance with the result of a previous review article on different types of intervention for preventing GDM, we found that probiotics were possibly effective in reducing the incidence of GDM in pregnant women.[58] Evidence from previous studies also suggests that the risk of developing GDM is inversely associated with regular physical activity both before or during pregnancy.[59] Regular physical activity leads to increased energy expenditure, glucose consumption, muscle mass, and blood flow through the capillary surface for glucose exchange.[60,61] Therefore, glucose tolerance and insulin sensitivity are likely to improve, and the improvement continues beyond the exercise period.[62] Similar to our findings, physical activity alone was beneficial in preventing GDM in several other systematic reviews.[7,63,64] Future work should focus on the type, duration, frequency, and timing of probiotic intervention and physical activity.

In our study, dietary intervention, a combination of physical activity and diet intervention, and inositol supplementation did not significantly alter GDM risk, though this does not exclude benefit for other health outcomes. Previous systematic reviews indicated that a combined diet and exercise intervention did not clearly reduce the risk of GDM, and suggested the reason for this was that simultaneously changing eating behavior and doing regular physical activity was too difficult.[63,65] We found no significant differences between the effectiveness of physical activity and the other interventions in preventing GDM. However, these summary effect sizes were mainly small to medium with some uncertainty, resulting from the small number of patients included and wide credible intervals.

Our review has several limitations. First, according to the CINEMA assessment, the quality of most comparisons was low or very low. Many trials did not report adequate information about allocation concealment, and it is difficult to use a double-blind design for patients in trials of diet, which would influence the transitivity of the whole network and restrict the interpretation of these results.[66] We did a sensitivity analysis

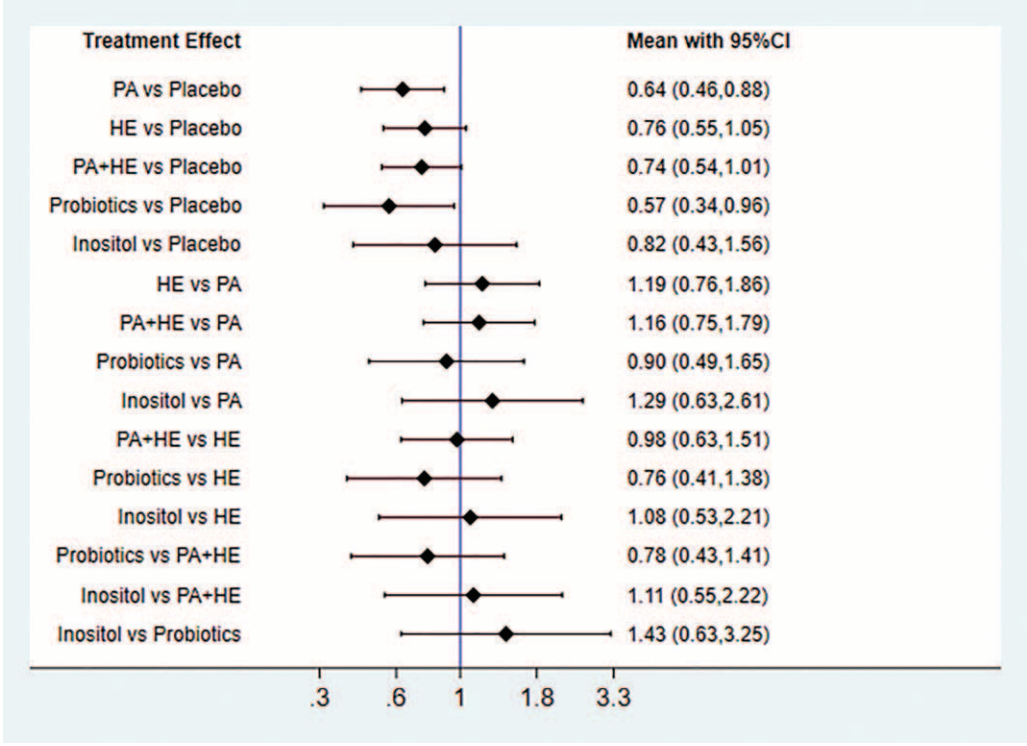

Figure 3. The forest map based on the pairwise comparison among interventions.

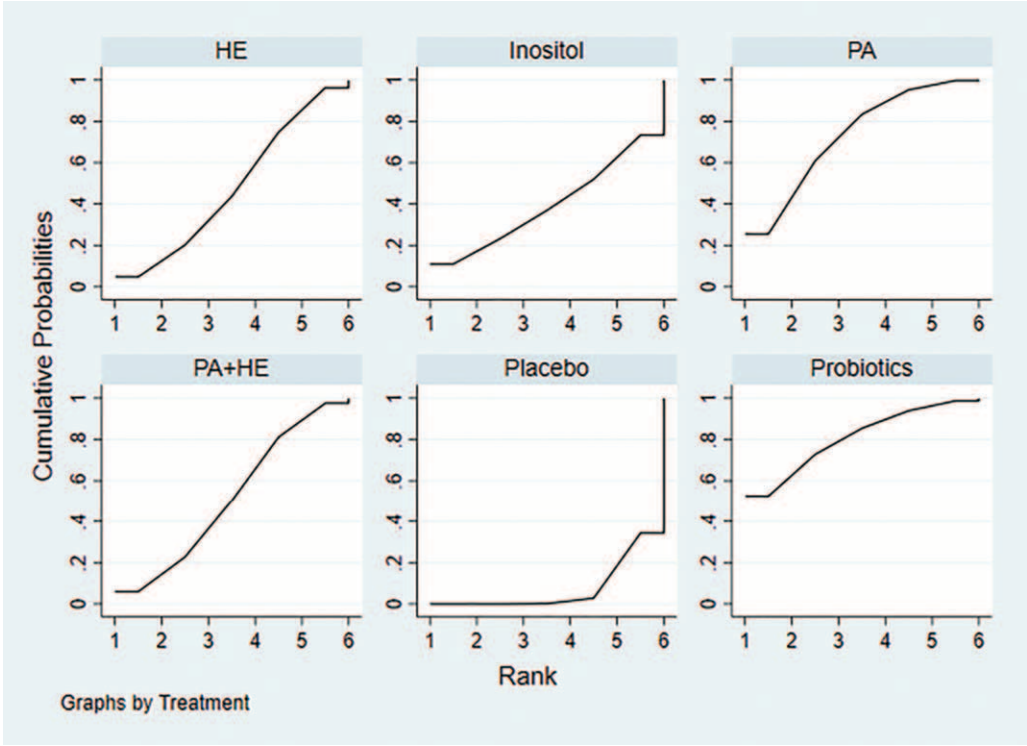

Figure 4. The SUCRA curves of 5 interventions. SUCRA = surface under the cumulative ranking curve.

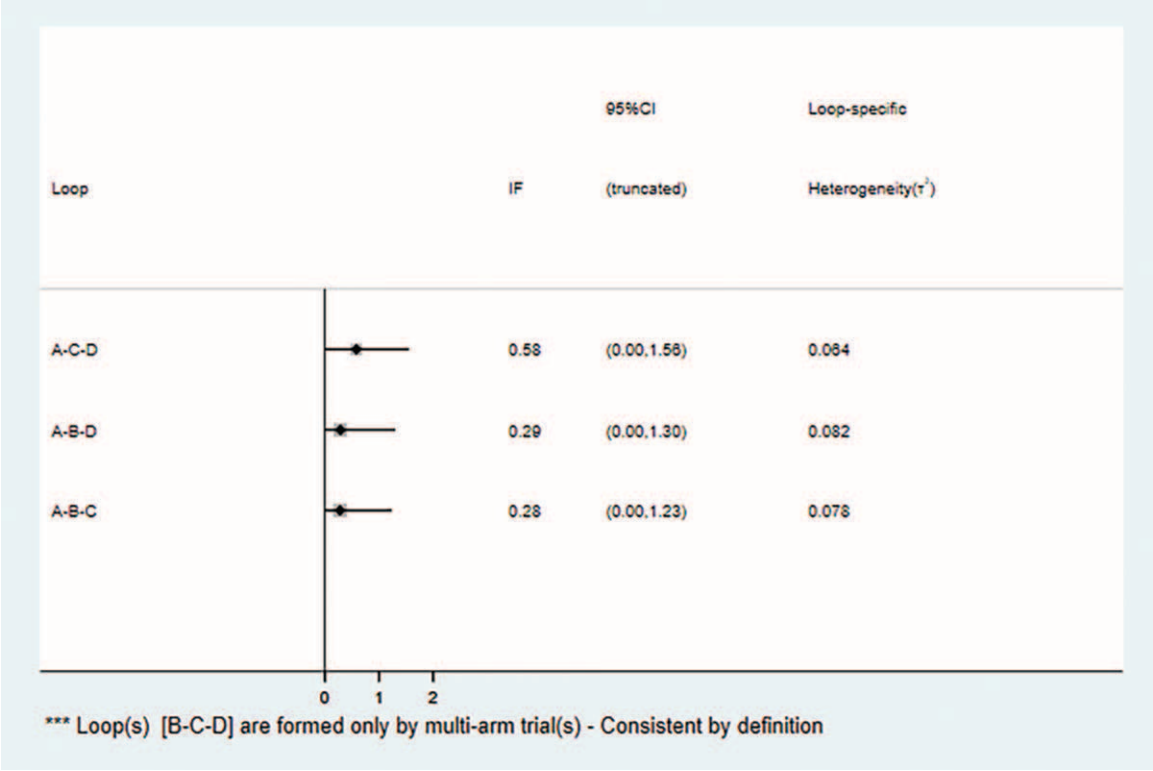

Figure 5. The results of loop inconsistency.

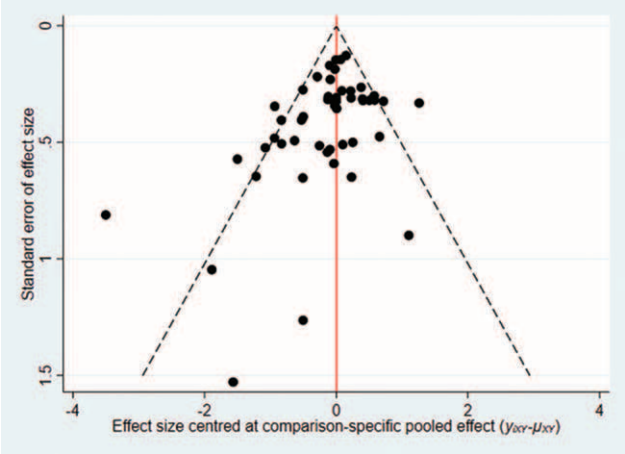

Figure 6. The funnel plot used for publication bias.

excluding nonblinded trials, the findings of which were not materially different from those of the primary analysis. Second, we found some global and local inconsistencies in efficacy outcomes in the network, perhaps because the proportion of patients who withdrew was a more consistently measured outcome across studies. Third, to support the transitivity assumption in the network, the review was restricted to trials involving pregnancies without gestational diabetes. We excluded studies in which participants were described as having subsyndromal depressive symptoms, because antidepressants are not recommended in this group of patients. They do, however, form a substantial proportion of the patients seen in real-world clinical settings. We also excluded patients with other pregnancy complications such as gestational hypertension, eclampsia, and placental insufficiency. Augmentation therapy is usually required for these patients, and including them would have violated the transitivity required of the network meta-analysis. Fourth, despite Egger test showing no publication bias for the outcome, we found some potential asymmetry of funnel plots in this network meta-analysis. Thus, the clinical interpretation of these findings is limited by the potential bias from selective reporting. We did our best to retrieve all available unpublished information and contacted study authors for supplementary data, but we cannot rule out the possibility that some unpublished studies are still missing. Fifth, physical activity or dietary interventions with different levels might produce different treatment effects. Although we included physical activities or dietary interventions without therapeutic ranges, we should consider the potential dose effects in this review. Moreover, physical activities and dietary interventions have a wide range of half-lives, from 5 hours to 5 days. Activities with a long half-life (i.e., physical and dietary interventions) need to be titrated over 3 or 4 weeks, whereas inositol with a short half-life does not. These titrations might confuse the outcomes from the short trials. In this review, we have excluded trials with a treatment duration of fewer than 4 weeks, which could reduce the effect for the final analysis. Sixth, we limited our search only to English, and valuable data might have been left out. However, a manual search in the references list of relevant articles and reviews was used to maximize the identification of eligible studies. Finally, there were some limitations in the network meta-analysis method. In this network meta-analysis, a small number of trials compared the same treatments, and the assumption of transitivity over various control conditions was

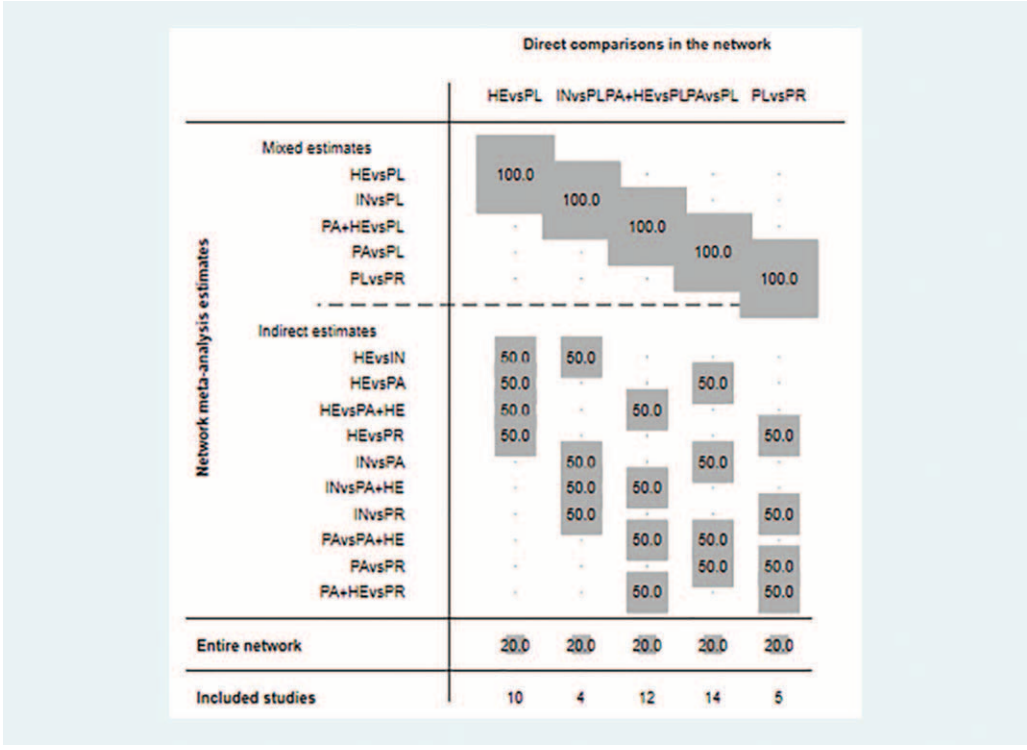

Figure 7. The contributional map for the included interventions.

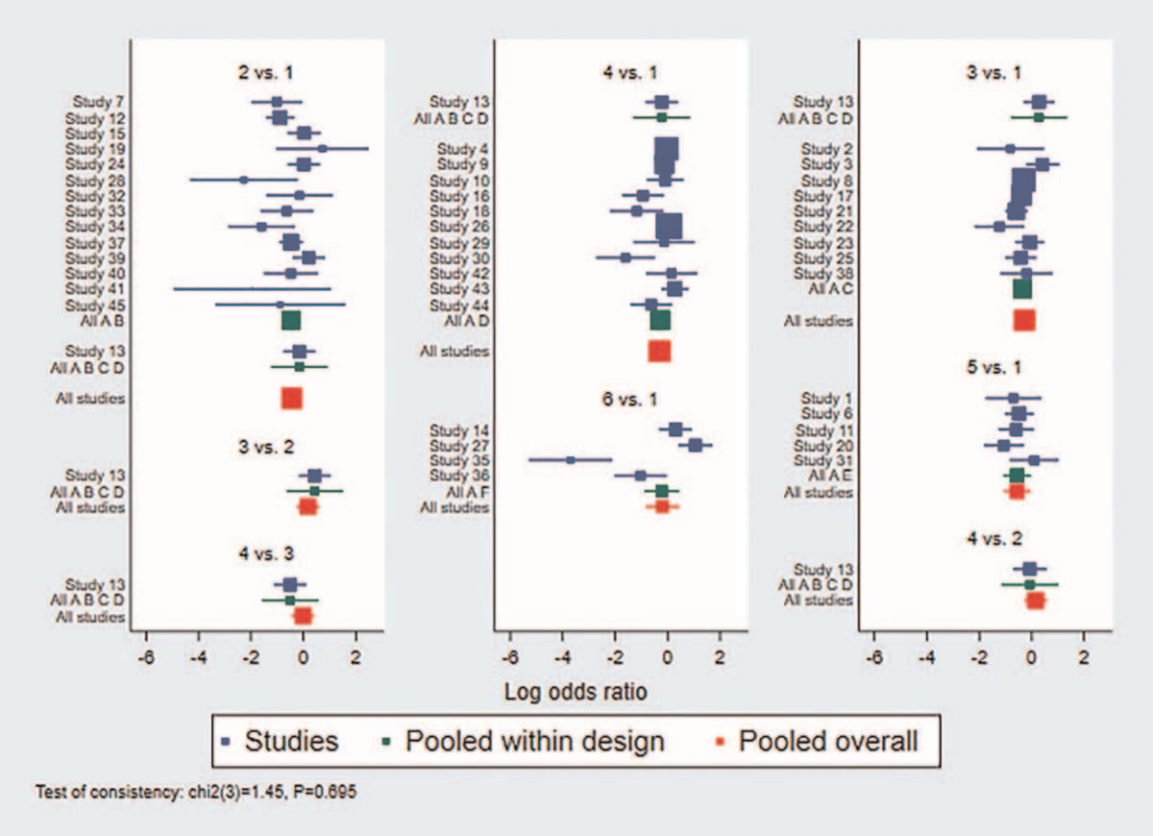

Figure 8. The forest map based on the pairwise comparison among interventions.

understated. These control conditions can reduce network connectivity in network meta-analyses and, therefore, low statistical power.[67] In addition, we excluded observational studies to decrease the heterogeneity in the network meta-analysis; however, observational studies can provide more information about real-world evidence on the interventions used in the studied population group.[68] Further meta-analyses with observational studies are warranted to reduce the limitations of the existing evidence.

5. Conclusion

Despite these limitations, the findings from this network meta-analysis represent the most comprehensive analysis of the available evidence on the interventions utilized to prevent GDM. Physical activity and probiotic intervention are more effective than placebo in reducing the risk of developing GDM. The present results suggest that these interventions may be considered adjunctive therapies for preventing GDM and reducing the short- and long-term health risks for pregnant women and their infants. Future work should focus on the type, duration, frequency, and timing of physical activity and probiotic intervention.

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