Effect of different nutrients on blood glucose, inflammatory response and oxidative stress in gestational diabetes mellitus: a network meta-analysis

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Abstract

We searched PubMed, Web of Science, Embase, The Cochrane Library, China Biomedical Literature Database and other databases from inception to June 2023. The included studies were randomised controlled trials (RCT). The studies were screened by four authors, divided into two independent pairs. A total of eighteen studies were included, including 1362 patients, involving twelve intervention measures. The different nutrients had a significant effect on improving blood glucose, reducing inflammation levels and reducing oxidative stress compared with placebo ($P < 0.05$). Cumulative probability ranking showed that vitamin A + vitamin D + vitamin E ranked first in lowering fasting blood glucose (standardised mean difference (SMD) = 41.30, 95 % CI (2.07, 825.60)) and postprandial 2-h blood glucose (SMD = 15.19, 95 % CI (4.16, 55.53)). In terms of insulin resistance index, the first highest probability ranking is vitamin D (SMD = 5.12, 95 % CI (0.76, 34.54)). In terms of reducing the high-sensitivity C-reactive protein level, the first in probability ranking is VE (SMD = 2.58, 95 % CI (1.87,3.55)). The results of cumulative probability ranking showed that Mg + Zn + Ca + VD ranked first in reducing TNF-α (SMD = 1.90, 95% CI (0.40, 9.08)) and IL-6 (SMD = 1.83, 95 % CI (0.37, 9.12)). In terms of reducing malondialdehyde levels, the first ranked probability is VB1 (SMD = 4.99, 95 % CI (1.85, 13.46)). Cumulative probability ranking results showed that Ca + VD ranked first in reducing total antioxidant capacity (SMD = 0.66,95 % CI (0.38, 1.15)) and glutathione (SMD = 1.39, 95 % CI (0.43, 4.56)). In conclusion, nutritional interventions have significant effects on improving blood glucose, inflammatory levels and oxidative stress in patients with gestational diabetes. Due to the high uncertainty in the results and differences in the number and quality of studies included, the reliability of the conclusions still needs to be validated by conducting large-sample, high-quality RCT studies.

Keywords: Nutrients: Gestational diabetes: Blood sugar: Inflammatory response: Oxidative stress: Network meta-analysis: Randomised controlled trial

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications[1]. Its incidence is increasing year by year, reaching 14·8% in the country[2], higher than the global prevalence rate of 14·0%[3]. Studies have shown that inflammation and oxidative stress are involved in the development of GDM and even contribute to poor pregnancy outcomes[4–6]. The reason for this may be that high blood glucose levels induce a significant increase in toll-like receptor expression in monocytes, elevated levels of oxidative stress and overproduction of reactive oxygen species, which further activate inflammatory transcription factors and increase the secretion of pro-inflammatory cytokines, which not only puts the organism in a chronic inflammatory state[7]. In addition, this can lead to adverse pregnancy events such as pre-eclampsia, the metabolic syndrome and gestational hypertension in both the fetus and

the mother[8]. In addition, inflammatory factors stimulate an increase in insulin secretion, and excessive insulin secretion further impairs pancreatic islet function, resulting in glucose metabolism disorders[9]. It is clear that disease control and therapeutic care for GDM have become important issues in public health.

Dietary therapy is the mainstay of GDM prevention and treatment, and since diet is a mixture of nutrients, it is particularly important to accurately assess the impact of the nutrient intake of different food groups on GDM patients. Several studies have now shown that nutrients such as vitamin D[10], *n*-3 fatty acids[11], Zn[12] and thiamine[13] are effective in improving inflammatory response and oxidative stress and maintaining glucose metabolic homoeostasis in GDM patients. However, it is also controversial that vitamin D[14] and *n*-3 fatty acids[15] have not been found to

be significantly effective in lowering blood glucose and improving inflammation levels. Currently, which nutrients have stronger anti-inflammatory efficacy and better glycaemic stabilisation in patients with GDM? The difference between different categories of nutrients still exists, has not yet been clarified and has not formed a unified conclusion. Most of the currently available studies have focused on the effect of a particular class of nutrient compared with placebo[16] or on the effect of nutrient interventions alone[17] or in combination[14] on pregnancy outcomes in GDM, and there is a lack of comparative evidence between different classes of nutrients.

Thus, this study used network meta-analysis to comprehensively evaluate the effects of different categories of nutrients on glucose metabolism, inflammation and oxidative stress in patients with GDM, with a view to providing evidence-based medical references for clinical dietary guidance in patients with GDM.

Methods

This network meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[18] and registered in the PROSPERO International prospective register of systematic reviews (CRD42023454432).

Search strategy

Electronic databases were searched, including PubMed, Web of Science, Embase, The Cochrane Library, China Biomedical Literature Database, China Knowledge Network, Wanfang Database and Wikipedia Database. The present study searched and screened all published RCTs related to the effects of different nutrient interventions on glycaemia, inflammation, and oxidative stress in patients with GDM from the time the database was established until June 20, 2023. The search terms were a combination of subject terms and free words, supplemented by hand searching and snowballing to obtain relevant studies. The following combination of keywords was used: ('nutrient' OR 'micronutrients' OR 'macronutrients' OR 'vitamin' OR 'mineral' OR 'lipids' OR 'fatty-acid' OR 'protein') AND ('gestational diabetes' OR 'gestational diabetes mellitus' OR 'GDM') AND ('blood sugar' OR 'glucose metabolism' OR 'inflammation' OR 'oxidative stress'). Moreover, we also searched the reference lists of pertinent studies for any missing studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. Study type: domestic and foreign published randomised controlled trials;
2. Subjects: GDM patients who met the diagnostic criteria of the Guidelines for the Diagnosis and Treatment of Hyperglycemia in Pregnancy (2022)[19];
3. Interventions: Dietary interventions for patients with GDM using nutrients alone or in combination in the intervention group and placebo or other diets in the control group;

4. Outcome indicators: blood glucose indicators included fasting blood glucose (FBG), 2h postprandial blood glucose (2hPG) and insulin resistance index (HOMA-1R); inflammatory response indicators included high-sensitivity C-reactive protein (hs-CRP), TNF-α and IL-6 and oxidative stress indicators included malondialdehyde (MDA), total antioxidant capacity (TAC) and glutathione (GSH).

Trials were excluded if:

1. studies in which the intervention nutrient contained in the intervention group was unclear;
2. literature with incomplete data or in which valid data could not be extracted;
3. poorly designed studies (no control group);
4. duplicated publications and (5) literature for which full text was not available.

Data extraction

Included studies were screened independently by two researchers in strict accordance with the inclusion and exclusion criteria; information was extracted and cross-checked; and in cases of disagreement, it was discussed and resolved, or a third-party expert was consulted to assist in the adjudication. Data extraction included the first author, year of publication, age of study participants, sample size of study participants, intervention, duration of intervention and outcome indicators.

Risk of bias in evaluation

Randomised controlled trials were evaluated independently by two investigators for quality according to the risk of bias assessment criteria recommended in the Cochrane Handbook version 5.1.0, and results were cross-checked. In the event of disagreement, discussions were held to resolve it, or third-party experts were consulted to assist in the adjudication. The evaluation included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases. Each category was judged to be low risk, unclear risk or high risk.

Grading the quality of evidence

The certainty of the evidence was assessed using the GRADE approach and GRADEpro[20]. The assessments were conducted independently by two investigators, with disagreements resolved through discussion or consultation with a third party. Each outcome had a high, moderate, low or very low evidence score, depending on study design, risk of bias, inconsistency, indirect evidence, imprecision and publication bias.

Statistical analysis

As the outcome indicators in this study were all continuous variables, a standardised mean difference (SMD) was used as the effect indicator, and a 95 % CI was selected for each effect size.
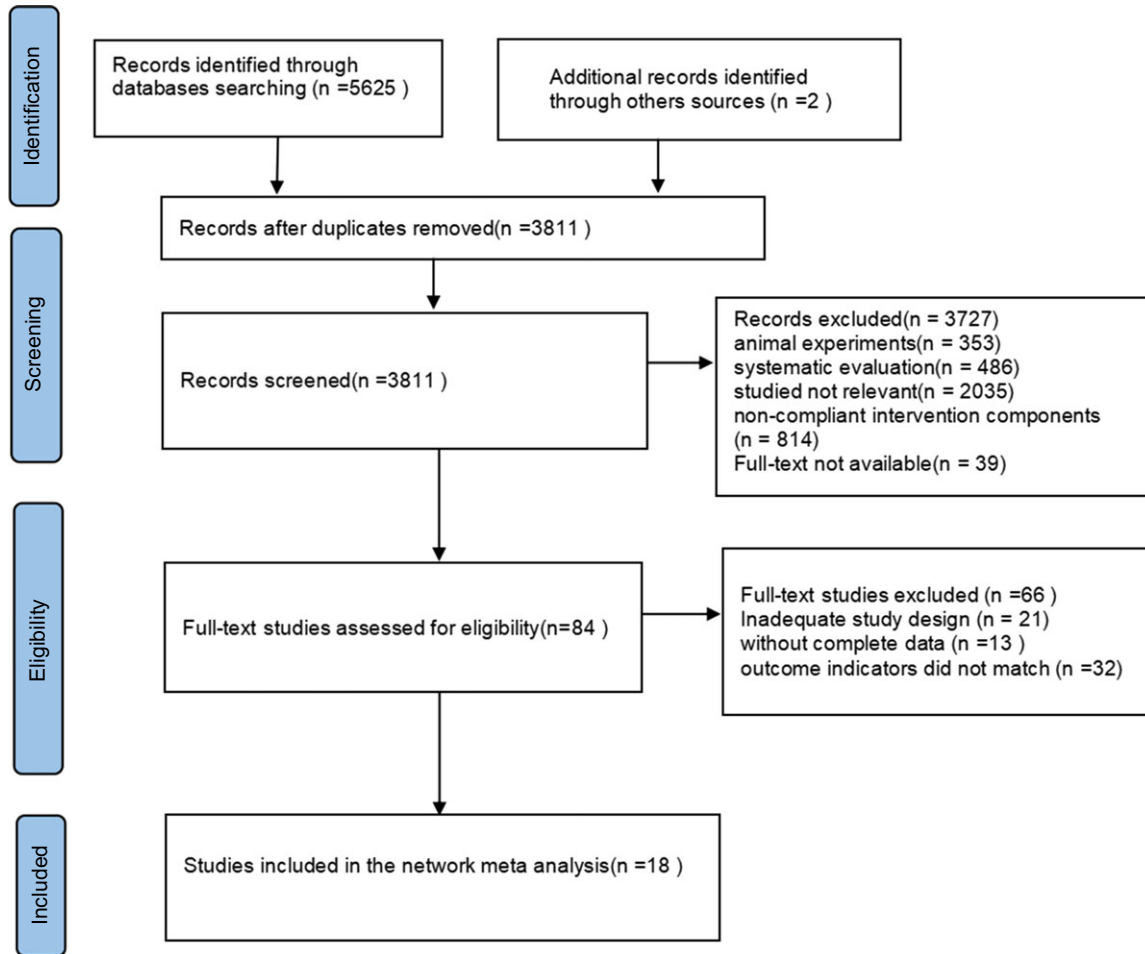
Fig. 1. PRISMA flow diagram of study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

The 95 % CI of the effect indicator was considered statistically significant by not crossing the effect line of zero. Based on the frequency-based framework, risk-bias maps were plotted using Rev Man 5·4 software, reticulated meta-analysis was performed using Stata 17.0 software and evidence network maps, comparison-correction funnel plots and the area under the cumulative probability ranking curve (surface under the cumulative ranking, SUCRA) were plotted. Evidence network diagrams showing closed loops required further inconsistency testing, and conversely, consistency models were selected. Comparison-correction funnels assessed publication bias and small-sample effects. SUCRA ranked the superior and inferior efficacy of interventions, with smaller values indicating better efficacy.

Results

Study selection and characteristics

A total of 5627 studies were retrieved from the database according to the established search strategy, and 1816 studies were removed due to duplication. Subsequently, 3727 studies were excluded during the screening process via title and abstract. We then further searched the full text of eighty-four studies to assess their eligibility, of which sixty-six were excluded. Eventually, we included eighteen original studies to investigate the effects of different nutrients on blood glucose, inflammatory response and oxidative stress in GDM[11–14, 16, 21–33]. The flow of the above-described procedures is shown in Fig. 1.

Overall, the included studies were published between 2013 and 2022 and enrolled a total of 1362 GDM patients. The duration of the included studies ranged between 6 weeks and 12 weeks, and the mean age of patients ranged between 27 and 32 years. The included studies included twelve nutrients interventions, namely vitamin D, Ca + vitamin D, vitamin E, n-3 fatty acids, n-3 fatty acids + vitamin D, vitamin A + vitamin D + vitamin E, Mg-Zn-Ca-vitamin D combination supplement, Se, folic acid + vitamin B_{12}, vitamin B_1, Zn and placebo. The details are shown in Table 1.

Risk of bias and GRADE

Regarding the particular elements of the Cochrane Collaboration's risk of bias assessment criteria, four studies did not mention randomisation, nine reported allocation concealment, three did not mention blinding of participants and personnel, ten reported incomplete outcome data and selective reporting bias and all studies mentioned no other biases. Details are shown in

Table 1. Characteristics of the included studies

Author	Publication year	Sample size (T/C)	Age (T/C)	Intervention measures T	Intervention measures C	Intervention duration (T/C)	Outcome indicators
E D[33]	2013	26/30	28 ± 5	VD	placebo	1 month/1 month	①③
Asemi Z[14]	2014	28/28	28·7 ± 6·0/30·80 ± 6·6	Ca + VD	placebo	6 weeks/6 weeks	①③④⑦⑧⑨
Jianrong H[32]	2015	87/80	28·32 ± 6·31/27·80 ± 6·46	VE	placebo	1 month/1 month	④⑥
Jamilian M[31]	2016	27/27	30·1 ± 5·3/30·0 ± 5·5	ω–3	placebo	6 weeks/6 weeks	④⑦⑧⑨
Razavi M[11]	2017	30/30	29·9 ± 4·0/29·2 ± 3·4	ω–3 + VD	placebo	6 weeks/6 weeks	④⑦⑧⑨
Yanmei Z[29]	2019	42/42	31 ± 5/30 ± 5	VD	placebo	12 weeks/12 weeks	①③
Xiangmei L[25]	2020	50/50	28·19 ± 0·16/28·21 ± 0·15	VA + VD + VE	placebo	6 weeks/6 weeks	①②③
Jing L[26]	2020	40/40	29·03 ± 5·63/28·46 ± 6·04	Mg + Zn + Ca + VD	placebo	6 weeks/6 weeks	④⑦⑧⑨
Baolian R[23]	2022	48/48	32·13 ± 5·07/31·13 ± 5·27	Mg + Zn + Ca + VD	placebo	6 weeks/6 weeks	④⑤⑥⑦⑧⑨
Jizhang H[27]	2020	38/42	27·5 ± 3·8/28·0 ± 3·5	VD	placebo	1 month/1 month	①③⑤⑥
Asemi Z[16]	2015	35/35	27·6 ± 5·3/29·6 ± 3·6	se	placebo	6 weeks/6 weeks	①③④⑦⑧⑨
Meng C[22]	2022	40/40	30·94 ± 6·46/30·63 ± 6·98	VB11 + VB12	placebo	/	①③
Yun C[21]	2022	50/50	27·69 ± 4·82/27·86 ± 4·95	VD	placebo	2months/2 months	①②③④
Amirani E[13]	2022	24/25	28·3 ± 5·7/29·5 ± 4·3	VB1	placebo	6 weeks/6 weeks	④⑦⑧⑨
Jamilian M[28]	2019	30/30	27·7 ± 4·0/29·1 ± 4·1	Mg + Zn + Ca + VD	placebo	6 weeks/6 weeks	①④⑦⑧⑨
Karamali M[30]	2018	30/30	30·0 ± 4·5/31·1 ± 4·2	Mg + Zn + Ca + VD	placebo	6 weeks/6 weeks	①③
Karamali M[12]	2016	25/25	29·9 ± 5·0/29·3·1 ± 3·8	Zn	placebo	6 weeks/6 weeks	④⑦⑧⑨
Jamilian M[24]	2020	30/30	29·5 ± 5·0/28·5 ± 4·1	ω–3	placebo	6 weeks/6 weeks	①③④⑦⑧⑨

T, intervention group; C, control group; VD, vitamin D; Ca + VD, calcium + vitamin D; VE, vitamin E; *n*-3, *n*-3 fatty acids; *n*-3 + VD, *n*-3 fatty acids + vitamin D; VA + VD + VE, vitamin A + vitamin D + vitamin E; Mg + Zn + Ca + VD, magnesium-zinc-calcium-vitamin D combination; se, selenium; VB11 + VB12, folic acid + vitamin B$_{12}$; VB1, vitamin B$_1$; Zn, zinc; ①, fasting blood glucose; ②, postprandial blood glucose; ③, insulin resistance index; ④, high-sensitivity C-reactive protein; ⑤, TNF-α; ⑥, IL-6; ⑦, malondialdehyde; ⑧, total antioxidant capacity; ⑨, glutathione.
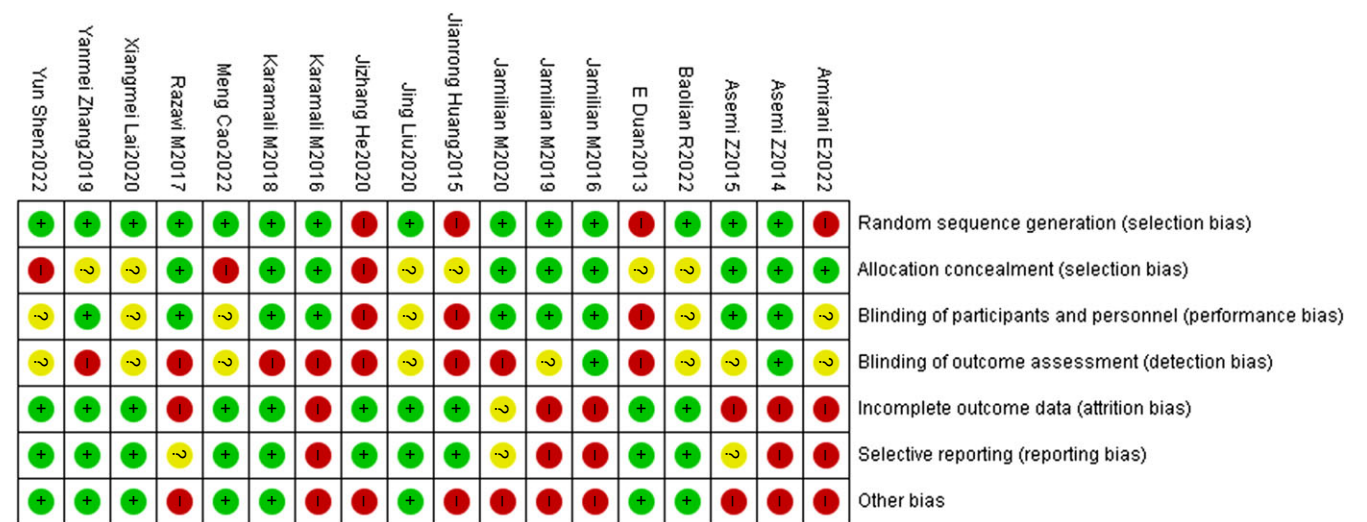

Fig. 2. Bias risk assessment results of included RCT. RCT, randomised controlled trial.

Figs. 2 and 3. The quality of evidence for all outcome indicators was evaluated according to the GRADE approach, with the majority of the evidence (74·5%) rated as having low credibility and a small proportion as moderate or very low. The details are shown in online Supplementary Table S1–S9.

Evidence network map

With no closed loops between any of the outcome indicators, the overall shape took the form of a diverging star that was centred on placebo. The dots in the figure represent the various nutrient interventions, their sizes indicate the number of sample sizes and the thickness of the line connecting the dots indicates the number of studies that directly compared the various nutrient interventions. Eleven studies reported on FBG, which involved seven interventions; two studies reported on 2hPG, which involved two interventions; ten studies reported on HOMA-1R, which involved seven interventions; twelve studies reported on hs-CRP, which involved nine interventions; two studies reported on TNF-α, which involved two interventions; three studies reported on IL-6, which involved three interventions; ten studies reported on MDA, which involved seven interventions; ten studies reported on TAC, which involved seven interventions; and ten studies reported on GSH, which involved seven interventions. The details are shown in Fig. 4.

Fasting blood glucose

A total of twenty-eight two-by-two comparisons were carried out in the network meta-analysis. The results demonstrate that VD
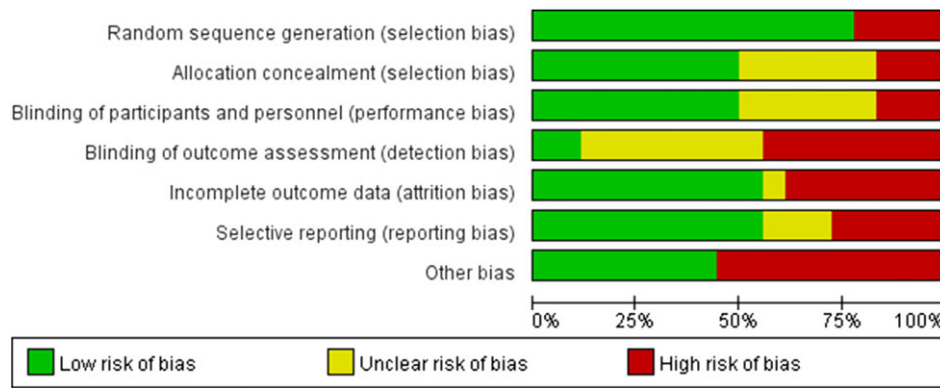
Fig. 3. Bar chart for bias risk of the included RCT. RCT, randomised controlled trial.

(SMD = 1·83, 95 % CI (0·42, 8·08)), Ca + VD (SMD = 1·62, 95 % CI (0·08, 31·65)), ω-3 (SMD = 2·65, 95 % CI (0·13, 52·17)), VA + VD + VE (SMD = 41·30, 95 % CI (2·07, 825·60)), Mg + Zn + Ca + VD (SMD = 2. 28, 95 % CI (0·28, 18·66)), se (SMD = 1·26, 95 % CI (0·07, 24·25)) and VB11 + VB12 (SMD = 5·56, 95 % CI (0·29, 108·21)) are statistically significant when compared with placebo control, in terms of lowering FBG levels ($P < 0.05$). The findings of the two-by-two assessment on the impact of diverse nutrient interventions in reducing FBG levels were statistically meaningful ($P < 0.05$), as demonstrated in Table 2.

The SUCRA results showed that VA + VD + VE was most likely to be the best nutrient intervention to reduce blood glucose levels, with the SUCRA ranking of VA + VD + VE (93·0 %) > VB11 + VB12 (65·8 %) > ω-3 (50·4 %) > Mg + Zn + Ca + VD (48·6 %) > VD (43·7 %) > Ca + VD (40·3 %) > se (34·6 %) > placebo (23·6 %), as detailed in Fig. 5(a).

Two-hour postprandial blood glucose

A total of three two-by-two comparative results were achieved by network meta-analysis, and the differences were statistically significant ($P < 0.05$) in terms of improvement of 2hPG levels with VD (SMD = 2·18, 95 % CI (0·17, 28·45)) and VA + VD + VE (SMD = 15·19, 95 % CI (4·16, 55·53)) compared with placebo control. In the results of a two-by-two comparison of the effects of using different nutrient interventions on reducing 2hPG levels, the differences were all statistically significant ($P < 0.05$), as shown in Table 3.

The SUCRA results showed that VA + VD + VE was most likely to be the best nutrient intervention to improve 2hPG levels, and the SUCRA ranking was VA + VD + VE (95·5 %) > VD (40·4 %) > placebo (14·2 %), as shown in Fig. 5(b).

HOMA-1R

A total of twenty-eight two-by-two comparisons of results were achieved by network meta-analysis, and in terms of stabilising HOMA-1R levels, VD (SMD = 5·12, 95 % CI (0·76, 34·54)), Ca + VD (SMD = 2·13, 95 % CI (0·05, 96·57)), ω-3 (SMD = 1·98, 95 % CI (0·04, 90·08)), VA + VD + VE (SMD = 2·60, 95 % CI (0·06115·98)), Mg + Zn + Ca + VD (SMD = 2·31, 95 % CI (0·05104·36)), se (SMD = 2·54, 95 % CI (0·06114·09)) and VB11 + VB12 (SMD = 1·82, 95 % CI (0·04, 81·46)) were

statistically significant when compared with placebo control ($P < 0.05$). In the two-by-two comparison results of the effect of using different nutrient interventions on stabilising HOMA-1R levels, the differences were all statistically significant ($P < 0.05$), as shown in Table 4.

The SUCRA results showed that VD was most likely the best nutrient intervention for stabilising HOMA-1R levels, and the SUCRA ranking was VD (69·5 %) > VA + VD + VE (53·1 %) > se (52·9 %) > Mg + Zn + Ca + VD (51·1 %) > Ca + VD (49·1 %) > ω-3 (47·8 %) > VB11 + VB12 (46·5 %) > placebo (30·0 %), as detailed in Fig. 5(c).

High-sensitivity C-reactive protein

A total of forty-five two-by-two comparisons of results were achieved by network meta-analysis, and in terms of reducing hs-CRP levels, VD (SMD = 1·71, 95 % CI (1·15, 2·55)), Ca + VD (SMD = 0·75, 95 % CI (0·44, 1·27)), VE (SMD = 2·58, 95 % CI (1·87, 3·55)) ω-3 (SMD = 1·72, 95 % CI (1·16, 2·55)), ω-3 + VD(SMD = 1·50, 95 % CI (0·90, 2·51)), Mg + Zn + Ca + VD(SMD = 1·75, 95 % CI (1·35, 2·27)) se(SMD = 1·90, 95 % CI (1·17, 3·07)) VB1 (SMD = 1·85, 95 % CI (1·04, 3·29)), and Zn (SMD = 2·34, 95 % CI (1·31, 4·18)) were statistically significant when compared with placebo control ($P < 0.05$). The results of the two-by-two comparison of the effects of using different nutrient interventions on the reduction of hs-CRP levels were statistically significant ($P < 0.05$), as shown in Table 5.

The SUCRA results showed that VE was most likely to be the best nutrient intervention to reduce hs-CRP levels, and the SUCRA ranking was VE (90·2 %) > Zn (78·8 %) > se (62·0 %) > VB1 (59·4 %) > Mg + Zn + Ca + VD (53·3 %) > ω-3 (51·8 %) > VD (51·5 %) > ω-3 + VD (40·3 %) > placebo (10·6 %) > Ca + VD (2·3 %), as detailed in Fig. 5(d).

TNF-α

A total of three two-by-two comparative results were achieved by network meta-analysis, and the differences were statistically significant ($P < 0.05$) when comparing VD (SMD = 0·30, 95 % CI (0·04, 2·09)) and Mg + Zn + Ca + VD (SMD = 1·90, 95 % CI (0·40, 9·08)) with placebo control in terms of lowering the TNF-α level. In the two-by-two comparison results of the effect of using different nutrient interventions on lowering TNF-α levels, the differences were all statistically significant ($P < 0.05$), see Table 6 for details.
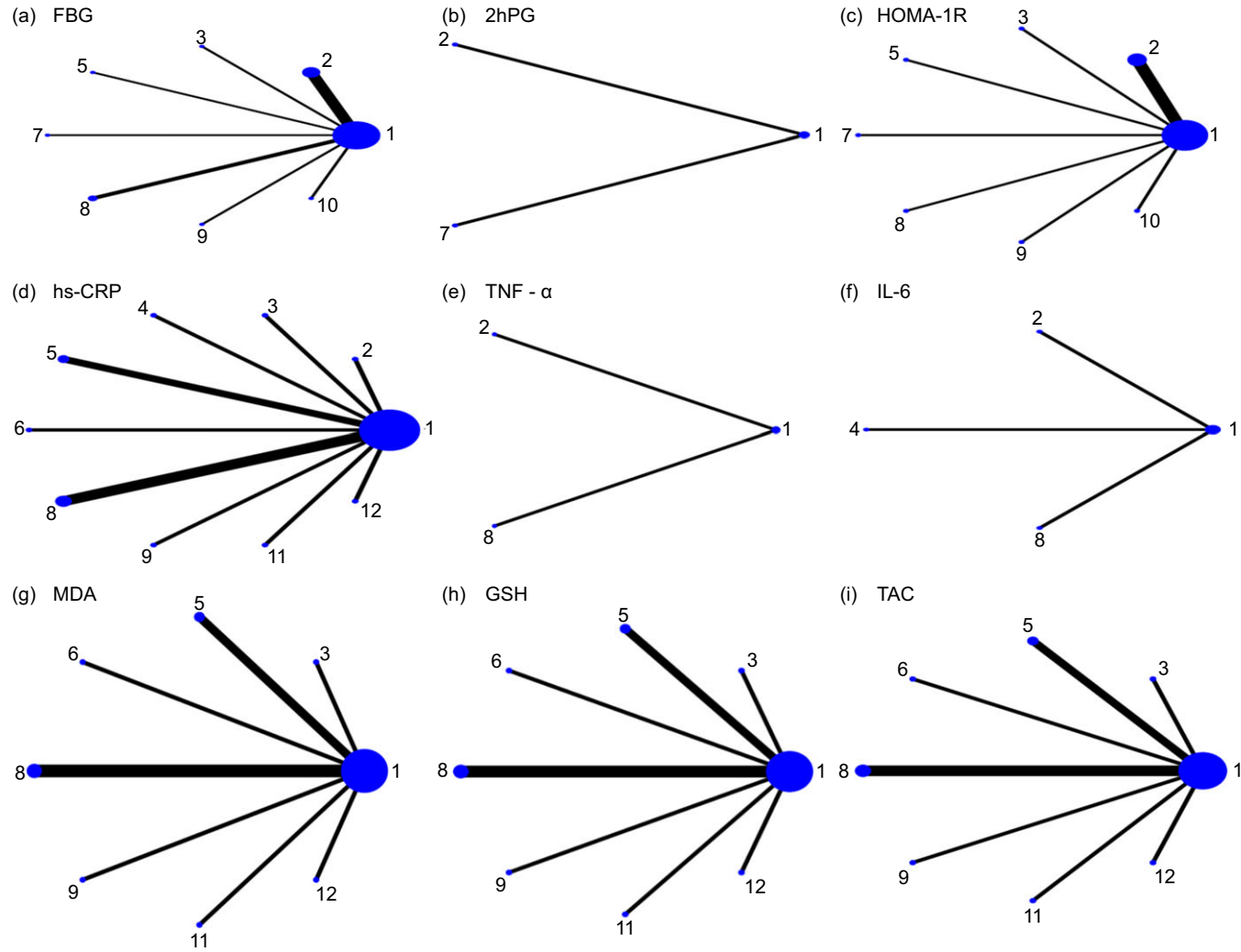
Fig. 4. Network relationship diagram for different outcome indicators. The dots in the figure indicate the different nutrient interventions, the size of the dots indicates the sample size and the thickness of the line connecting the dots indicates the number of studies in which direct comparisons of nutrient interventions were made. FBG, fasting blood glucose; 2hPG, 2h postprandial blood glucose; HOMA-1R, insulin resistance index; hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; GSH, glutathione; TAC, total antioxidant capacity; 1, placebo; 2, VD; 3, Ca + VD; 4, VE; 5, ω-3; 6, ω-3 + VD; 7, VA + VD + VE; 8, Mg + Zn + Ca + VD; 9, se; 10, VB11 + VB12; 11, VB1; 12, Zn.

Table 2. Results of network meta-analysis of FBG (SMD (95 % CI))

Intervention measures	Placebo		VD		Ca + VD		ω-3		VA + VD + VE		Mg + Zn + Ca + VD		se		VB11 + VB12
	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	
Placebo	0	–	–		–		–		–		–		–		–
VD	1·83	0·42, 8·08*	0	–	–		–		–		–		–		–
Ca + VD	1·62	0·08, 31·65*	0·89	0·03, 24·50*	0	–	–		–		–		–		–
ω-3	2·65	0·13, 52·17*	1·44	0·05, 40·33*	1·63	0·02109·67*	0	–	–		–		–		–
VA + VD + VE	41·30	2·07825·60*	22·53	0·80 637·39*	25·45	0·371 728·69*	15·61	0·231 068·21*	0	–	–		–		–
Mg + Zn + Ca + VD	2·28	0·28, 18·66*	1·25	0·10, 16·31*	1·41	0·04, 53·51*	0·86	0·02, 33·11*	18·08	0·47 701·18*	0	–	–		–
se	1·26	0·07, 24·25*	0·69	0·02, 18·79*	0·77	0·01, 51·30*	0·47	0·01, 31·70*	32·87	0·492 216·49*	0·55	0·01, 20·73*	0	–	–
VB11 + VB12	5·56	0·29 108·21*	3·03	0·11, 83·78*	3·43	0·05228·39*	2·10	0·03141·13*	7·42	0·11 503·25*	2·44	0·06, 92·36*	4·43	0·07292·82*	0

FBG, fasting blood glucose; SMD, standardised mean difference.
* Denotes P < 0·05; –denotes no relevant data/data duplication.

The SUCRA results showed that Mg + Zn + Ca + VD was most likely to be the best nutrient intervention to reduce TNF-α levels, and the SUCRA ranking was Mg + Zn + Ca + VD (85·8 %) > placebo (54·8 %) VD (9·4 %), as shown in Fig. 5(e).

Il-6

A total of six two-by-two comparisons of results were achieved by network meta-analysis, and in terms of lowering IL-6 levels, VD (SMD = 51·23, 95 % CI (1·20, 2177·63), VE (SMD = 2·11, 95 % CI (0·05, 82·08), and Mg + Zn + Ca + VD (SMD = 1·83, 95 % CI (0·37, 9·12)) were statistically significant when compared with placebo control (P < 0·05). The results of the two-by-two comparison of the effect of using different nutrient interventions on the reduction of IL-6 levels were statistically significant (P < 0·05), see Table 7.

The SUCRA results showed that Mg + Zn + Ca + VD is the most likely optimal nutrient intervention to reduce IL-6 levels. The SUCRA ranking is Mg + Zn + Ca + VD (74·3 %)>VE (71·7 %) > placebo (51·6 %) > VD (2·4 %), as shown in Fig. 5(f).

Malondialdehyde

A total of twenty-eight two-by-two comparisons of results were achieved by network meta-analysis, and in terms of reducing MDA levels, Ca + VD (SMD = 1·50, 95 % CI (0·60, 3·75)), ω-3 (SMD = 2·14, 95 % CI (1·10, 4·15)), ω-3 + VD (SMD = 2·80, 95 % CI (1·11, 7·04)), Mg + Zn + Ca + VD (SMD = 3·72, 95 % CI (2·21, 6·25)), se (SMD = 1·34, 95 % CI (0·56, 3·25)) VB1 (SMD = 4·99, 95 % CI (1·85, 13·46)) and Zn (SMD = 0·90, 95 % CI (0·36, 2·29)) were statistically significant when compared with placebo control (P < 0·05). The results of the two-by-two comparison of the effect of using different nutrient interventions on the reduction of MDA levels were statistically significant (P < 0·05), as shown in Table 8.

The SUCRA results showed that VB1 was most likely the best nutrient intervention to reduce MDA levels, and the SUCRA ranking was VB1 (90·8 %) > Mg + Zn + Ca + VD (83·3 %) > ω-3 + VD (68·5 %) > ω-3 (56·4 %) > Ca + VD (38·1 %) > se (32·8 %) > Zn (15·1 %) > placebo (15·0 %), as detailed in Fig. 5(g).

Total antioxidant capacity

A total of twenty-eight two-by-two comparisons of results were achieved by network meta-analysis, and in terms of reducing TAC levels, Ca + VD (SMD = 1·27, 95 % CI (0·47, 3·46)), ω-3 (SMD = 0·95, 95 % CI (0·46, 1·94)), and ω-3 + VD (SMD = 0·06, 95 % CI (0·02, 0·18)) Mg + Zn + Ca + VD (SMD = 0·66, 95 % CI (0·38, 1·15) se (SMD = 0·61, 95 % CI (0·23, 1·63)) VB1 (SMD = 1·05, 95 % CI (0·38, 2·91)) and Zn (SMD = 0·89, 95 % CI (0·32, 2·45)) were statistically significant when compared with placebo control (P < 0·05). The results of the two-by-two comparison of the effect of using different nutrient interventions on the reduction of TAC levels were statistically significant (P < 0·05), as shown in Table 9.

The SUCRA results showed that Ca + VD was most likely the best nutrient intervention to reduce TAC levels, and the SUCRA ranking was Ca + VD (76·7 %) > placebo (67·1 %) > VB1
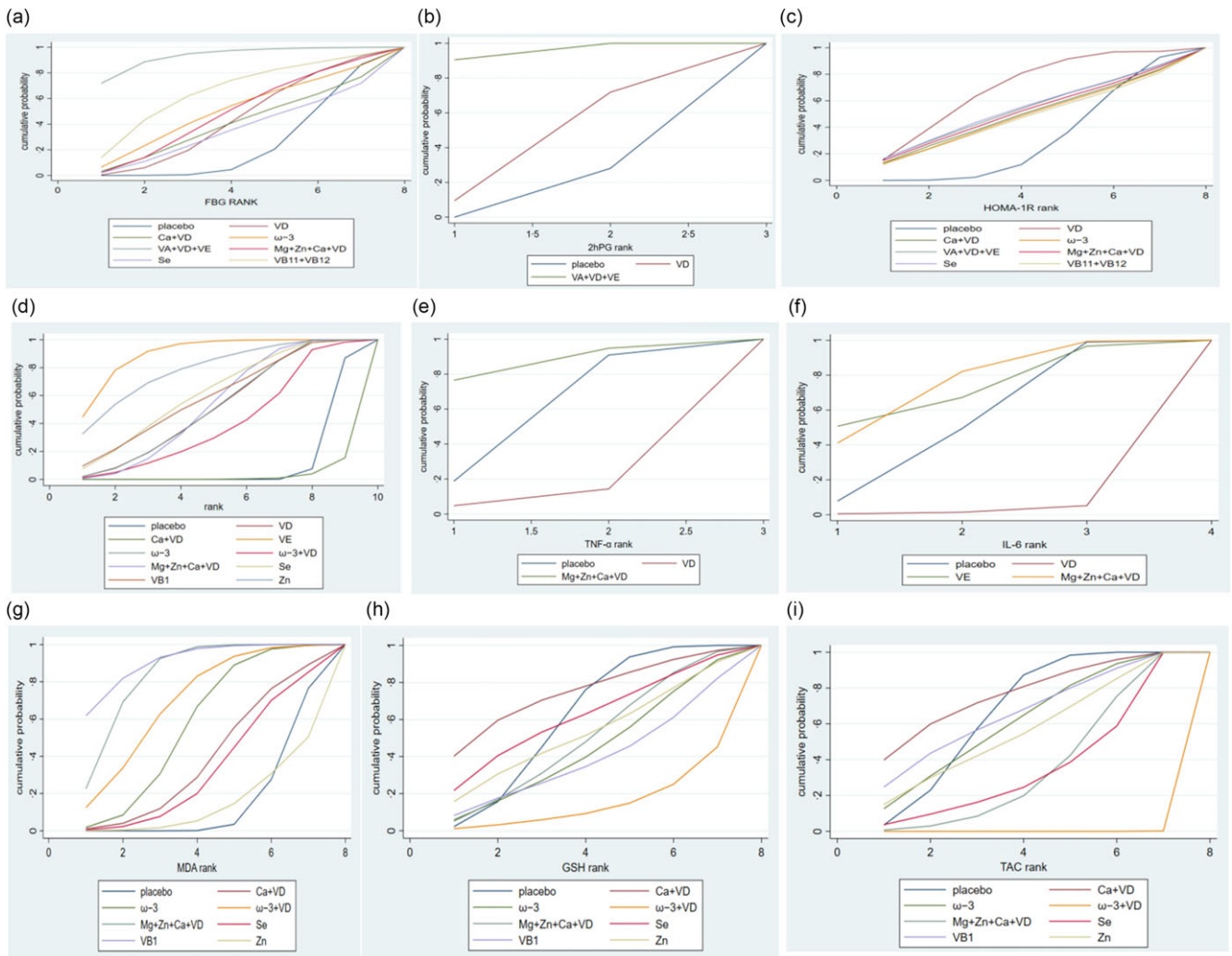
Fig. 5. Cumulative probability ranking of different outcome indicators. The larger the area under the curve in the graph, the larger the SUCRA value and the more likely the intervention is to be the best choice. Different colours represent different interventions.

Table 3. Results of network meta-analysis of 2hPG (SMD (95 % CI))

Intervention measures	Placebo		VD		VA + VD + VE
	SMD	95 % CI	SMD	95 % CI	
Placebo	0		–		–
VD	2·18	0·17, 28·45*	0		–
VA + VD + VE	15·19	4·16, 55·53*	6·96	0·39 123·51*	0

2hPG, 2h postprandial blood glucose; SMD, standardised mean difference.
* Denotes *P* < 0·05; –denotes no relevant data/data duplication.

(65·9 %) > ω-3 (61·3 %) > Zn (57·0 %) > se (36·4 %) > Mg + Zn + Ca + VD (35·5 %) > ω-3 + VD (0·0 %), as detailed in Fig. 5(h).

Glutathione

A total of twenty-eight two-by-two comparisons of results were achieved by network meta-analysis, and in terms of lowering GSH levels, Ca + VD (SMD = 1·39, 95 % CI (0·43, 4·56)), ω-3 (SMD = 0·80, 95 % CI (0·34, 1·87)), ω-3 + VD (SMD = 0·41, 95 % CI (0·12, 1·34)), Mg + Zn + Ca + VD (SMD = 0·87, 95 % CI (0·45, 1·69)) se (SMD = 1·05, 95 % CI (0·33, 3·35)) VB1 (SMD = 0·71, 95 % CI (0·21, 2·36)) and Zn (SMD = 0·92, 95 % CI (0·28, 3·03)) were statistically significant when compared with the placebo control (*P* < 0·05). The results of the two-by-two comparison of the effect of using different nutrient interventions on lowering GSH levels were statistically significant (*P* < 0·05), as shown in Table 10.

Table 4. Results of network meta-analysis of HOMA-1R (SMD (95 % CI))

Intervention measures	Placebo SMD	Placebo 95 % CI	VD SMD	VD 95 % CI	Ca + VD SMD	Ca + VD 95 % CI	ω−3 SMD	ω−3 95 % CI	VA + VD + VE SMD	VA + VD + VE 95 % CI	Mg + Zn + Ca + VD SMD	Mg + Zn + Ca + VD 95 % CI	se SMD	se 95 % CI	VB11 + VB12
Placebo	0		–		–		–		–		–		–		–
VD	5·12	0·76, 34·54*	0		–		–		–		–		–		–
Ca + VD	2·13	0·05, 96·57*	0·42	0·01, 29·59*	0		–		–		–		–		–
ω−3	1·98	0·04, 90·08*	0·39	0·01, 27·59*	0·93	0·00, 204·52*	0		–		–		–		–
VA + VD + VE	2·60	0·06115·98*	0·51	0·01, 35·60*	1·22	0·01264·90*	1·31	0·01285·99*	0		–		–		–
Mg + Zn + Ca + VD	2·31	0·05104·36*	0·45	0·01, 31·98*	1·08	0·00, 237·37*	1·17	0·01256·26*	0·89	0·00, 192·24*	0		–		–
se	2·54	0·06114·09*	0·50	0·01, 34·99*	1·19	0·01259·86*	1·28	0·01280·55*	0·97	0·00, 210·46*	1·10	0·01239·64*	0		–
VB11 + VB12	1·82	0·04, 81·46*	0·36	0·01, 24·99*	0·85	0·00, 185·84*	0·92	0·00, 200·64*	0·70	0·00, 150·51*	0·79	0·00, 171·38*	0·72	0·00, 155·52*	0

SMD, standardised mean difference.
* Denotes $P < 0.05$; –denotes no relevant data/data duplication.

Table 5. Results of network meta-analysis of hs-CRP (SMD (95 % CI))

Intervention measures	Placebo SMD	Placebo 95 % CI	VD SMD	VD 95 % CI	Ca + VD SMD	Ca + VD 95 % CI	VE SMD	VE 95 % CI	ω−3 SMD	ω−3 95 % CI	ω−3 + VD SMD	ω−3 + VD 95 % CI	Mg + Zn + Ca + VD SMD	Mg + Zn + Ca + VD 95 % CI	se SMD	se 95 % CI	VB1 SMD	VB1 95 % CI	Zn
Placebo	0		–		–		–		–		–		–		–		–		–
VD	1·71	1·15, 2·55*	0		–		–		–		–		–		–		–		–
Ca + VD	0·75	0·44, 1·27*	0·44	0·23, 0·85*	0		–		–		–		–		–		–		–
VE	2·58	1·87, 3·55*	1·51	0·90, 2·51*	3·42	1·85, 6·34*	0		–		–		–		–		–		–
ω−3	1·72	1·16, 2·55*	1·01	0·57, 1·76*	2·28	1·18, 4·41*	0·67	0·40, 1·11*	0		–		–		–		–		–
ω−3 + VD	1·50	0·90, 2·51*	0·88	0·46, 1·68*	2·00	0·96, 4·16*	0·58	0·32, 1·07*	0·87	0·46, 1·67*	0		–		–		–		–
Mg + Zn + Ca + VD	1·75	1·35, 2·27*	1·02	0·63, 1·65*	2·32	1·29, 4·18*	0·68	0·45, 1·03*	1·02	0·63, 1·63*	1·16	0·65, 2·06*	0		–		–		–
se	1·90	1·17, 3·07*	1·11	0·60, 2·08*	2·53	1·24, 5·15*	0·74	0·41, 1·32*	1·11	0·59, 2·06*	1·26	0·63, 2·55*	1·09	0·63, 1·88*	0		–		–
VB1	1·85	1·04, 3·29*	1·08	0·54, 2·18*	2·46	1·13, 5·37*	0·72	0·37, 1·39*	1·08	0·54, 2·16*	1·23	0·57, 2·66*	1·06	0·56, 1·99*	0·98	0·46, 2·06*	0		–
Zn	2·34	1·31, 4·18*	1·37	0·68, 2·77*	3·11	1·42, 6·80*	0·91	0·47, 1·76*	1·36	0·67, 2·74*	1·55	0·72, 3·37*	1·34	0·71, 2·53*	1·23	0·58, 2·61*	1·26	0·56, 2·85*	0

hs-CRP, high-sensitivity C-reactive protein; SMD, standardised mean difference.
* Denotes $P < 0.05$; –denotes no relevant data/data duplication.

Table 6. Results of network meta-analysis of TNF-α (SMD (95 % CI))

Intervention measures	Placebo		VD		Mg + Zn + Ca + VD
	SMD	95 % CI	SMD	95 % CI	
Placebo	0		–		–
VD	0·30	0·04, 2·09*	0		–
Mg + Zn + Ca + VD	1·90	0·40, 9·08*	6·36	0·52, 77·21*	0

SMD, standardised mean difference.
* Denotes $P < 0.05$; –denotes no relevant data/data duplication.

Table 7. Results of network meta-analysis of IL-6 (SMD (95 % CI))

Intervention measures	Placebo		VD		VE		Mg + Zn + Ca + VD
	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	
Placebo	0		–		–		–
VD	51·23	1·20, 2177·63*	0		–		–
VE	2·11	0·05, 82·08*	108·12	0·57, 20405·88*	0		–
Mg + Zn + Ca + VD	1·83	0·37, 9·12*	93·75	1·59, 5541·00*	0·87	0·02, 47·23*	0

SMD, standardised mean difference.
* Denotes $P < 0.05$; –denotes no relevant data/data duplication.

The SUCRA results showed that Ca + VD was most likely the best nutrient intervention to reduce GSH levels, and the SUCRA ranking was Ca + VD (75·2 %) > placebo (61·7 %) > se (61·3 %) > Zn (53·7 %) > Mg + Zn + Ca + VD (49·4 %) > ω-3 (44·5 %) > VB1 (39·2 %) > ω-3 + VD (15·1 %), as detailed in Fig. 5(i).

Assessment of publication bias

Comparison-correction funnel plots were drawn for each outcome indicator included in this study to assess publication bias, and the results showed that the scatters in the plots were distributed on both sides of the funnel plots, roughly symmetrically, suggesting that there was a low likelihood of publication bias, as detailed in Fig. 6.

Discussion

The results of this study showed that the differences between different nutrients in improving blood glucose, reducing inflammation levels and oxidative stress were all statistically significant, as well as the optimal ranking of different outcome indicators. In our study, we compared the effectiveness of twelve different nutrient interventions (VD, Ca + VD, VE, ω-3, ω-3 + VD, VA + VD + VE, Mg + Zn + Ca + VD, se, VB11 + VB12, VB1, Zn and placebo) in order of their effects on reducing blood glucose, reducing inflammation levels and reducing oxidative stress in patients with GDM. All nutrient interventions were more effective in reducing fasting glucose (5·56–1·83 mmol/l), 2hPG (15·19–2·18 mmol/l) and HOMA-1R (1·82–5·12) compared with the placebo. However, the findings of the network meta-analysis of FBG for VA + VD + VE (SMD = 41·30, 95 % CI (2·07, 825·60)) may be highly uncertain, which may be due to the small sample sizes of the included studies or because of the inconsistency in the content of the nutrient interventions in the included studies, which resulted in low stability of the findings. This suggests that future scholars should include larger sample sizes to improve the reliability of study results. The ranking according to SUCRA showed the highest value for VA + VD + VE (93·0 %), followed by VB11 + VB12 (65·8 %), and ω-3 (50·4 %) for FBG, whereas VA + VD + VE (95·5 %) had the highest SUCRA value for 2hPG, followed by VD (40·4 %). VD (69·5 %) had the highest SUCRA value for HOMA-1R, followed by VA + VD + VE (53·1 %) and se (52·9 %). Among them, VA + VD + VE may be the best intervention to improve FBG and 2hPG levels in GDM patients, while VD may be the best intervention to modulate HOMA-1R levels. This suggests that future scholars recommend that GDM patients consume foods rich in VA, VD and VE vitamin groups, such as liver, nuts and milk. In addition, combined vitamin supplementation may also have an important role in glycaemic regulation in GDM. This is consistent with the findings of Li D *et al.*[34] that combined vitamin supplementation significantly reduced blood glucose levels and maintained glycaemic homoeostasis in GDM patients. The reason for this may be that VA can indirectly reduce insulin resistance by regulating the level of the secreted adipokine RBP4[35, 36], while VE regulates the level of inflammation and oxidative stress in the body and reduces lipid peroxidation, which results in the regulation of glucose and insulin levels in the body[37].In contrast, VD increases insulin sensitivity by activating vitamin D receptors in pancreatic β-cells[38], while promoting an increase in glucose uptake in peripheral tissues and glycogen synthesis in the liver[39], which allows blood glucose to become homoeostatic. Nutrients work in concert with each other through different pathways to exert optimal effects. This suggests that combined nutrients may have more benefits for glycaemic control in GDM than single-nutrient interventions, but there is no conclusive evidence on the optimal recommended intake and composition of combined vitamin supplementation or the optimal form of combination, and large-sample, multicentre, high-quality clinical trials are still needed to validate the optimal dosage and range of different nutrient interventions. In addition, the current dietary interventions for GDM during pregnancy are mostly focused on

Table 8. Results of network meta-analysis of MDA (SMD (95 % CI))

Intervention measures	Placebo SMD	Placebo 95 % CI	Ca + VD SMD	Ca + VD 95 % CI	ω−3 SMD	ω−3 95 % CI	ω−3 + VD SMD	ω−3 + VD 95 % CI	Mg + Zn + Ca + VD SMD	Mg + Zn + Ca + VD 95 % CI	se SMD	se 95 % CI	VB1 SMD	VB1 95 % CI	Zn
Placebo	0		–		–		–		–		–		–		–
Ca + VD	1·50	0·60, 3·75*	0		–		–		–		–		–		–
ω−3	2·14	1·10, 4·15*	1·43	0·46, 4·42*	0		–		–		–		–		–
ω−3 + VD	2·80	1·11, 7·04*	1·87	0·51, 6·86*	1·31	0·42, 4·09*	0		–		–		–		–
Mg + Zn + Ca + VD	3·72	2·21, 6·25*	2·48	0·87, 7·12*	1·74	0·75, 4·05*	1·33	0·46, 3·83*	0		–		–		–
se	1·34	0·56, 3·25*	0·90	0·25, 3·21*	0·63	0·21, 1·90*	0·48	0·13, 1·73*	0·36	0·13, 1·01*	0		–		–
VB1	4·99	1·85, 13·46*	3·33	0·86, 12·86*	2·34	0·71, 7·71*	1·78	0·46, 6·92*	1·34	0·44, 4·11*	3·71	0·98, 14·02*	0		–
Zn	0·90	0·36, 2·29*	0·60	0·16, 2·23*	0·42	0·13, 1·33*	0·32	0·09, 1·20*	0·24	0·08, 0·70*	0·67	0·19, 2·42*	0·18	0·05, 0·70*	0

MDA, malondialdehyde; SMD, standardised mean difference.
* Denotes $P < 0.05$; –denotes no relevant data/data duplication.

Table 9. Results of network meta-analysis of TAC (SMD (95 % CI))

Intervention measures	Placebo SMD	Placebo 95 % CI	Ca + VD SMD	Ca + VD 95 % CI	ω−3 SMD	ω−3 95 % CI	ω−3 + VD SMD	ω−3 + VD 95 % CI	Mg + Zn + Ca + VD SMD	Mg + Zn + Ca + VD 95 % CI	se SMD	se 95 % CI	VB1 SMD	VB1 95 % CI	Zn
Placebo	0		–		–		–		–		–		–		–
Ca + VD	1·27	0·47, 3·46*	0		–		–		–		–		–		–
ω−3	0·95	0·46, 1·94*	0·74	0·22, 2·54*	0		–		–		–		–		–
ω−3 + VD	0·06	0·02, 0·18*	0·05	0·01, 0·21*	0·06	0·02, 0·23*	0		–		–		–		–
Mg + Zn + Ca + VD	0·66	0·38, 1·15*	0·52	0·16, 1·62*	0·69	0·28, 1·71*	11·22	3·21, 39·18*	0		–		–		–
se	0·61	0·23, 1·63*	0·48	0·12, 1·95*	0·65	0·19, 2·17*	10·48	2·38, 46·21*	0·93	0·30, 2·87*	0		–		–
VB1	1·05	0·38, 2·91*	0·83	0·20, 3·44*	1·11	0·32, 3·85*	17·97	3·96, 81·56*	1·60	0·50, 5·11*	1·71	0·42, 7·01*	0		–
Zn	0·89	0·32, 2·45*	0·70	0·17, 2·90*	0·94	0·27, 3·24*	15·17	3·35, 68·70*	1·35	0·42, 4·30*	1·45	0·35, 5·90*	0·84	0·20, 3·55*	0

TAC, total antioxidant capacity; SMD, standardised mean difference.
* Denotes $P < 0.05$; –denotes no relevant data/data duplication.

Table 10. Results of network meta-analysis of GSH (SMD (95 % CI))

Intervention measures	Placebo		Ca + VD		ω-3		ω-3 + VD		Mg + Zn + Ca + VD		se		VB1		Zn
	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	SMD	95 % CI	
Placebo	0	–	–		–		–		–		–		–		–
Ca + VD	1·39	0·43, 4·56*	0	–	–		–		–		–		–		–
ω-3	0·80	0·34, 1·87*	0·57	0·13, 2·46*	0	–	–		–		–		–		–
ω-3 + VD	0·41	0·12, 1·34*	0·29	0·05, 1·57*	0·51	0·12, 2·22*	0	–	–		–		–		–
Mg + Zn + Ca + VD	0·87	0·45, 1·69*	0·62	0·16, 2·43*	1·09	0·37, 3·22*	2·12	0·54, 8·29*	0	–	–		–		–
se	1·05	0·33, 3·35*	0·75	0·14, 3·96*	1·32	0·31, 5·57*	2·56	0·49, 13·50*	1·21	0·32, 4·60*	0	–	–		–
VB1	0·71	0·21, 2·36*	0·51	0·09, 2·75*	0·89	0·20, 3·88*	1·73	0·32, 9·37*	0·81	0·21, 3·22*	0·67	0·13, 3·58*	0	–	–
Zn	0·92	0·28, 3·03*	0·66	0·12, 3·54*	1·15	0·26, 5·00*	2·24	0·41, 12·09*	1·05	0·27, 4·15*	0·87	0·16, 4·62*	1·29	0·24, 7·07*	0

GSH, glutathione; SMD, standardised mean difference.
* Denotes $P < 0.05$; – denotes no relevant data/data duplication.

knowledge education, distribution of health brochures, nutritional counselling during pregnancy and recommendation of recipes during pregnancy[40], and the accessibility, practicability and adherence of dietary interventions often fail to achieve the expected goals. At the same time, follow-up studies can establish a multidisciplinary nutrition management team for GDM[41] to develop individualised and precise nutrition management plans based on the dietary characteristics of pregnant women and disease conditions. At the same time, the scope of out-of-hospital medical services should be broadened, and offline online appointments with dietitians should be encouraged to form an in-hospital and out-of-hospital linkage chain, so as to improve the level of self-nutrition management of GDM patients.

In our study, the ranking according to SUCRA showed the highest value for VE (90·2 %), followed by Zn (78·8 %) and se (62·0 %) for hs-CRP, whereas Mg + Zn + Ca + VD (85·8 %) had the highest SUCRA value for TNF-α. Mg + Zn + Ca + VD (74·3 %) had the highest SUCRA value for IL-6. Most studies have shown that vitamin and micronutrient interventions can significantly reduce inflammation and oxidative stress levels in GDM patients[34]. The results of this study found that Mg + Zn + Ca + VD may be the best intervention to reduce TNF-α and IL-6 levels in GDM patients, while VE may be the best intervention to reduce hs-CRP levels. This is similar to the findings of Jing *et al.*[26] that simultaneous supplementation of VD and trace elements such as Mg, Zn and Ca could reduce the inflammation level of GDM patients to a certain extent, and exploring the reason for this may be that the nutrients could play an anti-inflammatory role by antagonising the activity of the NF-κB pathway and reducing the secretion of inflammatory factors[42]. This suggests that inflammation levels in GDM patients can be reduced not only by nutrient intake but also by micronutrient supplementation. In our study, the ranking according to SUCRA showed the highest value for VB1 (90·8 %), followed by Mg + Zn + Ca + VD (83·3 %) for MDA, whereas Ca + VD (76·7 %) had the highest SUCRA value for TAC. Ca + VD (75·2 %) had the highest SUCRA value for GSH. Meanwhile, in terms of reducing the level of oxidative stress, Ca + VD may be the optimal intervention to reduce the level of TAC and GSH, while VB1 may be the optimal intervention to reduce the level of MDA, followed by Mg + Zn + Ca + VD. The reason may be that Ca + VD can reduce oxidative stress by affecting cellular signalling[43]. However, the exact mechanism of the effect is not clear[14], and further clinical trials are still needed to explore the potential mechanism of its effect in GDM in the future. In addition, Mg and Zn may reduce the level of oxidative stress by decreasing the production of reactive oxygen species and decreasing the amount of peroxynitrite produced as a result of redox activity[44]. VB1 may play an antioxidant role by increasing the activity of transketolase, reducing lipid peroxidation[45] and eliminating the production of ROS induced by hyperglycaemia[46]. The combined intervention of macronutrients and micronutrients is particularly important in reducing the levels of inflammation and oxidative stress in GDM patients. This suggests that future nutritional interventions for patients with GDM should not be limited to specific food range interventions but may combine nutrients with micronutrients or minerals to explore the role of diet or nutrients in inflammation or oxidative stress in patients with GDM from multiple perspectives,
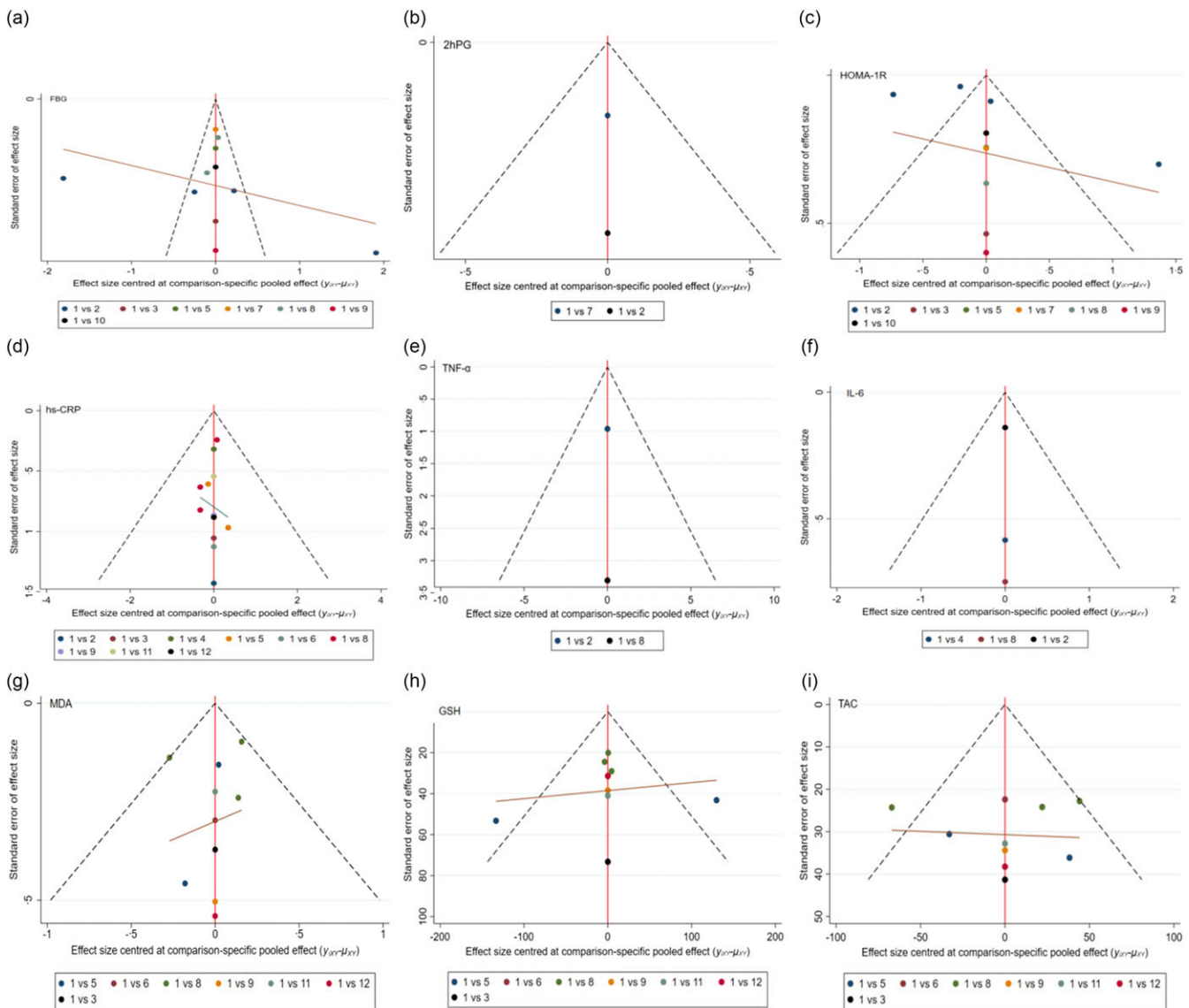
Fig. 6. Inverted funnel plot of different outcome measures. 1, placebo; 2, VD; 3, Ca + VD; 4, VE; 5, ω-3; 6, ω-3 + VD; 7, VA + VD + VE; 8, Mg + Zn + Ca + VD; 9, se; 10, VB11 + VB12; 11, VB1; 12, Zn.

with a view to providing new ideas for slowing down the disease process and reducing adverse pregnancy outcomes.

Currently, the number of interventional studies on nutrients is increasing, but the anti-inflammatory or pro-inflammatory efficacy of nutrients themselves and the level of inflammatory efficacy are still unclear. Tools such as the dietary inflammatory index[47] and the empirical dietary inflammatory index[48] have been used to evaluate the inflammatory efficacy of nutrients. There is still a lack of a Chinese nutrient inflammation scoring tool due to differences in nutrient inflammation scoring calculation methods, hetero-geneity of clinically validated populations and food databases that are biased towards dietary content from Europe and the USA. This suggests that a localised nutrient inflammation assessment tool based on Chinese dietary preferences could be constructed in the future to differentiate the inflammatory efficacy of different categories of nutrients. At the same time, the dietary inflammation assessment tool can be applied with the help of virtual

technologies such as artificial intelligence and cloud computing, which can be embedded into WeChat applets or APP, in order to clarify the overall inflammation score of dietary intake and provide a suitable assessment tool for the selection of anti-inflammatory diets for patients with GDM.

Limitations

However, some limitations of this study should be considered when interpreting its results. First, this study lacked direct comparative evidence between different nutrients, the evidence network did not form a closed loop and the superiority of intervention effects between different nutrients was evaluated only through indirect comparisons. The limited number of studies included, the age of the subjects included, who were mostly around 30 years old, and the duration of the studies, which were mostly around 6 weeks, did not allow for stratified

analyses, which may have reduced the reliability of the findings. Second, there were some differences in the measurement of intervention dose, duration and outcome indicators for different categories of nutrients, which may have led to increased heterogeneity; finally, some outcome indicators were under-reported or not yet studied, such as glycated Hb, IL-8 and GSH, which may have led to a lack of sufficient evidence for evaluating the effects of nutrient interventions from multiple perspectives.

Conclusion

Various nutrient interventions were significantly effective in improving blood glucose, inflammation levels and oxidative stress in GDM patients, with vitamin-based combined nutrient interventions such as VA + VD + VE and VD likely to be more effective in improving blood glucose levels in GDM patients, whereas micronutrient- or mineral-based combined interventions such as Mg + Zn + Ca + VD and Ca + VD may be more advantageous in reducing the inflammatory response and oxidative stress levels in GDM patients. However, multi-centre, large-sample, high-quality clinical studies are needed to validate the inflammatory efficacy of other different nutrients with a view to developing a practical and precise anti-inflammatory diet for patients with GDM.

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Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114523003069

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