Original Article

Effects of water-soluble vitamins on glycemic control and insulin resistance in adult type 2 diabetes: an umbrella review of meta-analyses

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Background and Objectives: Growing evidence has explored the effects of water-soluble vitamins supplementation on glycemic control and insulin resistance in diabetic patients; however, the results of previous meta-analyses are inconsistent. To address this, we conducted an umbrella review to synthesize the evidence on these effects. **Methods and Study Design:** A systematic literature search in Web of science, PubMed, and Cochrane Database of Systematic Reviews was performed from 2012 to November 2022. he quality of the meta-analyses was assessed using AMSTAR-2 and GRADE. **Results:** Fourteen systematic reviews and meta-analyses met the inclusion criteria, examining the effects of five water-soluble vitamins (B-1, B-3, biotin, B-9, and C) on glycemic control and insulin resistance. The findings suggest that vitamin C supplementation can improve glycemic control in type 2 diabetes, as indicated by reduced FBG and HbA1c, with more significant effects observed for durations longer than 30 days. **Conclusions:** Insulin resistance is improved by folic acid supplementations. More well-designed individual randomized controlled trials are needed in the future, as well as meta-analysis of higher quality.

Key Words: water-soluble vitamin, type 2 diabetes, glycemic control, insulin resistance, umbrella review

INTRODUCTION

"Diabetes mellitus, a leading cause of death and disability worldwide, is a significant public health issue.[1] As of 2021, 5.1 billion adults have diabetes, with a prevalence rate of 10.5%. By 2045, this number is projected to rise to 6.4 billion, with a prevalence rate of 12.2%.[2] Additionally, diabetes was linked to 6.7 million deaths and healthcare expenditures of at least $966 billion in 2021.[2] Type 2 diabetes mellitus (T2DM), the most common type of diabetes, accounted for more than 96% of diabetes cases globally in 2021.[1] The mechanism of T2DM is mainly associated with impaired insulin sensitivity, namely insulin resistance, as well as pancreatic β-cell dysfunction.[3, 4] Increased oxidative stress, endothelial cell dysfunction, and inflammation generation may contribute to the progression of T2DM.[5, 6] For instance, MAPK signaling pathway, a key regulator for insulin signaling, has reported to be activated under oxidative stress, resulting in insulin resistance.[7]

Mounting evidence suggests that glycemic control, the primary target in diabetes treatment, significantly impacts the development of complications.[8-11] It is widely accepted that glycosylated hemoglobin (HbA1c) is the most important indicator of long-term glycemic control, while fasting blood glucose (FBG) reflects short-term glycemic control.[12] Moreover, variations in FBG and HbA1c are strongly associated with an increased risk of retinopathy, nephropathy, and all-cause mortality in diabetic patients.[13,14] Therefore, maintaining good glycemic management is essential to reduce the risk of these complications.[15] Finding effective strategies for glycemic control in diabetic patients has become a central public health issue.

There are several recommended approaches in the existing diabetes guidelines to deal with the development of diabetes and its complications,[16, 17] such as exercise interventions,[18, 19] improvement of dietary pattern,[20, 21] as well as pharmacological control. In recent years, dietary supplements such as probiotics,[22] soluble fiber,[23] resveratrol,[24] vitamins and minerals have aroused intensive interests in scientific field and been reported to exert good effects on diabetes control.[25] Water-soluble vitamins, including B vitamins and vitamin C, primarily function as coenzymes or coenzyme components in the body's metabolism, playing crucial roles in processes such as energy metabolism and antioxidation.[26, 27] We conducted a search for all meta-analyses on water-soluble vitamin supplementation, assessing the quality of these meta-analyses and the randomized controlled trials (RCTs) they included. We also identified the number of identical RCTs across different meta-analyses and calculated the corrected coverage area (CCA) of the RCTs. It has been reported that water-soluble vitamins, such as vitamin C, folate, thiamine and biotin,

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Manuscript received 13 April 2024. Initial review completed 16 May 2024. Revision accepted 15 August 2024.
doi: 10.6133/apjcn.202502_34(1).0012

had a significant impact on diabetes and its complications.[28] The possible underlying mechanisms were related to improve oxidative stress, inflammation, and insulin resistance.[29] For instance, ascorbic acid (AA) has been reported to scavenge reactive oxygen and nitrogen species *in vitro* and *in vivo*,[30, 31] enhance insulin sensitivity in skeletal muscle through ameliorating oxidative stress;[32] folic acid supplementation has been shown to reduce c-Jun N-terminal protein kinase (JNK) activation and TNF gene expression, thereby reducing glucose uptake and inhibiting inflammatory processes;[33, 34] thiamine can activate glucose metabolism and insulin synthesis,[35] thus plays a role in blocking pathways that are responsible for hyperglycemia induced damage;[36] and biotin may compensate for low-concentration insulin exposure by inhibiting FOXO1 levels, increasing insulin expression and secretion.[37, 38]

There are several systematic reviews and meta-analyses (SRMAs) of RCTs summarizing the effects of water-soluble vitamin supplementations on insulin resistance and glycemic control; however, previous evidence of the pooled analysis shows inconsistent results. For example, two pooled studies showed that folic acid supplementation reduced FBG concentrations,[39, 40] but one study showed no such effect.[41] Three studies showed that vitamin C supplementation reduced HbAc1,[25, 42, 43] while two studies did not.[44, 45] Of the two niacin supplementation trials,[46, 47] no statistically significant effects on blood glucose were found. As for the effects of thiamine and biotin supplementations,[37, 48] only one systematic review and meta-analysis exists for each, and neither found a statistically significant effect on FBG. An umbrella review primarily analyzes evidence from different interventions for the same problem or disease condition, or from multiple studies that have investigated the same interventions and conditions but reported different outcomes. It provides a summary of the synthesis of existing studies on a given topic or problem, rather than a re-synthesis.[49] There have been some umbrella reviews that describe the effects of probiotics, minerals, and individual vitamins such as vitamin C and vitamin D on glycemic control and insulin resistance.[50] However, an umbrella review specifically summarizing the effects of water-soluble vitamin supplementation on glycemic control and insulin resistance is not yet available.

The purpose of this umbrella review is to re-evaluate SRMAs on the role of water-soluble vitamin supplementation in glycemic management for patients with T2DM. The quality of the SRMAs was assessed using the AMSTAR-2 tool, and evaluated the evidence with GRADE. This analysis aims to identify differences and associations among various water-soluble vitamins concerning different outcome indicators and to provide a comprehensive summary of their impact on glycemic control. Our study may offer important scientific evidence for developing nutritional recommendations for T2DM patients.

METHODS

Search strategy

We conducted an extensive search of SRMAs using three databases—Web of Science, PubMed, and the Cochrane Database of Systematic Reviews—limited to English-language articles, with data search dates up to November 2022. The search strategy is presented in Supplementary Table 1.

Study selection

Two researchers (Yin and Wang) independently completed the review of studies based on criteria for inclusion and exclusion. Firstly, relevant studies were selected based on the title and abstract of the studies. Secondly, selected studies were further screened by reading the full content of the included studies. Finally, disagreements were resolved by the judgment of the third author (Chen). SRMAs were selected based on the following inclusion criteria: (1) systematic reviews and meta-analysis of randomized controlled trials in adults aged 18 years or older; (2) used water-soluble vitamin supplementation as intervention, and results were compared with a control group; (3) reported weighted or standardized mean differences (MDs) and corresponding 95% confidence intervals (CIs) in glycemic control as the outcome of interest, the measured indices consisted of FBG, HbA1c, insulin, and HOMA-IR.

Exclusion criteria included: (1) primary studies that were experimental in animals, *in vivo*, *in vitro*, or *ex vivo*; and (2) systematic reviews and meta-analyses that did not report a summary effect size (e.g., systematic reviews without meta-analyses).

Quality assessment

We assessed the methodological quality of the SRMAs using AMSTAR 2,[51] which evaluates systematic reviews of randomized or non-randomized studies of healthcare interventions and consists of 16 scored items, including 7 critical items. AMSTAR 2 focuses on methodological flaws in these critical items and rates overall confidence in the systematic review results accordingly. Additionally, we used GRADE to assess the quality of evidence for the meta-analyses.[52, 53] There are five main components that influence the downgrading of GRADE evaluations: (1) Risk of bias; (2) Imprecision; (3) Inconsistency; (4) Indirectness; (5) Publication bias. When a risk factor is present in the evidence, the certainty needs to be downgraded by one or two levels (e.g., from high to moderate).

Data extraction

Two investigators (Yin and Wang) independently extracted studies information for the meta-analysis that was eligible for inclusion. Information collected included the first author's name, publication year, sample sizes (number of RCTs and total participants in intervention and control groups), study type, vitamin species, doses and durations of interventions, study locations, and conflicts of interest. Additionally, we extracted pooled effect sizes and 95%CIs for outcome indicators such as FBG, HbA1c, insulin, and HOMA-IR, as well as study heterogeneity, p-values for heterogeneity, and publication bias (assessed using Egger's test and Funnel plots).

Table 1. Characteristics of included systematic reviews and meta-analysis

SR Author and year	Primary studies, n	Population	Age (years)	Intervention		
				Vitamin species	Dose (mg/day)	Duration
Arti Muley, 2022[48]	6	T2DM	mean 52-65.3	B-1	100-900	1-3 months
Yi Ding, 2015[46]	7	T2DM	59-67	B-3	150-4500	8-64 weeks
Maryam Akbari, 2018[41]	16	T2DM/metabolic syndrome/Overweight and obese people/polycystic ovary syndrome	NR	B-9	1-10	2-12 weeks
Zhao JV, 2018[40]	18	T2DM / Other metabolic diseases	24.6-67.3	B-9	0.15-10	2weeks-7.3years
Patcharaporn Sudchada, 2012[54]	4	T2DM	mean 55-66	B-9	5	4 weeks-6 months
Omid Asbaghi, 2021[39]	24	T2DM / metabolic syndrome/Overweight and obese people/polycystic ovary syndrome/ hypertension/ coronary artery disease	24-65	B-9	0.8-15	3-234 weeks
Shaun A. Mason, 2021[42]	28	T2DM	38-71	VC	500-1000	1-6 months
Yoonhye Kim, 2022[25]	12	T2DM	NR	VC	200–1000	3-48weeks
AW Ashor, 2017[44]	22	T2DM / healthy individuals / T1DM / coronary artery diseases patients	22-60	VC	72-6000	14-120 days
Asma Kazemi, 2022[43]	19	T2DM / Diabetic Hyperlipidaemia	29.3-77 (median 56.5)	VC	NR	2-52 weeks
Mehrnoosh Khodaeian, 2015[78]	3	T2DM	20-75	VC	800–1000	4-16 weeks
Ozra Tabatabaei-Malazy, 2014[45]	12	T2DM	18-89	VC	120-2000	4 weeks-9 years
Yujia Zhang, 2022[37]	5	T2DM	46-59	B-7	1.5-15	4 weeks-3 months
Dan Xiang, 2020[47]	6	T2DM	mean 59-65	B-3	1500-4500	8 weeks-12 months

SR Author and year	Comparator	Outcome				Method of pooling estimates	Funding	COI	Country of author
		FBG	HbAc1	HOMA-IR	Insulin				
Arti Muley, 2022[48]	Placebo: 5, Thiamine: 1	√	√			random effect	NO	NR	Australia
Yi Ding, 2015[46]	Placebo: 3	√				random effect	National Foundation	NO	China
Maryam Akbari, 2018[41]	Placebo	√	√		√	random effect	a grant from the Vice-chancellor for Research	NO	Iran
Zhao JV, 2018[40]	Placebo	√	√	√	√	random effect	NO	NO	Hong Kong
Patcharaporn Sudchada, 2012[54]	Placebo		√			random effect	NO	NO	Thailand
Omid Asbaghi, 2021[39]	No intervention: 6, Placebo: 18	√	√	√	√	random effect	NO	NO	Iran
Shaun A. Mason, 2021[42]	Placebo	√	√	√	√	random effect	NR	NO	Australia
Yoonhye Kim, 2022[25]	Placebo	√	√	√		random effect	National Foundation	NO	Korea
AW Ashor, 2017[44]	Placebo: 13	√	√		√	random effect	National Foundation	NO	UK
Asma Kazemi, 2022[43]	No intervention: 1, Placebo: 18	√	√	√	√	random effect	NR	NO	Iran
Mehrnoosh Khodaeian, 2015[78]	Placebo			√		random effect	NO	NO	Iran
Ozra Tabatabaei-Malazy, 2014[45]	Placebo	√	√			random effect	NO	NO	Iran
Yujia Zhang, 2022[37]	Placebo	√	√		√	random effect	Faculty Research Grants	NO	Macau
Dan Xiang, 2020[47]	Placebo: 3, Statins:3	√	√			random effect	NR	NO	China

FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, SR: systematic review and meta-analysis.

Table 2. The locations where randomized controlled trials of water-soluble vitamin interventions were conducted

Area	No	B-1	B-3	B-7	B-9	VC	Area	No.	B-1	B-3	B-7	B-9	VC
Australia	8	1	2	0	1	4	New Zealand	1	0	0	0	1	0
Belgium	1	0	0	0	1	0	Norway	1	0	0	0	1	0
Brazil	2	0	0	0	1	1	Oman	1	0	0	0	0	1
Canada	2	0	1	0	1	0	Pakistan	1	1	0	0	0	0
China	5	0	0	0	5	0	Palestine	1	0	0	0	0	1
Denmark	1	0	0	0	0	1	Saudi Arabia	1	0	0	0	0	1
Egypt	1	0	0	0	0	1	Sweden	1	0	0	0	0	1
Greece	1	0	0	0	0	1	Switzerland	1	0	1	0	0	0
India	4	0	0	0	0	4	Taiwan	1	0	0	0	1	0
Iran	17	0	0	0	11	6	Thailand	2	0	0	0	0	2
Israel	1	0	0	0	1	0	the Netherlands	1	1	0	0	0	0
Italy	7	0	0	0	5	2	Turkey	3	0	0	0	2	1
Japan	1	0	0	1	0	0	UK	6	0	0	0	2	4
Malaysia	1	0	0	0	0	1	USA	13	0	5	2	1	5
Mexico	3	1	0	2	0	0	New Zealand	1	0	0	0	1	0

RESULTS

We searched a total of 2829 studies from three databases, and a total of 14 SRMAs of RCTs were included in our umbrella review (one of which was a network meta-analysis) after reading not only the titles and abstracts of the studies but also the full text according to the previously established exclusion criteria for inclusion in the studies (Figure 1). The intervention trials in the SRMAs included the following 5 individual water-soluble vitamins: vitamin B-1 (N=1), vitamin B-3 (N=2), biotin (N=1), vitamin B-9 (N=4), and vitamin C (N=6).

Characteristics of the included systematic reviews and meta-analyses

The 14 included SRMAs were published between 2014 and 2022, the characteristics of which were summarized in Table 1. In this study, T2DM patients were the target population, also, individuals with other metabolic disorders including obesity, polycystic ovary syndrome, metabolic syndrome, etc. were also included with the purpose to compare the effects. One systematic review reported thiamine intervention (dose: 100-900 mg/day) ranging from 1 to 3 months. Two systematic reviews reported niacin interventions for durations ranging from 8 to 64 weeks (dose: 150-4500 mg/day). One systematic review reported biotin interventions with durations ranging from 4 weeks to 3 months (dose: 1.5-15 mg/day). Primary studies included in the four systematic reviews examined the effects of folic acid interventions over durations ranging from 2 weeks to 7.3 years, with doses between 0.5 and 15 mg/day. Notably, the duration of vitamin C interventions varied widely, from 14 days to 9 years, with doses ranging from 72 to 6000 mg/day. All systematic reviews employed random effects models for pooled estimation. Most primary RCTs used placebo controls, while a small proportion used blank controls.

Among the 14 included systematic reviews, there were 162 primary RCTs. After excluding duplicates, 88 primary RCTs were included, conducted across 89 regions. These RCTs investigated the effects of vitamin B1, vitamin B3, biotin, vitamin B9, and vitamin C supplementation, with 4, 8, 5, 34, and 37 studies, respectively (Supplementary Table 2). Additionally, 17 RCTs were conducted in Iran, with 11 focusing on vitamin B-9 interventions, while 13 studies were conducted in the United States, including 5 each on vitamin B-3 and vitamin C interventions (Table 2). We observed that the quality of the primary RCTs was closely related to the economic status of the study locations, with higher quality studies typically found in countries with better economic conditions.

Estimating the corrected coverage area (CCA) for the included SRMAs revealed high overlap in supplementation trials for vitamin B-3 (CCA = 62.50%), vitamin B-9 (CCA = 24.51%), and vitamin C (CCA = 18.54%). When the meta-analyses were grouped according to study outcomes, the CCA was recalculated, and the results continued to show high levels of overlap (Table 3).

The corresponding authors of the systematic reviews were primarily from Iran (5/14), Australia (2/14), China (4/14), the UK (1/14), Korea (1/14), and Thailand (1/14). Funding sources for the systematic reviews were mainly national foundations (3/14), while 64% of the reviews did not report any funding. Most of the systematic reviews reported no conflicts of interest.

Risk of bias and quality assessment of included meta-analyses

The AMSTAR-2 assessment results for the studies are presented in Figure 2. One study was a network meta-analysis and thus AMSTAR-2 was not applicable.[43] The remaining thirteen systematic reviews and meta-analyses were rated as high, moderate, and low at rates of 2 (3/13), 2 (2/13) and 8 (8/13), respectively. The most common critical flaw in the included studies was the failure to consider the risk of bias when interpreting the results, occurring in 9 out of 13 studies. According to AMSTAR-2 and GRADE assessments, most of the included SRMAs were of low quality. About 61.5% of the articles were rated low by AMSTAR-2, primarily due to inadequate quality assessment in interpreting results. Additionally, approximately 31.6% and 26.3% of the articles were rated low and very low by GRADE, respectively, mainly due to high heterogeneity among primary RCTs and the presence of publication bias in the meta-analysis.

The quality of evidence was assessed for 38 outcome indicators extracted from the included studies, resulting in three of high-quality evidence, thirteen of moderate quality evidence, twelve of low-quality evidence, and ten of very

low-quality evidence. Inconsistency was the main factor affecting the downgrading, followed by risk of bias, indirectness, imprecision and publication bias (Figure 3, Supplementary Table 4). Also, Figure 4 shows the effects of water-soluble vitamin interventions on glycemic control and insulin resistance as reported in the included systematic reviews. This review found that conclusions with significant differences were often based on low-quality evidence. The inclusion of low and very low-quality evidence affects the reliability and stability of the final results, making the conclusions potentially uncertain and insufficient to support clinical practice robustly. This highlights the need for further high-quality research to validate these findings.

We assessed the quality of the RCTs from each meta-analysis using three methods: the JBI Evidence-Based Center's Quality Assessment Tool (N=1), the Jadad Scale (N=5), and the Cochrane Collaboration's Tool for Assessing Risk of Bias (N=8). Seven meta-analyses of vitamin B3, folic acid, and vitamin C had more than 50% of their primary RCTs rated as moderate or low quality (Figure 4).

The effect of water-soluble vitamin supplementation on FBG

Twelve systematic reviews explored the effects of the supplementation of five water-soluble vitamins including vitamin B-1, vitamin B-3, biotin, vitamin B-9, and vitamin C on FBG (Table 3, Figure 6).

There was only one meta-analysis targeting type 2 diabetic patients claiming that folic acid supplementation could reduce FBG,[39] with pooled effect sizes -2.17 (95% CI: -3.69, -0.65). In agreement, another pooled analysis in metabolism-related diseases including T2DM, metabolic syndrome, overweight and obese, polycystic ovary syndrome, coronary artery disease also found folic acid supplementation could reduce FBG with pooled effect sizes ranging from -2.17 (95% CI: -3.69, -0.65) to -0.15 (95% CI: -0.29, -0.01).[39, 40] However, Maryam et al. found no statistically significant effects of folic acid on FBG in the same population with metabolism-related diseases mentioned earlier.[41] Consistent evidence indicated that vitamin C supplementation could reduce FBG, with pooled effect sizes ranging from -20.59 (95% CI: -40.77 to -0.4) to -0.44 (95% CI: -0.81 to -0.07).[25, 42, 44, 45] Subgroup analysis further revealed that durations longer than 30 days had a statistically more significant positive effect on FBG, with pooled effect sizes ranging from -0.53 (95% CI: -0.97 to -0.10).[44]

Consistent evidence indicated that thiamine and biotin supplementation had no statistically significant effect on FBG.[37, 48] For the two niacin supplementation trials, no statistically significant effects on blood glucose were found. However, subgroup analysis revealed that high doses or supplementation durations longer than 20 weeks were significantly effective for reducing FBG.[46, 47]

Overall, regarding the influence of water-soluble vitamins on FBG, there were two SAMAs with high quality, three with intermediate quality, three with low quality, and four with very low quality (Figure 5).

The effect of water-soluble vitamin supplementation on HbA1c

Twelve meta-analyses explored the effect of the supplementation of five water-soluble vitamins including vitamin B-1, vitamin B-3, biotin, vitamin B-9, and vitamin C on HbA1c (Table 4, Figure 6). Two (50%) of the four meta-analyses found that vitamin C supplementation could reduce HbA1c with pooled effect sizes ranging from -0.54 (95% CI: -0.9, -0.17) to -0.37 (95% CI: -0.57, -0.17).[25, 42] Consistent evidence indicated that thiamine, niacin, and folic acid supplementation had no statistically significant effects on HbA1c.[39, 54] However, subgroup analysis found that high-dose niacin intervention had a statistically significant positive effect on HbA1c, with a pooled effect size of 0.90 (95% CI: 0.21 to 2.41).[47] In the single biotin supplementation trial, no statistically significant effect on HbA1c was found.[37] Overall, among the ten pooled studies, one systematic review and meta-analysis (SAMA) provided high-quality evidence on HbA1c, four provided moderate-quality evidence, two provided low-quality evidence, and three provided very low-quality evidence (Figure 3).

The effect of water-soluble vitamin supplementation on insulin resistance

Seven meta-analyses investigated the effects of supplementing three water-soluble vitamins—biotin, folic acid, and vitamin C—on fasting serum insulin (Table 4, Figure 7).

Only one meta-analysis targeting type 2 diabetic patients found that folic acid supplementation could reduce insulin levels, with a pooled effect size of -1.63 (95% CI: -2.53, -0.73).[39] Similarly, another pooled analysis in patients with metabolism-related diseases found that folic acid supplementation could reduce insulin levels, with pooled effect sizes ranging from -1.94 (95% CI: -3.28 to -0.61) to -1.28 (95% CI: -1.99 to -0.56).[39-41] In the single biotin supplementation trial, no statistically significant effects on insulin were found.[37] Similarly, the two vitamin C supplementation trials showed no statistically significant effects on insulin.[42, 44] In conclusion, there were two SAMAs with moderate-quality evidence, three with low quality, and one with very low quality (Figure 3).

We also analyzed the effects of these vitamins on HOMA-IR. Seven meta-analyses explored the effects of two water-soluble vitamins including folic acid and vitamin C on HOMA-IR (Table 4, Figure 8).

Only one meta-analysis reported that folic acid supplementation could reduce HOMA-IR, with a pooled effect size of -0.40 (95% CI: -0.70 to -0.09).[39] Similarly, another pooled analysis in patients with metabolism-related diseases found that folic acid supplementation could reduce

Table 3. The overlapping among included systematic reviews and meta-analyses

Vitamin species	Number of reviews	Number of included studies	CA statistic (%)	CCA statistic (%)	Degree of overlapping
Niacin	2	8	81.3%	62.5%	Very high
Folate	4	34	43.4%	24.5%	Very high
VC	6	41	32.1%	18.5%	Very high

CA: coverage area; CCA: corrected coverage area.

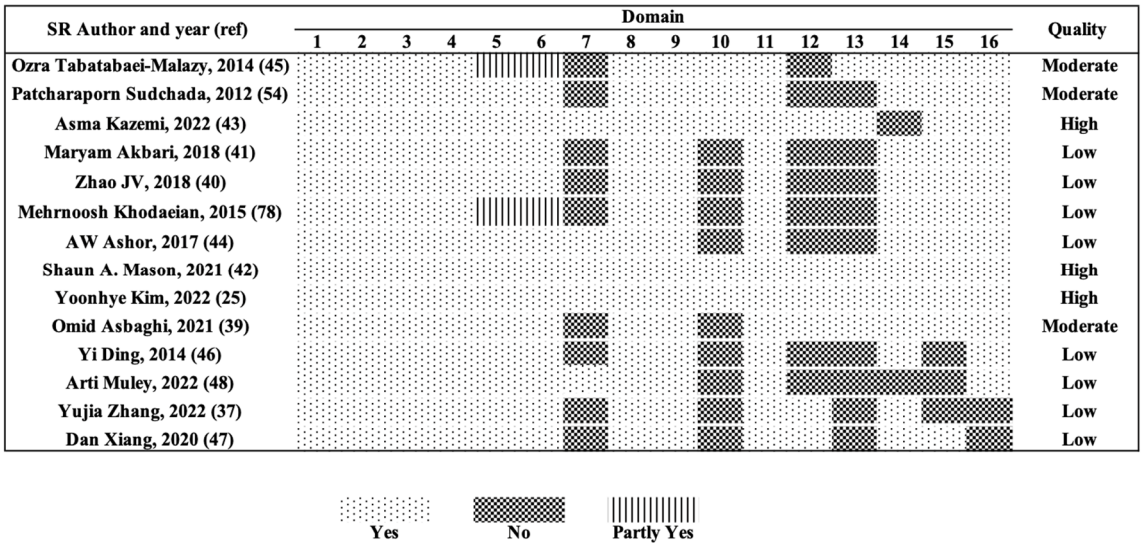

Figure 2. Results of assess the methodological quality of meta-analysis

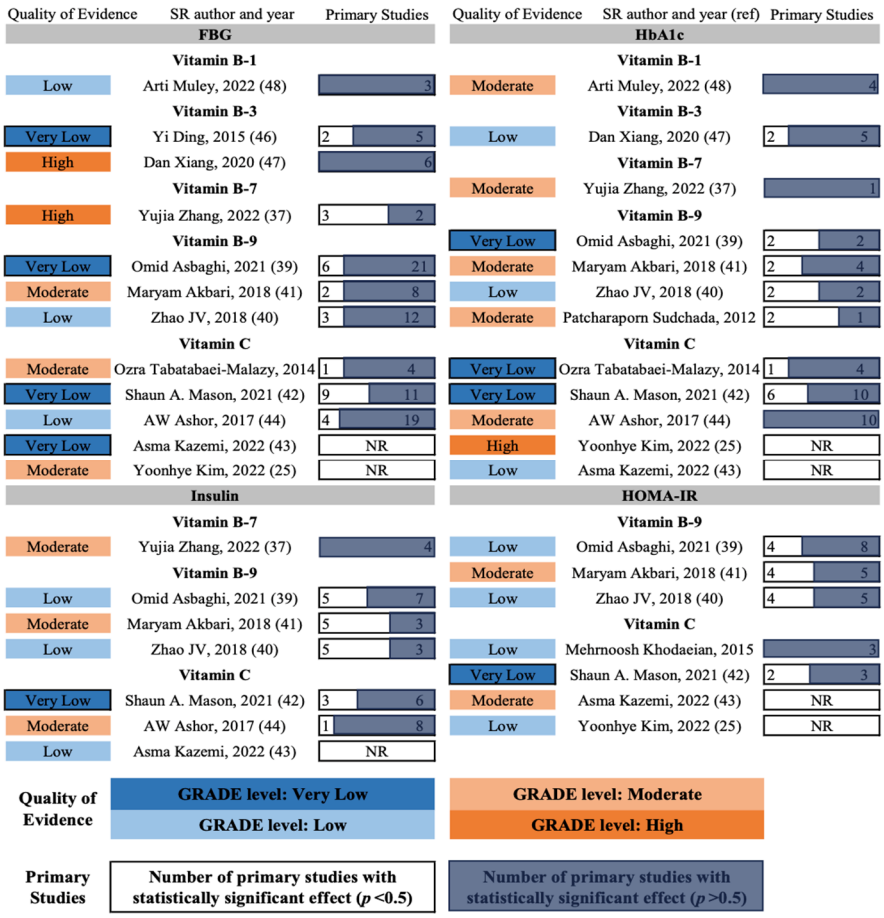

Figure 3. Summary of the strength of evidence for the effects of water-soluble vitamin supplementations. The left column indicates the meta-analyses with GRADE ratings that were very low, low, moderate, or high. Numbers in the right column indicate the modified consistency rating (number of primary randomized controlled trials with a statistically significantly positive effect or no statistically significant effect for each outcome).

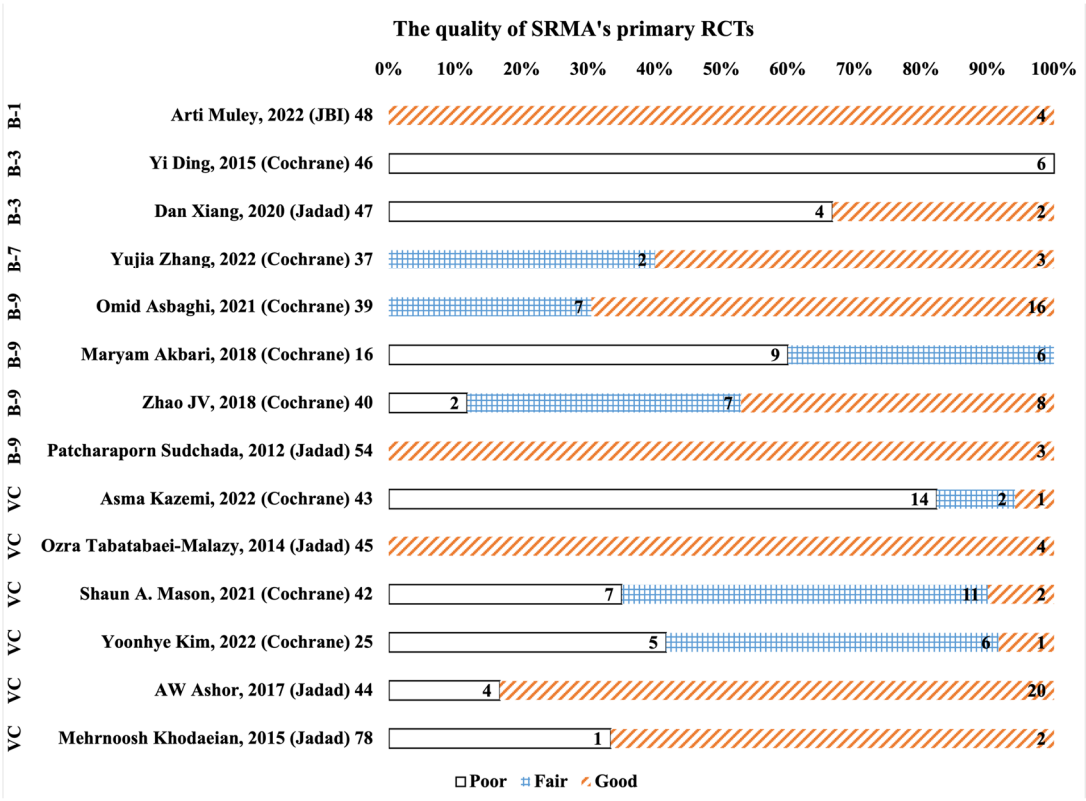

Figure 4. The quality of primary randomized controlled trials in meta-analysis

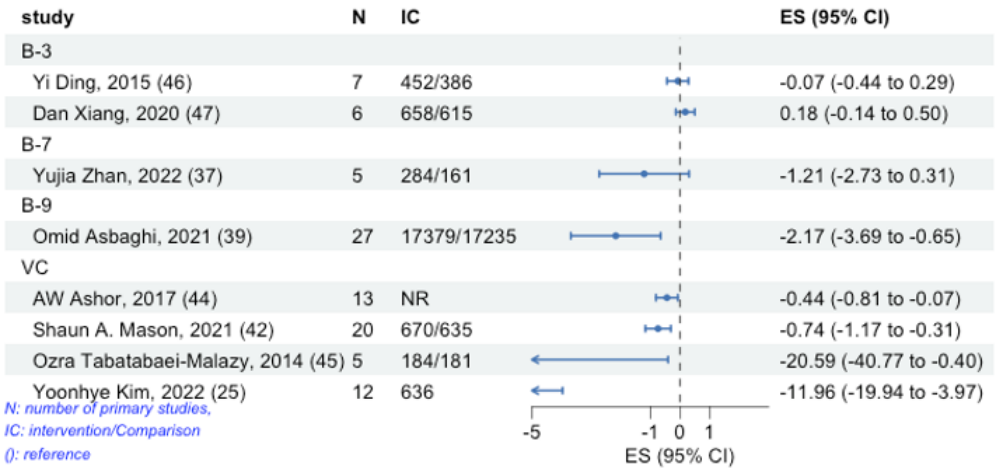

Figure 5. The effects of water-soluble vitamin supplementation on FBG

HOMA-IR, with pooled effect sizes ranging from -1.07 (95% CI: -1.80, -0.33) to -0.40 (95% CI: -0.70, -0.09).[39-41] As to the three vitamin C supplementation trials, no statistically significant effects on insulin were found.[25, 42, 43] In brief, regarding insulin resistance, there were two SAMAs with moderate-quality evidence, four with low quality, and one with very low quality (Figure 3).

DISCUSSION

This umbrella review summarizes the effects of water-soluble vitamins on glycemic management in T2DM. We included a total of 14 manuscripts of systematic reviews and meta-analyses containing 92 primary RCTs of the effects of five water-soluble vitamin supplementations (vitamin B-1, vitamin B-3, biotin, folic acid, and vitamin C) on glycemic control and insulin resistance. We found that folic acid improved insulin concentrations and HOMA-IR and vitamin C supplementation improved FBG and HbA1c in T2DM.

Folic acid (vitamin B-9) significantly improved insulin resistance indicated by reduced serum/plasma insulin concentrations and HOMA-IR. Vitamin B-9 acts as a key one-carbon donor in the body that plays an essential role in cellular metabolism. Low concentrations of vitamin B-9 lead to hyperhomocysteinemia, which has been reported to be associated with the development of insulin resistance.[55-57] The supplementation of folic acid could reduce serum homocysteine concentrations and improve glucose-induced oxidative stress and inflammation in T2DM.[58, 59] This is consistent with our findings. Regarding FBG, one study specifically in type 2 diabetes found a statistically significant effect. However, in populations with metabo-

Table 4. Efficacy of water-soluble vitamin supplementation on glycemic control and insulin resistance

SR author and year (number of studies)	I/C	Outcomes	Relative effect (95% CI)	I^2 (%)	Publication bias
Vitamin B1					
Arti Muley, 2022[48]					
2	24/24	FBG (<3 Mon)	MD=−0.20 (−0.69, 0.29)	0	YES
1	40/40	FBG (>3 Mon)	MD=1.30 (−0.12,2.72)	NR	YES
2	51/55	HbA1c (<3 Mon)	MD=−0.02% (−0.35, 0.31)	0	YES
2	79/83	HbA1c (>3 Mon)	MD=0.19% (−0.17,0.55)	0	YES
Vitamin B3					
Yi Ding,2015[46]					
7	452/386	FBG	WMD=-0.07 (-0.44, 0.29)	68.5	NO
Dan Xiang, 2020[47]					
6	658/615	FBG	WMD=0.18 (-0.14, 0.50)	5.20	NO
5	646/603	HbAc1	WMD=0.39 (-0.15, 0.94)	57.6	NO
Vitamin B7					
Yujia Zhang, 2022[37]					
5	284/161	FBG	MD=-1.21(-2.73, 0.31)	0.00	NR
1	226	HbAc1	MD=-0.18 (-0.39, 0.03)	NR	NR
4	266/151	insulin	MD=1.88(-13.44, 17.21)	58	NR
Vitamin B9					
Omid Asbaghi, 2021[39]					
27	17379/17235	FBG	WMD=-2.17 (-3.69, -0.65)	81.5	YES
4	85/85	HbAc1	WMD=−0.27 (−0.73, 0.18)	74.9	NO
12	322/295	HOMA-IR	WMD=−0.40 (−0.70, −0.09)	80.9	NO
12	315/291	insulin	WMD=−1.63 (−2.53, −0.73)	65.8	NO
Maryam Akbari, 2018[41]					
10	254/257	FBG	SMD=–0.30 (–0.63, 0.02)	69.1	NO
6	144/134	HbAc1	SMD=–0.29 (–0.61, 0.03)	40.6	NO
8	226/227	insulin	SMD= –1.28 (–1.99, –0.56)	91.5	NO
9	240/244	HOMA-IR	SMD= –1.07 (– 1.80, –0.33)	92.5	NO
Zhao JV, 2018[40]					
15	8369/8399	FBG	MD=-0.15 (-0.29, -0.01)	53.3	NO
4	157/156	HbAc1	MD=-0.17 (-0.49, 0.16)	77.8	NO
8	190/190	insulin	MD=-1.94 (-3.28, -0.61)	66.1	NO
9	221/214	HOMA-IR	MD=-0.83 (-1.31, -0.34)	80.9	NO
Patcharaporn Sudchada, 2012[54]					
3	71/71	HbAc1	WMD=-0.37 (-1.10, 0.35)	83.8	NO
Vitamin C					
AW Ashor, 2017[44]					
13	NR	FBG	WMD=-0.44 (-0.81, -0.07)	NR	NR
10	NR	HbAc1	WMD=-0.02 (-0.19, 0.15)	0.00	NR
6	NR	insulin	WMD=-13.63 (-22.73, -4.54)	NR	NR
Shaun A. Mason, 2021[42]					
20	670/635	FBG	MD=-0.74 (-1.17, -0.31)	75	NO
16	570/563	HbAc1	MD=-0.54% (-0.9, -0.17)	88.7	NO
5	222/214	HOMA-IR	MD=-1.43 (-2.88, 0.01)	61	NO
9	133/130	insulin	MD=-0.74 (-2.09, 0.61)	85.4	NO
Ozra Tabatabaei-Malazy, 2014[45]					
5	184/181	FBG	MD=-20.59 (-40.77, -0.4)	NR	NO
5	184/181	HbAc1	MD=-0.46 (-1.75, 0.84)	NR	YES
Asma Kazemi, 2022[43]					
19 (18)†	676/610	FBG	MD=-12.03 (-19.43, -4.63)	93.3	YES
15	543/538	HbAc1	MD=-0.48 (-0.75, -0.21)	83	YES
5 (4)†	131/126	HOMA-IR	MD=-0.06 (-1.15, 1.02)	75.3	NO
8 (7)†	215/207	insulin	MD=-1.164 (-3.21,0.86)	71.2	YES
Mehrnoosh Khodaeian, 2015[78]					
3	92	HOMA-IR	SMD=- 0.15 (- 0.49, 0.19)	35.4	NO
Yoonhye Kim, 202225					
12	318/318	FBG	MD=−11.96 (−19.94, −3.97)	60	NO
8	225/224	HbAc1	MD=−0.37 (−0.57, −0.17)	0	NO
3	75/77	HOMA-IR	MD=−1.86 (−4.10, 0.39)	61	NO

SR: systematic reviews and meta-analyses; FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance; I/C: intervention/comparison; NR: no report; MD: mean difference; SMD: standard mean difference; WMD: weighted mean difference.†The number of RCTs actually found in the meta-analysis.

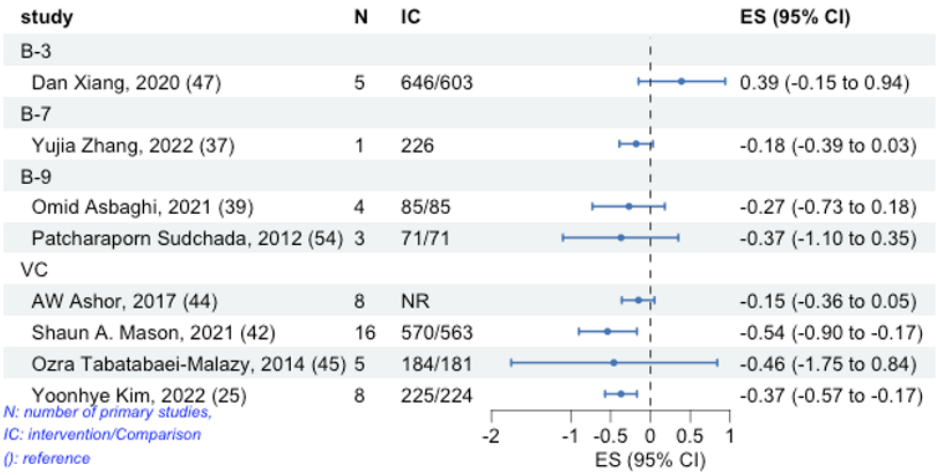

Figure 6. The effects of water-soluble vitamin supplementation on HbA1c

lism-related diseases—including T2DM, metabolic syndrome, overweight and obesity, polycystic ovary syndrome, and coronary artery disease—there were discrepancies among the pooled studies. Two systematic reviews and meta-analyses (SAMAs) indicated that folic acid supplementation could reduce FBG,[39, 40] while one SAMA did not find the same effect. However, sensitivity analysis revealed that supplementation was associated with a reduction in FBG.[41] Therefore, significant confounding may exist in the study. Additionally, folic acid supplementation did not show a significant effect on HbA1c, likely because HbA1c reflects long-term glycemic control, which may not be significantly altered by relatively short intervention periods (duration <12 weeks) in the included studies.[60] Furthermore, the number of RCTs investigating the effect of folic acid on HbA1c in the SRMAs was relatively small.[40, 54]

This umbrella review found that vitamin C supplementation had a significant effect on glycemic control, as indicated by reductions in both FBG and HbA1c. Oxidative stress, predisposing to insulin resistance, beta-cell dysfunction, impaired glucose tolerance, as well as mitochondrial dysfunction, is a major pathophysiological mechanism for diabetes and its complications.[61] Ascorbic acid (AA), the most potent water-soluble antioxidants in the body, has been reported to scavenge reactive oxygen and nitrogen species *in vitro* and *in vivo*,[30, 31] resulting in ameliorated oxidative stress.[62] Therefore, the role of VC on glycemic control in our study mainly attributes to its potent antioxidant function in the body. For FBG, the results of the included meta-analysis were consistent. However, the discrepancy of the effects on HbA1c concentrations were found. The possible reason is that high concentrations of glucose in the blood lead to intracellular VC deficiency, in addition, VC bioavailability is affected by transport proteins, which is impaired in T2DM.[45] Additionally, discrepancies may be attributed to small sample sizes and relatively early publication dates of some studies.[45]

AA supplementation did not show significant effects on insulin resistance in the present study. The possible reason is the high risk of bias in some studies as reported by Kim et al.[25] Additionally, the small number of included studies, high heterogeneity (I > 50%) among them, and significant overlap of primary RCTs across the three SRMAs may also contribute to these discrepancies.

Mitochondria are the site of production of important metabolites that regulate insulin secretion, and ATP/ADP ratio is significantly associated with insulin secretion.[63, 64] Also, in subjects with T2DM, impaired secretory response to glucose in pancreatic beta cells was associated with significant alterations in mitochondrial function and morphology.[65] Thiamine plays a crucial role in energy production within mitochondria, impacting intracellular glucose metabolism.[66, 67] Additionally, it regulates insulin secretion. Thiamine deficiency impairs insulin secretion by reducing glucose oxidation, which leads to beta-cell dysfunction and impaired glucose tolerance.[68-70] Niacin, mainly present in the body as coenzyme 1 (NAD) and coenzyme 2 (NADP), also is an important substance involved in the process of

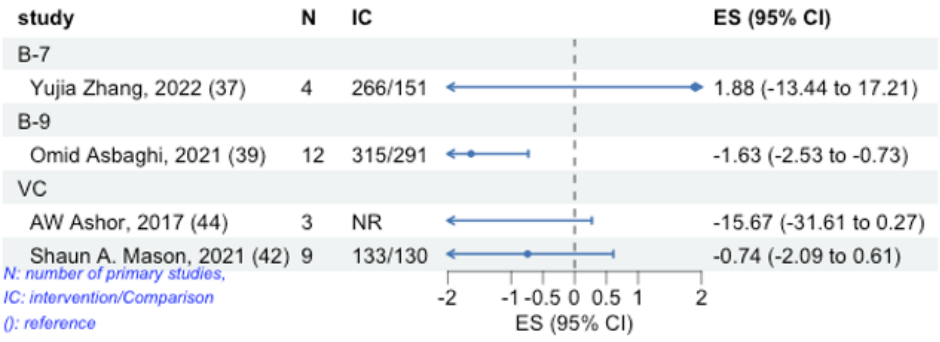

Figure 7. The effects of water-soluble vitamin supplementation on insulin

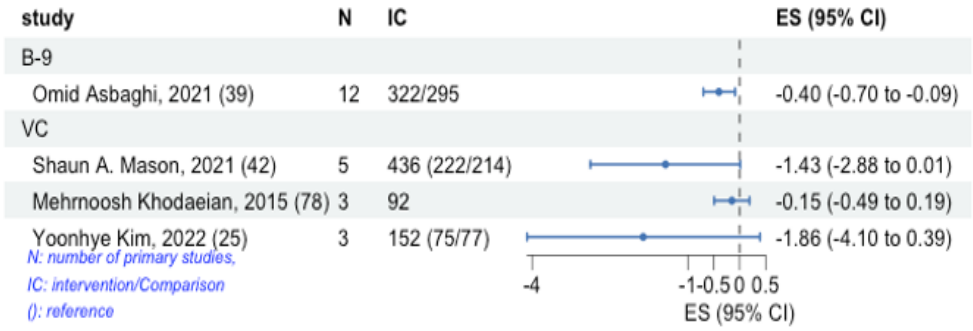

Figure 8. The effects of water-soluble vitamin supplementation on HOMA-IR

mitochondrial ATP production. At present, although studies did not find that thiamine (vitamin B-1) and niacin (vitamin B-3) supplementations improve blood glucose control, in the context of hyperglycemia, thiamine and niacin supplementations were revealed to prevent diabetic complications.[71-73] The possible reasons include the small number of included RCTs and populations, early publication of the primary RCTs, very low study quality, and a high degree of overlap between studies. Additionally, one study found that excess thiamine and niacin caused oxidative stress and insulin resistance in rats.[74] More rigorous studies are warranted in the future to investigate the effects of thiamine and niacin on glycemic control.

We did not find a significant effect of biotin supplementation on glycemic management or insulin resistance. In contrast, Zhang et al. found that biotin deficiency was associated with hyperglycemia and decreased insulin secretion and sensitivity.[75] Their study also showed that biotin supplementation increased insulin secretion and expanded the size of the islets by increasing the proportion of beta cells in rats.[76] The discrepancy may be due to the fact that only one SRMA investigated the effects of biotin supplemmentation on glycemic control and insulin concentrations, including just five RCTs with a relatively small pooled sample size. Additionally, AMSTAR-2 and GRADE assessments revealed low quality in the meta-analysis, primarily due to the lack of reporting on publication bias. Thus, more high-quality studies are needed in the future.

Strengths and limitations

Our study is the first umbrella review to systematically summarize the extensive evidence on the effects of water-soluble vitamin supplementation on glycemic control and insulin resistance. We evaluated the effects of various water-soluble vitamins and identified five—vitamin B-1, vitamin B-3, biotin, vitamin B-9, and vitamin C—that were included in the analysis. In our umbrella review, we categorized the primary RCTs by interventions and outcome indicators, analyzed the quality and overlap rate of included SRMAs, and explored reasons for inconsistencies among them. Additionally, we mapped the locations of the primary RCTs, which may help identify regional influences on study outcomes and guide future research.

Nevertheless, our umbrella review has some shortcomings. First, there was a high degree of overlap or corrected coverage area (CCA) among the included studies, with folic acid and vitamin C being the most common interventions in the primary RCTs. Second, the quality assessment revealed that the SRMA authors did not account for the risk of bias in the included RCTs when interpreting results. Additionally, high heterogeneity among the SRMAs was a major factor contributing to the downgrading of the GRADE evidence quality. Third, our review focused solely on RCTs evaluating single water-soluble vitamin supplementation. Future studies should investigate the effects of multivitamin supplementation or vitamin supplementation combined with other nutrients on glycemic control and insulin resistance. For instance, combined supplementation of vitamin C and vitamin E can improve glucose metabolism and oxidative stress in T2DM.[77] Fourth, we only extracted relevant information from the primary RCTs without performing a new meta-analysis, and we summarized the results and quality assessments of the included SRMAs. Future research should adopt rigorous study designs to enhance the overall quality of the studies. Finally, while we visualized the study sites, we did not account for or measure regional differences in our analysis. Most primary RCTs were conducted in countries with varying levels of development, where economic conditions and social factors could potentially impact the study outcomes.

Conclusion

Vitamin C supplementation can improve glycemic control in type 2 diabetes mellitus by reducing FBG and HbA1c, while folic acid supplementation can improve insulin resistance. Future research should include well-designed individual RCTs and higher-quality meta-analyses to further investigate these effects.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request.

ACKNOWLEDGEMENTS

We thank the participants and their families who made this study possible.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

All authors certify that they have no affiliations with or involvement in any organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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