Effects of water-soluble vitamin supplementations on glycemic control and insulin resistance in adult type 2 diabetes: an umbrella review of meta-analyses of randomized controlled trials

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Yi Chai MSc, Chengyu Chen BSc, Xueru Yin BSc, Xinru Wang BSc, Wenyan Yu BSc, Haochen Pan BSc, Ruiying Qin BSc, Xiyue Yang BSc, Qiuzhen Wang PhD

School of Public Health, Qingdao University, Qingdao, China

Authors' email addresses and contributions:
Yi Chai and Qiuzhen Wang: contributed to study concept and protocol development; Haochen, Ruiying Qin and Wenyan Yu: were responsible for study selection; Xueru Yin and Xinru Wang were responsible for data extraction and quality appraisal of the literature; Chengyu Chen: resolved conflicts with study selection, data extraction, and quality appraisal, and was responsible for GRADE assessments together with Yi Chai; Yi Chai: led data synthesis and drafting of the manuscript; Yi Chai and Qiuzhen Wang: revised the manuscript; Qiuzhen Wang: was responsible for study oversight and approval of the final content; and all authors: read and approved the final manuscript.

Corresponding Author: Prof. Qiuzhen Wang, Department of School of Public Health, Qingdao University, No. 308 Ningxia, Qingdao, 266071, China. Tel:. Email: qdwangqiuzhen@126.com

ABSTRACT

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. In this regard, we performed an umbrella review to synthesize evidence on the effects of water-soluble vitamin supplementation on glycemic control and insulin resistance. **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. Quality assessment of the meta-analyses was performed using AMSTAR-2 and GRADE. **Results:** Fourteen systematic reviews and meta-analyses were eligible, which studied the effects of five water-soluble vitamins (vitamin B-1, vitamin B-3, biotin, vitamin B-9, and vitamin C supplementation) supplements on glycemic control and insulin resistance. Results of the review suggest that vitamin C supplementations can improve glycemic control in type 2 diabetes indicated by reduced FBG and HbA1c, and having more significant effects with durations >30days on FBG. **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, meta-analysis

INTRODUCTION

Diabetes mellitus, one of the leading causes of death and disability worldwide, is a significant public health issue.[1] Until 2021, the number of adults with diabetes has reached 5.1 billion worldwide, with a prevalence rate of 10.5%; it is estimated that by 2045, the number will reach 6.4 billion worldwide, with a prevalence rate of 12.2%.[2] In addition, diabetes is related to 6.7 million deaths and an expenditure of at least $966 billion on healthcare 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 core target of treatment in diabetes, affects the development of its complications to a large extent.[8-11] It is widely accepted that glycosylated hemoglobin (HbA1c) is the most important indicator to reflect the long-term glycemic control status of diabetic patients, while fasting blood glucose (FBG) indicates a relatively short-term glycemic control status.[12] What's more, the variants of FBG and HbAc1 were strongly associated with the risk of developing retinopathy, nephropathy and all-cause mortality in diabetic patients.[13, 14] Therefore, it is essential to maintain good glycemic management, especially for the purpose of decreasing the risk of various complications of diabetes mellitus.[15] To find effective ways for glycemic control in diabetic patients has already 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 minerals25 have aroused intensive interests in scientific field and been reported to exert good effects on diabetes control. Water-soluble vitamins, including B vitamins and vitamin C, mainly act as coenzymes or coenzymes component molecules involved in the body's metabolism, playing an important role in vital activities of the body including energy metabolism, antioxidation, etc.[26, 27] We searched for all meta-analyses of water-soluble vitamin supplementation and assessed the quality of the meta-analyses and the randomized controlled trials (RCTs) they included, as well as counting the number of identical RCTs from different meta-analyses and calculating corrected coverage area (CCA) of RCTs vital activities of the body including energy metabolism, antioxidation, etc. It has been reported that water-soluble vitamins, such as vitamin C, folate, thiamine and biotin, 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] enhancing insulin sensitivity in skeletal muscle through ameliorating the 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] As to the two niacin supplementation trials,[46, 47] no statistically significant effects on blood glucose were found neither. As for the effects of thiamine and biotin supplementations,[37, 48] there is only one SRMA for both, and no statistically significant effect was found on FBG. Umbrella review is primarily an analysis of the evidence given for different interventions for the same problem or disease condition, or evidence from multiple studies that synthesize studies that have investigated the same interventions and disease conditions but have addressed and reported different outcomes, providing a summary of the synthesis of existing studies related to 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, umbrella review that specifically summarizes the effects of water-soluble vitamin supplementations on glycemic control and insulin resistance is still not available till now.

The purpose of this umbrella review is to re-evaluate SRMAs of the role of water-soluble vitamin supplementations in glycemic management in T2DM patients. The quality of the SRMAs was assessed by using the methodological quality assessment tool AMSTAR-2 and the quality of evidence evaluation tool GRADE to analyze the differences and associations of various water-soluble vitamins under different outcome indicators and to more comprehensively summarize the impact of water-soluble vitamin supplementation on glycemic control. Our study may provide important scientific evidence for proposing the nutritional recommendations targeting patients with type 2 diabetes.

MATERIALS AND METHODS

Search strategy

We performed an extensive search of the SRMAs using three databases, Web of science, PubMed, and Cochrane Database of Systematic Reviews, including only English-language articles, with data search dates ending in 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). We selected SRMAs by the appropriate inclusion criteria: (1) systematic reviews and meta-analysis of randomized controlled trials in adults aged 18 years or older; (2) reported supplementation with water-soluble vitamin as intervention, and 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.

The criterion for exclusion includes: (1) the primary study was experimental in animals, *in vivo*, *in vitro* or *ex vivo*; (2) no summary effect size was reported in the systematic review and meta-analysis (e.g., systematic review without meta-analysis).

Quality assessment

We assessed the methodological quality of the SRMAs using AMSTAR 2,[51] which is mainly used to assess systematic reviews that randomized or non-randomized studies of healthcare interventions, or both, and consists of 16 scored items, of which 7 are the critical items. AMSTAR 2 is concerned with the presence or absence of methodological flaws in critical items and rates the overall confidence in the results of the systematic reviews accordingly. Additionally, we used GRADE to assess the quality of evidence for the meta-analysis.[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, years of publication, sample sizes (including the number of RCTs in the meta-analysis and the total number of participants in the intervention and control groups), type of study, vitamin species, doses and durations of interventions, study locations, and conflict of interest, etc. Besides, the pooled effect sizes and 95%CI for outcome indicators such as FBG, HbA1c, insulin, and HOMA-IR as well as the heterogeneity of the studies, p-values for heterogeneity and publication bias (p-values determined by Egger's test and Funnel plot) were extracted.

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 (see 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, persons 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) for durations ranged from 1 to 3 months. Two systematic reviews reported niacin interventions for durations ranged from 8 to 64 weeks (dose: 150 ~ 4500 mg/day). One systematic review reported biotin interventions with durations ranged from 4 weeks to 3 months (dose: 1.5-15 mg/day). Primary studies of the 4 systematic reviews that examined the effect of folic acid interventions for longer durations of 2weeks to 7.3years (dose: 0.5-15 mg/day). It worth noting that the duration of vitamin C interventions varied greatly between the primary studies, with durations ranged from 14 days to 9 years (dose: 72-6000 mg/day). All systematic reviews used random effects models for pooled estimation. Most of the primary RCTs used placebo controls, and a small proportion used blank controls.

There were 162 primary RCTs in the 14 included systematic reviews, and after excluding duplicate studies, there were totally 88 primary RCTs implemented in 89 regions, of which 4, 8, 5, 34, and 37 primary RCTs conducted vitamin B-1, vitamin B-3, biotin, vitamin B-9, and vitamin C supplementations, respectively (Supplementary Table 2). In addition, 17 RCTs were conducted in Iran, 11 of which had vitamin B-9 interventions, and 13 studies were conducted in the United States, with vitamin B-3 or vitamin C interventions in 5 studies each (Figure 2). We noticed that the quality of the primary RCTs was closely related to the economic status of the places where the studies were conducted, which were significantly higher in countries with better economic status.

Estimating the degree of overlap or corrected coverage area (CCA) for the included SRMAs, high CCAs were found in the supplementation trials of vitamin B-3 (CCA=62.50%), vitamin B-9 (CCA=24.51%) and vitamin C (CCA=18.54%). If the meta-analysis were grouped according to the study outcomes, the degree of overlap or CCA) was calculated again, and the results showed that the CCAs remained high. (Table 2)

The corresponding authors of the systematic reviews were mainly from Iran (5/14), Australia (2/14), China (4/14), UK (1/14), Korea (1/14), and Thailand (1/14). The source of funding for the systematic reviews was mainly national foundation (3/14), and 64% of the systematic reviews did not report a source of funding. Most of the systematic reviews reported no conflict of interest.

Risk of bias and quality assessment of included meta-analyses

The assessment results of AMSTAR-2 for the studies are presented in Figure 3. One study was a network meta-analysis and 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 in the included studies when the investigator interpreted the results of each study (9/13). According to the assessment details of AMSTAR-2 and GRADE, most of the included SRMAs were low-quality articles with about 61.5% of the articles assessed as low by AMSTAR-2, mainly because the SRMAs did not consider quality assessment when interpreting the results; and about 31.6% and 26.3% of the articles assessed as low and very low by GRADE, mainly due to high heterogeneity among primary RCTs and publication bias also existed in meta-analysis studies.

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 4, Supplementary Table 3). Also, Figure 4 shows the effects of water-soluble vitamin interventions on glycemic control and insulin resistance as reported in the included systematic reviews. In this review, we found that conclusions with significant differences were often derived from low-quality evidence. The inclusion of low and very low-quality evidence impacts the reliability and stability of the final results, rendering the conclusions of the review potentially uncertain and insufficient to provide robust support for clinical practice. This underscores the need for further high-quality research to validate these findings.

We assessed the quality of the RCTs extracted from each meta-analysis with three quality assessment methods, namely JBI evidence-based center's quality assessment tool (N=1), Jadad scale (N=5), and Cochrane collaboration' s tool for assessing risk of bias (N=8), and seven meta-analyses of vitamin B-3, folic acid and vitamin C having more than 50% of the primary RCTs of moderate and low quality (Figure 5).

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, no statistically significant effects of folic acid on FBG were found by Maryam et al in the population with the same metabolism-related diseases aforementioned.[41] There was consistent evidence that vitamin C supplementation could reduce FBG with pooled effect sizes ranging from -20.59 (95% CI: -40.77, -0.4) to -0.44 (95% CI: -0.81, -0.07);[25, 42, 44, 45] and further subgroup analysis found that durations >30 days had a statistically more significant positive effect on FBG with pooled effect sizes ranging from -0.53 (95% CI: -0.97, -0.10).[44]

There was consistent evidence that thiamine and biotin supplementation had no statistically significant effect on FBG.[37, 48] As to the two niacin supplementation trials, no statistically significant effects on blood glucose were found neither; however, subgroup analysis found that high doses or >20 weeks' supplementation of niacin were significantly effective for FBG.[46, 47]

Totally, as to the influence of water-soluble vitamin on FBG, there were two SAMAs with high quality, three with intermediate quality, three with low quality, and four with very low quality (Figure 4).

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 3, Figure 7). 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] There was consistent evidence that thiamine, niacin and folic acid supplementation had no statistically significant effects on HbA1c;[39, 54] however, subgroup analysis found that high-doses niacin intervention had a statistically significant positive effect on HbA1c with pooled effect sizes 0.90 (95% CI: 0.21, 2.41).[47] As to the one biotin supplementation trial, no statistically significant effect on HbA1c was found.[37] Overall, among the ten pooled studies, one SAMA provided evidence on HbA1c with high quality, four with moderate, two with low and three with very low quality. (See in Figure 4)

The effect of water-soluble vitamin supplementation on insulin resistance

Seven meta-analyses explored the effect of the supplementation of three water-soluble vitamins including biotin, folic acid, and vitamin C on fasting serum insulin (Table 3, Figure 8).

There was only one meta-analysis targeting type 2 diabetic patients claiming that folic acid supplementation could reduce insulin, with pooled effect sizes ranging from -1.63 (95% CI: -2.53, -0.73).[39] In agreement, another pooled analysis in the previously mentioned metabolism-related diseases also found folic acid supplementation could reduce insulin, with pooled effect sizes ranging from -1.94 (95% CI: -3.28, -0.61) to -1.28 (95% CI: -1.99, -0.56).[39-41] As to the one biotin supplementation trials, no statistically significant effects on insulin were found.[37] For the two vitamin C supplementation trials, no statistically significant effects on insulin were found neither.[42, 44] In conclusion, two SAMAs with moderate quality of evidence, three with low quality and one with very low quality (Figure 4).

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 3, Figure 9).

There was only one meta-analysis reporting that folic acid supplementation could reduce HOMA-IR, with pooled effect sizes -0.40 (95% CI: -0.70, -0.09).[39] In agreement, another pooled analysis in the metabolism-related diseases also found folic acid supplementation could reduce 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, as to insulin resistance, two SAMAs with moderate quality of evidence, four with low quality, and one with very low quality (Figure 4).

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. As to FBG, there was one study implemented specifically in type 2 diabetes and found a statistically significant effect, while in the population of metabolism-related diseases including T2DM, metabolic syndrome, overweight and obese, polycystic ovary syndrome, coronary artery disease, there exists discrepancies in the pooled studies, two SAMAs showed that folic acid supplementation could reduce FBG,[39, 40] while one SAMA did not find the same effect; however, when sensitivity analysis was performed, the supplementation was found to decreased FBG again.[41] Therefore, there may exist major confounding in the study. Besides, it did not show a significant effect of folic acid supplementation on HbA1c, probably because HbA1c tends to reflect an estimation of long-term glycemic control, which cannot be significantly modified in the case of a relatively short intervention period (duration <12 weeks) in the included studies.[60] Also, the number of RCTs investigating the possible role of folic acid on HbA1c in the SRMAs was relatively small.[40, 54]

In the present umbrella review, vitamin C supplementation was discovered to have a significant effect on glycemic control indicated by 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] Besides, this may be also due to the small sample size and relatively early publication in some studies.[45]

Ascorbic acid 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] In addition, the small number of included studies, high heterogeneity (I > 50%) among the studies and the high overlaps of the primary RCTs included in the three SRMAs may also contribute.

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 As we all know, thiamine participates the process of energy production within mitochondria, affecting intracellular glucose metabolism.[66, 67] In addition, it was reported to regulate insulin secretion, when thiamine deficiency, insulin secretion is impaired by reduced glucose oxidation, leading 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 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 reason is the small number of included RCTs and populations and may be related to the early publication of the primary RCTs, the very low quality of the studies, and the very high degree of overlap between studies. Besides, one study even 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.

Also, we did not find a significant effect of biotin supplementation on glycemic management or insulin resistance. Unlikely, Zhang et al found that hyperglycemia and decreased insulin secretion and sensitivity was associated with biotin deficiency,[75] and biotin supplementation was able to increase insulin secretion and increase the proportion of beta cells by expanding the size of the islets in rats.[76] Considering the reason of the discrepancy, we found only one SRMA investigated the effects of biotin supplementation on glycemic control and insulin concentrations, and that study included only five RCTs and the pooled sample size of the RCTs was relatively small. In addition, by AMSTAR-2 and GRADE we found a low quality of the meta-analysis mainly due to not reporting publication bias. Therefore, 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 searched for the effects of all water-soluble vitamin supplementation on glycemic control and insulin resistance and finally found 5 vitamins (vitamin B-1, vitamin B-3, biotin, vitamin B-9, and vitamin C supplementation). In our umbrella review, after categorizing the primary RCTs according to interventions and outcome indicators, we analyzed the quality and the overlap rate of included SRMAs, which is beneficial to the exploration of the reasons for inconsistencies among SRMAs. In addition, we mapped the locations where the primary RCTs were conducted, which may facilitate further studies to explore the potential impact of the region where the study was conducted on outcomes.

Nevertheless, there are still some shortcomings in our umbrella review. First, the degree of overlap or CCA in these included studies was very high and that the interventions in most of the primary RCTs were folic acid and vitamin C. Second, the quality assessment showed that the authors of these SRMAs did not consider the risk of bias in the included RCTs when interpreting the results; and the high heterogeneity of the SRMAs was one of the main factors influencing the downgrading of the quality of the GRADE evidence. Third, in our review, the interventions of RCTs included in the SRMAs were all supplementing single water-soluble vitamin, and thus future studies are needed to investigate the role and effects of multivitamin supplementation or vitamin supplementation in combination 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 collected relevant information from the primary RCTs without subjecting them to a new meta-analysis, and also only summarized the results of the included SRMAs and their quality assessment. Therefore, future studies should adopt a rigorous study design to improve the quality of the studies. Finally, we only visualized the study sites and did not consider or measure the regional differences when discussing and analyzing the results of each study. However, most of the primary RCTs were conducted in countries with unbalanced development, for which economic conditions and social factors had potential impacts on the studies.

Conclusion

Vitamin C supplementations can improve glycemic control in type 2 diabetes mellitus by reduced FBG and HbA1c, and folic acid supplementations improve insulin resistance. More well-designed individual RCTs were needed in the future. More well-designed individual randomized controlled trials are needed in the future, as well as meta-analysis of higher quality.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request.

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Table 1. 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

SR Author and year	Comparator	Outcome FBG	HbAc1	HOMA-IR	Insulin	Method of pooling estimates	Funding	COI	Country of author
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

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

SR Author and year	Primary studies, n	Population	Age (years)	Intervention Vitamin species	Dose (mg/day)	Duration
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	4weeks-9years
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 FBG	HbAc1	HOMA-IR	Insulin	Method of pooling estimates	Funding	COI	Country of author
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 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	81.25%	62.50%	Very high
Folate	4	34	43.38%	24.51%	Very high
VC	6	41	32.11%	18.54%	Very high

CA: coverage area; CCA: corrected coverage area.

Table 3. 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)	68.50	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)	57.60	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)	58.00	NR
Vitamin B9					
Omid Asbaghi, 2021[39]					
27	17379/17235	FBG	WMD=-2.17 (-3.69, -0.65)	81.50	YES
4	85/85	HbAc1	WMD=−0.27 (−0.73, 0.18)	74.90	NO
12	322/295	HOMA-IR	WMD=−0.40 (−0.70, −0.09)	80.90	NO
12	315/291	insulin	WMD=−1.63 (−2.53, −0.73)	65.80	NO
Maryam Akbari, 2018[41]					
10	254/257	FBG	SMD=–0.30 (–0.63, 0.02)	69.10	NO
6	144/134	HbAc1	SMD=–0.29 (–0.61, 0.03)	40.60	NO
8	226/227	insulin	SMD= –1.28 (–1.99, –0.56)	91.50	NO
9	240/244	HOMA-IR	SMD= –1.07 (– 1.80, –0.33)	92.50	NO
Zhao JV, 2018[40]					
15	8369/8399	FBG	MD=-0.15 (-0.29, -0.01)	53.30	NO
4	157/156	HbAc1	MD=-0.17 (-0.49, 0.16)	77.80	NO
8	190/190	insulin	MD=-1.94 (-3.28, -0.61)	66.10	NO
9	221/214	HOMA-IR	MD=-0.83 (-1.31, -0.34)	80.90	NO
Patcharaporn Sudchada, 2012[54]					
3	71/71	HbAc1	WMD=-0.37 (-1.10, 0.35)	83.80	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)	74.95%	NO
16	570/563	HbAc1	MD=-0.54% (-0.9, -0.17)	88.70%	NO
5	222/214	HOMA-IR	MD=-1.43 (-2.88, 0.01)	60.98%	NO
9	133/130	insulin	MD=-0.74 (-2.09, 0.61)	85.44%	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)	93.30%	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)	75.30%	NO
8 (7)†	215/207	insulin	MD=-1.164 (-3.21,0.86)	71.20%	YES

CA: coverage area; CCA: corrected coverage area.

Table 3. Efficacy of water-soluble vitamin supplementation on glycemic control and insulin resistance (cont.)

SR author and year (number of studies)	I/C	Outcomes	Relative effect (95% CI)	I^2 (%)	Publication bias
Vitamin C					
Mehrnoosh Khodaeian, 2015[78]					
3	92	HOMA-IR	SMD=- 0.15 (- 0.49, 0.19)	35.40%	NO
Yoonhye Kim, 2022[25]					
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.

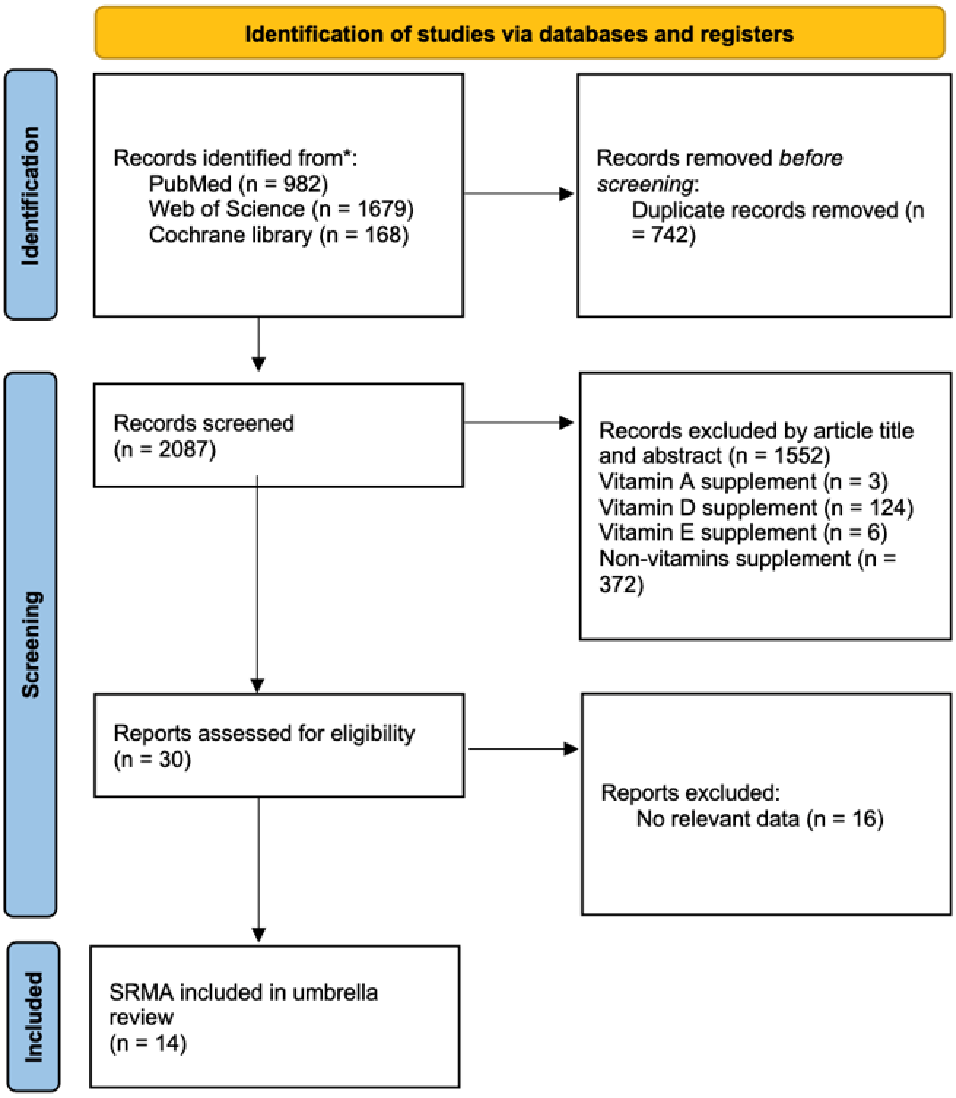

Figure 1. PRISMA Flow chart for search strategy exploring the effects of water-soluble on glycemic control and insulin resistance

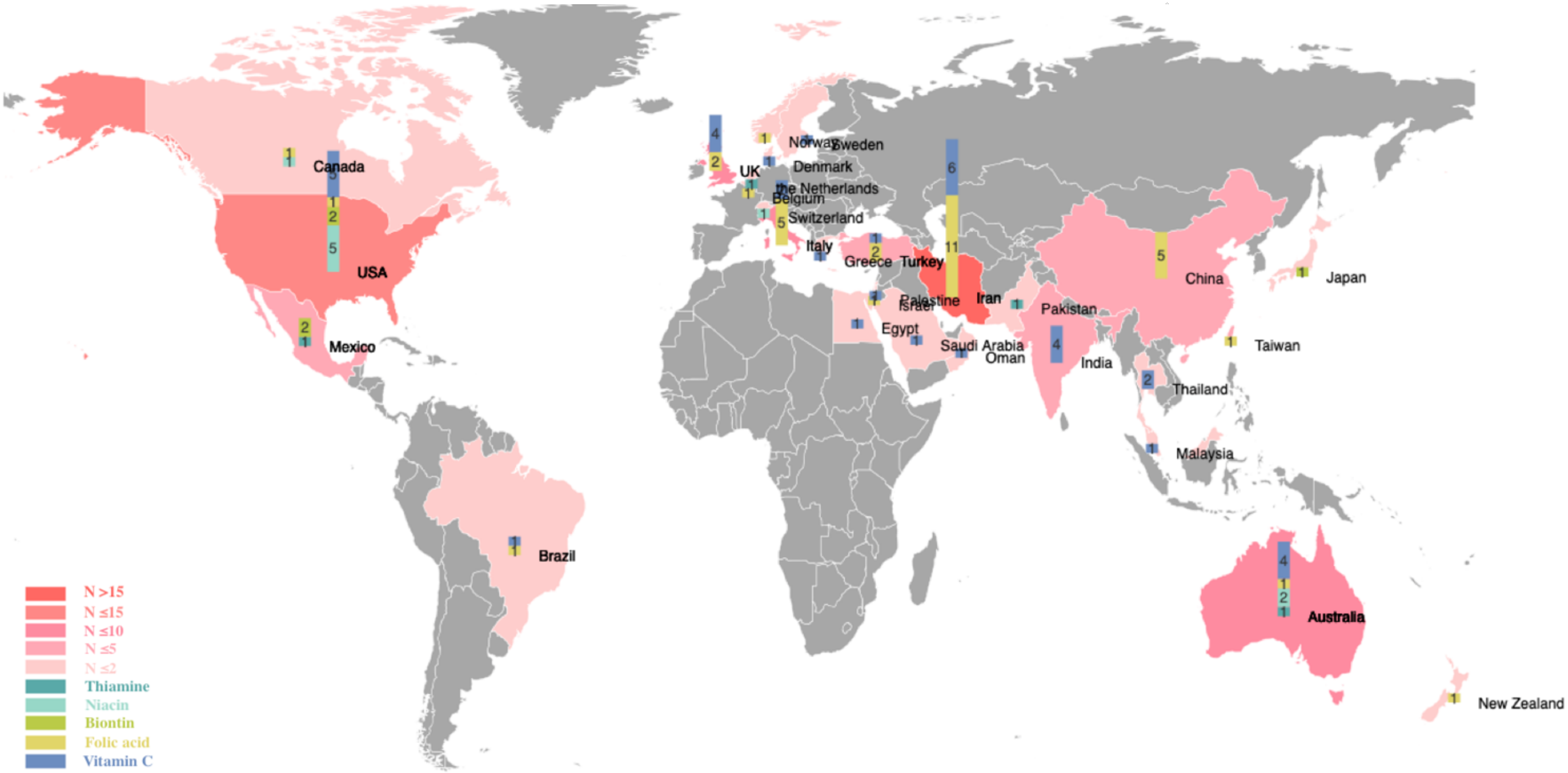

Figure 2. The locations where randomized controlled trials of water-soluble vitamin interventions were conducted

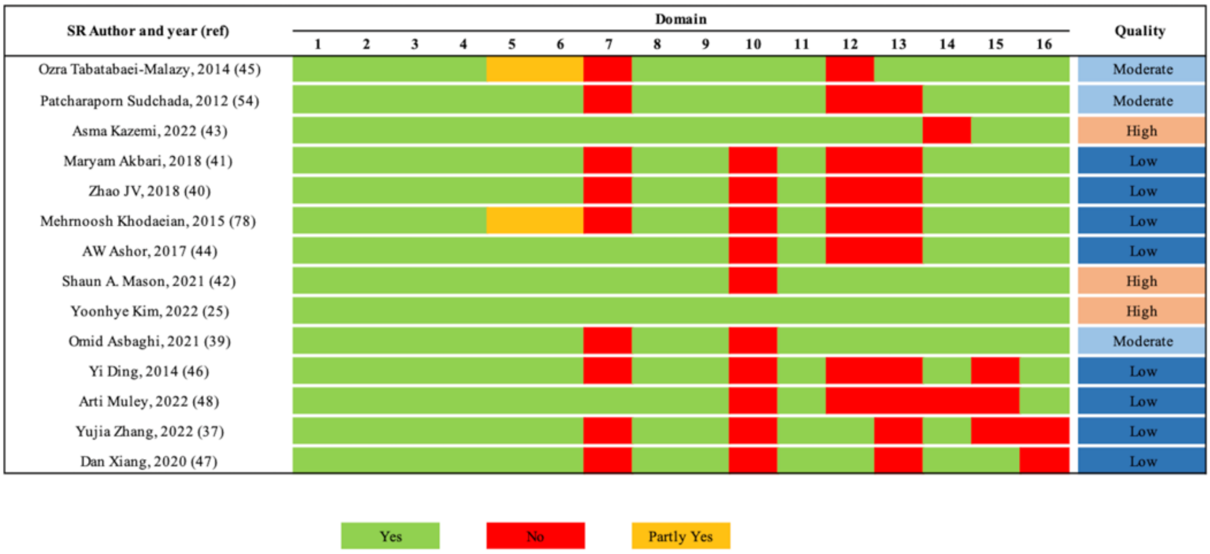

Figure 3. Results of assess the methodological quality of meta-analysis

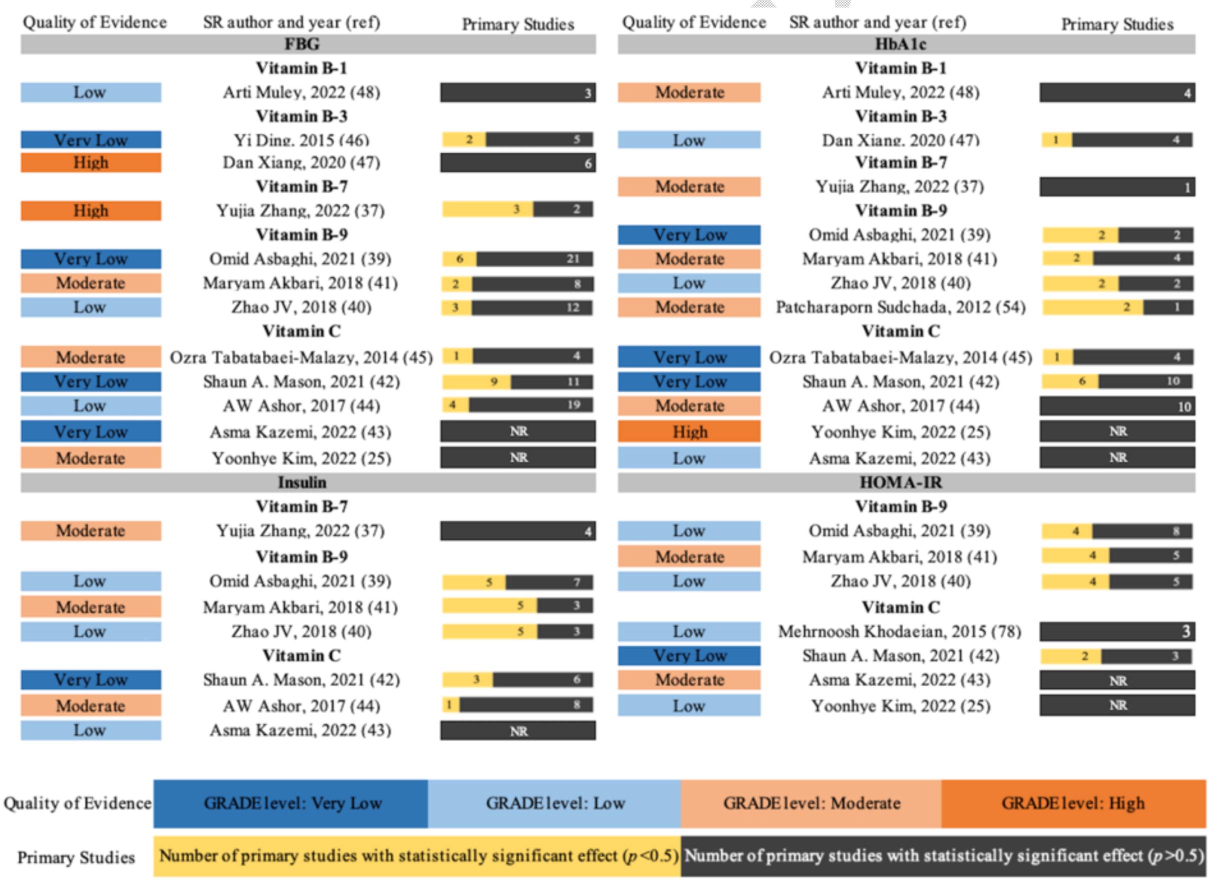

Figure 4. Summary of the strength of evidence for the effects of water-soluble vitamin supplementations. The left column indicates the meta-analyses with GRADE ratings that were very low, low, moderate, or high. Numbers in the right column indicate the modified consistency rating (number of primary randomized controlled trials with a statistically significantly positive effect or no statistically significant effect for each outcome).

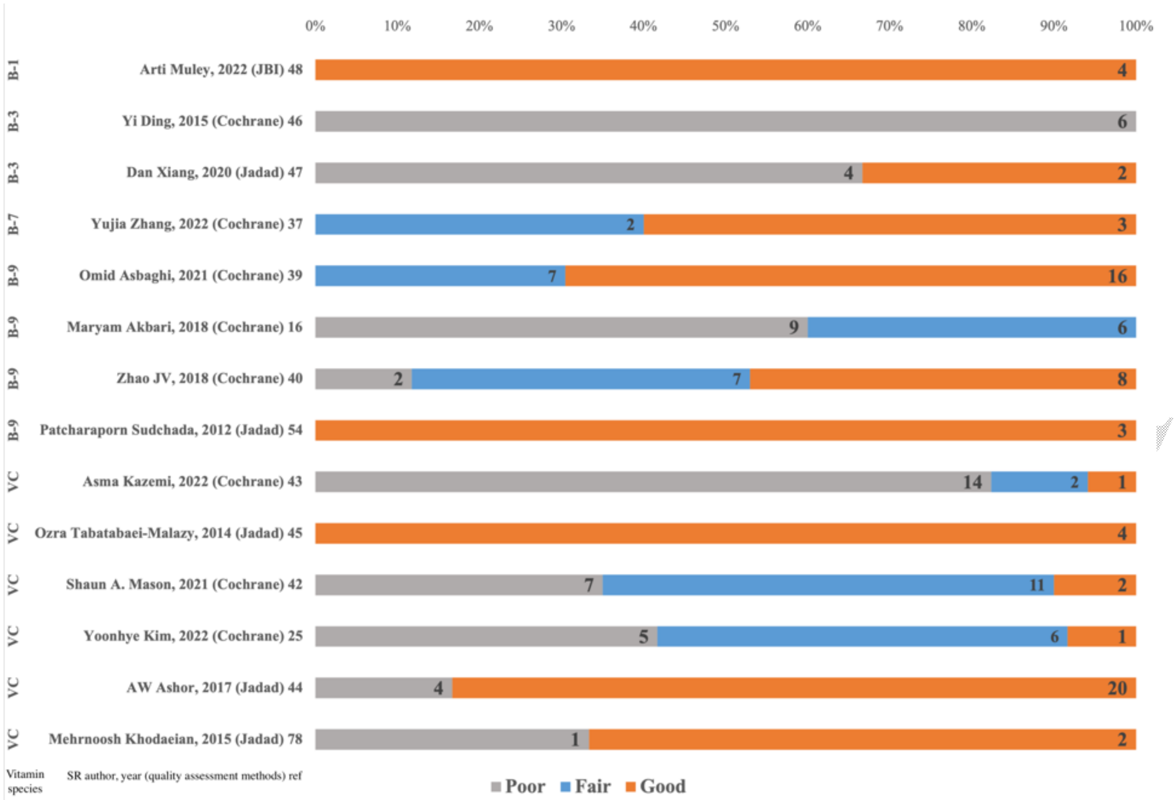

Figure 5. The quality of primary randomized controlled trials in meta-analysis

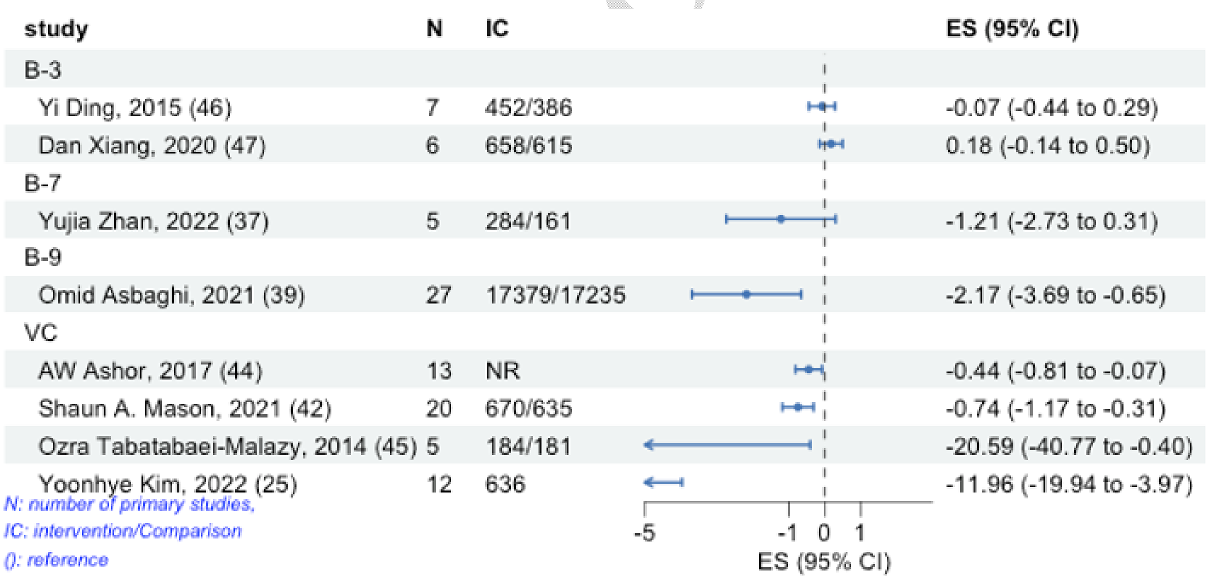

Figure 6. The effects of water-soluble vitamin supplementation on FBG

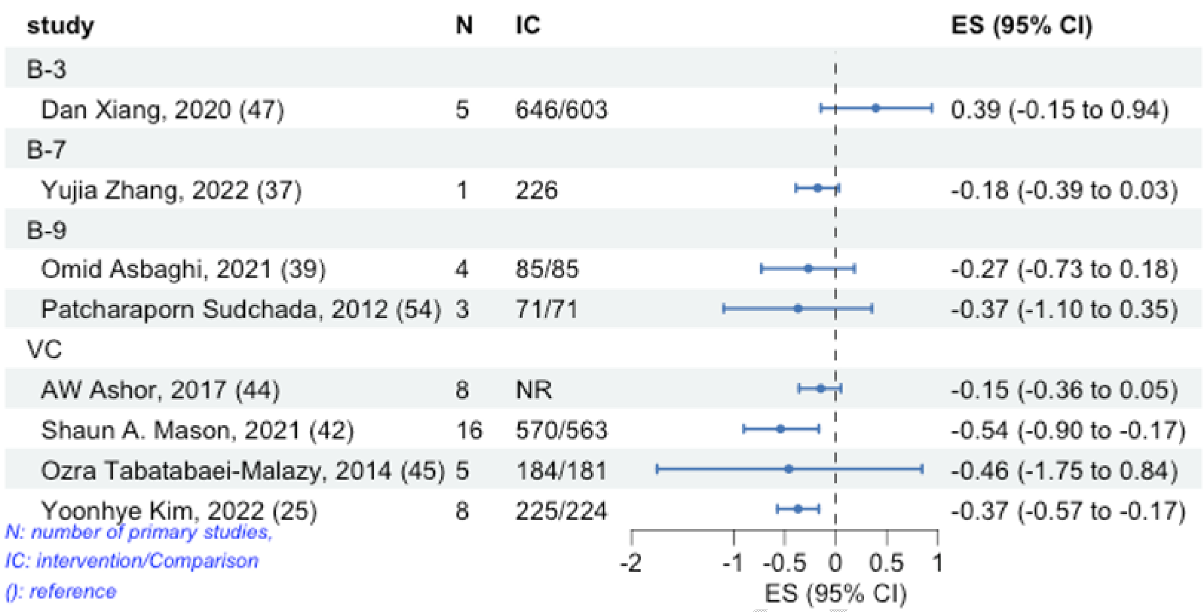

Figure 7. The effects of water-soluble vitamin supplementation on HbA1c

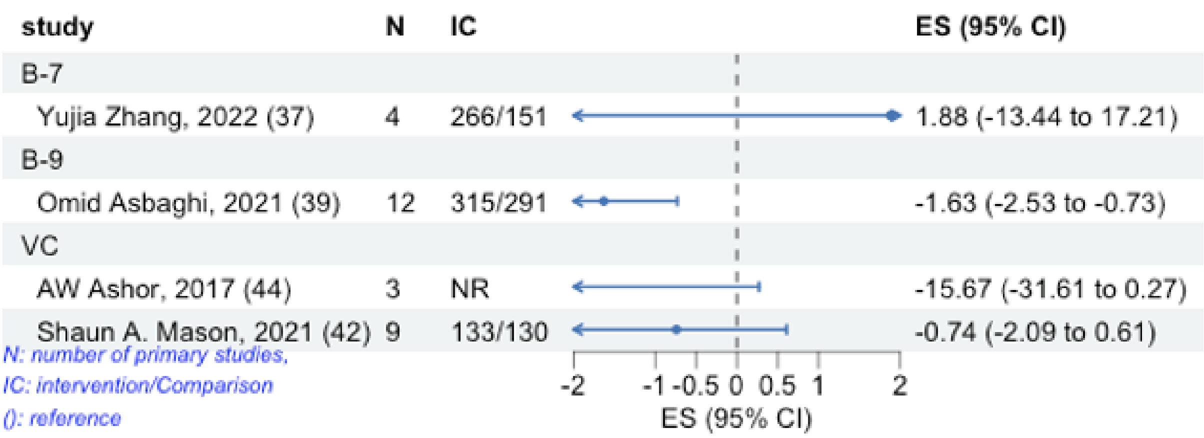

Figure 8. The effects of water-soluble vitamin supplementation on insulin

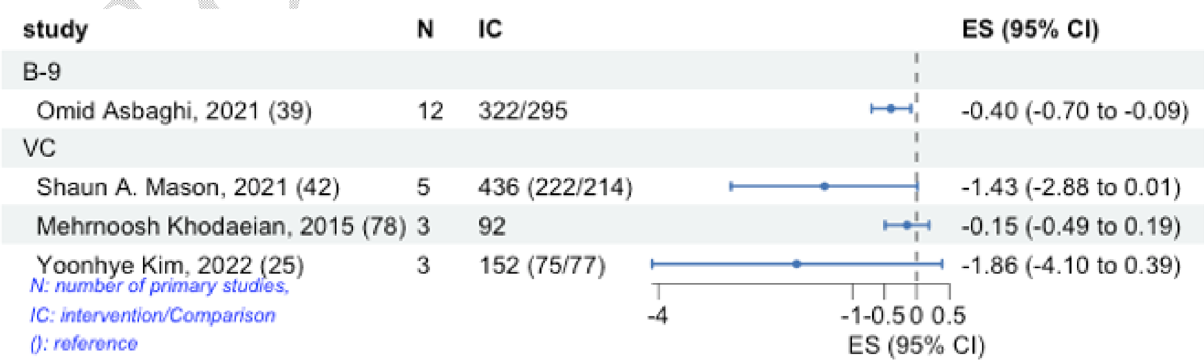

Figure 9. The effects of water-soluble vitamin supplementation on HOMA-IR

Supplementary Tables

Supplementary Table 1. Search strategy

Database	
PubMed	
#1	(((("Vitamins"[Mesh] OR "Vitamins" [Pharmacological Action]) OR "Vitamin B Complex"[Mesh]) OR "Dietary Supplements"[Mesh]) OR "Provitamins"[Mesh])
#2	(((((((((((((((((((("Thiamine"[Mesh]) OR "Thiamine Monophosphate"[Mesh]) OR "Riboflavin"[Mesh]) OR "Niacinamide"[Mesh]) OR "Nicorandil"[Mesh]) OR "Nicotinic Acids"[Mesh]) OR "Pantothenic Acid"[Mesh]) OR "Vitamin B 6"[Mesh]) OR "Biotin"[Mesh]) OR "Folic Acid"[Mesh]) OR "Hydroxocobalamin"[Mesh]) OR "Inositol"[Mesh]) OR "Levoleucovorin"[Mesh]) OR "Pyridoxal Phosphate"[Mesh]) OR "Pyridoxamine"[Mesh]) OR "Pyridoxine"[Mesh]) OR "Tetrahydrofolates"[Mesh]) OR "Thioctic Acid"[Mesh]) OR "Vitamin B 12"[Mesh]) OR "Cobamides"[Mesh]) OR "Ascorbic Acid"[Mesh]
#3	#1 OR #2
#4	((Multivitamins[Title/Abstract]) OR (dietary supplements[Title/Abstract])) OR (vitamin* supplement*[Title/Abstract])) OR (vitamin B[Title/Abstract])) OR (B Vitamins[Title/Abstract])) OR (B Vitamin[Title/Abstract])) OR (Vitamin, B[Title/Abstract])) OR (Neurobion[Title/Abstract])) OR (Thiamin[Title/Abstract])) OR (Vitamin B1[Title/Abstract])) OR (Aneurin[Title/Abstract])) OR (Vitamin B 1[Title/Abstract])) OR (Thiamine Mononitrate[Title/Abstract])) OR (Mononitrate, Thiamine[Title/Abstract])) OR (Vitamin G[Title/Abstract])) OR (Vitamin B2[Title/Abstract])) OR (Vitamin B 2[Title/Abstract])) OR (Riboflavin[Title/Abstract])) OR (Vitamin B3[Title/Abstract])) OR (B3, Vitamin[Title/Abstract])) OR (Vitamin PP[Title/Abstract])) OR (Nicotinamide[Title/Abstract])) OR (3-Pyridinecarboxamide[Title/Abstract])) OR (3 Pyridinecarboxamide[Title/Abstract])) OR (Vitamin B 3[Title/Abstract])) OR (B 3, Vitamin[Title/Abstract])) OR (Nicotinsäureamid Jenapharm[Title/Abstract])) OR (Jenapharm, Nicotinsäureamid[Title/Abstract])) OR (Nicobion[Title/Abstract])) OR (Vitamin B 5[Title/Abstract])) OR (B 5, Vitamin[Title/Abstract])) OR (Vitamin B5[Title/Abstract])) OR (B5, Vitamin[Title/Abstract])) OR (Pantothenate[Title/Abstract])) OR (Pantothenic Acid[Title/Abstract])) OR (Vitamin B6[Title/Abstract])) OR (Vitamin H[Title/Abstract])) OR (Medebiotin[Title/Abstract])) OR (Biodermatin[Title/Abstract])) OR (Biokur[Title/Abstract])) OR (Biotin Gelfert[Title/Abstract])) OR (Rombellin[Title/Abstract])) OR (Vitamin M[Title/Abstract])) OR (Vitamin B9[Title/Abstract])) OR (B9, Vitamin[Title/Abstract])) OR (Pteroylglutamic Acid[Title/Abstract])) OR (Folic Acid, Monopotassium Salt[Title/Abstract])) OR (Folic Acid, Monosodium Salt[Title/Abstract])) OR (Folic Acid, Potassium Salt[Title/Abstract])) OR (Folic Acid, (DL)-Isomer[Title/Abstract])) OR (Folvite[Title/Abstract])) OR (Folacin[Title/Abstract])) OR (Folate[Title/Abstract])) OR (B 12, Vitamin[Title/Abstract])) OR (Vitamin B12[Title/Abstract])) OR (B12, Vitamin[Title/Abstract])) OR (Cyanocobalamin[Title/Abstract])) OR (Cobalamins[Title/Abstract])) OR (Cobalamin[Title/Abstract])) OR (Acid, Ascorbic[Title/Abstract])) OR (L-Ascorbic Acid[Title/Abstract])) OR (Acid, L-Ascorbic[Title/Abstract])) OR (L Ascorbic Acid[Title/Abstract])) OR (Vitamin C[Title/Abstract])
#5	#3 OR #4
#6	(((((("Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Mellitus, Lipoatrophic"[Mesh] OR "Diabetes, Gestational"[Mesh]) OR "Hyperglycemia"[Mesh]) OR ("Blood Glucose"[Mesh] OR "Glycemic Control"[Mesh])) OR "Glucose Tolerance Test"[Mesh]) OR "Glycated Hemoglobin A"[Mesh]) OR "Insulin"[Mesh]) OR "Insulin Resistance"[Mesh]
#7	(((((((((((((((((((((((diabetes[Title/Abstract]) OR (diabetes mellitus[Title/Abstract])) OR (T2DM[Title/Abstract])) OR (hyperglycemia[Title/Abstract])) OR (hyperglycaemia[Title/Abstract])) OR (glucose[Title/Abstract])) OR (HbA1c[Title/Abstract])) OR (hemoglobin A1c[Title/Abstract])) OR (glycated hemoglobin[Title/Abstract])) OR (insulin resistance[Title/Abstract])) OR (insulin sensitivity[Title/Abstract])) OR (HOMA[Title/Abstract])) OR (HOMA-IR[Title/Abstract])) OR (glucose homeostasis[Title/Abstract])) OR (insulin secretion[Title/Abstract])) OR (insulin[Title/Abstract])) OR (beta-cell function[Title/Abstract])) OR (glycemic control[Title/Abstract])) OR (glucose tolerance[Title/Abstract])) OR (glucose metabolism[Title/Abstract])) OR (homeostatic model assessment[Title/Abstract])) OR (fasting blood sugar[Title/Abstract])) OR (FBS[Title/Abstract])) OR (OGTT[Title/Abstract])
#8	#6 OR #7
#9	#5 AND #8
#10	Filters: Meta-Analysis; Systematic Reviews; published in the last 10 years

Supplementary Table 1. Search strategy (cont.)

Database	
Web of Science	
#1	(((((TS=(Vitamins)) OR TS=(Vitamin B Complex)) OR TS=(Antioxidants)) OR TS=(Multivitamins)) OR TS=(Multivitamins)) OR TS=(vitamin* supplement*)
#2	(((((((((((((((((((((((((((((((((((((TS=(Thiamin)) OR TS=(Vitamin B1)) OR TS=(Aneurin)) OR TS=(Thiamine Mononitrate)) OR TS=(Vitamin G)) OR TS=(Vitamin B2)) OR TS=(Riboflavin)) OR TS=(Vitamin B3)) OR TS=(Vitamin PP)) OR TS=(Nicotinamide)) OR TS=(3-Pyridinecarboxamide)) OR TS=(Papulex)) OR TS=(Papulex)) OR TS=(Nicotinsäureamid Jenapharm)) OR TS=(Enduramide)) OR TS=(Nicobion)) OR TS=(Vitamin B 5)) OR TS=(Zinc Pantothenate)) OR TS=(Calcium Pantothenate)) OR TS=(Pantothenic Acid)) OR TS=(Vitamin B6)) OR TS=(Vitamin H)) OR TS=(Deacura)) OR TS=(Gabunat)) OR TS=(Medebiotin)) OR TS=(Biodermatin)) OR TS=(Biotin Gelfert)) OR TS=(Biotin Hermes)) OR TS=(Rombellin)) OR TS=(Vitamin M)) OR TS=(Vitamin B9)) OR TS=(Pteroylglutamic Acid)) OR TS=(Folic Acid)) OR TS=(Folvite)) OR TS=(Folacin)) OR TS=(Folate)) OR TS=(Vitamin B12)) OR TS=(Cyanocobalamin)) OR TS=(Cobalamin)) OR TS=(Eritron)) OR TS=(Ascorbic Acid)) OR TS=(Vitamin C)) OR TS=(Hybrin)) OR TS=(Magnorbin)) OR TS=(Sodium Ascorbate)) OR TS=(Ferrous Ascorbate)) OR TS=(Magnesium Ascorbate)) OR TS=(Magnesium di-L-Ascorbate)
#3	#1 OR #2
#4	((((((((((((((((((((((TS=(diabetes)) OR TS=(diabetes mellitus)) OR TS=(T2DM)) OR TS=(hyperglycemi)) OR TS=(hyperglycaemia)) OR TS=(glucose)) OR TS=(HbA1c)) OR TS=(hemoglobin A1c)) OR TS=(glycated hemoglobin)) OR TS=(insulin resistance)) OR TS=(insulin sensitivity)) OR TS=(HOMA)) OR TS=(HOMA-IR)) OR TS=(glucose homeostasis)) OR TS=(insulin secretion)) OR TS=(insulin)) OR TS=(beta-cell function)) OR TS=(glycemic control)) OR TS=(glucose tolerance)) OR TS=(glucose metabolism)) OR TS=(homeostatic model assessment)) OR TS=(fasting blood sugar)) OR TS=(FBS)) OR TS=(OGTT)
#5	#3 AND #4
#6	(TS=(meta analyses*)) OR TS=(systematic review*)
#7	#5 AND #6
Cochrane Library	
#1	MeSH descriptor: [Vitamins] explode all trees
#2	MeSH descriptor: [Vitamin B Complex] explode all trees
#3	MeSH descriptor: [Antioxidants] explode all trees
#4	MeSH descriptor: [Biotin] explode all trees
#5	MeSH descriptor: [Folic Acid] explode all trees
#6	MeSH descriptor: [Formyltetrahydrofolates] explode all trees
#7	MeSH descriptor: [Inositol] explode all trees
#8	MeSH descriptor: [Leucovorin] explode all trees
#9	MeSH descriptor: [Niacin] explode all trees
#10	MeSH descriptor: [Niacinamide] explode all trees
#11	MeSH descriptor: [Nicorandil] explode all trees
#12	MeSH descriptor: [Nicotinic Acids] explode all trees
#13	MeSH descriptor: [Pyridoxal] explode all trees
#14	MeSH descriptor: [Pyridoxal Phosphate] explode all trees
#15	MeSH descriptor: [Pyridoxamine] explode all trees
#16	MeSH descriptor: [Pyridoxine] explode all trees
#17	MeSH descriptor: [Riboflavin] explode all trees
#18	MeSH descriptor: [Tetrahydrofolates] explode all trees
#19	MeSH descriptor: [Thiamine] explode all trees
#20	MeSH descriptor: [Thioctic Acid] explode all trees
#21	MeSH descriptor: [Vitamin B 12] explode all trees
#22	MeSH descriptor: [Vitamin B 6] explode all trees
#23	MeSH descriptor: [Ascorbic Acid] explode all trees
#24	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25	((thiamin*) or (niacin*) or (riboflavin*) or (folic acid) or (folate*) or (cobalamin*) or (biotin*) or (neurobion*) or (pantothenic acid*) or (pyridox*) or (vitamin b*)):ti,ab,kw AND ("ascorbic acid" or "vitamin C" or "L-Ascorbic Acid" or "Acid, L-Ascorbic" or "L Ascorbic Acid" or " Hybrin" or "Magnorbin" or "Sodium Ascorbate" or " Ascorbate, Sodium" or " Ascorbic Acid, Monosodium Salt' or "Ferrous Ascorbate' or " Ascorbate, Ferrous" or "Magnesium Ascorbate" or "Ascorbate, Magnesium" or "Magnesium di-L-Ascorbate" or "Magnesium di L Ascorbate" or "di-L-Ascorbate, Magnesium" or "Magnesium Ascorbicum"):ti,ab,kw (Word variations have been searched)
#26	#24 or #25
#27	MeSH descriptor: [Diabetes Mellitus] explode all trees
#28	MeSH descriptor: [Hyperglycemia] explode all trees

Supplementary Table 1. Search strategy (cont.)

Database	
Cochrane Library	
#29	MeSH descriptor: [Glycemic Control] explode all trees
#30	MeSH descriptor: [Blood Glucose] explode all trees
#31	MeSH descriptor: [Glucose Tolerance Test] explode all trees
#32	MeSH descriptor: [Glycated Hemoglobin A] explode all trees
#33	#26 or #27 or #28 or #29 or #30 or #31 or #32
#34	("diabetes" OR "diabetes mellitus" OR "T2DM" OR "hyperglycemia" OR "hyperglycaemia glucose" OR "HbA1c" OR "hemoglobin A1c" OR "glycated hemoglobin" OR "insulin resistance" OR "insulin sensitivity" OR "HOMA" OR "HOMA-IR" OR "glucose homeostasis" OR "insulin secretion" OR "insulin" OR "beta-cell function" OR "glycemic control" OR "glucose tolerance" OR "glucose metabolism" OR "homeostatic model assessment" OR "fasting blood sugar" OR "FBS" OR "OGTT"):ti,ab,kw
#35	#33 or #34
#36	#34 and #35
#37	Filters: Reviews; published in the last 10 years

TWI: total water intake; TDF: total drinking fluids; WFF: water from food; EFI: exercise-related fluid intake; NEFI: non-exercise-related fluid intake.
Values were shown as medians (QR).
[*]$p<0.05$ there were statistically significant differences between different PAEE or MET groups; [**]$p<0.05$ there was statistically significant trend with the PAEE or MET level increase.
[†]$p<0.05$ compared with Gp1; [‡]$p<0.05$ compared with Gp2; [§]$p<0.05$ compared with Gm1; [¶]$p<0.05$ compared with Gm2; [††]$p<0.05$ compared with Gm3.

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin B-1			
Arti Muley, 2022 [48]	Rabbani N, 2009	T2DM	40
	González-Ortiz M, 2011	T2DM or overweight or obesity	24 (12/12)
	Alaei Shahmiri F, 2013	hyperglycemic subjects	17
Vitamin B-3			
Yi Ding, 2015 [46]	Pang, 2014	T2DM	(12/12)
	MacLean, 2011	T2DM	(298/277)
	Hamilton, 2010	T2DM	(7/8)
	Sorrentino, 2010	T2DM	(15/15)
	Fazio, 2010	MetS	(58/31)
	Elam, 2000	DM	(49/55)
	Garg, 1990	T2DM	(13/13)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin B-1							
Arti Muley, 2022 [48]	Unequal distribution	300 mg/day	3months	placebo	parallel	Pakistan	JBI, 24/26
	Unequal distribution	150 mg/day	1months	placebo	parallel	Mexico	JBI, 23/26
	Unequal distribution	100 mg/day	3weeks	placebo	crossover	Australia	JBI, 25/26
Vitamin B-3							
Yi Ding, 2015 [46]	NR	1-2 g/day	12weeks	Rosuvastatin	Crossover	Australia	Cochrane, poor
	NR	1-3 g/day	36weeks	Placebo with lipid-modifying regimen	Parallel; DB	USA	Cochrane, poor
	NR	1500 mg/day	20weeks	Statin	Parallel; SB	Australia	Cochrane, poor
	NR	500-1500 mg/day	3months	placebo	Parallel	Switzerland	Cochrane, poor
	NR	500-2000 mg/day	64weeks	E/S (10/20 mg)	Parallel; DB	USA	Cochrane, poor
	NR	1500-3000 mg/day	18weeks	placebo	Parallel; DB	USA	NR
	NR	150-4500 mg/day	8weeks	placebo	Crossover	USA	Cochrane, poor

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin B-3			
Dan Xiang, 2020 [47]	Garg, 1990	T2DM	13/13
	Elam 2000	T2DM	64/61
	Hamilton 2010	T2DM	7/8
	Sorrentino 2010	T2DM	15/15
	Pang 2014	T2DM	12/12
	Goldberg 2016	T2DM	547/506
Vitamin B-7			
Yujia Zhang, 2022 [37]	Cristina. 2006	T2MD	18 (10/8)
	Cesar . 2007	T2MD	348 (226/122)
	Armida,2004	T2MD	15 (10/5)
	Gregory,2006	T2MD	36 (20/16)
	Masaru,1993	T2MD	28 (18/10)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin B-3							
Dan Xiang, 2020 [47]	26M/F	4.5 g/d	8.0wk	Placebo	Crossover	US	Jadad, poor
	109M/16F	3000 mg/d	18.0weeks	Placebo	Parallel; DB	US	Jadad, good
	NR	1500 mg/d	20.0weeks	Statin	Parallel; DB	Australia	Jadad, poor
	0M/30F	1500 mg/d	3.0months	Placebo	Parallel; DB	Switzerland	Jadad, poor
	58.8%M	NR	12.0week	Rosuvastatin	Crossover	Australia	Jadad, poor
	1053M	NR	12.0months	Simvastatin/ezetimibe	Parallel; DB	USA and Canada	Jadad, good
Vitamin B-7							
Yujia Zhang, 2022 [37]	11/7	15mg/day	28days	PC	parallel	Mexico	Cochrane, good
	140/208	2mg/day	90days	PC	parallel	United States	Cochrane, good
	NR	6.14μmol/d	28days	PC	parallel	Mexico	Cochrane, good
	NR	2mg/day	4weeks	PC	parallel	USA	Cochrane, fair
	NR	9mg/day	NR	PC	parallel	Japan	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Gargari, 2011	Overweight and obese men with type 2 diabetes	48 (24/24)
	Cagnacci, 2009	Postmenopausal	30 (15/15)
	Mangoni, 2005	T2DM	26 (13/13)
	Moens, A.L, 2007	Acute myocardial infarction	40 (20/20)
	Aarsand, 1998	T2DM	28 (14/14)
	Doshi, 2001	Coronary artery disease	50 (50/50)
	Doshi, 2002	Coronary artery disease	33
	Sheu, 2005	Obese women	74 (36/38)
	Villa, 2005	Postmenopausal	20 (10/10)
	Moat, 2006 (A)	Coronary artery disease	59 (30/15)
	Moat, 2006 (B)	Coronary artery disease	54 (25/14)
	Solini, 2006	Overweight subjects	60 (30/30)
	Title, 2006	T2DM	19 (19/19)
	Mao, 2008 (A)	Mild to moderate primary hypertension	295 (146/75)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin B-9							
Omid Asbaghi, 2021 [39]	48M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	30F	15mg/d	3weeks	PC	parallel; DB	Italy	Cochrane, good
	14/12	5mg/d	4weeks	PC	parallel; DB	Australia	Cochrane, fair
	35/5	10mg/d	6weeks	PC	crossover; DB	Belgium	Cochrane, good
	21/7	0.25mg/d	12weeks	PC	parallel; DB	Norway	Cochrane, fair
	44/6	5mg/d	6weeks	PC	parallel	United Kingdom	Cochrane, fair
	30/3	5mg/d	6weeks	PC	crossover	United Kingdom	Cochrane, fair
	74F	5mg/d	12weeks	PC	parallel; DB	Taiwan	Cochrane, good
	20F	7.5mg/d	8weeks	PC	parallel	Italy	Cochrane, fair
	52/7	0.4mg/d	6weeks	PC	parallel; DB	USA	Cochrane, good
	46/8	5mg/d	6weeks	PC	parallel; DB	USA	Cochrane, good
	19/41	2.5mg/d	12weeks	PC	parallel	Italy	Cochrane, fair
	9/10	10mg/d	2weeks	PC	crossover; DB	Canada	Cochrane, good
	120/175	0.4mg/d	8weeks	No intervention	parallel; DB	China	Cochrane, good

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Mao, 2008 (B)	Mild to moderate primary hypertension	297 (148/74)
	Palomba, 2010	Polycystic ovary syndrome	47 (23/24)
	Aghamohammad, 2011	T2DM	68 (34/34)
	Grigoletti, 2013	HIV-infected individuals	30 (15/15)
	Asemi, 2014 (A)	Overweight women with polycystic ovary syndrome	81 (27/14)
	Asemi, 2014 (B)	Overweight women with polycystic ovary syndrome	81 (27/13)
	Asemi, 2016	Cervical intraepithelial neoplasia grade 1	58 (29/29)
	Hashemi, 2016	Pre-eclamptic patients	85 (43/42)
	Qin, 2016	Hypertension	20030 (10014/10016)
	Talari, 2016	Metabolic syndrome	60 (30/30)
	Li Y, 2017 (A)	Diabetics	1636 (800/836)
	Li Y, 2017 (B)	Nondiabetics	11435 (5711/5724)
	Bahmani, 2018	Endometrial hyperplasia	60 (30/30)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin B-9							
Omid Asbaghi, 2021 [39]	126/171	0.8mg/d	8weeks	No intervention	parallel; DB	China	Cochrane, good
	47F	0.4mg/d	25weeks	PC	parallel; DB; non-random	Italy	Cochrane, good
	68M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	14/16	5mg/d	4weeks	PC	parallel; DB	Brazil	Cochrane, good
	81F	1mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	81F	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	58F	5mg/d	25weeks	PC	parallel; DB	Iran	Cochrane, good
	85F	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	8295/11735	0.8mg/d	234 days	No intervention	parallel; DB	China	Cochrane, good
	26/34	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, good
	585/1051	0.8mg/d	229days	No intervention	parallel; DB	China	NR
	4444/6991	0.8mg/d	229days	No intervention	parallel; DB	China	NR
	60F	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, good

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin B-9			
Maryam Akbari, 2018 [16]	Gargari BP, 2011	Overweight and obese men with type 2 diabetes	48 (24/24)
	Mangoni AA, 2005	T2DM	26 (13/13)
	Asemi Z, 2014	Women with polycystic ovary syndrome	54 (27/27)
	Talari HR, 2016	Patients with metabolic syndrome	60 (30/30)
	Khiavi A, 2011	T2DM	64 (34/34)
	Setola E, 2004	Patients with metabolic syndrome	50 (25/25)
	Solini A, 2006	Overweight subjects	60 (30/30)
	Title LM, 2006	T2DM	38 (19/19)
	Doshi SN, 2002	Patients with coronary artery disease	33 (16/17)
	Sheu WH-H, 2005	Obese women	74 (36/38)
Zhao JV, 2018 [40]	Talari, 2016	With type 2 diabetes at baseline； Overweight and stable CHD	60 (30/30)
	Qin, 2016	Hypertension	15951 (7960/7991)
	Asemi, 2016	Cervical intraepithelial neoplasia grade 1	58 (29/29)
	Asemi, 2014	Overweight or obesity, and PCOS	54 (27/27)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin B-9							
Maryam Akbari, 2018 [16]	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, fair
	NR	5mg/d	4weeks	PC	parallel; DB	Australia	Cochrane, poor
	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, poor
	NR	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, poor
	NR	5mg/d	8weeks	PC	NR	Iran	Cochrane, fair
	NR	Folate plus vitamins B6 or B12, 5mg/d	8weeks	PC	parallel; DB	Italy	Cochrane, fair
	NR	2.5mg/d	12weeks	PC	NR	Italy	Cochrane, poor
	NR	10mg/d	2weeks	PC	crossover	Canada	Cochrane, poor
	NR	5mg/d	6weeks	PC	NR	UK	Cochrane, fair
	NR	5mg/d	12weeks	PC	parallel; DB	Taiwan	Cochrane, fair
Zhao JV, 2018 [40]	both	5mg/d	12weeks	placebo	parallel	Iran	Cochrane, good
	both	0.8mg/d	4.5years	placebo	parallel	China	Cochrane, fair
	58F	5mg/d	6months	placebo	parallel	Iran	Cochrane, fair
	54F	1mg/d	8weeks	placebo	parallel	Iran	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin B-9			
Zhao JV, 2018 [40]	Gargari, 2011	With type 2 diabetes at baseline、Overweight	48 (24/24)
	Liu, 2011	With type 2 diabetes at baseline、BMI≥22 kg/m2	182 (92/90)
	Kurt, 2010	Vitamin B12 deficiency	44 (24/20)
	Mashavi, 2008	T2DM	57 (28/29)
	Mao, 2008	Baseline fasting glucose≥6.1	60 (28/32)
	Gu, 2008	T2DM	60 (30/30)
	Solini, 2006	NO	60 (30/30)
	Title, 2006	T2DM	38 (19/19)
	Mangoni, 2005	type 2 diabetes, microalbuminuria	26 (13/13)
	Villa, 2005	NO	20 (10/10)
	Setola, 2004	metabolic syndrome, hyperinsulinemia	50 (25/25)
	Masaru,1993	T2MD	28 (18/10)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin B-9							
Zhao JV, 2018 [40]	48M	5mg/d	8weeks	placebo	parallel	Iran	Cochrane, fair
	both	0.15mg/d	6months	placebo	parallel	China	Cochrane, good
	both	5mg/d	8weeks	placebo	parallel	Turkey	Cochrane, fair
	both	1mg/d	4months	placebo	parallel	Israel	Cochrane, good
	both	0.8mg/d	8weeks	placebo	parallel	China	Cochrane, good
	both	5mg/d	2weeks	placebo	parallel	China	Cochrane, fair
	both	2.5mg/d	12weeks	placebo	parallel	Italy	Cochrane, poor
	both	10mg/d	2 weeks	placebo	Crossover	Canada	Cochrane, good
	both	5mg/d	4weeks	placebo	parallel	UK	Cochrane, good
	20F	7.5mg/d	8weeks	placebo	parallel	Italy	Cochrane, poor
	both	5mg/day	2months	placebo	parallel	Italy	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin C			
Asma Kazemi, 2022 [43]	Tousoulis, 2007	T2DM	(13/13)
	Nayaka, 2013	T2DM	30
	Ghaffari, 2015	T2DM	(17/14)
	Bishop, 1984	Diabetic Hyperlipidemia,25/25	25/25
	Dakhale, 2011	T2DM	33
	Siavash, 2014	T2DM	15/15
	Lu, 2005	T2DM	17
	Gillani, 2017	T2DM	139/142
	Bhatt, 2012	T2DM	30/29
	Devanandan, 2020	T2DM	68/67
	Kunsongkeit, 2019	T2DM	15/16
	Mason, 2018	T2DM	27/ 27/ 27
	El-Aal, 2018	T2DM	10/10
	Ramzy Ragheb, 2020	T2DM	20/13

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin C							
Asma Kazemi, 2022 [43]	NR	2g/day	4weeks	No intervention	Parallel	Greece	Cochrane, poor
	NR	1g/d	8weeks	Placebo	Parallel	India	Cochrane, poor
	NR	800 mg/d	8weeks	Placebo	Parallel	Iran	Cochrane, poor
	NR	500mg/d	52weeks	Placebo	Cross-over	UK	Cochrane, poor
	NR	1000mg/d	12weeks	Placebo	Parallel	India	Cochrane, fair
	NR	1000mg	6weeks	No intervention	Parallel	Iran	Cochrane, poor
	NR	3g/d	2weeks	Placebo	Cross-over	Sweden	Cochrane, poor
	NR	500mg/d	52weeks	Placebo	Parallel	Saudi Arabia	Cochrane, poor
	NR	500mg/d	12weeks	Placebo	Parallel	Oman	Cochrane, poor
	NR	500mg/d	36weeks	Placebo	Parallel	India	Cochrane, poor
	NR	500mg/d	8weeks	Placebo	Parallel	Thailand	Cochrane, poor
	NR	1000mg/d	17weeks	Placebo	Parallel	Australia	Cochrane, good
	20M	800mg/d	12weeks	Placebo	Parallel	Palestine	Cochrane, poor
	NR	500mg/d	8weeks	placebo	Parallel	Egypt	Cochrane

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin C			
Asma Kazemi, 2022 [43]	Sanguanwong, 2016	T2DM	50
	Froghi, 2018	T2DM	21/21
	Chen, 2006	T2DM	15/17
	Paolisso, 1995	T2DM	40
Ozra Tabatabaei-Malazy, 2014 [45]	Bhatt J, 2012	T2DM	30/29
	Shakouri, 2011	T2DM	32/33
	Delvarianzadeh M, 2008	T2DM	68/68
	Farvid M, 2000 (A)	diabetics	28/28
	Farvid M, 2000 (B)	diabetics	26/23
Shaun A. Mason, 2021 [42]	Bhatt, 2012	T2DM	59 (30/29)
	Hui Chen, 2006	T2DM	32(15/17)
	Dakhale, 2011	T2DM	70(35/35)
	Devanandan, 2020	T2DM	135(68/67)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin C							
Asma Kazemi, 2022 [43]	NR	1000mg/d	8weeks	Placebo	Parallel	Thailand	Cochrane, fair
	NR	500mg/d	8weeks	Placebo	Parallel	Iran	Cochrane, poor
	NR	800mg/d	4weeks	Placebo	Parallel	USA	Cochrane, poor
	both	1000 mg/d	12 weeks	Placebo	Cross-over	Italy	Cochrane, poor
Ozra Tabatabaei-Malazy, 2014 [45]	NR	500mg/d, AA	3month	placebo	open label; cross over	NR	Jadad, good
	65M	200mg/d, AA	8weeks	500mg/d; EPA	DB; cross over	Iran	Jadad, good
	NR	1250mg/d, AA	3month	placebo	DB; cross over	NR	Jadad, good
	NR	500mg/d, AA	4weeks	placebo, VE	crossover	NR	Jadad, good
	NR	500mg/d, AA	9weeks	placebo, VE	crossover	NR	Jadad, good
Shaun A. Mason, 2021 [42]	42/17	500mg/day	90days	active control	parallel	India	Cochrane, poor
	13/19	800mg/day	28days	placebo	parallel; DB	US	Cochrane, fair
	28/38	1000mg/day	84days	placebo	parallel; DB	India	Cochrane, good
	84/51	1000mg/day	270days	placebo	parallel	India	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin C			
Shaun A. Mason, 2021 [42]	El-Aal, 2018	T2DM	40(10/10/10/10)
	Foroghi, 2018	T2DM	78(38/40)
	Ghaffari, 2015	T2DM	31(17/14)
	Gillani, 2017	T2DM	304(152/152)
	Kunsongkeit, 2019	T2DM	31(15/16)
	Lu, 2005	T2DM	(17/17)
	Mahmoudabadi, 2011	T2DM	34(17/17)
	Mason, 2016	T2DM	(7/7)
	Mason, 2019	T2DM	(27/27)
	Paolisso, 1995	T2DM	（40/40）
	Rafighi, 2013	T2DM	84(44/40)
	Dakhale, 2011	T2DM	70(35/35)
	Devanandan, 2020	T2DM	135(68/67)
	Ragheb, 2020	T2DM	33(20/13)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin C							
Shaun A. Mason, 2021 [42]	40M	1000mg/day	90days	placebo	parallel	Palestine	Cochrane, poor
	41/37	500mg/day	60days	placebo	parallel; DB	Iran	Cochrane, fair
	13/18	800mg/day	60days	placebo	parallel	Iran	Cochrane, fair
	183/121	500mg/day	365days	placebo	parallel	Malaysia	Cochrane, poor
	9/22	500mg/day	60days	placebo	crossover; DB	Thailand	Cochrane, poor
	12/5	3000mg/day	14days	placebo	crossover; DB	Sweden	Cochrane, fair
	34M	200mg/day	56days	placebo	parallel; DB	Iran	Cochrane, fair
	12/1	1000mg/day	120days	placebo	crossover; DB	Australia	Cochrane, fair
	26/5	1000mg/day	120days	placebo	crossover; DB	Australia	Cochrane, good
	19/21	1000mg/day	120days	placebo	crossover; DB	Italy	Cochrane, fair
	44/40	800mg/day	90 days	placebo	parallel	Iran	Cochrane, fair
	28/38	1000mg/day	84days	placebo	parallel; DB	India	Cochrane, good
	84/51	1000mg/day	270days	placebo	parallel	India	Cochrane, fair
	10/23	500mg/day	56days	only received anti-diabetes treatment	parallel	Egypt	Cochrane, poor

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin C			
Shaun A. Mason, 2021 [42]	Rekha, 2013	T2DM	(55/28)
	Sanguanwong, 2016	T2DM	(50/50)
	Siavash, 2014	T2DM	30(15/15)
	Tousoulis, 2007	T2DM	26(13/13)
Yoonhye Kim, 2022[25]	Hui Chen, 2006	T2DM	(15/17)
	Ali Abd El-Aal, 2018	T2DM	(10/10)
	Ganesh, 2011	T2DM	(35/35)
	M Evans, 2003	T2DM	20(10/10)
	Ghaffari, 2015	T2DM	（17/14）
	Mahmoudabadi, 2014	T2DM	40(20/20)
	Mason, 2019	T2DM	(27/27)
	Paolisso, 1995	T2DM	(40/40)
	Rekha, 2013	T2DM	(30/30)
	Sanguanwong, 2016	T2DM	(50/50)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin C							
Shaun A. Mason, 2021 [42]	NS	1000 or 2000mg/day	56days	active cotrol	parallel	India	Cochrane, poor
	NS	1000mg/day	60days	placebo	parallel; DB	Thailand	Cochrane, fair
	12/18	1000mg/day	42days	active cotrol	parallel	Iran	Cochrane, fair
	14/12	200mg/day	28days	active cotrol	parallel	Greece	Cochrane, poor
Yoonhye Kim, 2022[25]	NR	800mg/day	4weeks	PC	parallel; DB	USA	Cochrane, poor
	NR	1000mg/day	12weeks	PC	parallel	USA	Cochrane, fair
	NR	1000mg/day	12weeks	PC	parallel; DB	India	Cochrane, good
	17/3	1000mg/day	6weeks	PC	parallel	UK	Cochrane, fair
	NR	800mg/day	8weeks	placebo	parallel	NR	Cochrane, poor
	40M	200mg/day	8weeks	placebo	parallel; DB	Iran	Cochrane, fair
	NR	1000mg/day	16weeks	placebo	crossover; DB	Australia	Cochrane, fair
	NR	1000mg/day	16weeks	placebo	crossover; DB	Italy	Cochrane, fair
	NR	1000mg/day	8weeks	placebo	parallel	NR	Cochrane, poor
	NR	1000mg/day	8weeks	placebo	parallel; DB	NR	Cochrane, poor

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin C			
Yoonhye Kim, 2022[25]	Bhatt JK, 2012	T2DM	(33/32)
	Ellulu MS, 2015	T2DM	(36/36)
AW Ashor, 2017 [44]	Ganesh, 2011	T2DM	(33/33)
	Ellulu, 2015	T2DM	(31/33)
	Tousoulis, 2007	T2DM	26 (13/13)
	Hui Chen, 2006	T2DM	32 (17/15)
	Mahmoudabadi, 2011	T2DM	34 (17/17)
	Zahra Rafighi, 2013	T2DM	170
	Mansour Siavash, 2014	T2DM	35 (20/15)
	Shaun A Mason, 2016	T2DM	14 (7/7)
	Davison, 2008 (B)	T1DM	26
	F Klein, 1995	T1DM	24 (12/12)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin C							
Yoonhye Kim, 2022[25]	NR	500mg/day	12weeks	PC	parallel	NR	Cochrane, poor
	NR	1000mg/day	8weeks	PC	parallel	Malaysia	Cochrane, fair
AW Ashor, 2017 [44]	28/33	1000mg/day	84days	placebo	parallel; DB	India	Jadad, 3
	22/50	1000mg/day	56days	No intervention	parallel	Malaysia	Jadad, 4
	14/12	2000mg/day	30days	No intervention	parallel	Athens, Greece	Jadad, 3
	13/19	800mg/day	28days	placebo	parallel; DB	USA	Jadad, 5
	34M	200mg/day	56days	placebo	parallel; DB	Iran	Jadad, 3
	40/39	VC: 800mg/day; vitamin C (266.7 mg), vitamin E (300 IU), vitamin C+E (300IU+266.7mg)	90 days	placebo	parallel	Iran	Jadad, 4
	12/23	1000mg/day	42days	600 mg gemfibrozil	parallel	Iran	Jadad, 2
	12/2	1000mg/day	120days	placebo	crossover; DB	Australia	Jadad, 5
	12M	1000mg/day	1days	placebo	parallel; DB	UK	Jadad, 3
	24M	6000mg/day	28days	placebo	parallel; DB	Denmark	Jadad, 3

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin C			
AW Ashor, 2017 [44]	Bhatt JK, 2012	T2DM	59
	Gutierrez AD, 2013	Healthy	28
	Ghaffari , 2015	T2DM	31
	N Bishop, 1985 (B)	T2DM	25
	N Bishop, 1985 (A)	T2DM	50
	C S Johnston, 1994	Healthy	9
	L Pirbudak, 2004	Healthy	22 (11/11)
	G W Davison, 2008 (A)	Healthy	26
	Johannes Pleiner, 2002	Healthy	10
	Simona Bo, 2007	Healthy	78 (40/38)
	N Gokce, 1999	CAD	46 (21/25)
	Brian A Mullan, 2005	Healthy	9
	David C Nieman, 1985	Healthy	28 (15/13)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin C							
AW Ashor, 2017 [44]	17/42	500mg/day	90 days	placebo	parallel	NR	Jadad, 2
	5/9	1000 mg/day	120days	placebo	Parallel	USA	Jadad, 3
	13/17	800mg/day	56days	placebo	Parallel	Iran	Jadad, 2
	11/14	500mg/day	60days	placebo	crossover; DB	UK	Jadad, 3
	13/12	500mg/day	60days	placebo	crossover; DB	UK	Jadad, 3
	2/7	1000mg/day	14days	placebo	crossover; DB	USA	Jadad, 5
	22F	AA 500 mg, fentanyl 1–2 mg/kg and etomidate 0.3–0.4 mg/kg	1days	fentanyl 1–2 mg/kg and etomidate 0.3–0.4 mg/kg	parallel	Turkey	Jadad, 2
	12M	1000mg/day	1days	placebo	parallel; DB	UK	Jadad, 3
	10M	72mg/day	1days	placebo	crossover; DB	Australia	Jadad, 3
	24/54	2000mg/day	14days	No intervention	parallel	Italy	Jadad, 3
	42/4	500mg/day	30days	placebo	DB	USA	Jadad, 3
	9M	2000mg/day	1days	placebo	crossover; DB	UK	Jadad, 3
	NR	1500mg/day	1days	placebo	parallel; DB	USA	Jadad, 4

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
FBG			
Vitamin C			
AW Ashor, 2017 [44]	Bhatt JK, 2012	T2DM	59
	Gutierrez AD, 2013	Healthy	28
	Ghaffari , 2015	T2DM	31
	N Bishop, 1985 (B)	T2DM	25
	N Bishop, 1985 (A)	T2DM	50
	C S Johnston, 1994	Healthy	9
	L Pirbudak, 2004	Healthy	22 (11/11)
	G W Davison, 2008 (A)	Healthy	26
	Johannes Pleiner, 2002	Healthy	10
	Simona Bo, 2007	Healthy	78 (40/38)
	N Gokce, 1999	CAD	46 (21/25)
	Brian A Mullan, 2005	Healthy	9
	David C Nieman, 1985	Healthy	28 (15/13)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
FBG							
Vitamin C							
AW Ashor, 2017 [44]	17/42	500mg/day	90 days	placebo	parallel	NR	Jadad, 2
	5/9	1000 mg/day	120days	placebo	Parallel	USA	Jadad, 3
	13/17	800mg/day	56days	placebo	Parallel	Iran	Jadad, 2
	11/14	500mg/day	60days	placebo	crossover; DB	UK	Jadad, 3
	13/12	500mg/day	60days	placebo	crossover; DB	UK	Jadad, 3
	2/7	1000mg/day	14days	placebo	crossover; DB	USA	Jadad, 5
	22F	AA 500 mg, fentanyl 1–2 mg/kg and etomidate 0.3–0.4 mg/kg	1days	fentanyl 1–2 mg/kg and etomidate 0.3–0.4 mg/kg	parallel	Turkey	Jadad, 2
	12M	1000mg/day	1days	placebo	parallel; DB	UK	Jadad, 3
	10M	72mg/day	1days	placebo	crossover; DB	Australia	Jadad, 3
	24/54	2000mg/day	14days	No intervention	parallel	Italy	Jadad, 3
	42/4	500mg/day	30days	placebo	DB	USA	Jadad, 3
	9M	2000mg/day	1days	placebo	crossover; DB	UK	Jadad, 3
	NR	1500mg/day	1days	placebo	parallel; DB	USA	Jadad, 4

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HbA1C			
Vitamin B-1			
Arti Muley, 2022[48]	Alkhalaf, 2010	T2MD	82
	González-Ortiz, 2011	T2DM or overweight or obesity	24 (12/12)
	Rabbani, 2009	T2MD	40
	Alkhalaf, 2010	T2MD	82
Vitamin B-3			
Dan Xiang, 2020[47]	Garg, 1990	T2DM	13/13
	Elam, 2000	T2DM	64/61
	Hamilton, 2010	T2DM	7, 8
	Sorrentino, 2010	T2DM	15/15
	Pang, 2014	T2DM	547/506
Vitamin B-7			
Yujia Zhang, 2022 [37]	Cesar, 2007	T2MD	348 (226/122)
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Gargari, 2011	Overweight and obese men with type 2 diabetes	48 (24/24)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HbA1C							
Vitamin B-1							
Arti Muley, 2022[48]	77%/33%	900mg/day	12weeks	placebo	parallel	the Netherlands	JBI, 23/26
	NR	150mg/day	1months	placebo	parallel	Mexico	JBI, 23/26
	NR	300mg/day	3months	placebo	parallel	Pakistan	JBI, 24/26
	77%/33%	900mg/day	12weeks	placebo	parallel	the Netherlands	JBI, 23/26
Vitamin B-3							
Dan Xiang, 2020[47]	26M	4.5 g/d	8weeks	placebo	Crossover	US	Jadad, poor
	109M/16F	3000mg/d	18weeks	placebo	Parallel; DB	US	Jadad, good
	15F	1500mg/d	20weeks	Statin	Parallel; DB	Australia	Jadad, poor
	25M/5F	1501mg/d	3month	Placebo	Parallel; DB	Switzerland	Jadad, poor
	874M/179F	NR	12month	Simvastatin/ezetimibe	Parallel; DB	USA and Canada	Jadad, poor
Vitamin B-3							
Yujia Zhang, 2022 [37]	140/208	2mg/day	90 days	PC	parallel	United States	Cochrane, good
Vitamin B-9							
Omid Asbaghi, 2021 [39]	48M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HbA1C			
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Mangoni, 2005	T2DM	26 (13/13)
	Aarsand, 1998	T2DM	28 (14/14)
	Aghamohammadi Khiavi, 2011	T2DM	68 (34/34)
Maryam Akbari, 2018 [16]	Gargari BP, 2011	Overweight and obese men with type 2 diabetes	48 (24/24)
	Mangoni AA, 2005	T2DM	26 (13/13)
	Khiavi A, 2011	T2DM	64 (34/34)
	Alian Z, 2012	T1DM	55 (34/21)
	Mosavi Z, 2015	T2DM	45 (24/21)
	Peña AS, 2004	T1DM	36 (15/21)
Zhao JV, 2018 [40]	Gargari, 2011	With type 2 diabetes at baseline, Overweight	48 (24/24)
	Liu, 2011	With type 2 diabetes at baseline、BMI≥22 kg/m2	182 (92/90)
	Mashavi, 2008	T2DM	57 (28/29)
	Mangoni, 2005	With type 2 diabetes at baseline; Hypertension in 16 patients; microalbuminuria in 8 patients	26 (13/13)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HbA1C							
Vitamin B-9							
Omid Asbaghi, 2021 [39]	14/12	5mg/d	4weeks	PC	parallel; DB	Australia	Cochrane, fair
	21/7	0.25mg/d	12weeks	PC	parallel; DB	Norway	Cochrane, fair
	68M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
Maryam Akbari, 2018 [16]	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, fair
	NR	5mg/d	4weeks	PC	parallel; DB	Australia	Cochrane, poor
	NR	5mg/d	8weeks	PC	NR	Iran	Cochrane, fair
	NR	5mg/d	8weeks	PC	crossover; DB	Iran	Cochrane, poor
	NR	1mg/d	12weeks	PC	NR	Iran	Cochrane, poor
	NR	5mg/d	8weeks	PC	crossover; DB	New Zealand	Cochrane, poor
Zhao JV, 2018 [40]	48M	5mg/d	8weeks	placebo	parallel	Iran	Cochrane, fair
	both	0.15mg/d	6months	placebo	parallel	China	Cochrane, good
	both	1mg/d	4months	placebo	parallel	Israel	Cochrane, good
	both	5mg/d	4weeks	placebo	parallel	UK	Cochrane, good

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HbA1C			
Vitamin B-9			
Patcharaporn Sudchada, 2012[54]	Bahram Pourghassem Gargari, 2011	T2DM	24/24
	Vahide Aghamohammadi, 2011	T2DM	34/34
	Mangoni AA, 2005	T2DM	13/13
Vitamin C			
Asma Kazemi, 2022 [43]	Bishop, 1984	Diabetic Hyperlipidemia	25/25
	Dakhale, 2011	T2DM	33
	Siavash, 2014	T2DM	15/ 15
	Lu, 2005	T2DM	17
	Gillani, 2017	T2DM	139/ 142
	Bhatt, 2012	T2DM	30/29
	Devanandan et al, 2020	T2DM	68/67
	Kunsongkeit, 2019	T2DM	15/16
	Mason, 2018	T2DM	27/ 27/ 27

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HbA1C							
Vitamin B-9							
Patcharaporn Sudchada, 2012[54]	48M	5mg/day	8weeks	Placebo	parallel	Iran	Jadad, good
	68M	5mg/day	8weeks	Placebo	parallel; DB	Iran	Jadad, good
	14M/12F	5mg/day	4weeks	Placebo	parallel; DB	Australia	Jadad, good
Vitamin C							
Asma Kazemi, 2022 [43]	NR	VC, 500 mg/d	52weeks	Placebo	Cross-over	UK	Cochrane, poor
	NR	VC, 1000 mg/d	12weeks	Placebo	Parallel	India	Cochrane, fair
	NR	VC, 1000 mg	6weeks	No intervention	Parallel	Iran	Cochrane, poor
	NR	VC, 3 g/d	2weeks	Placebo	Cross-over	Sweden	Cochrane, poor
	NR	VC, 500 mg/d	52weeks	Placebo	Parallel	Saudi Arabia	Cochrane, poor
	NR	VC, 500 mg/d	12weeks	Placebo	Parallel	Oman	Cochrane, poor
	NR	VC, 500 mg/d	36weeks	Placebo	Parallel	India	Cochrane, poor
	NR	VC, 500 mg/d	8weeks	Placebo	Parallel	Thailand	Cochrane, poor
	NR	VC, 1000 mg/d	17weeks	Placebo	Parallel	Australia	Cochrane, good

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HbA1C			
Vitamin C			
Asma Kazemi, 2022 [43]	El-Aal, 2018	T2DM	10,10
	Sanguanwong, 2016	T2DM	50
	Froghi, 2018	T2DM	21/21
	Chen, 2006	T2DM	15/17
	Paolisso, 1995	T2DM	40
Ozra Tabatabaei-Malazy, 2014 [45]	Bhatt J, 2012	T2DM	30/29
	Shakouri Mahmoudabadi, 2011	T2DM	32/33
	Delvarianzadeh M, 2008	T2DM	68/68
	Farvid M, 2000 (A)	diabetics	28/28
	Farvid M, 2000 (B)	diabetics	26/23
Shaun A. Mason, 2022 [42]	Bhatt, 2012	T2DM	59 (30/29)
	Dakhale, 2011	T2DM	70 (35/35)
	Devanandan, 2020	T2DM	135 (68/67)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HbA1C							
Vitamin C							
Asma Kazemi, 2022 [43]	20 Male	VC, 800 mg/d	12weeks	Placebo	Parallel	Palestine	Cochrane, poor
	NR	VC, 1000 mg/d	8weeks	Placebo	Parallel	Thailand	Cochrane, fair
	NR	VC, 500 mg/d	8weeks	Placebo	Parallel	Iran	Cochrane, poor
	NR	VC, 800 mg/d	4weeks	Placebo	Parallel	USA	Cochrane, poor
	both	1000 mg/d	12 weeks	Placebo	Cross-over	Italy	Cochrane, poor
Ozra Tabatabaei-Malazy, 2014 [45]	NR	500mg/d; AA	3month	placebo	open label; cross over	NR	Jadad, good
	65M	200mg/d; AA	8weeks	500mg/d; EPA	DB; cross over	Iran	Jadad, good
	NR	1250mg/d; AA	3month	placebo	DB; cross over	NR	Jadad, good
	NR	500mg/d; AA	4weeks	placebo, VE	cross over	NR	Jadad, good
	NR	500mg/d; AA	9weeks	placebo, VE	cross over	NR	Jadad, good
Shaun A. Mason, 2022 [42]	42/17	500mg/day	90days	active cotrol	parallel	India	Cochrane, poor
	28/38	1000mg/day	84days	placebo	parallel; DB	India	Cochrane, good
	84/51	1000mg/day	270days	placebo	parallel	India	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HbA1C			
Vitamin C			
Shaun A. Mason, 2022 [42]	El-Aal, 2018	T2DM	40 (10/10/10/10)
	Foroghi, 2018	T2DM	78 (38/40)
	Gillani, 2017	T2DM	304 (152/152)
	Kunsongkeit, 2019	T2DM	31 (15/16)
	Lu, 2005	T2DM	(17/17)
	Mahmoudabadi, 2011	T2DM	34(17/17)
	Mason, 2016	T2DM	(7/7)
	Mason, 2019	T2DM	(27/27)
	Paolisso, 1995	T2DM	(40/40)
	Rafighi, 2013	T2DM	84 (44/40)
	Ragheb, 2020	T2DM	33 (20/13)
	Sanguanwong, 2016	T2DM	(50/50)
	Siavash, 2014	T2DM	30 (15/15)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HbA1C							
Vitamin C							
Shaun A. Mason, 2022 [42]	40M	1000mg/day	90days	placebo	parallel	Palestine	Cochrane, poor
	41/37	500mg/day	60days	placebo	parallel; DB	Iran	Cochrane, fair
	9/22	500mg/day	365days	placebo	parallel	Malaysia	Cochrane, poor
	45191	500mg/day	60days	placebo	crossover; DB	Thailand	Cochrane, poor
	12/5	3000mg/day	14days	placebo	crossover; DB	Sweden	Cochrane, fair
	34M	200mg/day	56days	placebo	parallel; DB	Iran	Cochrane, fair
	12/1	1000mg/day	120days	placebo	crossover; DB	Australia	Cochrane, fair
	26/5	1000mg/day	120days	placebo	crossover; DB	Australia	Cochrane, good
	19/21	1000mg/day	120days	placebo	crossover; DB	Italy	Cochrane, fair
	44/40	800mg/day	90days	placebo	parallel	Iran	Cochrane, fair
	10/23	500mg/day	56days	No	parallel	Egypt	Cochrane, poor
	NS	1000mg/day	60days	placebo	parallel; DB	Thailand	Cochrane, fair
	12/18	1000mg/day	42days	active control	parallel	Iran	Cochrane, poor

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HbA1C			
Vitamin C			
Yoonhye Kim, 2022 [25]	Ali Abd El-Aal, 2018	T2DM	(10/10)
	Ganesh N Dakhale, 2011	T2DM	(35/35)
	Mahmoudabadi, 2014	T2DM	40 (20/20)
	Mason, 2019	T2DM	(27/27)
	Paolisso, 1995	T2DM	(40/40)
	Bhatt JK, 2012	T2DM	(33/32)
	M Evans, 2003	T2DM	20 (10/10)
	Sanguanwong, 2016	T2DM	(50/50)
AW Ashor, 2017[44]	Ganesh N Dakhale, 2011	T2DM	(33/33)
	Mahmoudabadi, 2011	T2DM	34 (17/17)
	Zahra Rafighi, 2011	T2DM	170
	Mansour Siavash, 2014	T2DM	35 (20/15)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HbA1C							
Vitamin C							
Yoonhye Kim, 2022 [25]	NR	1000mg/day	12weeks	PC	parallel	NR	Cochrane, fair
	NR	1000mg/day	12weeks	PC	parallel; DB	India	Cochrane, good
	40M	200mg/day	8weeks	placebo	parallel; DB	Iran	Cochrane, fair
	NR	1000mg/day	16weeks	placebo	crossover; DB	Australia	Cochrane, fair
	NR	1000mg/day	16weeks	placebo	crossover; DB	Italy	Cochrane, fair
	NR	500mg/day	12weeks	PC	parallel	NR	Cochrane, poor
	17/3	1000mg/day	6weeks	PC	parallel	UK	Cochrane, fair
	NS	1000mg/day	60days	placebo	parallel; DB	Thailand	Cochrane, fair
AW Ashor, 2017[44]	28/33	1000mg/day	84days	placebo	parallel; DB	India	Jadad, 3
	34M	200mg/day	56days	placebo	parallel; DB	Iran	Jadad, 3
	40/39	VC: 800mg/day; vitamin C was (266.7 mg), vitamin C+E (300 IU+266.7 mg)	90days	placebo	parallel	Iran	Jadad, 4
	12/23	1000mg/day	42days	600 mg gemfibrozil	parallel	Iran	Jadad, 2

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HbA1C			
Vitamin C			
AW Ashor, 2017[44]	Shaun A Mason, 2016	T2DM	14 (7/7)
	Bhatt JK, 2012	T2DM	59
	N Bishop, 1985（A）	T2DM	25
	N Bishop, 1985（B）	T2DM	25
	F Klein, 1995	T1DM	24 (12/12)
	Joíza L Camargo, 2006	Healthy	14 (7/7)
HOMA-IR			
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Kilicdag, 2005	Polycystic ovarian syndrome patients	31(17/14)
	Sheu, 2005	Obese women	74(36/38)
	Solini, 2006	Overweight subjects	60(30/30)
	Cagnacci, 2009	Postmenopausal	30(15/15)
	Palomba, 2010	Polycystic ovary syndrome	47(23/24)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HbA1C							
Vitamin C							
AW Ashor, 2017[44]	12/2	1000mg/day	120days	placebo	crossover; DB	Australia	Jadad, 5
	17/42	500mg/day	90days	NR	parallel	NR	Jadad, 2
	11/14	500mg/day	60days	placebo	crossover; DB	UK	Jadad, 3
	13/12	500mg/day	60days	placebo	crossover; DB	UK	Jadad, 3
	24M	6000mg/day	28days	placebo	parallel; DB	Denmark	Jadad, 3
	5/9	1000mg/day	120days	No intervention	parallel	Brazil	Jadad, 5
HOMA-IR							
Vitamin B-9							
Omid Asbaghi, 2021 [39]	31F	0.348mg/d	12weeks	No intervention	parallel	Turkey	Jadad, 3
	74F	5mg/d	12weeks	PC	parallel; DB	Taiwan	Jadad, 3
	19/41	2.5mg/d	12weeks	PC	parallel	Italy	Jadad, 4
	30F	15mg/d	3weeks	PC	parallel; DB	Italy	Jadad, 2
	47F	0.4mg/d	25weeks	PC	parallel; DB; non-random	Italy	

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HOMA-IR			
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Gargari, 2011	Overweight and obese men with type 2 diabetes	48(24/24)
	Aghamohammadi Khiavi, 2011	T2DM	68(34/34)
	Asemi, 2014 (A)	Overweight women with polycystic ovary syndrome	81(27/14)
	Asemi, 2014 (B)	Overweight women with polycystic ovary syndrome	81(27/13)
	Asemi, 2016	Cervical intraepithelial neoplasia grade 1	58(29/29)
	Talari, 2016	Metabolic syndrome	60(30/30)
	Bahmani, 2018	Endometrial hyperplasia	60(30/30)
Maryam Akbari, 2018 [16]	Gargari BP, 2011	Overweight and obese men with type 2 diabetes	48(24/24)
	Asemi Z, 2014	Women with polycystic ovary syndrome	54(27/27)
	Talari HR, 2016	Patients with metabolic syndrome	60(30/30)
	Khiavi A, 2011	T2DM	64(34/34)
	Setola E, 2004	Patients with metabolic syndrome	50(25/25)
	Solini A, 2006	Overweight subjects	60(30/30)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HOMA-IR							
Vitamin B-9							
Omid Asbaghi, 2021 [39]	48M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	68M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	81F	1mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	81F	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	58F	5mg/d	25weeks	PC	parallel; DB	Iran	Cochrane, good
	26/34	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, good
	60F	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, good
Maryam Akbari, 2018 [16]	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, poor
	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, poor
	NR	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, poor
	NR	5mg/d	8weeks	PC	NR	Iran	Cochrane, fair
	NR	Folate plus vitamins B6 or B12，5mg/d	8weeks	PC	parallel; DB	Italy	Cochrane, fair
	NR	2.5mg/d	12weeks	PC	NR	Italy	Cochrane, poor

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HOMA-IR			
Vitamin B-9			
Maryam Akbari, 2018 [16]	Sheu WH-H, 2005	Obese women	74(36/38)
	Dehkordi EH, 2016	Overweight and obese children and adolescents	39(20/19)
	Kilicdag EB, 2005	Women with polycystic ovary syndrome	31(14/17)
Zhao JV, 2018[40]	Talari, 2016	With type 2 diabetes; Overweight and stable CHD	60(30/30)
	Asemi, 2016	Cervical intraepithelial neoplasia grade 1	58(29/29)
	Asemi, 2014	Overweight or obesity, and PCOS	54(27/27)
	Gargari, 2011	With type 2 diabetes at baseline; Overweight	48(24/24)
	Kurt, 2010	Vitamin B12 deficiency	44(24/20)
	Solini, 2006	NO	60(30/30)
	Setola, 2004	With metabolic syndrome and hyperinsulinemia	50(25/25)
	Cagnacci, 2015	NO	30(15/15)
	Kilicdag, 2005	PCOS	40(20/20)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HOMA-IR							
Vitamin B-9							
Maryam Akbari, 2018 [16]	NR	5mg/d	12weeks	PC	parallel; DB	Taiwan	Cochrane, fair
	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, fair
	NR	2.5mg/d	12weeks	PC	NR	Turkey	Cochrane, poor
Zhao JV, 2018[40]	both	5mg/d	12weeks	placebo	parallel	Iran	Cochrane, good
	58F	5mg/d	6months	placebo	parallel	Iran	Cochrane, fair
	54F	1mg/d	8weeks	placebo	parallel	Iran	Cochrane, fair
	48M	5mg/d	8weeks	placebo	parallel	Iran	Cochrane, fair
	both	5mg/d	8weeks	placebo	parallel	Turkey	Cochrane, fair
	both	2.5mg/d	12weeks	placebo	parallel	Italy	Cochrane, poor
	both	5mg/day	2months	placebo	parallel	Italy	Cochrane, fair
	30F	15mg/d	3weeks	placebo	parallel	Italy	Cochrane, good
	40F	0.35mg/day	3months	placebo	parallel	Turkey	Cochrane, good

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HOMA-IR			
Vitamin C			
Mehrnoosh Khodaeian, 2015 [78]	Chen, 2006	T2DM	NR
	Evans, 2003	T2DM	NR
	Paolisso, 1995	T2DM	NR
Asma Kazemi, 2022 [43]	Ramzy Ragheb, 2020	T2DM	20/13
	Sanguanwong, 2016	T2DM	50
	Froghi, 2018	T2DM	21/21
	Chen, 2006	T2DM	15/17
Shaun A. Mason, 2022 [42]	Ragheb, 2020	T2DM	33(20/13)
	El-Aal, 2018	T2DM	40(10/10/10/10)
	Foroghi, 2018	T2DM	78(38/40)
	Sanguanwong, 2016	T2DM	(50/50)
	Hui Chen, 2006	T2DM	32(15/17)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HOMA-IR							
Vitamin C							
Mehrnoosh Khodaeian, 2015 [78]	both	800 mg/d	4weeks	Placebo	DB	USA	Jadad, 4 good
	both	1000 mg/d VC + 0.2 IU/kg insulin Lispro	6weeks	Placebo + 0.2 IU/kg insulin Lispro	DB	UK	Jadad, 1 poor
	both	1000 mg /d	16w/4 w wash out	Placebo	DB	Italy	Jadad, 3 good
Asma Kazemi, 2022 [43]	NR	VC, 500 mg/d	8weeks	placebo	Parallel	Egypt	Cochrane
	NR	VC, 1000 mg/d	8weeks	Placebo	Parallel	Thailand	Cochrane, fair
	NR	VC, 500 mg/d	8weeks	Placebo	Parallel	Iran	Cochrane, poor
	NR	VC, 800 mg/d	4weeks	Placebo	Parallel	USA	Cochrane, poor
Shaun A. Mason, 2022 [42]	10/23	500mg/day	56days	only received anti-diabetes treatment	parallel	Egypt	Cochrane, poor
	40M	1000mg/day	90days	placebo	parallel	Palestine	Cochrane, poor
	41/37	500mg/day	60days	placebo	parallel; DB	Iran	Cochrane, fair
	NS	1000mg/day	60days	placebo	parallel; DB	Thailand	Cochrane, fair
	13/19	800mg/day	28days	placebo:500 mg citric acid/25 ml	parallel; DB	US	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
HOMA-IR			
Vitamin C			
Yoonhye Kim, 2022 [25]	Ali Abd El-Aal, 2018	T2DM	(10/10)
	Hui Chen, 2006	T2DM	(15/17)
	Sanguanwong, 2016	T2DM	(50/50)
Fasting insulin			
Vitamin B-7			
Yujia Zhang, 2022[37]	Cristina, 2006	T2MD	18 (10/8)
	Cesar, 2007	T2MD	348 (226/122)
	Armida, 2004	T2MD	15 (10/5)
	Gregory, 2006	T2MD	36 (20/16)
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Gargari, 2011	Overweight and obese men with type 2 diabetes	48 (24/24)
	Cagnacci, 2015	Postmenopausal	30 (15/15)
	Sheu, 2005	Obese women	74 (36/38)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
HOMA-IR							
Vitamin C							
Yoonhye Kim, 2022 [25]	NR	1000mg/day	12weeks	PC	parallel	NR	Cochrane, fair (unclear)
	NR	800mg/day	4weeks	PC	parallel; DB	USA	Cochrane, poor
	NR	1000mg/day	60days	placebo	parallel; DB	Thailand	Cochrane, fair
Fasting insulin							
Vitamin B-7							
Yujia Zhang, 2022[37]	11/7	15mg/day	28days	PC	parallel	Mexico	Cochrane, good
	140/208	2mg/day	90days	PC	parallel	United States	Cochrane, good
	NR	6.14μmol/d	28days	PC	parallel	Mexico	Cochrane, good
	NR	2mg/day	4weeks	PC	parallel	USA	Cochrane, fair
Vitamin B-9							
Omid Asbaghi, 2021 [39]	48M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	30F	15mg/d	3weeks	PC	parallel; DB	Italy	Cochrane, good
	74F	5mg/d	12weeks	PC	parallel; DB	Taiwan	Cochrane, good

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
Fasting insulin			
Vitamin B-9			
Omid Asbaghi, 2021 [39]	Villa, 2005	Postmenopausal	20 (10/10)
	Solini, 2006	Overweight subjects	60 (30/30)
	Palomba, 2010	Polycystic ovary syndrome	47 (23/24)
	Aghamohammadi Khiavi, 2011	T2DM	68 (34/34)
	Asemi, 2014 (A)	Overweight women with polycystic ovary syndrome	81 (27/14)
	Asemi, 2014 (B)	Overweight women with polycystic ovary syndrome	81 (27/13)
	Asemi, 2016	Cervical intraepithelial neoplasia grade 1	58 (29/29)
	Talari, 2016	Metabolic syndrome	60 (30/30)
	Bahmani, 2018	Endometrial hyperplasia	60 (30/30)
Zhao JV, 2018[40]	Talari, 2016	With type 2 diabetes at baseline；Overweight and stable CHD	60 (30/30)
	Asemi, 2016	Cervical intraepithelial neoplasia grade 1	58 (29/29)
	Asemi, 2014	Overweight or obesity, and PCOS	54 (27/27)
	Gargari, 2011	With type 2 diabetes at baseline、Overweight	48 (24/24)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
Fasting insulin							
Vitamin B-9							
Omid Asbaghi, 2021 [39]	20F	7.5mg/d	8weeks	PC	parallel	Italy	Cochrane, Fair
	19/41	2.5mg/d	12weeks	PC	parallel	Italy	Cochrane, Fair
	47F	0.4mg/d	25weeks	PC	parallel; DB; non-random	Italy	Cochrane, good
	68M	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	81F	1mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	81F	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, good
	58F	5mg/d	25weeks	PC	parallel; DB	Iran	Cochrane, good
	60F	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, good
	40M	1000mg/day	90days	placebo	parallel	Palestine	Cochrane, poor
Zhao JV, 2018[40]	both	5mg/d	12weeks	placebo	parallel	Iran	Cochrane, good
	58F	5mg/d	6months	placebo	parallel	Iran	Cochrane, fair
	54F	1mg/d	8weeks	placebo	parallel	Iran	Cochrane, fair
	48M	5mg/d	8weeks	placebo	parallel	Iran	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
Fasting insulin			
Vitamin B-9			
Zhao JV, 2018[40]	Solini, 2006	NO	60 (30/30)
	Villa, 2005	NO	20 (10/10)
	Setola, 2004	With metabolic syndrome and hyperinsulinemia	50 (25/25)
	Cagnacci, 2015	NO	30 (15/15)
Maryam Akbari, 2018 [16]	Gargari BP, 2011	Overweight and obese men with type 2 diabetes	48 (24/24)
	Asemi Z, 2014	Women with polycystic ovary syndrome	54 (27/27)
	Talari HR, 2016	Patients with metabolic syndrome	60 (30/30)
	Khiavi A, 2011	T2DM	64 (34/34)
	Setola E, 2004	Patients with metabolic syndrome	50 (25/25)
	Solini A, 2006	Overweight subjects	60 (30/30)
	Sheu WH-H, 2005	Obese women	74 (36/38)
	Dehkordi EH, 2016	Overweight and obesity	39 (20/19)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
Fasting insulin							
Vitamin B-9							
Zhao JV, 2018[40]	both	2.5mg/d	12weeks	placebo	parallel	Italy	Cochrane, poor
	20F	7.5mg/d	8weeks	placebo	parallel	Italy	Cochrane, poor
	both	5mg/day	2months	placebo	parallel	Italy	Cochrane, fair
	30F	15mg/d	3weeks	placebo	parallel	Italy	Cochrane, good
Maryam Akbari, 2018 [16]	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, fair
	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, poor
	NR	5mg/d	12weeks	PC	parallel; DB	Iran	Cochrane, poor
	NR	5mg/d	8weeks	PC	NR	Iran	Cochrane, fair
	NR	Folate + vitamins B6 or B12, 5mg/d	8weeks	PC	parallel; DB	Italy	Cochrane, fair
	NR	2.5mg/d	12weeks	PC	NR	Italy	Cochrane, poor
	NR	5mg/d	12weeks	PC	parallel; DB	Taiwan	Cochrane, fair
	NR	5mg/d	8weeks	PC	parallel; DB	Iran	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
Fasting insulin			
Vitamin C			
Asma Kazemi, 2022 [43]	Mason, 2018	T2DM	27/ 27/ 27
	El-Aal, 2018	T2DM	10, 10
	Ramzy Ragheb, 2020	T2DM	20/13
	Sanguanwong, 2016	T2DM	50
	Froghi, 2018	T2DM	21/21
	Chen, 2006	T2DM	15/17
	Ghaffari, 2015	T2DM	(17/14)
	Paolisso, 1995	T2DM	40
Shaun A. Mason, 2022 [42]	Paolisso, 1995	T2DM	(40/40)
	Mason, 2016	T2DM	(7/7)
	Mason, 2019	T2DM	(27/27)
	Ragheb, 2020	T2DM	33 (20/13)
	El-Aal, 2018	T2DM	40 (10/10/10/10)
	Foroghi, 2018	T2DM	78 (38/40)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
Fasting insulin							
Vitamin C							
Asma Kazemi, 2022 [43]	NR	VC, 1000mg/d	17weeks	Placebo	Parallel	Australia	Cochrane, good
	20 Male	VC, 800mg/d	12weeks	Placebo	Parallel	Palestine	Cochrane, poor
	NR	VC, 500mg/d	8weeks	placebo	Parallel	Egypt	Cochrane
	NR	VC, 1000mg/d	8weeks	Placebo	Parallel	Thailand	Cochrane, fair
	NR	VC, 500mg/d	8weeks	Placebo	Parallel	Iran	Cochrane, poor
	NR	VC, 800mg/d	4weeks	Placebo	Parallel	USA	Cochrane, poor
	NR	VC, 800mg/d	8weeks	Placebo	Parallel	Iran	Cochrane, poor
	both	1000 mg/d	12 weeks	Placebo	Cross-over	Italy	Cochrane, poor
Shaun A. Mason, 2022 [42]	19/21	1000mg/day	120days	placebo	crossover; DB	Italy	Cochrane, fair
	12/1	1000mg/day	120days	placebo	crossover; DB	Australia	Cochrane, fair
	26/5	1000mg/day	120days	placebo	crossover; DB	Australia	Cochrane, good
	10/23	500mg/day	56days	PC	parallel	Egypt	Cochrane, poor
	40M	1000mg/day	90days	placebo	parallel	Palestine	Cochrane, poor
	41/37	500mg/day	60days	placebo	parallel; DB	Iran	Cochrane, fair

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 2. Characteristics of included randomized controlled trials of meta-analysis exploring the effects of water-soluble vitamin on glycemic control and insulin resistance (cont.)

Variables and vitamin species (SR Author and year (ref))	Primary study's author and year	Population	Total, n (intervention/comparison)
Fasting insulin			
Vitamin C			
Shaun A. Mason, 2022 [42]	Sanguanwong, 2016	T2DM	(50/50)
	Hui Chen, 2006	T2DM	32 (15/17)
	Ghaffari, 2015	T2DM	31 (17/14)
AW Ashor, 2017 [44]	Hui Chen, 2006	T2DM	32 (17/15)
	L Pirbudak, 2004	Healthy	22 (11/11)
	Johannes Pleiner, 2002	Healthy	10
	Simona Bo, 2007	Healthy	78 (40/38)
	Shaun A Mason, 2016	T2DM	14 (7/7)
	Gaffari, 2015	T2DM	31
	C S Johnston, 1994	Healthy	9
	Brian A Mullan, 2005	Healthy	9
	David C Nieman, 2002	Healthy	(15/13)

SR Author and year	Male / female	Intervention		Comparator	Study design	Setting	Quality assessment
		Dose	Duration				
Fasting insulin							
Vitamin C							
Shaun A. Mason, 2022 [42]	NS	1000mg/day	60days	placebo	parallel; DB	Thailand	Cochrane, fair
	13/19	800mg/day	28days	placebo:	parallel; DB	US	Cochrane, fair
	13/18	800mg/day	60days	placebo	parallel	Iran	Cochrane, fair
AW Ashor, 2017 [44]	13/19	800mg/day	28days	placebo	parallel; DB	USA	Jadad, 5
	22F	AA 500 mg, fentanyl 1–2 mg/kg and etomidate 0.3–0.4 mg/kg	1days	fentanyl 1–2 mg/kg and etomidate 0.3–0.4 mg/kg	parallel	Turkey	Jadad, 2
	10M	72mg/day	1days	placebo	crossover; DB	Australia	Jadad, 3
	24/54	2000mg/day	14days	no intervention	parallel	Italy	Jadad, 3
	12/2	1000mg/day	120days	placebo	crossover; DB	Australia	Jadad, 5
	13/17	800mg/ day	56days	placebo	parallel	Iran	Jadad, 2
	2/7	1000mg/day	14days	placebo	crossover; DB	USA	Jadad, 5
	9M	2000mg/day	1days	placebo	crossover; DB	UK	Jadad, 3
	NR	1500mg/day	1days	placebo	parallel; DB	USA	Jadad, 4

AA: ascorbic acid, T2DM: type 2 diabete, T1DM: type 1 diabetes, FBG: fasting blood glucose, HbA1c: glycosylated hemoglobin, HOMA-IR: homeostatic model assessment for insulin resistance, COI: conflict of interest, NR: no report, DB: double blind, F: female; M, male, PC: placebo

Supplementary Table 3. Results of assess quality of evidence in meta-analysis

SR author and year (ref)	Vitamin species	Outcomes	Risk of bias	Inconsistency
Arti Muley, 2022 [48]	Thiamine	FBG	No serious limitations	Serious limitations b
		HbAc1	No serious limitations	No serious limitations
Yi Ding, 2014 [46]	Niacin	FBG	Serious limitations a1	Serious limitations b
Dan Xiang, 2020 [47]	Niacin	BG	No serious limitations	No serious limitations
		HbAc1	No serious limitations	Serious limitations b
Yujia Zhang, 2022 [37]	Biotin	FBG	No serious limitations	No serious limitations
		HbAc1	No serious limitations	No serious limitations
		insulin	No serious limitations	No serious limitations
Omid Asbaghi, 2021[39]	Folic acid	FBG	No serious limitations	Very serious limitations b
		HbAc1	No serious limitations	Serious limitations b
		HOMA-IR	No serious limitations	Very serious limitations b
		insulin	No serious limitations	Serious limitations b
Maryam Akbari, 2018[16]	Folic acid	FBG	No serious limitations	Serious limitations b
		HbAc1	No serious limitations	No serious limitations
		HOMA-IR	No serious limitations	Serious limitations b
		insulin	No serious limitations	Serious limitations b

SR author and year (ref)	Indirectness	Imprecision	Publication bias	Quality
Arti Muley, 2022 [48]	No serious limitations	No serious limitations	Serious limitations e1	Low
	No serious limitations	No serious limitations	Serious limitations e1	Moderate
Yi Ding, 2014 [46]	No serious limitations	No serious limitations	Serious limitations e1	Very low
Dan Xiang, 2020 [47]	No serious limitations	No serious limitations	No serious limitations	High
	No serious limitations	serious limitations [d3]	No serious limitations	Low
Yujia Zhang, 2022 [37]	No serious limitations	No serious limitations	No serious limitations	High
	No serious limitations	Serious limitations [d2]	No serious limitations	Moderate
	No serious limitations	Serious limitations [d3]	No serious limitations	Moderate
Omid Asbaghi, 2021[39]	Serious limitations c1	No serious limitations	Serious limitations e2	Very low
	Serious limitations c1	Serious limitations [d1]	No serious limitations	Very low
	Serious limitations c1	No serious limitations	No serious limitations	Low
	Serious limitations c1	No serious limitations	No serious limitations	Low
Maryam Akbari, 2018[16]	No serious limitations	No serious limitations	No serious limitations	Moderate
	No serious limitations	Serious limitations [d1]	No serious limitations	Moderate
	No serious limitations	No serious limitations	No serious limitations	Moderate
	No serious limitations	No serious limitations	No serious limitations	Moderate

a1: high risk of bias regarding allocation concealment. a2: Bias risk was low for 17 studies, whereas a high risk of bias was found in five studies. a3: Of 12 trials, only 4 trials had score equal to 4 (high-quality studies) and the others were categorized as low-quality studies. a4: 93.75% of studies were at high risk. a5: 10 studies (77%) were at high risk. a6: 6 studies were at high risk. b: The test for heterogeneity is significant, and the I is moderate, >50%. b2: The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p < 0.0001). c1: Studies conducted subject to various conditions. c2: Surrogate outcome measure, not a patient-important end point. d1: Values are distributed within opposite direction across studies. d2: The sample size is small. d3: Upper bound 95% CI of estimate outside of clinical meaningfulness. e1: The risk of publication bias is high. e2: The Egger's test for publication bias. is significant(p=0.039). e3: The Egger's test for publication bias, is significant(p=0.01).

Supplementary Table 3. Results of assess quality of evidence in meta-analysis (cont.)

SR author and year (ref)	Vitamin species	Outcomes	Risk of bias	Inconsistency
Zhao JV, 2018 [40]	Folic acid	FBG	No serious limitations	Serious limitations b
		HbAc1	No serious limitations	Serious limitations b
		HOMA-IR	No serious limitations	Very serious limitations b
		insulin	No serious limitations	Serious limitations b
Patcharaporn Sudchada, 2012 [54]	Folic acid	HbAc1	No serious limitations	Serious limitations b
AW Ashor, 2017 [44]	Vitamin C	FBG	Serious limitations a2	Serious limitations b
		HbAc1	Serious limitations a2	No serious limitations
		insulin	Serious limitations a2	No serious limitations
Shaun A. Mason, 2021 [42]	Vitamin C	FBG	Serious limitations	Serious limitations b
		HbAc1	Serious limitations	Serious limitations b
		PPG	Serious limitations	Serious limitations b
		HOMA-IR	Serious limitations	Serious limitations b
		insulin	Serious limitations	Serious limitations b
Ozra Tabatabaei-Malazy, 2014 [45]	Vitamin C	FBG	Serious limitations a3	No serious limitations
		HbAc1	Serious limitations a3	Serious limitations b2

SR author and year (ref)	Indirectness	Imprecision	Publication bias	Quality
Zhao JV, 2018 [40]	No serious limitations	No serious limitations	Serious limitations e1	Low
	No serious limitations	No serious limitations	Serious limitations e1	Low
	No serious limitations	No serious limitations	No serious limitations	Low
	No serious limitations	No serious limitations	Serious limitations e1	Low
Patcharaporn Sudchada, 2012 [54]	No serious limitations	No serious limitations	No serious limitations	Moderate
AW Ashor, 2017 [44]	No serious limitations	No serious limitations	No serious limitations	Low
	No serious limitations	No serious limitations	No serious limitations	Moderate
	No serious limitations	No serious limitations	No serious limitations	Moderate
Shaun A. Mason, 2021 [42]	Serious limitations c2	Serious limitations d3	No serious limitations	Very low
	Serious limitations c2	Serious limitations d3	No serious limitations	Very low
	No serious limitations	Serious limitations d3	No serious limitations	Very low
	No serious limitations	Serious limitations d3	No serious limitations	Very low
	No serious limitations	Serious limitations d3	No serious limitations	Very low
Ozra Tabatabaei-Malazy, 2014 [45]	No serious limitations	No serious limitations	No serious limitations	Moderate
	No serious limitations	No serious limitations	Serious limitations e3	Very low

a1: high risk of bias regarding allocation concealment. a2: Bias risk was low for 17 studies, whereas a high risk of bias was found in five studies. a3: Of 12 trials, only 4 trials had score equal to 4 (high-quality studies) and the others were categorized as low-quality studies. a4: 93.75% of studies were at high risk. a5: 10 studies (77%) were at high risk. a6: 6 studies were at high risk. b: The test for heterogeneity is significant, and the I is moderate, >50%. b2: The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous ($p < 0.0001$). c1: Studies conducted subject to various conditions. c2: Surrogate outcome measure, not a patient-important end point. d1: Values are distributed within opposite direction across studies. d2: The sample size is small. d3: Upper bound 95% CI of estimate outside of clinical meaningfulness. e1: The risk of publication bias is high. e2: The Egger's test for publication bias. is significant(p=0.039). e3: The Egger's test for publication bias, is significant(p=0.01).

Supplementary Table 3. Results of assess quality of evidence in meta-analysis (cont.)

SR author and year (ref)	Vitamin species	Outcomes	Risk of bias	Inconsistency
Asma Kazemi, 2022[43]	Vitamin C	FBG	Very serious a4	Very serious
		HbAc1	Serious limitations a5	Serious limitations b
		insulin	Serious limitations a6	Serious limitations b
		HOMA-IR	No serious limitations	Serious limitations b
Mehrnoosh Khodaeian, 2015[78]	Vitamin C	HOMA-IR	Serious limitations a1	No serious limitations
Yoonhye Kim, 202[25]	Vitamin C	FBG	No serious limitations	Serious limitations b
		HbAc1	No serious limitations	No serious limitations
		HOMA-IR	No serious limitations	Serious limitations b

SR author and year (ref)	Indirectness	Imprecision	Publication bias	Quality
Asma Kazemi, 2022[43]	No serious limitations	No serious limitations	No serious limitations	Very low
	No serious limitations	No serious limitations	No serious limitations	Low
	No serious limitations	No serious limitations	No serious limitations	Low
	No serious limitations	No serious limitations	No serious limitations	Moderate
Mehrnoosh Khodaeian, 2015[78]	No serious limitations	Serious limitations d2	No serious limitations	Low
Yoonhye Kim, 202[25]	No serious limitations	No serious limitations	No serious limitations	Moderate
	No serious limitations	No serious limitations	No serious limitations	High
	No serious limitations	Serious limitations d2	No serious limitations	Low

a1: high risk of bias regarding allocation concealment. a2: Bias risk was low for 17 studies, whereas a high risk of bias was found in five studies. a3: Of 12 trials, only 4 trials had score equal to 4 (high-quality studies) and the others were categorized as low-quality studies. a4: 93.75% of studies were at high risk. a5: 10 studies (77%) were at high risk. a6: 6 studies were at high risk. b: The test for heterogeneity is significant, and the I is moderate, >50%. b2: The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous ($p < 0.0001$). c1: Studies conducted subject to various conditions. c2: Surrogate outcome measure, not a patient-important end point. d1: Values are distributed within opposite direction across studies. d2: The sample size is small. d3: Upper bound 95% CI of estimate outside of clinical meaningfulness. e1: The risk of publication bias is high. e2: The Egger's test for publication bias. is significant($p=0.039$). e3: The Egger's test for publication bias, is significant($p=0.01$).