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RECEIVED 09 April 2025

ACCEPTED 21 October 2025

PUBLISHED 19 November 2025

## CITATION

Deng F, Ji Y, Kong H, Fu Y, Zhang H and  
Zhang J (2025) Network meta-analysis of the  
effects of combined exercise and vitamin  
intervention on insulin resistance and related  
indicators in patients with type 2 diabetes.  
*Front. Nutr.* 12:1608634.  
doi: 10.3389/fnut.2025.1608634

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# Network meta-analysis of the effects of combined exercise and vitamin intervention on insulin resistance and related indicators in patients with type 2 diabetes

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**Objective:** This study aimed to evaluate the effects of vitamin supplementation, exercise, and their combined interventions on insulin resistance and related outcomes in patients with type 2 diabetes (T2D). Additionally, it examined the dose–response relationships between vitamin dosage, exercise intensity, and improvements in insulin resistance.

**Methods:** Relevant studies investigating the impact of vitamin supplementation and exercise interventions on insulin resistance in T2D patients were systematically retrieved from authoritative domestic and international databases, followed by comprehensive synthesis and analysis.

**Results:** Traditional meta-analyses revealed that both short-term (<12 weeks) and long-term (>12 weeks) interventions significantly improved insulin resistance and related outcomes. The exceptions included vitamin supplementation alone, which did not significantly improve glycated hemoglobin (HbA1c); neither exercise alone or vitamin supplementation alone, which failed to significantly reduce fasting blood glucose; and combined exercise interventions, which had no significant effects on insulin levels. All other interventions yielded significant benefits. Network meta-analysis revealed that, compared with the control group, probiotics provided the greatest improvement in insulin resistance. Vitamin D was most effective at improving HbA1c, whereas vitamin C had the strongest effects on fasting blood glucose and insulin indices. Dose-subgroup analysis indicated that vitamin supplementation up to 2000 IU/day most effectively reduced fasting blood glucose ( $p < 0.01$ ) but had no significant effects on HbA1c or insulin (all  $p > 0.05$ ). A dosage of 2,100–4,000 IU/day produced the most pronounced improvements in HbA1c ( $p < 0.01$ ) and insulin ( $p < 0.05$ ) but did not significantly affect insulin resistance or fasting blood glucose (all  $p > 0.05$ ). Supplementation at 4100–7500 IU/day yielded the greatest improvements in insulin resistance ( $p < 0.01$ ) but had no significant effect on HbA1c ( $p > 0.05$ ). Exercise interventions with an intensity of  $\leq 4$  METs, performed three times per week, significantly improved insulin resistance, HbA1c, and insulin indices. Sessions lasting  $\leq 60$  min produced optimal benefits for insulin resistance and insulin measures, whereas sessions  $\leq 45$  min were most effective for HbA1c and fasting blood glucose.

**Conclusion:** Vitamin supplementation at 4100–7500 IU/day combined with moderate-intensity exercise (approximately 4 METs) performed three times

per week with each session lasting 45–60 min, yielded the most favorable improvements in insulin resistance and related metabolic outcomes in T2DM patients.

**Systematic review registration:** <https://www.crd.york.ac.uk/PROSPERO/view/CRD420250655264>.

#### KEYWORDS

type 2 diabetes, insulin resistance, vitamin intervention, exercise intervention, network meta-analysis

## Introduction

According to the World Health Organization (WHO), approximately 180 million people worldwide have diabetes, and this number is projected to rise to 360 million by 2030. Each year, diabetes contributes to an estimated 2.9 million deaths, making it a major global public health challenge (1). Type 2 diabetes mellitus (T2DM), also known as non-insulin-dependent diabetes mellitus (NIDDM), accounts for more than 90% of all diabetes cases and occurs predominantly in middle-aged and older adults (1).

Insulin resistance (IR), a key pathophysiological feature of T2DM, is closely linked to the development and progression of the disease. Most patients with T2DM present with IR, which is defined as a diminished responsiveness of insulin-target tissues to elevated insulin levels. This impaired response reduces the body's ability to regulate blood glucose, leading to chronic hyperglycemia. Over time, persistent hyperglycemia induces  $\beta$ -cell dysfunction and failure, resulting in chronic hyperinsulinemia and ultimately progressing to T2DM (2, 3). Importantly, prediabetes represents a transitional stage between normal glucose tolerance and T2DM and serves as a critical warning period (4). Individuals in this stage already exhibit insulin resistance and  $\beta$ -cell dysfunction, both of which contribute to the onset and persistence of T2DM. Insulin resistance and impaired insulin secretion jointly characterize this stage. Furthermore, IR and T2DM are strongly associated with obesity (5).

Current interventions for prediabetes and T2DM include vitamin supplementation and exercise. Vitamin supplementation plays an important role in suppressing inflammation, controlling blood glucose, and enhancing insulin secretion. Exercise, considered one of the five cornerstones of T2DM management, is valued for its affordability, convenience, and systemic health benefits. Research has shown that exercise improves obesity-related outcomes and reduces glycated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting insulin (FINS) levels. However, the effects of vitamins on diabetes remain a subject of debate, and the optimal parameters of exercise—such as duration, intensity, and type—have not been clearly defined (1). In addition, although some studies suggest that combining exercise with dietary and lifestyle interventions achieves greater benefits in weight reduction and prevention or management of T2DM than exercise alone, the overall effectiveness of these combined approaches requires further validation.

To address these gaps, the present study employed a network meta-analysis to evaluate the effects of vitamin supplementation, exercise interventions, and their combination on insulin resistance in patients with T2DM. Furthermore, a dose–response meta-analysis was conducted to identify the optimal dosage of vitamin supplementation and exercise parameters, aiming to provide

evidence-based recommendations for the management of insulin resistance in T2DM patients.

## Research subjects and methods

This study followed the PRISMA 2020 guidelines for systematic reviews and meta-analyses and has been registered on the international PROSPERO platform, with the registration number CRD420250655264.

### Literature search strategy

A comprehensive search was conducted in both domestic and international academic databases, including PubMed, Web of Science, Embase, Scopus, Cochrane Library, the China Biomedical Literature Database, CNKI, the Wanfang Database, and the VIP Database. The search was limited to publications in Chinese and English, with a cutoff date of December 24, 2024. The Chinese search terms included: vitamin and exercise or training or “physical activity and type 2 diabetes and insulin resistance.” The English search terms included: “insulin resistance” OR “Insulin resistance” OR “Metabolic syndrome” OR “insulin resistance factor uremia” OR “Pseudoacromegaly with Severe Insulin Resistance” OR “HAIR-AN syndrome” AND “type 2 diabetes” OR “Diabetes Mellitus Type 2” OR “Maturity-Onset Diabetes of the Young” OR “Type 2” OR “T2DM” AND “vitamin” AND “sport” OR “exercise” OR “physical activity” OR “training.” Please refer to [Appendix 2](#) for the specific process.

### Inclusion and exclusion criteria

Studies were included according to the PICOST framework. Eligibility criteria: Population (P): Patients diagnosed with T2DM, regardless of age, sex, or disease duration. Patients with or without additional complications were considered. Intervention (I): Vitamin supplementation (e.g., vitamin D, vitamin E, folic acid), with no restrictions on dosage or frequency. Exercise interventions (including aerobic exercise, resistance training, traditional exercise, and aquatic exercise), with no restrictions on frequency, duration, or type. Combined interventions of exercise plus vitamin supplementation, with no restrictions on vitamin type, exercise modality, frequency, or dosage. Comparison (C): Control groups received placebo supplementation without vitamins and maintained usual physical activity. Outcomes (O): Insulin resistance and related metabolic indicators. Study design (S): Randomized controlled trials (RCTs), with no language restrictions. Time frame (T): No restrictions on intervention duration.

Exclusion criteria: Studies were excluded if they met any of the following conditions: reviews, theoretical studies, animal experiments, or conference abstracts; interventions not involving exercise, vitamin supplementation, or their combination; or data reported without means  $\pm$  standard deviations.

## Literature screening and data extraction

Two independent researchers screened the literature according to the predefined inclusion and exclusion criteria. A third researcher resolved any disagreements. The selection process included the following steps: 1. Identification and removal of duplicate records. 2. Title screening to exclude survey studies, reviews, studies with unrelated interventions, and animal experiments. 3. Abstract and full-text screening to exclude studies with incomplete data, unclear interventions, or undefined outcome measures; and 4. Verification of eligible studies was performed by a third researcher. Final confirmation of the included studies and extraction of relevant data. Data extraction included the following: study characteristics: first author and year of publication. Participant information: Age, sex, and sample size of the experimental and control groups. Study design: type of intervention, duration, frequency, and evaluation indicators. Outcomes of interest: IR, fasting blood sugar (FBS), HbA1c, FINS, TC, TG, LDL-C, and hHDL-C. To ensure consistency, all outcome measures were converted to international standard units. For example, blood glucose values reported in mg/dL were converted to mmol/L. Insulin resistance was assessed via the homeostasis model assessment of IR (HOMA-IR).

## Quality assessment

Two researchers independently evaluated the methodological quality of the included studies via the Cochrane risk of bias assessment tool. The assessment covered seven domains, including random sequence generation, allocation concealment, and blinding. A third researcher resolved any disagreements.

## Statistical analysis

This study used Stata software to conduct a meta-analysis of intervention effects on the outcome measures from the included studies. All primary indicators—including IR, FINS, FBS, and HbA1c—were treated as continuous variables. The network meta-analysis employed Stata to perform traditional meta-analysis and dose-subgroup analyses. R software (version 4.4.1) was used to test model consistency, assess convergence, generate cumulative ranking results, and evaluate publication bias.

## Assessment of evidence quality

This study applied the GRADE approach to evaluate the quality of evidence for the included outcomes. The assessment considered five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. On the basis of these domains, each outcome was graded as very low, low, moderate, or high quality.

# Results

## Literature selection results

A total of 4,766 articles were initially retrieved from domestic and international databases. After removing duplicates, animal studies, and other ineligible records, 295 articles remained for preliminary screening. Following full-text review, 37 studies met the inclusion criteria (Figure 1). These included 5 two-arm trials, 6 studies with dual interventions, and 12 studies with multiple interventions.

The baseline characteristics of the included studies are summarized in Table 1. Overall, 2,828 patients with type 2 diabetes were enrolled, with 1,672 participants in the test group (T) and 1,156 in the control group (C). Interventions included vitamin C, trace element, vitamin D, aerobic exercise, resistance training, unsaturated fatty acid, combined exercise, combined vitamin supplementation, and exercise plus vitamin supplementation. All interventions lasted at least 8 weeks.

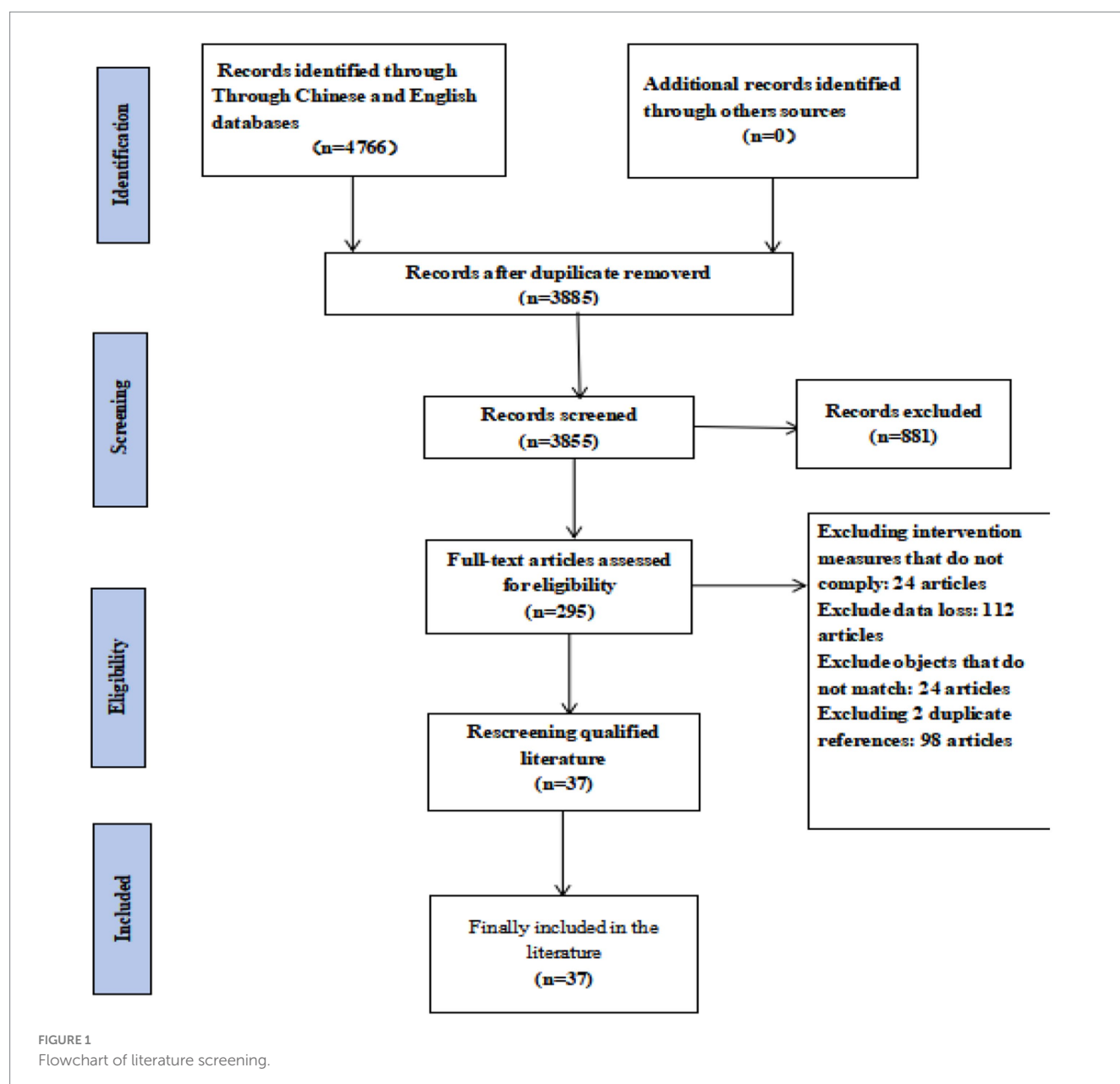
## Risk of bias assessment

All 37 included studies reported the use of randomization. However, 31 studies did not provide detailed descriptions of the randomization method. One study used computer-generated randomization, one applied block randomization, one adopted sealed envelopes, and one used a random number generator. Among the included studies, three explicitly implemented single-blinding, nine applied double-blinding, and the remaining studies did not mention blinding procedures. Three studies presented a potential risk of incomplete outcome data. With respect to participant characteristics, 29 studies included patients with comorbidities. The reported comorbidities included coronary heart disease in two studies, hyperlipidemia in one study, and hypertension in one study. The detailed results are presented in Figure 2.

## Traditional meta-analysis results

A total of 33, 21, 26, and 28 studies were included to assess the effects of interventions on IR, HbA1c, FBS, and FINS, respectively. Overall effect analyses indicated significant heterogeneity across studies (IR:  $p < 0.01$ ,  $I^2 = 90.8\%$ ; HbA1c:  $p < 0.01$ ,  $I^2 = 85.1\%$ ; FBS:  $p < 0.01$ ,  $I^2 = 93.8\%$ ; FINS:  $p < 0.01$ ,  $I^2 = 86.4\%$ ), suggesting the use of a random effects model. The results demonstrated that, compared with controls, interventions significantly reduced IR and associated metabolic indicators: IR: SMD =  $-1.217$ , 95% CI [ $-1.490$ ,  $-0.945$ ],  $p < 0.01$ ; HbA1c: SMD =  $-1.061$ , 95% CI [ $-1.315$ ,  $-0.807$ ],  $p < 0.01$ ; FBS: SMD =  $-1.122$ , 95% CI [ $-1.505$ ,  $-0.740$ ],  $p < 0.01$ ; FINS: SMD =  $-0.908$ , 95% CI [ $-1.152$ ,  $-0.665$ ],  $p < 0.01$ .

Subgroup analyses revealed that single exercise, combined exercise, single supplementation with vitamins, unsaturated fatty acids, or trace elements, and combined interventions with vitamins, unsaturated fatty acids, trace elements, or exercise significantly reduced IR (SMD range:  $-0.854$  to  $-1.916$ , all  $p < 0.05$ ). Single exercise significantly reduced IR (SMD range:  $-0.854$  to  $-1.916$ , all  $p < 0.05$ ). Single exercise, combined exercise, single supplementation, and combined interventions significantly improved HbA1c (SMD range:  $-0.957$  to  $-1.534$ , all  $p < 0.05$ ). However, combined supplementation with vitamins, unsaturated



fatty acids, and trace elements alone did not significantly affect HbA1c (SMD =  $-0.247$ , 95% CI [ $-1.169$ ,  $0.676$ ],  $p > 0.05$ ). Single exercise and single supplementation did not significantly reduce FBS (SMD =  $-0.684$ , 95% CI [ $-1.543$ ,  $0.174$ ],  $p > 0.05$ ; SMD =  $-1.063$ , 95% CI [ $-1.505$ ,  $0.621$ ],  $p > 0.05$ ). In contrast, combined vitamin/unsaturated fatty acids/trace elements, combined exercise, and unsaturated fatty acids/trace elements plus exercise significantly reduced the FBS (SMD range:  $-0.598$  to  $-5.001$ , all  $p < 0.01$ ). Single exercise, single supplementation, combined vitamin supplementation, and other combined interventions significantly reduced insulin levels (SMD range:  $-0.715$  to  $-1.718$ , all  $p < 0.05$ ), whereas combined exercise alone did not significantly affect insulin (SMD =  $0.024$ , 95% CI [ $-0.521$ ,  $0.568$ ],  $p > 0.05$ ).

Intervention duration analysis revealed that short-term (<12 weeks), medium-term (12 weeks), and long-term (>12 weeks) interventions significantly reduced IR, insulin, and HbA1c (all  $p < 0.01$ ). Interventions shorter than 12 weeks or longer than 12 weeks

also significantly reduced FBS, whereas 12-week interventions did not significantly affect FBS (SMD =  $-0.479$ , 95% CI [ $-1.094$ ,  $0.135$ ],  $p > 0.05$ ). The detailed results are presented in [Table 2](#).

## Dosage subgroup analysis

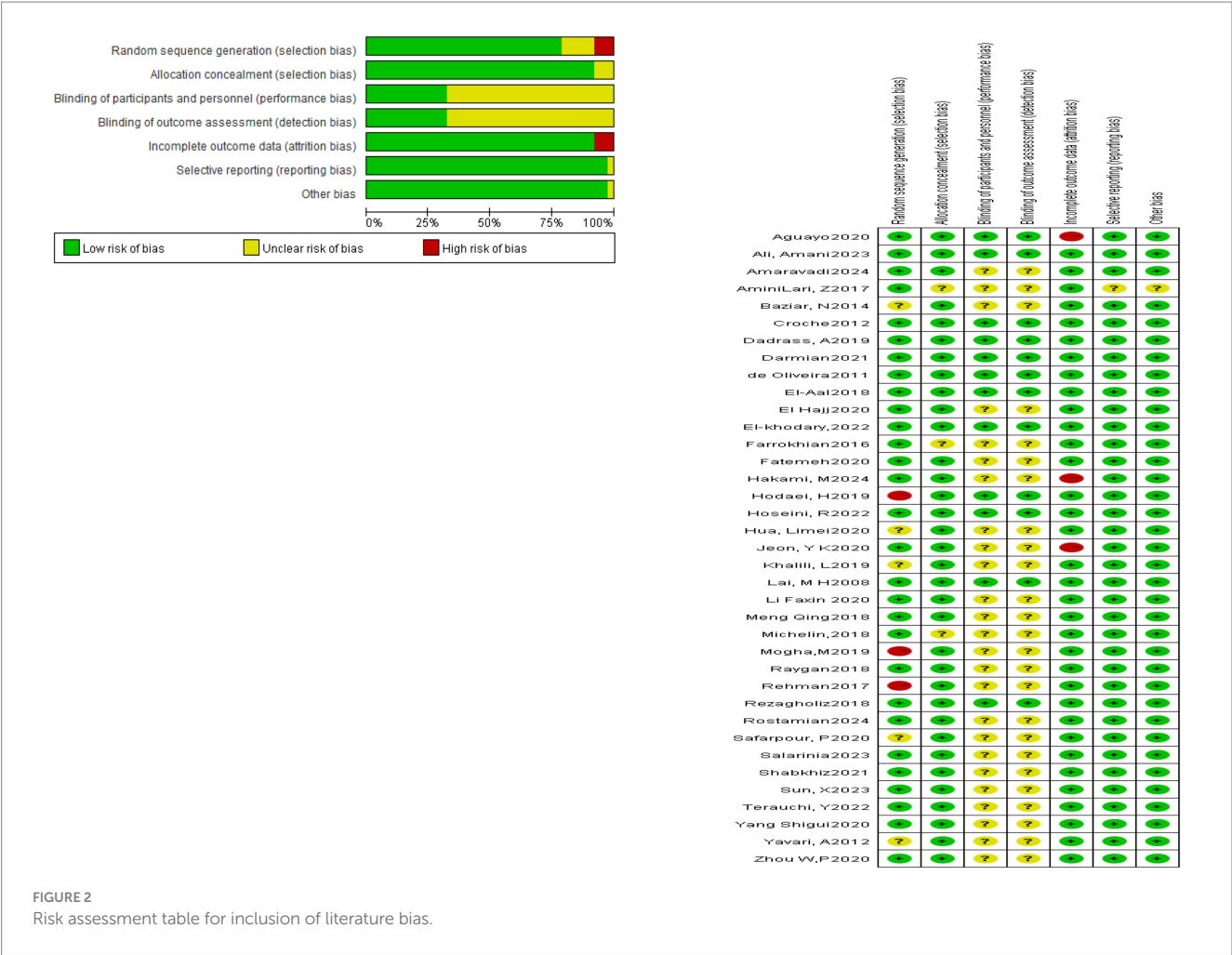
This study collected and standardized intervention doses to quantify the effects of vitamin supplementation and exercise on insulin resistance. For fat-soluble vitamin interventions, 0 IU/day served as the reference, and for exercise interventions, 0 MET·hour served as the reference. The study then conducted a quantitative assessment of the relationships between vitamin dose, exercise intensity, and IR in patients with type 2 diabetes. The dose-response meta-analysis revealed that fat-soluble vitamin supplementation up to 2,000 IU/day produced the greatest improvement in fasting blood glucose (FBS) ( $p < 0.01$ ) but had no significant effect on hemoglobin A1c (HbA1c) or

TABLE 1 Basic characteristics of included studies.

| First author and year   | Number of cases |     | Intervention measures |     | Intervention cycle (week) | Outcome indicators  |
|-------------------------|-----------------|-----|-----------------------|-----|---------------------------|---------------------|
|                         | EX              | CON | EX                    | CON |                           |                     |
| Meng Qing 2018 (25)     | 40              | 40  | B, N                  | A   | 12                        | 1, 2, 3             |
| Fatemeh 2020 (26)       | 23              | 23  | D, K, R               | A   | 16                        | 1, 2, 4, 5, 6, 7    |
| Amini Lari, Z 2017 (22) | 15              | 15  | B, C, N               | A   | 12                        | 1, 4                |
| El-Aal 2018 (27)        | 10              | 10  | F, E, O               | A   | 12                        | 1, 2, 3, 4, 5, 6, 7 |
| Mogha, M 2019 (21)      | 10              | 10  | B, C                  | A   | 10                        | 1, 4                |
| Aguayo 2020 (28)        | 12              | 12  | D, O                  | A   | 12                        | 1, 4, 7             |
| Sun, X 2023 (12)        | 15              | 15  | D, B, P               | A   | 12                        | 1, 2, 3, 4          |
| Raygan 2018 (29)        | 30              | 30  | S                     | A   | 12                        | 1, 2, 3             |
| Darmian 2021 (30)       | 11              | 10  | I, B, T               | A   | 8                         | 1, 2, 3, 4, 7       |
| de Oliveira 2011 (31)   | 25              | 26  | U, E, O               | A   | 16                        | 1, 4, 5, 6, 7       |
| Hua, Limei 2020 (32)    | 54              | 54  | G, Q                  | A   | 12                        | 1, 2, 3, 4, 5, 6, 7 |
| Amaravadi 2024 (19)     | 75              | 71  | B                     | A   | 12                        | 1, 2, 3, 4          |
| Yavari, A 2012 (33)     | 20              | 20  | B, C, N               | A   | 52                        | 2, 3, 7             |
| Ali, Amani 2023 (34)    | 45              | 45  | H                     | A   | 24                        | 1, 2, 3, 4, 5, 6    |
| Michelin,2018 (20)      | 8               | 8   | M                     | A   | 12                        | 1, 2, 3, 4          |
| Shabkhiz 2021 (35)      | 10              | 10  | B                     | A   | 12                        | 1, 3, 4             |
| Rehman 2017 (36)        | 51              | 51  | B                     | A   | 25                        | 1, 3, 4             |
| Farrokhian 2016 (37)    | 30              | 30  | L                     | A   | 8                         | 1, 3, 4, 5, 6, 7    |
| Hakami, M 2024 (38)     | 34              | 34  | B                     | A   | 12                        | 2, 3                |
| Terauchi, Y 2022 (39)   | 97              | 107 | N                     | A   | 12                        | 1, 3, 4, 5, 6       |
| Jeon, Y K 2020 (40)     | 21              | 14  | N                     | A   | 12                        | 1, 2, 5, 6          |
| Hodaei, H 2019 (41)     | 33              | 23  | I                     | A   | 10                        | 1, 2, 3, 4          |
| Khalili, L 2019 (42)    | 20              | 20  | J                     | A   | 8                         | 1, 2, 3, 4          |
| Croche 2012 (43)        | 14              | 14  | G                     | A   | 4                         | 1, 4, 5, 6          |
| Li Faxin 2020 (44)      | 40              | 40  | N                     | A   | 12                        | 1, 2, 3, 5, 6, 7    |
| Yang Shigui 2020 (15)   | 40              | 30  | D, B, P               | A   | 28                        | 1, 2, 3, 4          |
| Rostamian 2024 (14)     | 10              | 10  | D, B, P               | A   | 8                         | 1, 3, 4, 5, 6, 7    |
| Salarinia 2023 (45)     | 10              | 10  | D, B, P               | A   | 8                         | 1, 3, 4, 5, 6, 7    |
| Dadrass, A 2019 (46)    | 12              | 12  | D, C, P               | A   | 12                        | 1, 2, 3, 4, 5, 6, 7 |
| Hoseini, R 2022 (47)    | 10              | 10  | D, B, P               | A   | 8                         | 1, 2, 3, 4          |
| El Hajj 2020 (48)       | 45              | 43  | D                     | A   | 24                        | 1, 2, 3             |
| Zhou W, P 2020 (49)     | 45              | 44  | B                     | A   | 12                        | 1, 3, 4             |
| El-khodary, 2022 (50)   | 50              | 50  | H                     | A   | 12                        | 1, 2, 3, 4          |
| Rezagholiz 2018 (51)    | 20              | 20  | D                     | A   | 8                         | 1, 2, 3, 4          |
| Baziar, N 2014 (13)     | 43              | 44  | D                     | A   | 8                         | 1, 3, 4             |
| Safarpour, P 2020 (52)  | 42              | 43  | D                     | A   | 8                         | 1, 2                |
| Lai, M H 2008 (53)      | 10              | 10  | G, O                  | A   | 24                        | 1, 2, 3, 4          |

Intervention measures: A: control group, B: aerobic exercise, C: resistance exercise, D: vitamin D, E: vitamin E, F: vitamin C, G: unsaturated fatty acids, H: vitamin K, I: curcumin, J: probiotics, K: dietary supplements, L: trace elements, M: interval exercise, N: combined vitamin, O: combined vitamin, P: vitamin combined exercise, Q: fatty acid combined exercise, R: vitamin combined dietary supplements, S: vitamin combined probiotics, T: exercise combined curcumin, U: vitamin B. Outcome measures: 1. Insulin resistance model (HOMA-IR), 2. Glycated hemoglobin (HbA1c), 3. Blood glucose (FBG), 4. Insulin, 5. Low density lipoprotein cholesterol (LDL-C), 6. High density lipoprotein cholesterol (HDL-C), 7. Triglycerides (TG). EX, experimental group; CON, control group.

insulin levels (both  $p > 0.05$ ). Doses of 2,100–4,000 IU/day optimized improvements in HbA1c ( $p < 0.01$ ) and insulin ( $p < 0.05$ ) but did not significantly affect insulin resistance or FBS (both  $p > 0.05$ ). Doses of 4,100–7,500 IU/day achieved the greatest reduction in insulin resistance ( $p < 0.01$ ) without significantly affecting HbA1c ( $p > 0.05$ ). With respect to exercise interventions, intensities  $\leq 4$  MET significantly improved insulin resistance and insulin levels (both  $p < 0.01$ ) and significantly affected HbA1c ( $p < 0.01$ ) and FBS ( $p < 0.05$ ). Intensities



of 4.1–8 MET optimized HbA1c outcomes ( $p < 0.01$ ) but did not significantly affect FINS levels ( $p > 0.05$ ). Intensities of 8.1–15 MET significantly improved HbA1c and FBS (both  $p < 0.01$ ) but did not significantly influence IR or FINS (both  $p > 0.05$ ). An intervention frequency of three sessions per week significantly improved IR, HbA1c, and FINS outcomes. Single-session durations  $\leq 60$  min produced the greatest improvements in IR and FINS levels, whereas durations  $\leq 45$  min were most effective for HbA1c and FBS.

On the basis of these findings, fat-soluble vitamin supplementation at 4,100–7,500 IU/day combined with exercise at approximately 4 METs, performed three times per week, with each session lasting 45–60 min, is recommended to achieve optimal improvements in insulin resistance and related metabolic indicators in patients with type 2 diabetes. The detailed results are presented in [Tables 3–5](#).

## Network meta-analysis results

### Network plot

[Figures 3–6](#) illustrate the network relationships of various interventions—including vitamin supplementation, unsaturated fatty acids, trace elements, curcumin, aerobic exercise, resistance training, combined vitamin and exercise interventions, and combinations of vitamins with unsaturated fatty acids plus exercise—on insulin resistance and related metabolic indicators (glucose, insulin, and hemoglobin A1c)

in patients with type 2 diabetes. All the network plots were centered on the control group and did not form closed loops. Overall, the comparisons focused primarily on aerobic exercise, resistance training, vitamin D supplementation, and combined vitamin plus exercise interventions relative to the control group outcomes.

### Forest plot

This study included 33 trials on single vitamin supplementation, 21 trials on resistance training, 36 trials on aerobic exercise, and 28 trials on combined interventions, including vitamin plus exercise, combined vitamin supplementation, combined exercise, exercise plus probiotics, and exercise plus unsaturated fatty acids. The results of the network meta-analysis indicated that, compared with the control diet without exercise or corresponding vitamin interventions, probiotics produced the greatest improvement in insulin resistance. Vitamin D significantly improved HbA1c, whereas vitamin C had the most pronounced effects on FBS and insulin levels. The detailed results are presented in [Figures 7–10](#).

### Consistency test and model convergence diagnosis

In this study, trace plots were used to assess model convergence, whereas bandwidth indicators from density plots were used to evaluate model stability. Theoretically, as the number of iterations increases sufficiently, a bandwidth approaching zero indicates progressively

TABLE 2 Subgroup analysis of exercise combined with vitamin intervention on insulin resistance and corresponding indicators.

| Index                   | Compare types             | Effect value            | P     |
|-------------------------|---------------------------|-------------------------|-------|
| Insulin resistance      | Individual exercise       | −0.854 (−1.312, −0.396) | 0.000 |
|                         | United Movement           | 1.347 (−2.424, −0.269)  | 0.014 |
|                         | Individual vitamins       | −1.271 (−1.677, −0.865) | 0.000 |
|                         | Combined vitamins         | −1.909 (−3.621, −0.196) | 0.029 |
|                         | Vitamin combined exercise | −1.916 (−3.010, −0.823) | 0.001 |
|                         | <12 weeks                 | −0.949 (−1.289, −0.610) | 0.000 |
|                         | 12 weeks                  | −0.990 (−1.436, −0.544) | 0.000 |
|                         | >12 weeks                 | −1.836 (−2.421, −1.252) | 0.000 |
|                         | total                     | −1.217 (−1.490, −0.945) | 0.000 |
| Glycosylated hemoglobin | Individual exercise       | −1.163 (−1.598, −0.728) | 0.000 |
|                         | United movement           | −0.957 (−1.667, −0.247) | 0.008 |
|                         | Individual vitamins       | −1.019 (−1.419, −0.619) | 0.000 |
|                         | Combined vitamins         | −0.247 (−1.169, 0.676)  | 0.601 |
|                         | Vitamin combined exercise | −1.534 (−2.360, −0.708) | 0.000 |
|                         | <12 weeks                 | −1.738 (−2.478, −0.999) | 0.000 |
|                         | 12 weeks                  | −0.927 (−1.269, −0.585) | 0.000 |
|                         | >12 weeks                 | −0.907 (−1.347, −0.467) | 0.000 |
|                         | total                     | −1.061 (−1.315, −0.807) | 0.000 |
| Fasting blood sugar     | Individual exercise       | −0.684 (−1.543, 0.174)  | 0.118 |
|                         | United movement           | −0.598 (−1.367, −0.172) | 0.000 |
|                         | Individual vitamins       | −1.063 (−1.505, 0.621)  | 0.128 |
|                         | Combined vitamins         | −5.001 (−6.855, −3.147) | 0.000 |
|                         | Vitamin combined exercise | −2.242 (−3.722, −0.762) | 0.003 |
|                         | <12 weeks                 | −2.451 (−3.335, −1.567) | 0.000 |
|                         | 12 weeks                  | −0.479 (−1.094, 0.135)  | 0.126 |
|                         | >12 weeks                 | −1.178 (−1.762, −0.593) | 0.000 |
|                         | Total                     | −1.122 (−1.505, −0.740) | 0.000 |
| Insulin                 | Individual exercise       | −0.715 (−1.135, −0.296) | 0.001 |
|                         | United Movement           | 0.024 (−0.521, 0.568)   | 0.932 |
|                         | Individual vitamins       | 0.907 (−1.239, 0.574)   | 0.000 |
|                         | Combined vitamins         | −1.718 (−3.382, −0.055) | 0.043 |
|                         | Vitamin combined exercise | −1.704 (−2.715, −0.693) | 0.001 |
|                         | <12 weeks                 | −1.823 (−2.531, −1.115) | 0.000 |
|                         | 12 weeks                  | −0.551 (−0.857, −0.245) | 0.000 |
|                         | >12 weeks                 | −0.942 (−1.307, −0.577) | 0.000 |
|                         | total                     | −0.908 (−1.152, −0.665) | 0.000 |

enhanced model stability. The results revealed that insulin resistance values ranged from 0.08804 to 0.5455, with the highest value observed for d.A.S. (0.5455). HbA1c ranged from 0.4257 to 3.512, with a d.A.L. of 3.512 as the peak value. Insulin values ranged from 0.06296 to 0.2959, peaking at d.A.M. (0.2959), and FBS ranged from 0.4257 to 3.512, also peaking at d.A.L (3.512). Most sd.d values were low, whereas d.A.L represented a core high value across indicators. Overall, HbA1c and FBS exhibited greater density and more complete information (see Table 6).

This study employed the node-splitting method to evaluate consistency among interventions for IR, HbA1c, FBS, and FINS outcomes. The analysis indicated that insulin resistance outcomes for interventions B versus N, as well as insulin outcomes for interventions B versus N, demonstrated poor consistency ( $p < 0.05$ ). All the other outcome measures showed good consistency across the interventions ( $p > 0.05$ ). The detailed results are presented in Table 7.

TABLE 3 Subgroup reactions of vitamin supplementation to insulin resistance and corresponding indicator doses.

| Covariates and stratified subgroups | Number of studies | Effect size (confidence interval) | <i>P</i> | Heterogeneity     | <i>P</i> |
|-------------------------------------|-------------------|-----------------------------------|----------|-------------------|----------|
|                                     |                   |                                   |          | I <sup>2</sup> /% |          |
| Insulin resistance                  |                   |                                   |          |                   |          |
| 0–2000                              | 6                 | −0.906 (−1.651, −0.160)           | 0.017.   | 90.1              | 0.000    |
| 2,100–4,000                         | 3                 | −0.215 (−0.786, 0.355)            | 0.459    | 39.6              | 0.191    |
| 4,100–7,500                         | 5                 | −0.789 (−1.249, −0.330)           | 0.001    | 63.2              | 0.0028   |
| Glycated hemoglobin                 |                   |                                   |          |                   |          |
| 0–2000                              | 6                 | −0.638 (−1.339, 0.064)            | 0.075    | 87.9              | 0.000    |
| 2,100–4,000                         | 1                 | −1.397 (−2.297, −0.496)           | 0.002    | –                 | –        |
| 4,100–7,500                         | 4                 | −0.694 (−1.500, 0.113)            | 0.092    | 80.8              | 0.001    |
| Fasting blood glucose               |                   |                                   |          |                   |          |
| 0–2000                              | 4                 | −1.093 (−1.767, −0.419)           | 0.001    | 77.6              | 0.004    |
| 2,100–4,000                         | 2                 | −0.303 (−0.898, −0.292)           | 0.318    | 0.0               | 0.978    |
| 4,100–7,500                         | 4                 | −0.810 (−1.477, −0.144)           | 0.017    | 89.8              | 0.000    |
| Insulin                             |                   |                                   |          |                   |          |
| 0–2000                              | 4                 | −0.399 (−0.697, 1.496)            | 0.475    | 87.5              | 0.000    |
| 2,100–4,000                         | 3                 | −0.425 (−0.751, −0.100)           | 0.010    | 0.0               | 0.923    |
| 4,100–7,500                         | 4                 | −0.978 (−1.868, −0.088)           | 0.031    | 83.4              | 0.000    |

TABLE 4 Dose response of exercise intensity to insulin resistance and corresponding indicators.

| Covariates and stratified subgroups | Number of studies | Effect size (confidence interval) | <i>P</i> | Heterogeneity     | <i>P</i> |
|-------------------------------------|-------------------|-----------------------------------|----------|-------------------|----------|
|                                     |                   |                                   |          | I <sup>2</sup> /% |          |
| Insulin resistance                  |                   |                                   |          |                   |          |
| 0–4                                 | 9                 | −1.108 (−1.349, −0.630)           | 0.000    | 87.4              | 0.000    |
| 4.1–8                               | 8                 | −0.742 (−1.211, −0.273)           | 0.002    | 69.9              | 0.002    |
| 8.1–15                              | 6                 | −1.034 (−1.970, −0.099)           | 0.030    | 93.6              | 0.000    |
| Glycated hemoglobin                 |                   |                                   |          |                   |          |
| 0–4                                 | 4                 | −1.066 (−2.046, −0.086)           | 0.033    | 84.1              | 0.000    |
| 4.1–8                               | 8                 | −0.945 (−1.409, −0.482)           | 0.000    | 77.1.0            | 0.000    |
| 8.1–15                              | 4                 | −1.095 (−1.549, −0.640)           | 0.000    | 53.9              | 0.089    |
| Fasting blood glucose               |                   |                                   |          |                   |          |
| 0–4                                 | 6                 | −2.107 (−3.483, −0.731)           | 0.003    | 97.0              | 0.000    |
| 4.1–8                               | 8                 | −0.776 (−1.430, −0.121)           | 0.020    | 87.8              | 0.000    |
| 8.1–15                              | 5                 | −0.967 (−1.404, −0.530)           | 0.000    | 72.7              | 0.005    |
| Insulin                             |                   |                                   |          |                   |          |
| 0–4                                 | 9                 | −0.940 (−1.453, −0.427)           | 0.000    | 82.5              | 0.000    |
| 4.1–8                               | 5                 | −0.905 (−2.177, 0.367)            | 0.163    | 89.2              | 0.000    |
| 8.1–15                              | 5                 | −0.359 (−0.999, 0.280)            | 0.271    | 83.0              | 0.000    |

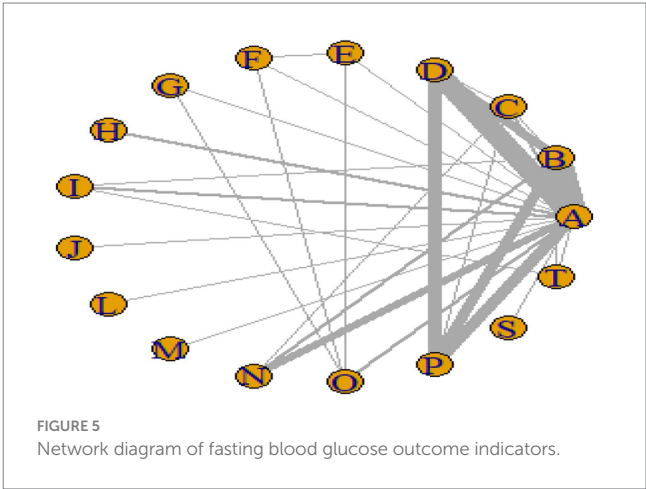
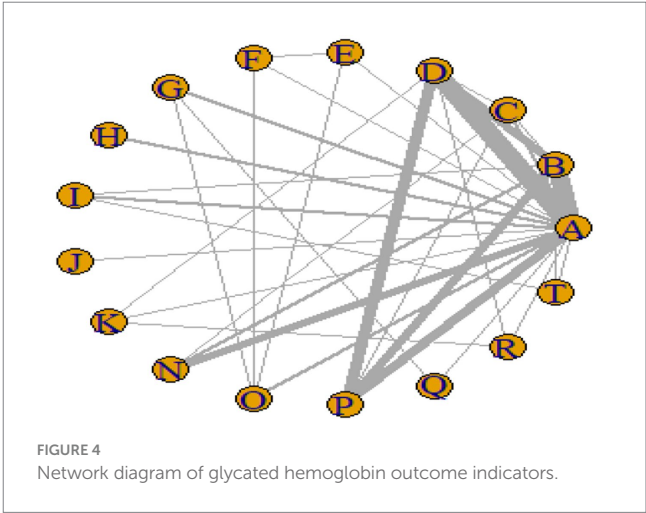
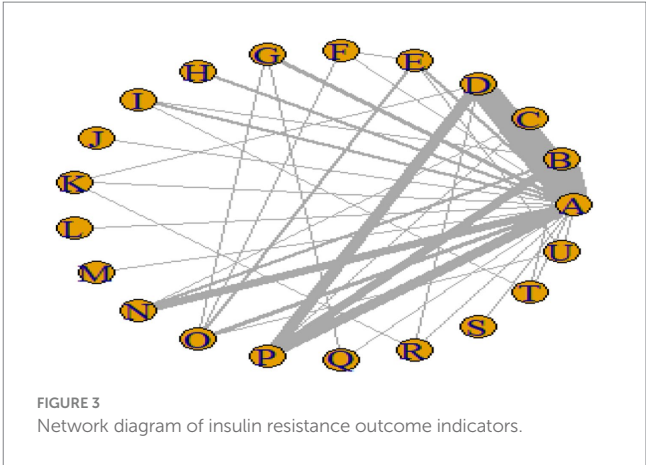
### Cumulative ranking results

This study ranked the effects of vitamin supplementation, exercise interventions, and combined vitamin plus exercise interventions on IR and related metabolic outcomes (FBS, FINS, and HbA1c) in patients with type 2 diabetes via SUCRA values. The SUCRA values range from 0 to 1, with values approaching 1 indicating maximal efficacy and values near 0 indicating minimal efficacy. The ranking results

demonstrated that probiotics produced the greatest improvement in insulin resistance. Combined vitamin plus exercise interventions achieved the most pronounced effect on hemoglobin A1c. Vitamin C supplementation significantly reduced FBS levels. Combined vitamin plus exercise interventions again had the optimal effect on hemoglobin A1c outcomes, whereas fatty acid plus exercise interventions produced the greatest improvement in insulin levels. The detailed results are presented in [Table 8](#) and [Appendix 1](#).

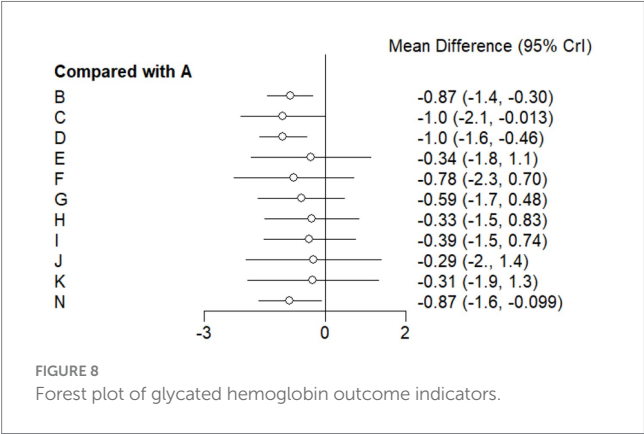
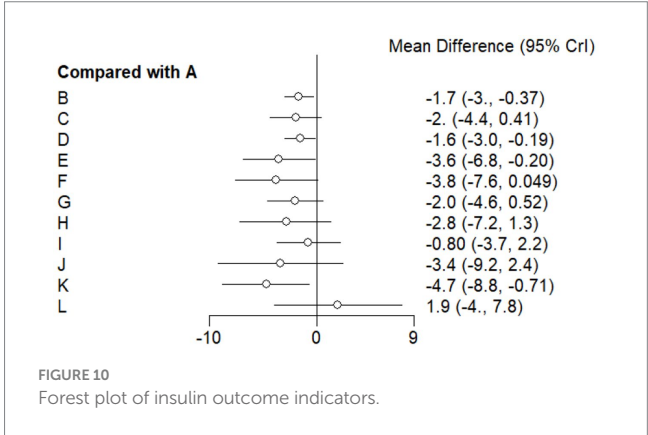
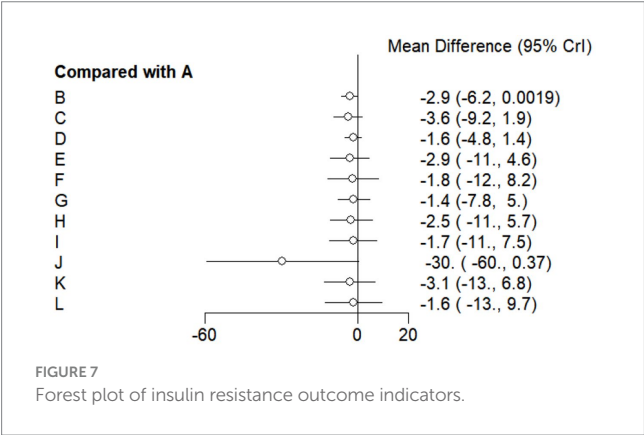
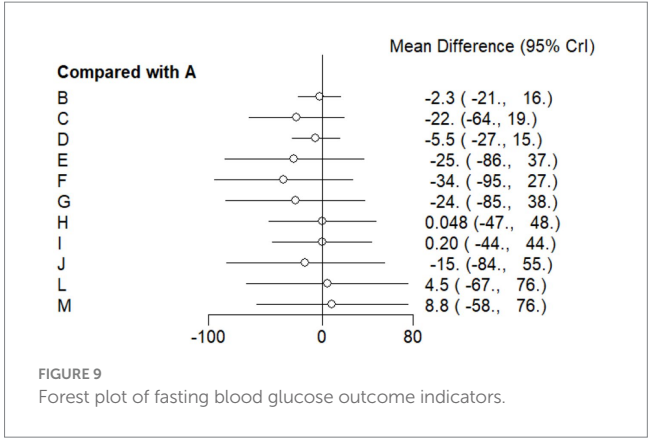
TABLE 5 Subgroup analysis of exercise intervention frequency and duration of single exercise intervention.

| Index                   | Compare types | Effect value            | <i>P</i> |
|-------------------------|---------------|-------------------------|----------|
| Insulin resistance      | 3 times/week  | −1.059 (−1.700, −0.418) | 0.001    |
|                         | >3 times/week | −0.455 (−1.028, 0.119)  | 0.120    |
|                         | 45 min        | −0.983 (−1.941, −0.024) | 0.044    |
|                         | 60 min        | −0.934 (−1.729, −0.139) | 0.021    |
|                         | 30 min        | −0.599 (−1.803, 0.605)  | 0.330    |
|                         | Total         | −0.868 (−1.364, −0.372) | 0.001    |
| Glycosylated hemoglobin | 3 times/week  | −1.068 (−1.495, −0.641) | 0.000    |
|                         | >3 times/week | −0.683 (−1.134, −0.231) | 0.003    |
|                         | 45 min        | −1.105 (−1.507, −0.703) | 0.000    |
|                         | 60 min        | −0.906 (−1.466, −0.345) | 0.002    |
|                         | 30 min        | −0.100 (−0.777, 0.577)  | 0.772    |
|                         | total         | −0.955 (−1.285, −0.624) | 0.000    |
| Fasting blood sugar     | 3 times/week  | −0.270 (−0.926, 0.386)  | 0.419    |
|                         | >3 times/week | 0.053 (−0.945, 1.052)   | 0.916    |
|                         | 45 min        | −1.108 (−1.838, −0.379) | 0.003    |
|                         | 60 min        | 0.933 (−0.063, 1.928)   | 0.066    |
|                         | 30 min        | −0.730 (−1.318, −0.143) | 0.015    |
|                         | total         | −0.214 (−0.746, 0.318)  | 0.430    |
| Insulin                 | 3 times/week  | −1.133 (−1.856, −0.410) | 0.002    |
|                         | >3 times/week | −0.144 (−1.471, 1.036)  | 0.811    |
|                         | 45 min        | −0.878 (−1.814, 0.059)  | 0.066    |
|                         | 60 min        | −1.375 (−2.731, −0.020) | 0.047    |
|                         | 30 min        | −0.525 (−2.005, 0.954)  | 0.486    |
|                         | total         | −0.896 (−1.471, −0.320) | 0.002    |



Sensitivity analysis

This study conducted sensitivity analyses via R software, as shown in Figures 11–14. The meta-analysis results for IR, HbA1c, FBS, and FINS outcomes remained stable, with no evidence of significant heterogeneity detected.



## Heterogeneity test

This study used Egger's and Begg's tests to assess heterogeneity among the included outcome measures. The results indicated significant heterogeneity for IR, HbA1c, FBS, and FINS outcomes. The detailed results are presented in [Table 9](#).

## Regression analysis

This study employed Stata software to perform meta-regression analyses to identify sources of heterogeneity among the included

studies. We treated the pooled effect sizes as the dependent variable and used intervention duration and frequency as covariates to construct the meta-regression model. The results indicated that combined exercise and vitamin interventions did not reveal significant sources of heterogeneity for IR, FBS, or FINS outcomes ( $p > 0.05$ ). Similarly, intervention duration and frequency did not account for heterogeneity in hemoglobin A1c outcomes ( $p > 0.05$ ). However, heterogeneity in HbA1c outcomes was detected ( $p < 0.05$ ). The detailed results are presented in [Table 10](#).

## Evaluation of evidence quality

This study used the GRADE framework to evaluate the quality of the included outcome measures. The assessment indicated that IR, HbA1c, FBS, and FINS outcomes were moderate. The detailed results are presented in [Figure 15](#).

## Discussion

This study employed network meta-analysis to evaluate the effects of combined exercise and vitamin interventions on insulin resistance and related metabolic indicators in patients with T2D. The traditional meta-analysis results indicated that intervention periods of both  $<12$  weeks and  $>12$  weeks significantly improved insulin resistance

TABLE 6 Inclusion of study trajectory density information.

| Index                   | Compare types    | Bandwidth |
|-------------------------|------------------|-----------|
| Insulin resistance      | Density of d.A.B | 0.1498    |
|                         | Density of d.A.C | 0.2709    |
|                         | Density of d.A.D | 0.1507    |
|                         | Density of d.A.E | 0.3672    |
|                         | Density of d.A.F | 0.4794    |
|                         | Density of d.A.G | 0.3052    |
|                         | Density of d.A.H | 0.3952    |
|                         | Density of d.A.I | 0.447     |
|                         | Density of d.A.J | 0.1483    |
|                         | Density of d.A.K | 0.48      |
|                         | Density of d.A.L | 0.5443    |
|                         | Density of d.A.M | 0.5435    |
|                         | Density of d.A.N | 0.2284    |
|                         | Density of d.A.O | 0.3037    |
|                         | Density of d.A.P | 0.1962    |
|                         | Density of d.A.Q | 0.4927    |
|                         | Density of d.A.R | 0.479     |
|                         | Density of d.A.S | 0.5455    |
|                         | Density of d.A.T | 0.4794    |
|                         | Density of d.A.U | 0.4929    |
|                         | Density of sd.d  | 0.08804   |
| Glycosylated hemoglobin | Density of d.A.B | 0.8906    |
|                         | Density of d.A.C | 2.052     |
|                         | Density of d.A.D | 1.033     |
|                         | Density of d.A.E | 2.971     |
|                         | Density of d.A.F | 2.962     |
|                         | Density of d.A.G | 2.969     |
|                         | Density of d.A.H | 2.301     |
|                         | Density of d.A.I | 2.139     |
|                         | Density of d.A.J | 3.409     |
|                         | Density of d.A.L | 3.512     |
|                         | Density of d.A.M | 3.265     |
|                         | Density of d.A.N | 1.505     |
|                         | Density of sd.d  | 0.4257    |
| Insulin                 | Density of d.A.B | 0.06296   |
|                         | Density of d.A.C | 0.1177    |
|                         | Density of d.A.D | 0.06826   |
|                         | Density of d.A.E | 0.1613    |
|                         | Density of d.A.F | 0.1845    |
|                         | Density of d.A.G | 0.1234    |
|                         | Density of d.A.H | 0.2068    |
|                         | Density of d.A.I | 0.1412    |
|                         | Density of d.A.J | 0.2884    |
|                         | Density of d.A.K | 0.1979    |

(Continued)

TABLE 6 (Continued)

| Index               | Compare types    | Bandwidth |
|---------------------|------------------|-----------|
|                     | Density of d.A.L | 0.2945    |
|                     | Density of d.A.M | 0.2959    |
|                     | Density of d.A.N | 0.1466    |
|                     | Density of d.A.O | 0.1252    |
|                     | Density of d.A.P | 0.07999   |
|                     | Density of d.A.Q | 0.1897    |
|                     |                  |           |
| Fasting blood sugar | Density of d.A.B | 0.8906    |
|                     | Density of d.A.C | 2.052     |
|                     | Density of d.A.D | 1.033     |
|                     | Density of d.A.E | 2.971     |
|                     | Density of d.A.F | 2.962     |
|                     | Density of d.A.G | 2.969     |
|                     | Density of d.A.H | 2.301     |
|                     | Density of d.A.I | 2.139     |
|                     | Density of d.A.J | 3.409     |
|                     | Density of d.A.L | 3.512     |
|                     | Density of d.A.M | 3.165     |
|                     | Density of d.A.N | 1.505     |
|                     | Density of d.A.O | 2.258     |
|                     | Density of d.A.P | 1.19      |
|                     | Density of d.A.S | 3.347     |
|                     | Density of d.A.T | 2.709     |
|                     | Density of sd.d  | 0.4257    |
|                     |                  |           |

and related indicators. Except for the effects of combined vitamin interventions on HbA1c, single exercise or single vitamin interventions on fasting blood glucose, and combined exercise interventions on FINS levels, all other intervention strategies produced significant improvements in IR and associated metrics. Dose–response subgroup analysis revealed that vitamin supplementation at 4,100–7,500 IU/day combined with exercise at approximately 4 MET, performed three times per week with each session lasting 45–60 min, produced optimal improvements in insulin resistance and related metabolic indicators.

Network meta-analysis further demonstrated that probiotic supplementation most effectively improved insulin resistance in T2D patients; combined exercise and vitamin interventions had the greatest effect on HbA1c; vitamin C supplementation most significantly improved FBS and insulin levels; and combined fatty acid and exercise interventions had the strongest effect on FINS levels. Specifically, interventions with periods >12 weeks or <12 weeks, exercise performed three times per week, and single-session durations of 45–60 min at ~4 MET, combined with weekly vitamin supplementation of 5,000 IU achieved the most pronounced effects on IR and related outcomes. These findings provide evidence-based guidance for designing exercise plus vitamin intervention programs for T2D patients.

The results highlight the importance of specific intervention doses and intensities. Exercise at  $\leq 4$  MET significantly improved insulin resistance and insulin levels ( $p < 0.01$ ) and significantly

modulated HbA1c ( $p < 0.01$ ) and FBS ( $p < 0.05$ ). Vitamin supplementation at 4,100–7,500 IU/day significantly affected all measured outcomes except HbA1c. Furthermore, combining exercise with vitamin and nutrient supplementation produced even greater improvements in IR and related indicators. Exercise not only reduces body weight but also enhances glycemic control, decreases body fat, and improves insulin responsiveness. Vitamins reduce oxidative stress by scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby improving insulin signaling pathways.

Insulin serves as a central regulator of metabolic homeostasis, and dysregulation of insulin secretion and action is closely linked

TABLE 7 Consistency test of insulin resistance and corresponding indicators.

| Index                   | Compare types | <i>P</i> |
|-------------------------|---------------|----------|
| Insulin resistance      | d.B.C         | 0.099550 |
|                         | d.B.D         | 0.473625 |
|                         | d.B.I         | 0.984200 |
|                         | d.B.N         | 0.023125 |
|                         | d.B.P         | 0.643725 |
|                         | d.C.D         | 0.717500 |
|                         | d.C.N         | 0.781750 |
|                         | d.C.P         | 0.776525 |
| Glycosylated hemoglobin | d.B.C         | 0.565375 |
|                         | d.B.D         | 0.567775 |
|                         | d.B.I         | 0.738125 |
|                         | d.B.N         | 0.206625 |
|                         | d.B.P         | 0.736200 |
|                         | d.C.D         | 0.640075 |
|                         | d.C.N         | 0.341800 |
|                         | d.C.P         | 0.471850 |
|                         | d.G.O         | 0.714450 |
| Fasting blood sugar     | d.B.C         | 0.688525 |
|                         | d.B.D         | 0.879550 |
|                         | d.B.I         | 0.975625 |
|                         | d.B.N         | 0.766325 |
|                         | d.B.P         | 0.554425 |
|                         | d.C.D         | 0.749575 |
|                         | d.C.N         | 0.641250 |
|                         | d.C.P         | 0.900200 |
| Insulin                 | d.B.C         | 0.251450 |
|                         | d.B.D         | 0.394850 |
|                         | d.B.I         | 0.678950 |
|                         | d.B.N         | 0.008875 |
|                         | d.B.P         | 0.916325 |
|                         | d.C.D         | 0.898250 |
|                         | d.C.N         | 0.133575 |
|                         | d.C.P         | 0.885075 |
|                         | d.G.O         | 0.196125 |

to modern sedentary lifestyles, overnutrition, and metabolic syndrome, which are key contributors to T2D development. When pancreatic  $\beta$ -cells fail to compensate for IR, hyperglycemia occurs, promoting T2D progression. This process involves  $\beta$ -cell oxidative stress, inflammation, and disrupted redox signaling, which are often triggered by chronic nutrient overload leading to lipotoxicity and glucotoxicity (6). Vitamin D (VitD) exerts multiple metabolic regulatory effects via its nuclear receptor: it protects mitochondrial function by upregulating components of the respiratory chain, thereby reducing oxidative stress-mediated vascular complications; for example, 2,000 IU/day VitD supplementation for 3 months reduces DNA oxidative damage (7, 8). VitD also regulates  $\beta$ -cell  $\text{Ca}^{2+}$  flux as a chemical messenger, influencing insulin secretion by modulating extracellular  $\text{Ca}^{2+}$  concentration and membrane  $\text{Ca}^{2+}$  transport. VitD deficiency impairs  $\beta$ -cell secretory function, while supplementation (2,000–7,500 IU/day) restores intracellular  $\text{Ca}^{2+}$  levels and enhances insulin secretion (9). VitD deficiency also elevates parathyroid hormone (PTH) and induces mild pancreatic inflammation, both of which are related to IR (10). Supplementation increases anti-inflammatory cytokine IL-10 and decreases the proinflammatory cytokines TNF- $\alpha$ , IL-6, IL-12, and IFN- $\gamma$ , thereby improving immune homeostasis and IR (11).

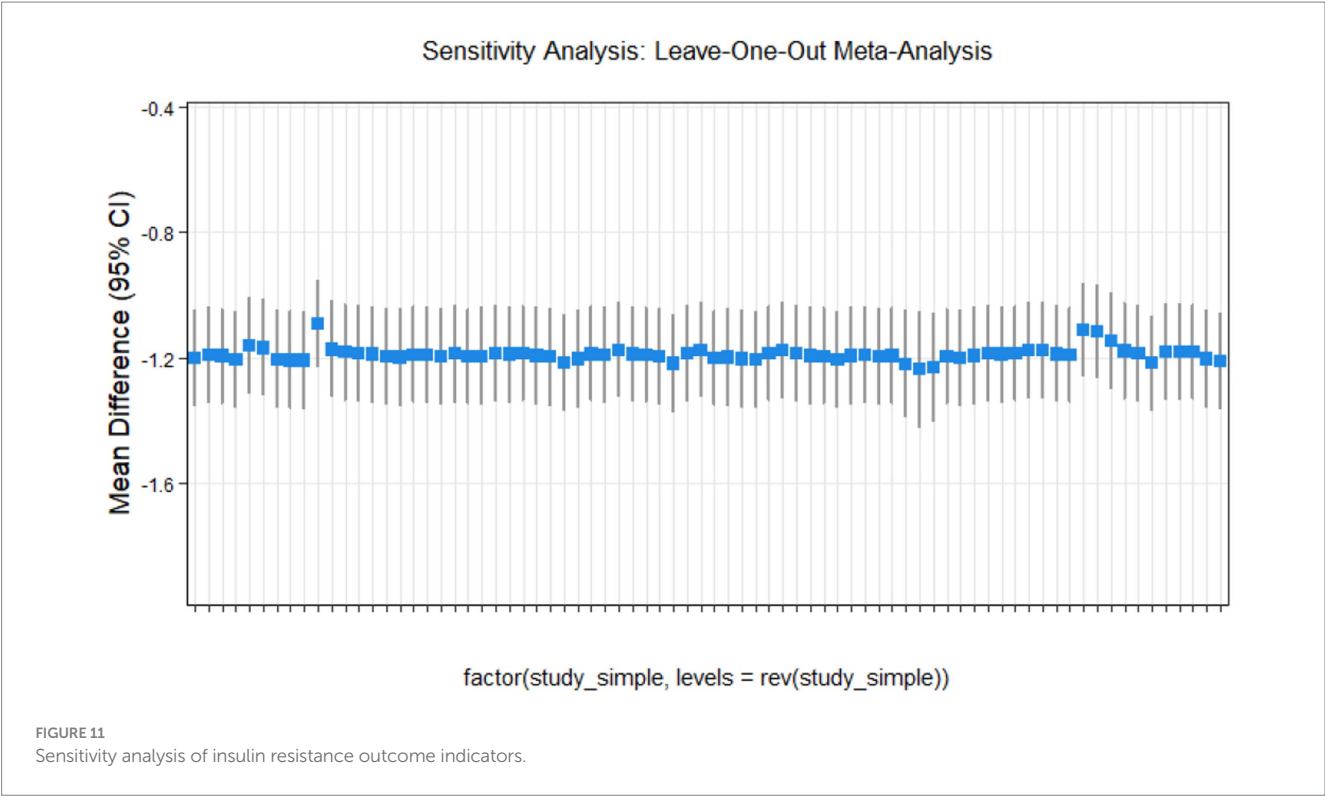
Clinical studies support these mechanisms. Twelve weeks of progressive endurance cycling (2–3 sessions/week, 1 h/session at 65–80% maximum heart rate) combined with 1,000 IU/day VitD3 did not improve HOMA-IR but significantly reduced FBS (11.9% change, effect size 0.65,  $p < 0.05$ ) (12). Higher-dose interventions (50,000 IU of VitD weekly for 8 weeks) normalized serum 25-hydroxyvitamin D levels ( $p < 0.001$ ) and significantly reduced FBS ( $p = 0.04$ ), FINS ( $p = 0.02$ ), and HOMA-IR ( $p = 0.007$ ) (13). Another multi-arm study also demonstrated that 8 weeks of aerobic exercise (30 min, 50–75% heart rate reserve, 3 times per week) combined with 25 min of resistance training, along with daily supplementation of 4,000 IU of vitamin D<sub>3</sub>, significantly reduced HOMA-IR [ $F = 24.07$ ;  $p < 0.001$ ], FINS levels [ $F = 17.97$ ;  $p < 0.001$ ], and FBS [ $F = 11.28$ ;  $p < 0.001$ ] compared to the placebo group. However, the combination of vitamin D<sub>3</sub> and exercise resulted in the highest percentage reductions (–20.73, –10.68%, –11.54%, respectively) (14). Furthermore, daily supplementation of 600 mg of calcium with 60 min of aerobic and resistance exercise also significantly reduced FBS, FINS, IR levels, and pro-inflammatory cytokines TNF- $\alpha$  and IL-6 ( $p < 0.005$ ) compared to either exercise alone, vitamin D intervention, or the placebo group. The combination group had higher levels of 25(OH)D and fasting C-peptide than the vitamin D group, exercise group, and placebo group, and lower HbA1c levels than the other groups ( $p < 0.05$ ). Additionally, the combination group exhibited lower levels of TNF- $\alpha$  and IL-6 compared to the vitamin D, exercise, and placebo groups, with statistically significant differences ( $p < 0.05$ ) (15).

Exercise improves glucose uptake and metabolism through multiple pathways, including enhancing insulin sensitivity, promoting cellular glucose transport, and reducing fat accumulation, making it a critical intervention for T2D management (16). The regulation of blood glucose and fatty acid levels depends on energy utilization patterns: short-duration, high-intensity exercise relies primarily on glycogen, whereas long-duration, low-intensity exercise depends on fatty acid metabolism. Exercise intensity modulates glucose utilization via the dynamic balance between FINS and counterregulatory hormones such as glucagon, epinephrine, and cortisol (17, 18).

TABLE 8 Cumulative probability results (SUCRA values) of network meta-analysis on insulin resistance and corresponding indicators under different intervention methods.

| Intervention measures | Insulin resistance | Fasting blood sugar | Insulin | Glycosylated hemoglobin |
|-----------------------|--------------------|---------------------|---------|-------------------------|
| A                     | 0.262              | 0.309               | 0.140   | 0.164                   |
| B                     | 0.574              | 0.356               | 0.376   | 0.610                   |
| C                     | 0.611              | 0.643               | 0.430   | 0.679                   |
| D                     | 0.438              | 0.415               | 0.357   | 0.706                   |
| E                     | 0.551              | 0.636               | 0.648   | 0.365                   |
| F                     | 0.463              | 0.729               | 0.671   | 0.553                   |
| G                     | 0.427              | 0.625               | 0.436   | 0.466                   |
| H                     | 0.509              | 0.363               | 0.552   | 0.350                   |
| I                     | 0.455              | 0.356               | 0.270   | 0.370                   |
| J                     | 0.959              | 0.534               | 0.604   | 0.358                   |
| K                     | 0.541              | *                   | 0.770   | 0.363                   |
| L                     | 0.454              | 0.350               | 0.124   | *                       |
| M                     | 0.323              | 0.304               | 0.094   | *                       |
| N                     | 0.523              | 0.561               | 0.348   | 0.608                   |
| O                     | 0.576              | 0.700               | 0.794   | 0.480                   |
| P                     | 0.538              | 0.593               | 0.539   | 0.968                   |
| Q                     | 0.442              | *                   | 0.822   | 0.510                   |
| R                     | 0.521              | *                   | 0.733   | 0.328                   |
| S                     | 0.401              | 0.479               | 0.496   | *                       |
| T                     | 0.476              | 0.547               | 0.747   | 0.622                   |
| U                     | 0.451              | *                   | 0.547   | *                       |

\*: None.



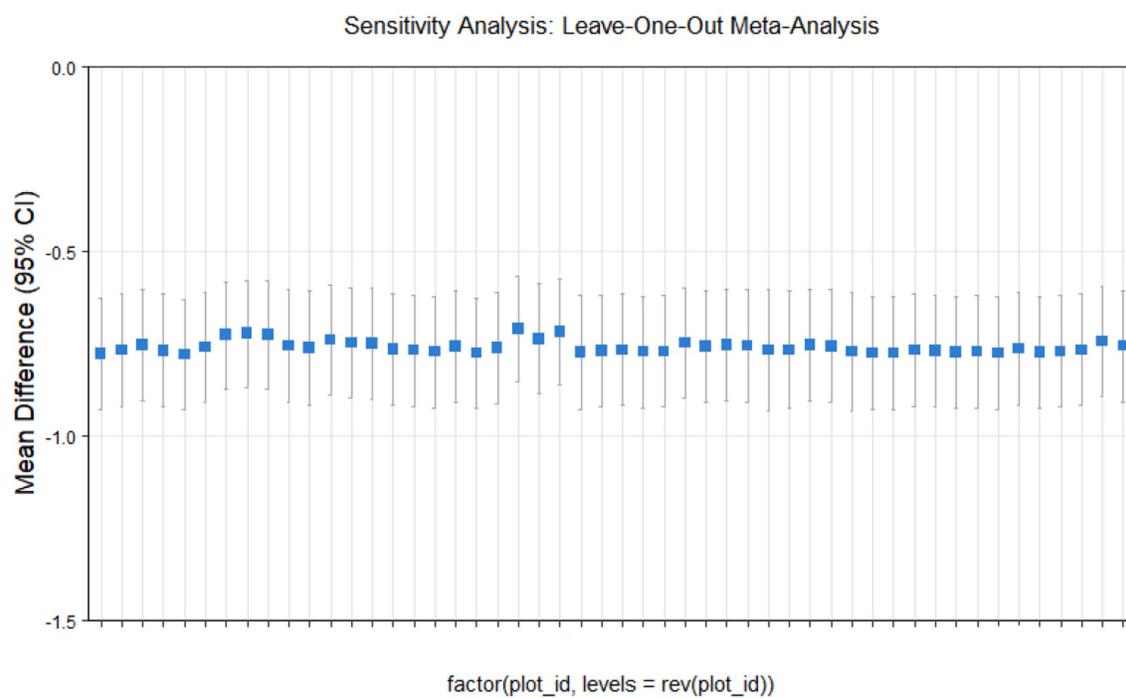


FIGURE 12  
Sensitivity analysis of glycated hemoglobin outcome indicators.

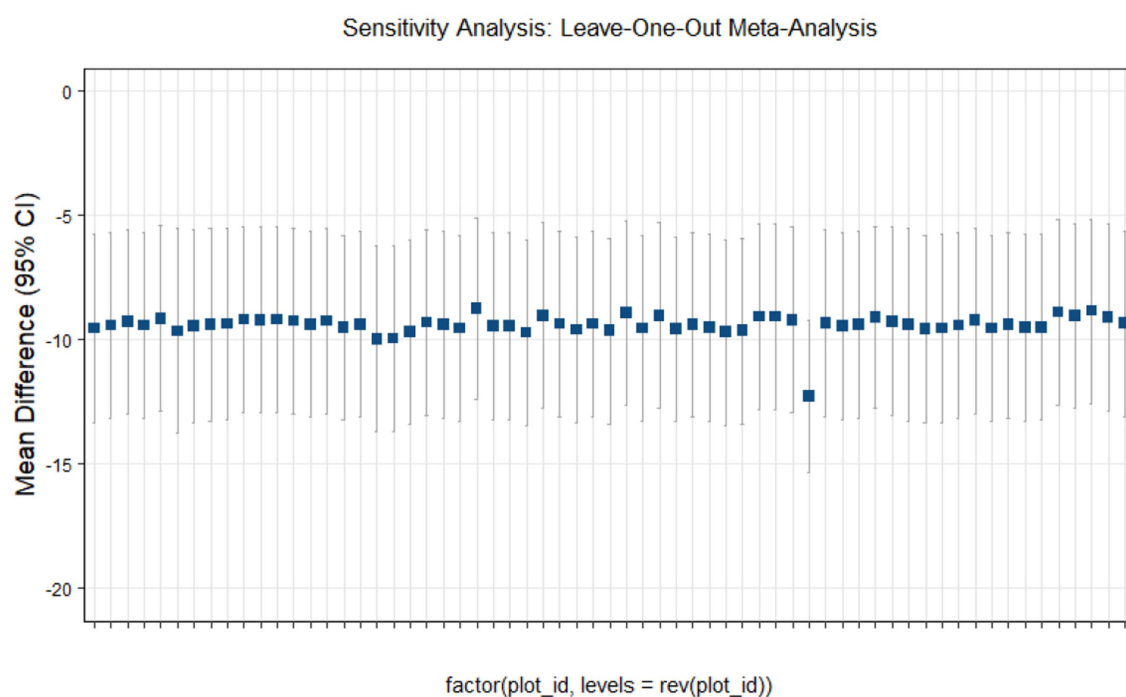


FIGURE 13  
Sensitivity analysis of fasting blood glucose outcome indicators.

Clinical evidence shows that 12 weeks of low- to moderate-intensity running (40 min/session) significantly improved HOMA-IR ( $F(1,144) = 89.29$ ,  $p < 0.001$ ), fasting insulin ( $F(1,144) = 129.10$ ,

$p < 0.001$ ), FINS ( $F(1,144) = 12.193$ ,  $p < 0.001$ ), postprandial glucose ( $F(1,144) = 53.015$ ,  $p < 0.001$ ), and HbA1c ( $F(1,144) = 80.050$ ,  $p < 0.001$ ) (19). Twelve weeks of combined moderate-intensity

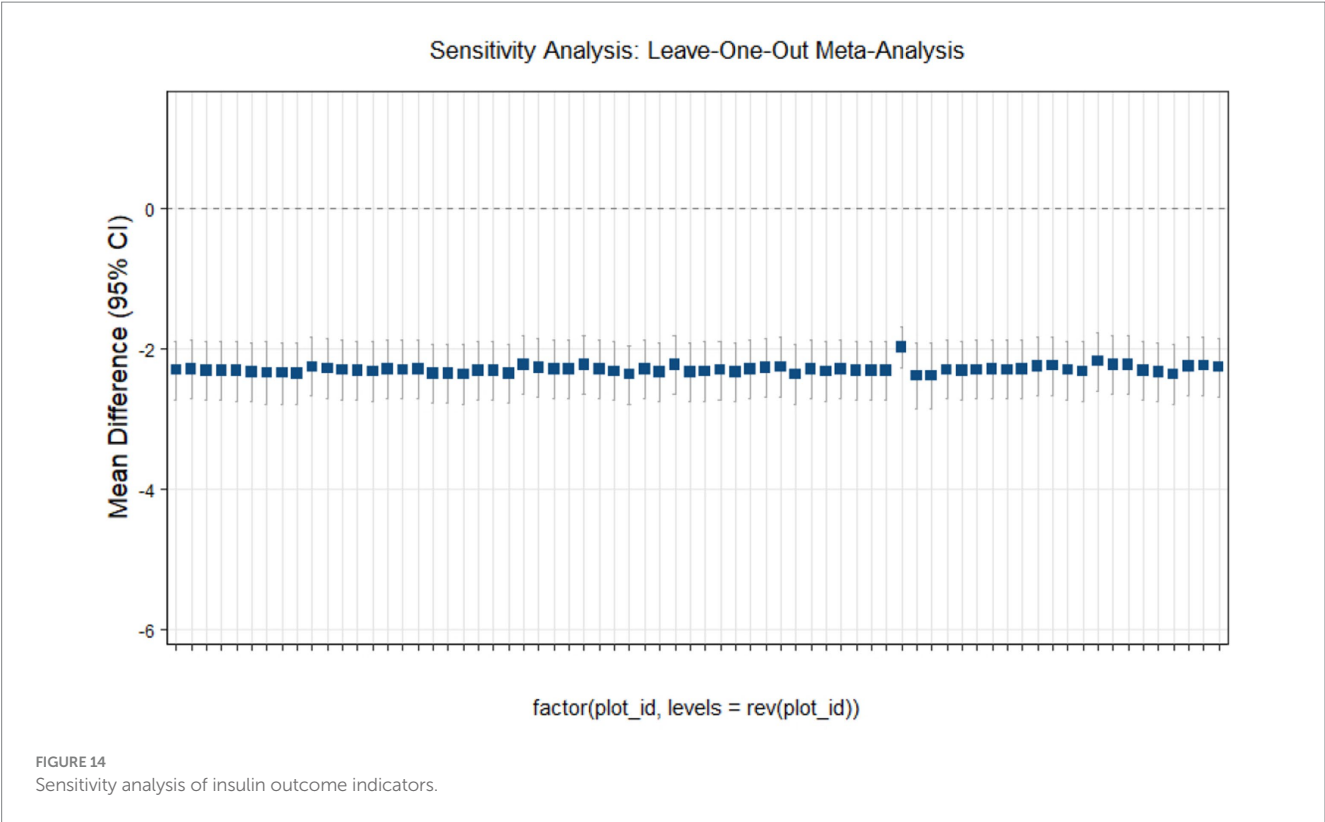


TABLE 9 Heterogeneity test table for insulin resistance and corresponding indicators.

| Outcome indicators      | Egger's test (P) | Begg's test (P) |
|-------------------------|------------------|-----------------|
| Insulin resistance      | 0.000            | 0.000           |
| Glycosylated hemoglobin | 0.030            | 0.001           |
| Fasting blood sugar     | 0.010            | 0.000           |
| Insulin                 | 0.000            | 0.000           |

walking (30 min) or high-intensity interval training (28 min) performed three times weekly also significantly improved fasting glucose, HbA1c, insulin, and HOMA-IR (20). Aerobic exercise performed three times per week for 25 weeks, totaling 75 min, or combined aerobic and resistance training, significantly reduced fasting blood glucose, improved glycemic control, and lowered plasma insulin and insulin resistance. However, the combined exercise group showed better outcomes in fasting blood glucose, HbA1c, insulin resistance index, peak exercise load, lean body mass, and overall quality of life scores compared to the aerobic-only group ( $p < 0.05$ ) (21).

However, exercise effects vary. Ten weeks of resistance or endurance training (3 sessions/week, 40 min/session) significantly reduced insulin resistance but did not significantly improve FINS levels ( $p > 0.05$ ) (21). Mechanistically, exercise enhances insulin-mediated glucose uptake in skeletal muscle, with resistance training resulting in particularly pronounced improvements, thereby reducing overall insulin dependence. A multiarm trial confirmed that 12 weeks of aerobic, resistance, or combined exercise (3 sessions/week, ~5.5 MET) reduced fasting glucose, but

TABLE 10 Regression analysis of insulin resistance and corresponding indicators.

| Outcome indicators      | _ES     | (95% Conf. Interval)    | T     | P     |
|-------------------------|---------|-------------------------|-------|-------|
| Insulin resistance      | Week    | (−1.189681, 0.1976864)  | −1.43 | 0.158 |
|                         | Methods | (−0.7155258, 0.1739014) | −1.22 | 0.228 |
|                         | –       | (−1.593843, 1.947468)   | 0.20  | 0.842 |
| Glycosylated hemoglobin | Week    | (−0.0714416, 0.7453682) | 1.67  | 0.103 |
|                         | Methods | (−0.2460263, 0.2547492) | 0.04  | 0.972 |
|                         | –       | (−2.940112, −0.669356)  | −3.21 | 0.003 |
| Fasting blood sugar     | Week    | (−0.2485223, 1.737867)  | 1.51  | 0.138 |
|                         | Methods | (−0.8904513, 0.1703226) | −1.37 | 0.178 |
|                         | –       | (−4.500902, 0.4960883)  | −1.61 | 0.113 |
| Insulin                 | Week    | (−0.2428625, 1.225148)  | 1.34  | 0.185 |
|                         | Methods | (−0.682556, 0.1502671)  | −1.28 | 0.205 |
|                         | –       | (−3.210808, 0.2367608)  | −1.73 | 0.089 |

Author(s):  
Date: 2025-08-16  
Question: Should Overall effect analysis be used for [health problem]?  
Settings:  
Bibliography: [Intervention] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

| Quality assessment                                                                                                                                   |                   |                      |                          |                         |                        |                      | No of patients          |         | Effect            |                                     | Quality           | Importance |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------|--------------------------|-------------------------|------------------------|----------------------|-------------------------|---------|-------------------|-------------------------------------|-------------------|------------|
| No of studies                                                                                                                                        | Design            | Risk of bias         | Inconsistency            | Indirectness            | Imprecision            | Other considerations | Overall effect analysis | Control | Relative (95% CI) | Absolute                            |                   |            |
| Effect of exercise combined with vitamin intervention on insulin resistance in type 2 diabetes patients (Better indicated by lower values)           |                   |                      |                          |                         |                        |                      |                         |         |                   |                                     |                   |            |
| 33                                                                                                                                                   | randomised trials | serious              | no serious inconsistency | no serious indirectness | no serious imprecision | none                 | 1370                    | 1374    | -                 | SMD 1.04 lower (1.3 to 0.79 lower)  | ⊕⊕⊕⊕O<br>MODERATE |            |
| Effect of exercise combined with vitamin intervention on glycosylated hemoglobin in patients with type 2 diabetes (Better indicated by lower values) |                   |                      |                          |                         |                        |                      |                         |         |                   |                                     |                   |            |
| 21                                                                                                                                                   | randomised trials | serious <sup>1</sup> | no serious inconsistency | no serious indirectness | no serious imprecision | none                 | 917                     | 909     | -                 | SMD 0.96 lower (1.21 to 0.71 lower) | ⊕⊕⊕⊕O<br>MODERATE |            |
| Effect of exercise combined with vitamin intervention on fasting blood glucose in patients with type 2 diabetes (Better indicated by lower values)   |                   |                      |                          |                         |                        |                      |                         |         |                   |                                     |                   |            |
| 26                                                                                                                                                   | randomised trials | serious <sup>1</sup> | no serious inconsistency | no serious indirectness | no serious imprecision | none                 | 1024                    | 1037    | -                 | SMD 1.02 lower (1.42 to 0.63 lower) | ⊕⊕⊕⊕O<br>MODERATE |            |
| Effect of exercise combined with vitamin intervention on insulin in patients with type 2 diabetes (Better indicated by lower values)                 |                   |                      |                          |                         |                        |                      |                         |         |                   |                                     |                   |            |
| 28                                                                                                                                                   | randomised trials | serious <sup>1</sup> | no serious inconsistency | no serious indirectness | no serious imprecision | none                 | 1130                    | 1138    | -                 | SMD 0.87 lower (1.12 to 0.62 lower) | ⊕⊕⊕⊕O<br>MODERATE |            |

<sup>1</sup> There are significant biases in randomization, allocation concealment, and blinding in the included studies

FIGURE 15  
Quality of evidence for insulin resistance and corresponding outcome indicators.

improvements in HOMA-IR were significant only in the aerobic and combined exercise groups (22).

Beyond metabolic regulation, exercise confers systemic benefits: it enhances cardiac function, lowers blood pressure, improves lipid profiles (reducing LDL-C and increasing HDL-C), and mitigates disease risk. Exercise also alleviates psychological stress, indirectly lowering glucose levels and reducing diabetes complications (18, 23). Studies have shown that exercise can improve HbA1c baseline levels by 10–20%, significantly optimizing T2D and insulin resistance status (24). This study also revealed marked improvements in HbA1c, which were further enhanced when vitamin supplementation was combined with vitamin C, suggesting a synergistic effect that warrants further investigation.

Limitations and implications

This study represents the first effort to apply network meta-analysis and dose–response analysis to evaluate the effects of combined exercise and vitamin interventions on insulin resistance and related metabolic indicators in patients with type 2 diabetes (t2d). However, several limitations should be noted: 1. Limited standardization of outcomes: the included studies used inconsistent measurement units for key outcomes such as blood glucose (mg/dl vs. mmol/l), which may increase heterogeneity and reduce the precision of effect size estimates. 2. Subgroup analysis constraints: The analysis did not fully account for covariates such as sex, disease duration, or comorbidities (e.g., obesity, cardiovascular disease), limiting the ability to detect differential intervention effects across specific populations. 3. Intervention heterogeneity: differences in exercise modality (aerobic, resistance, or combined), intensity control, and vitamin supplementation (e.g., d3 vs. d2, timing of administration) may obscure the specificity of optimal intervention protocols. 4. Limited strength of evidence: direct comparison

studies for some interventions, such as specific vitamin–plus–exercise combinations, are scarce. Network meta-analysis relies on indirect evidence to infer effects, which may reduce the robustness of conclusions. 5. Short follow-up periods: Most included trials had intervention durations ≤24 weeks, limiting the ability to assess long-term (≥1 year) effects on insulin resistance and diabetes-related complications.

Implications for future research: 1. To increase study design rigor, future large-scale, multidimensional RCTs should standardize outcome measurement and reporting, objectively monitor exercise intensity, evaluate vitamin bioavailability, and clearly document intervention details to minimize methodological heterogeneity. 2. Refined subgroup analyses: future studies should stratify t2d patients by sex, age, disease duration, and comorbidities to explore differential responses and support the development of individualized intervention strategies. 3. Precision intervention exploration: RCTs should investigate varying vitamin doses (e.g., 2000 iu vs. 4,100–7,500 iu), exercise intensities (4 met vs. higher), and combined intervention modes, using dose–response models to identify optimal thresholds. 4. Mechanistic investigation: Integrating molecular biology techniques, such as measuring inflammatory cytokines, oxidative stress markers, and gut microbiota composition, can clarify the biological mechanisms underlying exercise- and vitamin-mediated improvements in insulin resistance, including mitochondrial function regulation and the Ca<sup>2+</sup> signaling pathway. 5. Long-term effect evaluation: Cohort studies with ≥1 year follow-up should examine sustained the impacts on diabetes and related complications, while evaluating adherence to interventions to provide comprehensive evidence for clinical practice. 6. Integrated multimodal interventions: Future research should explore combined strategies involving exercise, vitamins, dietary modifications, and psychological interventions, evaluating their synergistic effects on metabolic syndrome management and enhancing overall t2d prevention and control.

## Conclusion

Combined vitamin interventions produced the greatest improvements in FINS levels in patients with type 2 diabetes; vitamin C supplementation most effectively reduced FBS; Probiotic intervention has the best effect on IR; probiotic intervention has the best effect on insulin resistance and intervention and combined vitamin-plus-exercise interventions achieved the optimal effect on HbA1c. Moreover, vitamin supplementation at 4,100–7,500 IU/day, exercise at approximately 4 MET, and exercise three times per week for 45–60 min per session produced maximal improvements in insulin resistance and related metabolic indicators. Given the limitations of this study, high-quality experimental research is still needed to further validate these findings.

## Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

## Author contributions

FD: Writing – original draft, Formal analysis, Software, Data curation. YJ: Funding acquisition, Supervision, Writing – review & editing. HK: Writing – review & editing, Supervision. YF: Data curation, Writing – review & editing. HZ: Data curation, Writing – review & editing. JZ: Data curation, Writing – review & editing.

## Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study has received financial support from the key project of the “2024 Higher Education Scientific Research Planning Project” — “Construction and Implementation of Safety First Aid Education in College Physical

Education Courses under the Healthy China Strategy” (Project No. 24BJ0305), funded by the Chinese Society of Higher Education. This support provides directional guidance at the macro level for college physical education research and ensures the smooth progress of the study.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2025.1608634/full#supplementary-material>

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