Meta-analysis

Which intervention is optimal to control blood glucose and improve physical performance in the elderly living with type 2 diabetes mellitus? A network meta-analysis

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Background and Objectives: This study aimed to find the optimal intervention available to both control blood glucose and improve physical function in the geriatric population with T2DM. **Methods and Study Design:** A systemic review and network meta-analysis (NMA) was conducted to assess and rank the comparative efficacy of different interventions on glycosylated hemoglobin A1c (HbAc1), fasting blood glucose (FBG), muscle mass, grip strength, gait speed, lower body muscle strength, and dynamic balance. A total of eight databases were searched for eligible randomized controlled trials (RCTs) that the elderly aged more than 60 years or with mean age ≥ 55 years, the minimal duration of the RCT intervention was 6 weeks, and those lacking data about glycemic level and at least one indicator of physical performance were excluded. The Cochrane risk of bias tool was used to assess the bias of each study included. Bayesian NMA was performed as the main results, the Bayesian meta regression and the frequentist NMA as sensitivity analysis. **Results:** Of the 2266 literature retrieved, 27 RCTs with a total of 2289 older adults were included. Health management provided by health workers exerts beneficial effects that is superior to other interventions at achieving glycemic control, but less marked improvement in physical performance. Exercise combined with cognitive training showed more pronounced improvement in muscle strength, gait speed, and dynamic balance, but ranked behind in decreasing the HbAc1 and FBG. **Conclusions:** Personalized health management combined with physical and cognitive training might be the optimal intervention to both accomplish glycemic control and improvement of physical performance. Further RCTs are needed to validate and assess the confidence of our results from this NMA.

Key Words: type 2 diabetes mellitus, network meta-analysis, aging, physical performance, intervention

INTRODUCTION

One fifth of the geriatric population (≥65 years of age) had diabetes worldwide in 2019,[1] and it is estimated that diabetes will double from 2019 to 2045 among older adults according to the Diabetes Atlas 2021, especially in Asia.[2,3] Type 2 diabetes mellitus (T2DM) has far reaching negative effects on aging health, increasing the risk of impaired physical performance related to fatal falls and life quality.[4,5]

Medications as well as lifestyle changes such as diet, and exercise are the main ways to treat T2DM in older adults.[6] In addition to effectively controlling blood glucose, impaired physical performance such as frailty and sarcopenia occur frequently in the elderly population with T2DM.[7,8] High-energy diet, resistance exercise, individualized health management, psychological training, and combined interventions are recommended to improve muscle mass, muscle strength, or physical performance in elder people with T2DM.[6,7] Several randomized controlled trials (RCTs) were conducted to find an optimal intervention to achieve glycemic control and improve physicalperformance, leading to inconsistent conclusions.[9-12] Identifying the superiority of the different interventions referring to single individual RCTs or pairwise meta-analysis faces challenges. RCTs were generally implemented to compare less than three specific interventions with routine care or no intervention; Traditional meta-analyses need sufficient head-to-head comparisons-covered all available interventions used- derived from published RCTs to assess comparative effectiveness, which is unpractical. While direct comparisons between interventions may not exist, indirect evidence is typically available. Network meta-analysis (NMA) is developed to combine indirect and direct comparisons to compare their relative effects simultaneously.[13]

There has been no systemic review assessing the relative effectiveness of all current interventions used to control blood glucose and improve physical performance in elder adults with T2DM. Therefore, the goal of this

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study is to perform NMA of RCTs to assess the comparative efficacy of different interventions on blood glucose control, muscle mass, muscle strength, and dynamic balance in older adults with T2DM, and establish a rank of these interventions.

METHODS

Search strategy

Four international electronic databases (PubMed, Scopus, Web of Science, and Cochrane Central Registry of Controlled Trials) and four Chinese electronic databases (National Knowledge Infrastructure [CNKI], SinoMed, Wang Fang, and China Science and Technology Journal Database [VIP]) were searched from establishment to until February 20, 2024. Search terms were constructed by the PICOS principle: (P) Population: elderly adults were formally diagnosed with Type 2 Diabetes Mellitus. (I) Intervention: any treatment to improve the glycemic control and physical performance; (C) Comparator: sham interventions, control intervention, or routine or standard health care; (O) Outcomes: HbAc1[%], fasting plasma glucose (FBG, mmol/l), and indicators of assessing physical performance, and (S) Study type: RCTs. Pharmacotherapy (PHARM): any medication to decrease blood glucose such as Metformin, empagliflozin, linagliptin, dapagliflozin, insulin injection, etc. Health management (HEALTH_MA): health care providers (such as nurse, doctors, etc) provide individualized nursing and lifestyle treatments, including weight management program or nutritional recommendation. Physical activity only (PHYS): any type of aerobic exercise, resistance exercise, and balance exercise. Mixed Physical activity (Mixed_PHYS): Any two or more forms of structured exercise including aerobic, resistance, flexibility, or balance exercise.Nutrition supplementation only (NUTR): this includes any nutritional supplementation (such as calcium/vitamin D, protein, etc.). Physical + Psycho-social or cognitive training (PHYS+PSYCH): any form of exercise with any form of psycho-social or cognitive training. Physical + Pharmacotherapy (PHYS+PHARM): any form of exercise with pharmacotherapy. Physical + nutrition supplementation (PHYS + NUTR): any form of exercise with nutritional supplementation (such as calcium/vitamin D, protein, etc.).Physical + Health management (PHYS + HEALTH_MA): any form of exercise with health management provided by health care providers (such as nurses, doctors, etc) with individualized nursing and lifestyle treatments, including weight management programs or nutritional recommendations. Placebo or standard care (PLAC/STD): usual /routine health care, no treatment, placebo. This NMA is described and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[14]

Eligibility criteria

Open published RCTs assessing at least one intervention [health management, mixed physical activity, physical activity only, nutritional supplements, pharmacotherapy] or combination of any two listed interventions for controlling glycemic level and improving physical performance. Studies eligible included: the elderly aged more than 60 years (also included those studies with mean age around or more than 55 years) with or without other chronic diseases or degenerative diseases; written in English or Chinese; the minimal duration of the RCT intervention is 6 weeks. There is no data about glucose indicator (HbAc1 and/or FBG), and at least one indicator of assessing physical activity (muscle mass[kg/m^2], grip strength (kg), gait speed (m/s), lower muscle strength, and dynamic balance) were excluded. In studies where interventions were summarized under the same type, any RCTs with before-after self-control or cross-over design were also excluded.

Outcomes

Glycemic indicators were HbAc1 and FBG (as measured by collecting the fasting venous blood samples using standard procedure). Physical performance measurements included muscle mass (gauged by dual-energy X-ray absorptiometry, bioelectrical impedance, and ultrasonography), grip strength (right handgrip), lower muscle strength (chair stand test in 30 s), gait speed, and dynamic balance (Five-time up and go test).

Study selection

A literature management software called EndNote X21 was employed to manage the search records. In the initial screening phase, the primary duplicates were detected and removed by the EndNote X21, and two reviewers (YXX, YZC) independently screened the studies based on abstract and title. In the deep screening phase, two reviewers (YZC, QYY) further reviewed the abstract of all studies selected from the initial screening phase and determined the eligible studies according to predetermined inclusion criteria. If a disagreement occurs, we resolved it by discussing between three reviewers (YZC and QYY) and the senior reviewer (QY). In the phase of data extraction and assessing risk bias of individual studies, the studies retained from the previous phase were fully reviewed by two independent reviewers (YZC, QYY) to extract data, assess potential risk biases, and exclude any studies according to the exclusion criteria. Any conflict between reviewers was also discussed and resolved in our team (YXX, YZC, QYY, and QY).

Data extraction

A data extraction form was used to record the data of interest: the first author, publication year, country, research setting (participants recruited from hospital or community), follow-up time (weeks), intervention categories and a brief summary of interventions used, sample size (total/female/male), sex-stratified average age (mean value with standard deviation or median value with interquartile range, years), other recorded disease conditions, duration of diabetes (mean value with standard deviation or median value with interquartile range, years), the outcomes of interest reported with mean ± standard deviation (SD) for each intervention or mean difference (MD) ± SD between interventions at the end of the study.

Risk of bias assessment

The risk of bias (ROB) of the RCTs included was assessed following the Cochrane Handbook version 6.1.0 by two independent reviewers (YZC, and QYY).[15] The assessment over seven domains included randomized sequence generation, treatment concealment, blinding of participants and personnel, incomplete outcome data, dropout rate (if retain rate > 10%, follow-up bias exists), and other sources of bias (significantly statistical baseline imbalance, data analysis without the intention-to-treat method). The ROB results for all RCTs were categorized into three levels of ROB regarding the number of domains for which high ROB existed possible: high risk (5 scores or more). Moderate (3 or 4 score), and low risk (2 scores or less). Any conflict was resolved by discussion with a senior reviewer (QY).

Data synthesis and statistical analysis

We began by demonstrating the included RCTs, their intervention characteristics, and their relative effect on the glycemic control and physical performance of evidence available. In each RCT with two-/three arms, under the assumption that the key confounding factors are evenly distributed in comparative interventions, mean difference and its SD at the end of the intervention versus baseline for each arm, or the change of the mean difference, and its SD in the experimental interventions versus control were extracted. If a study had three intervention arms where two arms were classified as the same intervention type, we separated it into two two-arm studies where the experimental intervention versus the control in each study. If the SDs at the end of the follow-up for one intervention group were missing, the SDs in follow-up means were assumed to be equal to SDs in baseline mean values. Missing SD difference between two intervention groups was calculated using the SD formulas according to the different situations of sample size in the two groups:

$\sqrt{[(n_1-1) \times s_1^2 + (n_2 - 1) \times s_2^2] / [n_1 + n_2 - 2]}$ (when the sample size in two groups both < 60)

$\sqrt{(S_1^2 / n_1) + (S_2^2 / n_2)}$ (when the sample size in two groups both ≥ 60)

Second, we conducted the traditional head-to-head frequentist meta-analysis with the random effects model or the fixed effects model according to the I^2 statistic which is the between-study variability (heterogeneity) of the treatment effects within each intervention comparison. If the I^2 statistic was more than 50%, the random effects model would be used, otherwise, the fixed effects model would used.

Third, for each outcome, we generate a network plot to illustrate the geometry of different types of interventions. The nodes represented different interventions and the edge thickness corresponds with the number of studies we included for that head-to-head intervention comparisons. We then conducted a Bayesian random effects NMA using Markov-chain Monte Carlo simulation to allow us to ensure model convergence to estimate the posterior distributions of the parameters and generate the results of the NMA, with model parameters: 1000 burn-in iterations, 100000 actual simulation iterations, and 10 thinning to reduce the required computer memory. A net splitting method was used to check the inconsistency between direct and indirect evidence, using a forest plot to visualize the net split results.[16] When a difference is p value < 0.05, it denotes a significant inconsistency between direct and indirect estimates. Interventions were ranked according to the surface under the cumulative ranking curve (SUCRA) scores, which range from 0% to 100%.[17] The SUCRA scores measure the probability that an intervention is better than another intervention, and the higher the SUCRA scores, the higher the likelihood that an intervention is in the top rank. The pooled effect size estimate for each intervention comparison based on our Bayesian NMA was reported with the posterior median values along with their 95% confidential intervals (CIs).

Fifth, frequentist NMA was performed as a sensitivity analysis to estimate indirect and direct effect size between intervention comparisons. Network meta-regression was performed with consideration of the overall risk of bias of individual study, with the assumption that a common fixed coefficient (β) for the effect of risk of bias across all interventions. When the 95% CI of β did include zero, the risk of bias would indeed not influence the results. When negative effect sizes denote “better” outcomes such as HbAc1, we could predict high overall effects under the situation where the risk of bias is high. Comparison-adjusted funnel plots were used to visually inspect the risk of publication bias in NMA. The funnel plots were applicable based on a specific hypothesis that effects of comparisons in which a new intervention was compared to an older one are asymmetrically distributed.[18] The Egger’s test was used to test the hypothesis. When the test is not significant (p value >0.05), this indicates there are not small-study effects in our NMA. That is there are no “innovative” interventions with superior effects that tend to be found in the published studies.

All NMA were done in R statistical software (version 4.3.1) using “netmeta” and “gemtc” packages that depends on the rjags package. The Just Another Gibbs Sampler (JAGS) software was installed to ensure the successful installation and loading the rjags package.

RESULTS

Literature selection

A total of 2266 studies were initially identified from 8 databases in our NMA. After removing duplicates by EndNote software, 2266 studies were selected to go through deeply screening by reviewing the title and abstract. Of these, 129 were eligible for full-text reviewing, of which 102 were excluded: 21 did not meet the inclusion of aging that participants’ age or mean age > 60 years; 68 did not report the outcomes of interest that demonstrated either the glycemic indicator or only the physical performance; 7 did not meet the RCTs design; 4 studies’ direct comparisons were classified as the same intervention categories; 1 did not be connected into the network graph;10 and 1 was duplicate in which was identified as the same ongoing study.19The study selection process is illustrated in Figure 1.

Characteristics of the included studies

The characteristics of the included studies were described in Table 1. The included RCTs were conducted in Asia (n = 15), America (n = 6),9,12,20-23 Europe (n = 4),[24-27] and Australia (n =2).28,29 Of 15 RCTs conducted in Asia, 6 were in China,[30-35] 5 were in Japan,[36-40] 2 were in Iran,[11,41] 1 was in South Korea,[42] and 1 was in Kuwait.[43] A total of 1889 elder adults with the average age of 66.3 years and

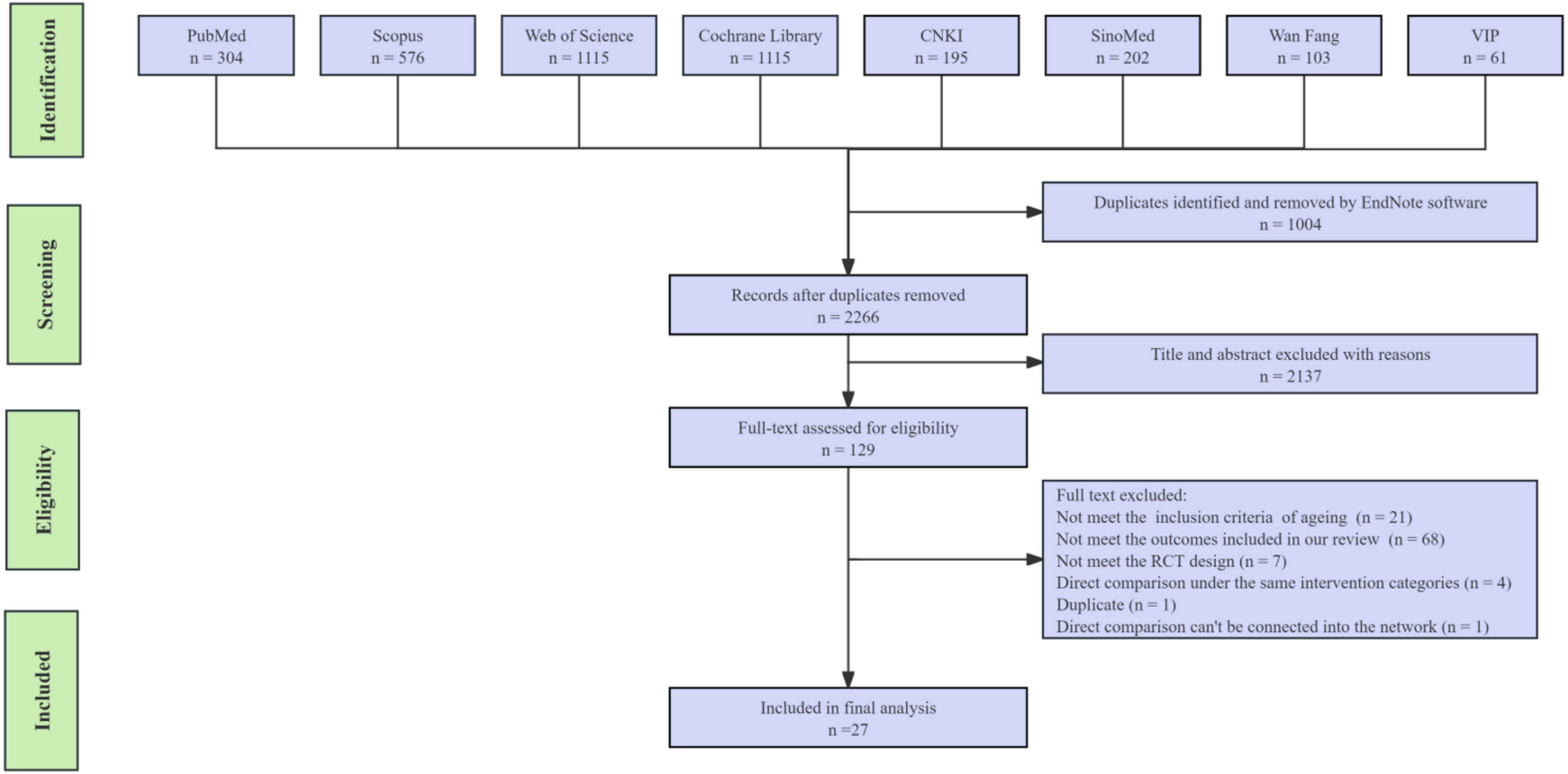

Figure 1. Flow diagram

Table 1. Overview of studies included

Author & Year	Country	Setting	Follow-up time (weeks)	Intervention category	Summary of intervention
Asian countries and regions					
M. M. Ghahfarrokhi, et al, 2024[41]	Iran	Hospital	6	PHYS PHYS PLAC/STD	Functional training (three sessions per week) with 120–125% of the lactate threshold Functional training (five sessions per week) with a 70–75% lactate threshold No exercise
Liu Yang, et al,2023[30]	China	Hospital	12	PHYS+PSYCH PLAC/STD	Baduanjin exercise(60 min per time, 3 times per week) andcognitive training (finger movement, recognition and recall over pictures, attention training using the Schulte Chart, and the counter-counter-counter exercise).25-30 min every time, 3 times per week Routine care
D. Yabe, et al, 2023[36]	Japan	Hospital	52	PHARM PLAC/STD	Oral empagliflozin 10 mg once daily Oral placebo once daily
E. A. Ozairi, et al, 2023[43]	Kuwait	Hospital	32	PHYS PLAC/STD	Home-based resistance exercise plus usual care Usual care
Yun-Da Huang, et al, 2022[31]	China	Hospital	26	Mixed_PHYS PLAC/STD	Yijinjing combined with elastic band exercise five times a week No exercise
Yu-Hsuan Chien, et al, 2022[32]	China	Community	12	PHYS PLAC/STD	Resistance exercises for the upper and lower extremities were performed using sandbags (0.5 kg at the beginning to 1 kg after 1 month) No exercise

Author & Year	Sample size N/F/M	Age[†], year	Additional disease condition	Duration of diabetes*, year	Outcome measures interested
Asian countries and regions					
M. M. Ghahfarrokhi, et al, 2024[41]	16/?/? 16/?/? 16/?/?	66.47±6.61 68.35±5.44 67.76±5.49	Cognitive impairment/dementia MMSE score>23	NA	HbA1c, FBG, hand grip strength, gait speed, FTUG, one-foot standing
Liu Yang, et al, 2023[30]	40/27/13 39/21/18	67.5 ± 3.1 67.4 ± 2.8	Cognitive frailty with MoCA score < 25	NA	HbA1c, grip strength, gait speed
D. Yabe, et al, 2023[36]	64/16/48 63/19/44	74.2 ± 4.9 74.0 ± 5.1	BMI ≥ 22 kg/m^2	12.4±8.2 11.8±7.6	HbA1c, muscle mass, Handgrip strength, Chair stand in 30 sec
E. A. Ozairi, et al, 2023[43]	64/23/41 56/23/33	59.45 ± 8.55 60.99 ± 10.32	None	NA	HbA1c, grip strength
Yun-Da Huang, et al, 2022[31]	26/20/6 21/16/5	63.5 ± 4.7 63.5 ± 4.7	Prediabetes mellitus (FBG< 7.8 mmol/Land/or 7.8 ≤ OGTT2h blood glucose < 11.1mmol/L)	NA	HbA1c, FBG, muscle mass, handgrip strength, gait speed,FTUG, one-foot standing
Yu-Hsuan Chien, et al, 2022[32]	20/15/5 20/18/2	67.6 ± 7.7 67.6 ± 7.7	Possible sarcopenia (recommendation of the 2019 Asian Working Group for Sarcopenia)	17.5±16.3 13.6±7.6	HbA1c, hand grip, muscle mass, chair stand in 30 sec

1RM = 1-repetition maximum, FBG = Fasting blood glucose, HbA1c = glycosylated hemoglobin A1c, IQR = inter-quartile range, SD =standard deviation, MoCA = Montreal cognitive assessment; MMSE = Mini–Mental State Examination; MoCA = Montreal Cognitive Assessment; FTUG = Five-Time up and go test, sec. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only.

[†]Duration of diabetes and age were represented as mean (SD) or median (IQR).

Table 1. Overview of studies included (cont.)

Author & Year	Country	Setting	Follow-up time (weeks)	Intervention category	Summary of intervention
Asian countries and regions					
N. Ghodrati, et al, 2022[11]	Iran	Community	12	Mixed_PHYS PLAC/STD	A combination of aerobic, resistance, and balance exercises performed 3 session per week, 65 min per session No training intervention
J. Matsushita, et al, 2022[37]	Japan	Community	8	PHYS PLAC/STD	Exercise instructions from physical therapists, ≥ 150 min per week at moderate speed, ≥ 30 min per day, with ambulatory accelerometers No exercise with ambulatory accelerometers.
T. Matsuda, et al, 2022[38]	Japan	Hospital	24	NUTR PLAC/STD	Supplementation of 8 g of branched-chain amino acids Supplementation of 7.5 g of soy protein
Chen-Chen Gui, et al, 2021[33]	China	Community	12	PHYS+NUTR PLAC/STD	Exercise prescription with nutritional support. Exercise included 40 regular items such as walking, biking, jogging, and skipping. At least 5 days per week. Nutritional support: individualized prescription over ratio of carbohydrate, protein, and fat according to participants' blood glucose, height, and weight Routine care
R. Bouchi, et al, 2021[39]	Japan	Hospital	24	PHYS+PHARM PHARM	Dapagliflozin 5 mg daily with intensive exercise therapy, including resistance training (three sets of 10 repetitions daily, each training session includes squats, push-ups exercise regarding, latissimus doris, gluteus maximus, and hamstring muscle) Dapagliflozin 5 mg daily with routine care

Author & Year	Sample size N/F/M	Age†, year	Additional disease condition	Duration of diabetes*, year	Outcome measures interested
Asian countries and regions					
N. Ghodrati, et al, 2022[11]	12/12/0 9/9/0	58.8 ± 1.5 55.8 ± 1.5	None	6.3±1.9 6.1±1.7	HbA1c, FBG, gait speed, chair stand in 30 sec, FTUG, one-foot standing
J. Matsushita, et al, 2022[37]	16/2/14 13/2/11	62 (51.5–77) 61 (50.5–68)	None	24.7 (22.5–28.7) 26.4 (22.0–31.1)	HbA1c, FBG, muscle mass, grip strength, gait speed,
T. Matsuda, et al, 2022[38]	21/8/13 15/5/10	73.0 ± 4.0 73.0 ± 4.0	None	21 (16–24) 19 (14–29)	HbA1c, FBG,serum insulin, muscle mass, lower body muscle strength, grip strength
Chen-Chen Gui, et al, 2021[33]	41/14/27 41/18/23	65.04 ± 6.11 66.77 ± 6.93	Sarcopenia identified by diagnosis standard from the Consensus report of the Asian Working Group for Sarcropenia.	11.86 ± 3.02 12.30 ± 2.99	HbA1c, FBG, muscle mass, grip strength,
R. Bouchi, et al, 2021[39]	72/26/46 69/26/43	59.0 ± 10.0 57.0 ± 11.0	None	10 (6–15) 10 (6–15)	HbA1c, FBG, muscle mass

1RM = 1-repetition maximum, FBG = Fasting blood glucose, HbA1c = glycosylated hemoglobin A1c, IQR = inter-quartile range, SD =standard deviation, MoCA = Montreal cognitive assessment; MMSE = Mini–Mental State Examination; MoCA = Montreal Cognitive Assessment; FTUG = Five-Time up and go test, sec. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only.

†Duration of diabetes and age were represented as mean (SD) or median (IQR).

Table 1. Overview of studies included (cont.)

Author & Year	Country	Setting	Follow-up time (weeks)	Intervention category	Summary of intervention
Asian countries and regions					
Y. Yamamoto, et al, 2021[40]	Japan	Hospital	48	PHYS+NUTR PHYS PLAC/STD	Daily bodyweight resistance training with elastic bands exercises at home, and took 6 g of a leucine-rich amino acid supplement daily Daily bodyweight resistance training with elastic bands exercises at home Routine care
P. L. Hsieh, et al, 2016[34]	China	Hospital	12	PHYS PLAC/STD	8 resistance training exercises in 3 sets of 8 to 12 repetitions at 75% 1-repetition maximum (1-RM) 3 times per week for 12 weeks Usual care and maintained their daily activities and lifestyle
Xiao-Ling Luo, et al, 2015[35]	China	Community	13	PHYS PLAC/STD	Individualized exercise prescription based on disease condition and personal demand Routine care
N. Ghodrati, et al, 2023[11]	Iran	Community	12	Mixed_PHYS PLAC/STD	A combination of aerobic, resistance, and balance exercises performed 3 session per week, 65 min per session No training intervention
J. Matsushita, et al, 2022[37]	Japan	Community	8	PHYS PLAC/STD	Exercise instructions from physical therapists, ≥ 150 min per week at moderate speed, ≥ 30 min per day, with ambulatory accelerometers No exercise with ambulatory accelerometers.

Author & Year	Sample size N/F/M	Age†, year	Additional disease condition	Duration of diabetes*, year	Outcome measures interested
Asian countries and regions					
Y. Yamamoto, et al, 2021[40]	18/9/9 18/9/9 17/7/10	72.1 ± 2.1 73.2 ± 2.6 73.3 ± 2.5	None	17.3±9.6 17.6±10.0 16.0±11.1	HbA1c, grip strength, gait speed
P. L. Hsieh, et al, 2016[34]	15/10/5 15/9/6	70.6 ±4.2 71.8 ± 4.5	None	11.1±7.8 13.9±6.7	HbA1c, FBG,muscle mass, chair stand in 30 sec
Xiao-Ling Luo, et al, 2015[35]	55/25/30 55/24/31	68.40 ± 5.22 68.34 ± 5.11	None	NA	FBG, grip strength, one foot standing time
N. Ghodrati, et al, 2023[11]	12/12/0 9/9/0	58.8 ± 1.5 55.8 ± 1.5	None	6.3±1.9 6.1±1.7	HbA1c, FBG, gait speed, chair stand in 30 sec, FTUG, one-foot standing
J. Matsushita, et al, 2022[37]	16/2/14 13/2/11	62 (51.5–77) 61 (50.5–68)	None	24.7 (22.5–28.7) 26.4 (22.0–31.1)	HbA1c, FBG, muscle mass, grip strength, gait speed,

1RM = 1-repetition maximum, FBG = Fasting blood glucose, HbA1c = glycosylated hemoglobin A1c, IQR = inter-quartile range, SD =standard deviation, MoCA = Montreal cognitive assessment; MMSE = Mini–Mental State Examination; MoCA = Montreal Cognitive Assessment; FTUG = Five-Time up and go test, sec. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only.
†Duration of diabetes and age were represented as mean (SD) or median (IQR).

Table 1. Overview of studies included (cont.)

Author & Year	Country	Setting	Follow-up time (weeks)	Intervention category	Summary of intervention
Asian countries and regions					
T. Matsuda, et al, 2022[38]	Japan	Hospital	24	NUTR PLAC/STD	Supplementation of 8 g of branched-chain amino acids Supplementation of 7.5 g of soy protein
Chen-Chen Gui, et al, 2021[33]	China	Community	12	PHYS+NUTR PLAC/STD	Exercise prescription with nutritional support. Exercise included 40 regular items such as walking, biking, jogging, and skipping. At least 5 days per week. Nutritional support: individualized prescription over ratio of carbohydrate, protein, and fat according to participants' blood glucose, height, and weight Routine care
K. Lee et al, 2013[42]	South Korea	Hospital	6	Mixed_PHYS PHYS PLAC/STD	Whole body vibration (up to 3 × 3 min, 3 times per week, for 6 weeks) with the balance exercise program (60 min per day, 2 times per week) The balance exercise program for 60 min per day, 2 times per week No exercise
European countries and regions					
C. Blioumpa, et al, 2023[24]	Greece	Hospital	6	Mixed_PHYS PLAC/STD	Experimental group: received a supervised exercise-based telerehabilitation program, 3 times a week, for 60 minutes per session, combination of areobic and resistance exercises Routine care

Author & Year	Sample size N/F/M	Age[†], year	Additional disease condition	Duration of diabetes*, year	Outcome measures interested
Asian countries and regions					
T. Matsuda, et al, 2022[38]	21/8/13 15/5/10	73.0 ± 4.0 73.0 ± 4.0	None	21 (16–24) 19 (14–29)	HbA1c, FBG,serum insulin, muscle mass, lower body muscle strength, grip strength
Chen-Chen Gui, et al, 2021[33]	41/14/27 41/18/23	65.04 ± 6.11 66.77 ± 6.93	Sarcopenia identified by diagnosis standard from the Consensus report of the Asian Working Group for Sarcopenia.	11.86 ± 3.02 12.30 ± 2.99	HbA1c, FBG, muscle mass, grip strength,
K. Lee et al, 2013[42]	19/10/9 18/11/7 18/10/8	76.31±4.78 74.05±5.42 75.77±5.69	Diabetic peripheral nephropathy	13.24±4.32 12.29±4.98 11.27±5.78	HbA1c, chair stand in 30 sec, FTUG
European countries and regions					
C. Blioumpa, et al, 2023[24]	11//3/8 11/4/7	60.3 ± 9.3 60.8±13.6	None	NA	HbA1c, grip strength, gait speed, chair stand in 30 sec

1RM = 1-repetition maximum, FBG = Fasting blood glucose, HbA1c = glycosylated hemoglobin A1c, IQR = inter-quartile range, SD =standard deviation, MoCA = Montreal cognitive assessment; MMSE = Mini–Mental State Examination; MoCA = Montreal Cognitive Assessment; FTUG = Five-Time up and go test, sec. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only.
[†]Duration of diabetes and age were represented as mean (SD) or median (IQR).

Table 1. Overview of studies included (cont.)

Author & Year	Country	Setting	Follow-up time (weeks)	Intervention category	Summary of intervention
European countries and regions					
K. S. Khan, et al, 2022[25]	Denmark	Hospital	12	PHYS PLAC/STD	Progressive resistance training: each supervisedsession lasted ~ 1 h. Training schedules were individualized and submaximal loads were calculated basedon the individual one-repetition maximum. No exercise
K. S. Khan, et al, 2022[25]	Denmark	Hospital	12	PHYS PLAC/STD	Progressive resistance training: each supervisedsession lasted ~ 1 h. Training schedules were individualized and submaximal loads were calculated basedon the individual one-repetition maximum No exercise
F. Galle, et al, 2018[26]	Italy	Community	39	PHYS+PSYCH PLAC/STD	Community-based exercise program and 12 motivational group meetings focused on physical activity Routine care
M. Leenders, et al, 2011[27]	Netherlands	Hospital	26	NUTR PLAC/STD	2.5 g L-leucine with each main meal (7.5 g/d leucine) Placebo with each main meal (7.5 g/d placebo)
Oceanian country					
E. G. Miller, et al, 2020[28]	Australia	Community	24	PHYS+NUTR PHYS	Progressive resistance training (2-3 days/week) with whey protein (20 g each morning plus 20 g postexercise) plus vitamin D3(2000 IU/day) Progressive resistance training (2-3 days/week)

Author & Year	Sample size N/F/M	Age†, year	Additional disease condition	Duration of diabetes*, year	Outcome measures interested
European countries and regions					
K. S. Khan, et al, 2022[25]	15/?/? 15/?/?	unclear	Distal symmetric diabetic polyneuropathy	8.0 ±5.0	HbA1c, gait speed, chair stand in 30 sec
K. S. Khan, et al, 2022[25]	13/?/? 17/?/?	unclear	None	8.0 ±5.0	HbA1c, gait speed
F. Galle, et al, 2018[26]	69/43/26 90/52/38	63 ± 5.2 64 ± 6.4	None	NA	HbA1c, chair stand in 30 sec, FTUG
M. Leenders, et al, 2011[27]	29/0/29 28/0/28	71.0 ± 1.0 71.0 ± 1.0	None	NA	HbA1c, FBG, muscle mass, 1-RM leg press
Oceanian country					
E. G. Miller, et al, 2020[28]	98/36/62 100/36/64	61.1 ± 6.2 62.0 ± 6.2	None	7.1±5.1 7.1±5.2	HbA1c, FBG, chair stand in 30 sec, FTUG

1RM = 1-repetition maximum, FBG = Fasting blood glucose, HbA1c = glycosylated hemoglobin A1c, IQR = inter-quartile range, SD =standard deviation, MoCA = Montreal cognitive assessment; MMSE = Mini–Mental State Examination; MoCA = Montreal Cognitive Assessment; FTUG = Five-Time up and go test, sec. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only.

†Duration of diabetes and age were represented as mean (SD) or median (IQR).

Table 1. Overview of studies included (cont.)

Author & Year	Country	Setting	Follow-up time (weeks)	Intervention category	Summary of intervention
Oceanian country					
Y. Mavros, et al, 2013[29]	Australia	Community	52	PHYS PLAC/STD	High-intensity, high-velocity progressive resistance training Sham exercise
American countries					
A. Celli, et al, 2022[20]	USA	Community	52	HEALTH_MA PLAC/STD	Diet and exercise at a facility transitioned into community-fitness centers and homes, consisting of a weight-management program and exercise training (Combined aerobic and resistance exercise) Group educational sessions about a healthful diet during monthly visits
E. R. Vieria, et al, 2021[21]	USA	Community	13	PHYS +NUTR NUTR PLAC/STD	Combined diet and exercise: 2 times/week, 30 min group exercise, 30 min of walking, & 2 times /week, 30 min group nutrition sessions Diet-only intervention: 2 times/week, 30 min group nutrition sessions Routine care without any intervention
R. Nielsen, et al, 2016[22]	USA	Hospital	17	HEALTH_MA PLAC/STD	Assessment of the daily blood glucose profile, adjustment of the insulin dosage, use of oral antidiabetics, and by supply of dietary advice provided by a trained dietitian during contacts to the outpatient clinic and tailored to the individual patient's needs Routine care
A. L. de S. Soares, et al, 2023[9]	Brazil	Community	12	PHYS+NUTR PHYS	Resistance training for 12 weeks, twice a week, protein supplementation was 20 g of whey protein isolate Resistance training for 12 weeks, twice a week, supplemented with an isocaloric drink, containing 20 g of maltodextrin

Author & Year	Sample size N/F/M	Age†, year	Additional disease condition	Duration of diabetes*, year	Outcome measures interested
Oceanian country					
Y. Mavros, et al, 2013[29]	47/23/24 53/27/26	67.1 ± 4.8 68.9 ± 6.0	None	7.0 ±5.0 9.0 ±7.0	HbA1c, muscle mass
American countries					
A. Celli, et al, 2022[20]	50/19/31 50/16/34	72.3 ± 4.0 71.4 ± 3.7	None	13.8±9.0 13.7±8.7	HbA1c, FBG, gait speed
E. R. Vieria, et al, 2021[21]	8/?/? 6/?/? 15/?/?	unclear	None	NA	HbA1c, muscle mass, grip strength, chair stand in 30 sec
R. Nielsen, et al, 2016[22]	20/?/? 20/?/?	67.0 ±6.0 67.0 ±9.0	Left ventricular ejection fraction	12±6 15±9	HbA1c, FBG, grip strength, gait speed
A. L. de S. Soares, et al, 2023[9]	13/0/13 13/0/13	68.1 ± 4.5 68.9 ± 4.1	None	12.7 ±3.8 12.8 ±6.4	HbA1c, FBG, gripstrength

1RM = 1-repetition maximum, FBG = Fasting blood glucose, HbA1c = glycosylated hemoglobin A1c, IQR = inter-quartile range, SD =standard deviation, MoCA = Montreal cognitive assessment; MMSE = Mini–Mental State Examination; MoCA = Montreal Cognitive Assessment; FTUG = Five-Time up and go test, sec. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only.

†Duration of diabetes and age were represented as mean (SD) or median (IQR).

Table 1. Overview of studies included (cont.)

Author & Year	Country	Setting	Follow-up time (weeks)	Intervention category	Summary of intervention
American countries					
C. E. Botton, et al, 2018[23]	Brazil	Community	12	PHYS	Resistance training 3 times a week, 2-3 sessions per time
				PLAC/STD	Stretching classes once a week
R. Cavalcante, et al, 2015[12]	Brazil	Hospital	12	NUTR	Vitamin D3 (6600 IU/week, AdderaD3, Farmasa Laboratories, Sao Paulo, Brazil) in extra virgin olive oil weekly
				PLAC/STD	Natural extra virgin olive oil intervention weekly

Author & Year	Sample size N/F/M	Age†, year	Additional disease condition	Duration of diabetes*, year	Outcome measures interested
American countries					
C. E. Botton, et al, 2018[23]	20/10/10	70.6 ± 6.70	None	10.7±7.9	HbA1c, FBG, chair stand in 30 sec, FTUG
	22/8/14	68.6 ± 7.06		11.31±7.4	
R. Cavalcante, et al, 2015[12]	19/19/0	62.16 ± 7.62	Postmenopausal women	11.16±7.46	HbA1c, handgrip strength
	19/19/0	68.95 ± 7.40		8.95±7.40	

1RM = 1-repetition maximum, FBG = Fasting blood glucose, HbA1c = glycosylated hemoglobin A1c, IQR = inter-quartile range, SD =standard deviation, MoCA = Montreal cognitive assessment; MMSE = Mini–Mental State Examination; MoCA = Montreal Cognitive Assessment; FTUG = Five-Time up and go test, sec. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only.

†Duration of diabetes and age were represented as mean (SD) or median (IQR).

the average duration of type 2 diabetes of 11.5 years, were performed across 27 studies. The sample size ranged from 21 to 198 participants, with the majority between 40 and 150 participants (n = 16, 59.2%). Four (14.8%) RCTs had an intervention duration of 12 weeks or less, and 11 (40.7%) RCTs had a duration of 24 weeks or more.

Given on intervention categories, 346 participants were included in the PHYS category, 178 participants were classified into the PHYS + NUTR category, 109 participants were in the PHYS + PSYCH category, 75 participants were in the NUTR category, 72 participants were in the PHYS+PHARM category, 70 participants were in the Health_MA category, 68 participants were in the Mixed_PHYS category, and 64 participants were in the PHARM category. The remaining 907 participants were included in the control group and no intervention, sham intervention, or routine health care provided. Detailed information involving the interventions is briefly described in Table 1.

Results of ROB assessment

The ROB assessment of per item for each study were shown in Table 2. Overall, 12 studies were assessed to be of low ROB,[9,12,20,22,23,30,33,34,36,41-43] 11 of moderate ROB,[21,24,27-29,31,32,35,37-39] and the remaining 4 study judged as at high ROB.[11,25,26,40] About each ROB domain, 11 studies were rated at high or unclear ROB in random sequence generation.[11,20,21,25,27,29,31,32,35,38,40] Seven studies were rated as at low ROB in adequate sequence generation,[9,22,23,28,37,39,41] and only two studies conducted blinding of participants.[29,36] More than half of the studies (n = 19, 70.4%) did not demonstrate the blinding of research personnel. All studies reported the outcomes they expected, but eight studies,[11,24-26,28,29,37,40] lost their participants during the intervention period > 10%. Eight studies used an intention-to-treat analysis,[9,20-23,35,41,43] and seven had imbalanced data at baseline between comparisons (p< 0.10) in key confounding factors such as BMI, HbAc1, frailty, grip strength, and duration of diabetes.[9,20,21,24,25,29,31]

Network meta-analysis

HbAc1was assessed in the NMA with twenty-seven studies (one study has two distinct populations),[25] including 1779 participants and nine intervention categories. The head-to-head comparisons between PHYS and PHYS+NUTR (I^2 = 82%), PHYS vs PLAC/STD (I^2 = 71%), and PHYS+NUTR and PLAC/STD (I^2 = 94%) represented inconsistency within designs. The reduction of HbAc1 was obvious, with mean values ranging from -0.01 to -0.87%. Interventions that included physical activity combined with nutritional supplements (PHYS+NUTR: -0.44 [95%CI: -0.84, -0.07]) and the-Health_MA (-0.90 [95%CI: -1.52, -0.28]) were more effective in decreasing HbAc1 than control, and the Health_MA were superior to NUTR interventions (Table 3). Health_MA had the highest probability of decreasing HbAc1 no matter which NMA was conducted (SUCRA score in Bayesian NMA = 0.89; SUCRA score in Bayesian meta regression = 0.84; P score in frequentist NMA = 0.95) (Table 4). The publication bias was with the p value of the Egger test = 0.744. For FBG, the physical activity only intervention (PHYS: -1.79, 95%CI: -2.92, -0.59) was found to be significantly more effective in reducing FBG than control (Table 3). Due to no significant difference between interventions but in the comparison between PHYS and control PLAC/STD, the intervention of PHYS became the best intervention in the network for reducing FBG (SUCRA score in Bayesian NMA = 0.80; SUCRA score in Bayesian meta regression = 0.81; P score in frequentist NMA = 0.71) (Table 4). The publication bias for HbAc1 (p = 0.74) and FBG (p = 0.55) was with the p value of the Egger test > 0.05.

Muscle mass was assessed in ten studies including 689 participants and seven intervention categories. The change in muscle mass was substantial, with the mean values ranging from 0.01 to 2.22 kg. Interventions that included a component of physical activity (PHYS: -2.03[95%CI: -3.44, -0.54]; Mixed_PHYS: -2.03[95%CI:-3.64, -0.41]; PHYS+PHARM: -2.22[95%CI: -4.14, -0.29]),PHARM (-2.12[95%CI:-3.77, -0.47]) and NUTR(-2.01[95%CI: -3.52, -0.51]) was less effective in increasing muscle mass than physical activity combined with nutritional supplements (Table 3). Obviously, the PHYS+NUTR intervention had the highest probability of increasing muscle mass no matter which NMA was conducted (SUCRA score in Bayesian NMA = 0.99; SUCRA score in Bayesian meta regression = 0.87; P score in frequentist NMA = 0.85) (Table 4). The publication bias for muscle mass was assessed with the p value of the Egger test = 0.43.

The NMA for grip strengthwas conducted with seventeen studies including 780 participants, across eight intervention categories. The head-to-head comparisons between NUTR and PLAC/STD (I^2 = 0%), PHYS and PHYS+NUTR (I^2 = 5%), and PHYS+NUTR and PLAC/STD (I^2 = 0%) represented consistency within designs. The increase in grip strength was with mean values ranging from -0.01 to 3.43 kg. The intervention of PHYS was found to significantly increase grip strength when compared with control (0.45[95%CI:0.12, 1.33]) (Table 3). Even the intervention of PHYS+PSYCH ranked first, but Mixed_PHYS ranked second that showed significantly more increased grip strength than the interventions of PHARM (1.81[95%CI: 0.81, 2.80]) and PHYS (1.11[95%CI: 0.52, 1.70]) using frequentist NMA with a fixed model (Table 5). The publication bias for grip strength was with the p value of the Egger test = 0.63.

The NMA for gait speed included nine studies with 369 participants and six of nine intervention categories. There was inconsistency within the PHYS-versus-control designs (I^2 = 91.6%), so frequentist NMA with a random model was used to calculate the effect size matrix: Mixed PHYS intervention was better than the PHYS intervention (0.05 [95%CI: 0.01, 0.10]) and the control (0.06 [95%CI: 0.01,0.11]) to increase the gait speed (Table 5). PHYS+PSYCH appeared as the best intervention to increase gait speed (SUCRA score in Bayesian NMA = 0.88; SUCRA score in Bayesian meta regression = 0.93; P score in frequentist NMA = 0.97), even though it had no significant difference in increasing gait speed compared with other interventions (Table 4). The intervention of PHYS + PYSYCH also appeared as the best intervention to increase lower muscle strength and improve

Table 2. Study quality assessment according to Cochrane Collaboration's tool for assessing risk of bias

Author Year	Random sequence generation	Allocation concealed	Blinding of participant	Blinding of research personnel	Complete outcome data reported	Dropout rate, %	Other secure of bias†
M. M. Ghahfarrokhi, et al, 2024[41]	Yes	Yes	No	Nil stated	Yes	10	No
Liu Yang, et al,2023[30]	Yes	No	No	Nil stated	Yes	6	Yes
D. Yabe, et al, 2023[36]	Yes	No	Yes	Yes	Yes	5	Yes
E. A. Ozairi, et al, 2023[43]	Yes	No	No	Yes	Yes	3	No
Yun-Da Huang, et al, 2022[31]	Unclear	No	No	Nil stated	Yes	10	Yes
Yu-Hsuan Chien, et al, 2022[32]	No	No	No	Nil stated	Yes	8	Yes
N. Ghodrati, et al, 2023[11]	Unclear	No	No	Nil stated	Yes	14	Yes
J. Matsushita, et al, 2022[37]	Yes	Yes	No	Nil stated	Yes	22	Yes
T. Matsuda, et al, 2022[38]	Unclear	No	No	Nil stated	Yes	5	Yes
Chen-Chen Gui, et al, 2021[33]	Yes	No	No	Nil stated	Yes	<5	unclear
R. Bouchi, et al, 2021[39]	Yes	Yes	No	Nil stated	Yes	10	Yes
Y. Yamamoto, et al, 2021[40]	Unclear	No	No	Nil stated	Yes	12	Yes
P. L. Hsieh, et al, 2016[34]	Yes	No	No	Yes	Yes	<5	Yes
Xiao-Ling Luo, et al, 2015[35]	Unclear	No	No	Nil stated	Yes	<5	No
K. Lee, et al, 2013[42]	Yes	No	No	Nil stated	Yes	8	Yes
C. Blioumpa, et al, 2023[24]	Yes	No	No	Yes	Yes	27	Yes
K. S. Khan, et al, 2022[25]	Unclear	No	No	Yes	Yes	17	Yes

Author Year	1	2	3	4	5	6	7	Overall score (category)
M. M. Ghahfarrokhi, et al, 2024[41]	L	L	H	H	L	H	L	2 (low)
Liu Yang, et al,2023[30]	L	H	H	H	L	L	L	2 (low)
D. Yabe, et al, 2023[36]	L	H	L	L	L	L	L	1 (low)
E. A. Ozairi, et al, 2023[43]	L	H	H	L	L	L	L	2 (low)
Yun-Da Huang, et al, 2022[31]	H	H	H	H	L	L	H	4 (moderate)
Yu-Hsuan Chien, et al, 2022[32]	H	H	H	H	L	L	L	3 (moderate)
N. Ghodrati, et al, 2023[11]	H	H	H	H	L	H	H	5 (high)
J. Matsushita, et al, 2022[37]	L	L	H	H	L	H	H	3 (moderate)
T. Matsuda, et al, 2022[38]	H	H	H	H	L	L	H	3 (moderate)
Chen-Chen Gui, et al, 2021[38]	L	H	H	H	L	L	L	2 (low)
R. Bouchi, et al, 2021[39]	L	L	H	H	L	H	H	3 (moderate)
Y. Yamamoto, et al, 2021[40]	H	H	H	H	L	H	H	5 (high)
P. L. Hsieh, et al, 2016[34]	L	H	H	L	L	L	H	2 (low)
Xiao-Ling Luo, et al, 2015[35]	H	H	H	H	L	L	L	3 (moderate)
K. Lee, et al, 2013[42]	L	H	H	H	L	L	H	2 (low)
C. Blioumpa, et al, 2023[24]	L	H	H	L	L	H	H	4 (moderate)
K. S. Khan, et al, 2022[25]	H	H	H	L	L	H	H	5 (high)

†Other secure of bias included balanced co-variate distribution between groups, and Per-Protocol analysis instead of Intention-To-Treat analysis to compare the effect difference between groups. If one study conducts multi-variable analysis methods and ITT analysis, it is assessed without other bias.

Table 2. Study quality assessment according to Cochrane Collaboration's tool for assessing risk of bias (cont.)

Author Year	Random sequence generation	Allocation concealed	Blinding of participant	Blinding of research personnel	Complete outcome data reported	Dropout rate, %	Other secure of bias†
F. Galle, et al, 2018[26]	Unclear	No	No	Nil stated	Yes	28	Yes
M. Leenders, et al, 2011[27]	Unclear	No	No	Nil stated	Yes	5	Yes
E. G. Miller, et al, 2020[28]	Yes	Yes	No	Yes	Yes	16	Yes
Y Mavros, et al, 2013[29]	Unclear	No	Yes	Yes	Yes	17	Yes
A. Celli, et al, 2022[20]	Yes	No	No	Nil stated	Yes	<5	Yes
E. R. Vieria, et al, 2021[21]	Unclear	No	No	Nil stated	Yes	<5	Yes
R. Nielsen, et al, 2016[22]	Yes	Yes	No	Nil stated	Yes	<5	No
A. L. de S. Soares, et al, 2023[9]	Yes	Yes	Yes	Yes	Yes	7	Yes
C. E. Botton, et al, 2018[23]	Yes	Yes	No	Nil stated	Yes	<5	No
R. Cavalcante, et al, 2015[12]	Yes	No	No	Nil stated	Yes	<5	unclear

Author Year	1	2	3	4	5	6	7	Overall score (category)
F. Galle, et al, 2018[26]	H	H	H	H	H	H	H	6 (high)
M. Leenders, et al, 2011[27]	H	H	H	H	L	L	H	3 (moderate)
E. G. Miller, et al, 2020[28]	L	L	H	L	L	H	H	3 (moderate)
Y Mavros, et al, 2013[29]	H	H	L	L	L	H	H	4 (moderate)
A. Celli, et al, 2022[21]	L	H	H	H	L	L	H	2 (low)
E. R. Vieria, et al, 2021[21]	H	H	H	H	L	L	H	4 (moderate)
R. Nielsen, et al, 2016[22]	L	L	H	H	L	L	L	1 (low)
A. L. de S. Soares, et al, 2023[9]	L	L	L	L	L	L	H	1 (low)
C. E. Botton, et al, 2018[23]	L	L	H	H	L	L	L	1 (low)
R. Cavalcante, et al, 2015[12]	L	H	H	H	L	L	L	2 (low)

†Other secure of bias included balanced co-variate distribution between groups, and Per-Protocol analysis instead of Intention-To-Treat analysis to compare the effect difference between groups. If one study conducts multi-variable analysis methods and ITT analysis, it is assessed without other bias.

Table 3. Bayesian Network meta-analysis matrix of results

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)				
HbAc1 (%)	PHYS_PSYCH	PLAC_STD	PHYS_NUTR	PHYS	Mixed_PHYS
PHYS+PSYCH		0.32 (-0.33, 0.98)	-0.12 (-0.88, 0.62)	0.11 (-0.60, 0.79)	0.05 (-0.76, 0.82)
PLAC/STD	-0.32 (-0.98, 0.33)		-0.44 (-0.84, -0.07)	-0.22 (-0.48, 0.01)	-0.27 (-0.74, 0.16)
PHYS+NUTR	0.12 (-0.62, 0.88)	0.44 (0.07, 0.84)		0.22 (-0.17, 0.61)	0.17 (-0.41, 0.73)
PHYS	-0.11 (-0.79, 0.60)	0.22 (-0.01, 0.48)	-0.22 (-0.61, 0.17)		-0.05 (-0.54, 0.41)
Mixed_PHYS	-0.05 (-0.82, 0.76)	0.27 (-0.16, 0.74)	-0.17 (-0.73 0.41)	0.05 (-0.41, 0.54)	
Health_MA	0.57 (-0.33, 1.47)	0.90 (0.28, 1.52)	0.46 (-0.29, 1.18)	0.68 (-0.01, 1.34)	0.63 (-0.17, 1.38)
PHYS+PHARM	0.25 (-1.09, 1.56)	0.58 (-0.59, 1.71)	0.14 (-1.11, 1.32)	0.36 (-0.84, 1.51)	0.31 (-0.98, 1.50)
PHARM	0.25 (-0.80, 1.29)	0.57 (-0.24, 1.38)	0.14 (-0.79, 1.00)	0.35 (-0.51, 1.18)	0.31 (-0.66, 1.19)
NUTR	-0.30 (-1.09, 0.49)	0.02 (-0.41, 0.47)	-0.41 (-0.98, 0.12)	-0.19 (-0.70, 0.29)	-0.24 (-0.90, 0.37)
FBG (mmol/L)					
PHYS+PSYCH					
PLAC/STD			-0.92 (-2.90, 1.13)	-1.79 (-2.92, -0.59)	-0.81 (-3.13, 1.38)
PHYS+NUTR		0.92(-1.13, 2.90)		-0.87 (-2.88, 1.16)	0.11 (-3.02, 3.02)
PHYS		1.79 (0.59, 2.92)	0.87 (-1.16, 2.88)		0.98 (-1.64, 3.43)
Mixed_PHYS		0.81 (-1.38, 3.13)	-0.11 (-3.02, 3.02)	-0.98 (-3.43, 1.64)	

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)			
HbAc1 (%)	Health_MA	PHYS_PHARM	PHARM	NUTR
PHYS+PSYCH	-0.57 (-1.47, 0.33)	-0.25 (-1.56, 1.09)	-0.25 (-1.29, 0.80)	0.30 (-0.49, 1.09)
PLAC/STD	-0.90 (-1.52, -0.28)	-0.58 (-1.71, 0.59)	-0.57 (-1.38, 0.24)	-0.02 (-0.47, 0.41)
PHYS+NUTR	-0.46 (-1.18, 0.29)	-0.14 (-1.32, 1.11)	-0.13 (-1.00, 0.79)	0.41 (-0.12, 0.98)
PHYS	-0.68 (-1.34, 0.01)	-0.37 (-1.51, 0.84)	-0.35 (-1.18, 0.51)	0.19 (-0.29, 0.70)
Mixed_PHYS	-0.62 (-1.38, 0.17)	-0.31 (-1.50, 0.98)	-0.31 (-1.19, 0.66)	0.25 (-0.37, 0.90)
Health_MA		0.32 (-0.97, 1.65)	0.32 (-0.69, 1.36)	0.87 (0.11, 1.64)
PHYS+PHARM	-0.32 (-1.65, 0.97)		0.01 (-0.82, 0.82)	0.55 (-0.70, 1.78)
PHARM	-0.32 (-1.35, 0.69)	-0.01 (-0.82, 0.82)		0.55 (-0.38, 1.46)
NUTR	-0.87 (-1.63, -0.11)	-0.55 (-1.78, 0.70)	-0.55 (-1.46, 0.38)	
FBG (mmol/L)				
PHYS+PSYCH				
PLAC/STD	-1.89 (-4.07, 0.23)			-0.11 (-2.01, 1.82)
PHYS+NUTR	-0.97 (-3.96, 1.92)			0.80 (-1.97, 3.55)
PHYS	-0.11 (-2.59, 2.25)			1.68 (-0.61, 3.89)
Mixed_PHYS	-1.09 (-4.14, 2.07)			0.69 (-2.19, 3.78)

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis

Table 3. Bayesian Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)				
FBG (mmol/L)	PHYS_PSYCH	PLAC_STD	PHYS_NUTR	PHYS	Mixed_PHYS
Health_MA		1.89 (-0.23, 4.07)	0.97 (-1.92, 3.96)	0.11 (-2.25, 2.59)	1.09 (-2.07, 4.14)
PHYS+PHARM					
PHARM					
NUTR		0.11 (-1.82, 2.01)	-0.80 (-3.55, 1.97)	-1.68 (-3.89, 0.60)	-0.69 (-3.78, 2.19)
Muscle mass (kg/m^2)					
PHYS+PSYCH					
PLAC/STD			2.04 (0.72, 3.36)	0.01 (-0.55, 0.67)	0.01 (-0.98, 1.01)
PHYS+NUTR		-2.04 (-3.36, -0.72)		-2.03 (-3.44, -0.54)	-2.03 (-3.64, -0.41)
PHYS		-0.01 (-0.67, 0.55)	2.03 (0.54, 3.44)		0.01 (-1.23, 1.14)
Mixed_PHYS		-0.01 (-1.01, 0.98)	2.03 (0.41, 3.64)	-0.013 (-1.14, 1.23)	
Health_MA					
PHYS+PHARM		0.18 (-1.25, 1.61)	2.22 (0.29, 4.14)	0.18 (-1.30, 1.79)	0.19 (-1.55, 1.95)
PHARM		0.08 (-0.95, 1.12)	2.12 (0.47, 3.77)	0.08 (-1.05, 1.33)	0.09 (-1.35, 1.51)
NUTR		-0.03 (-0.78, 0.70)	2.01 (0.51, 3.52)	-0.03 (-0.93, 0.99)	-0.02 (-1.274, 1.23)

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)			
FBG (mmol/L)	Health_MA	PHYS_PHARM	PHARM	NUTR
Health_MA				1.78 (-1.02, 4.66)
PHYS+PHARM				
PHARM				
NUTR	-1.78 (-4.66, 1.02)			
Muscle mass (kg/m^2)				
PHYS+PSYCH				
PLAC/STD		-0.18 (-1.61, 1.25)	-0.08 (-1.12, 0.95)	0.03 (-0.70, 0.78)
PHYS+NUTR		-2.22 (-4.14, -0.29)	-2.12 (-3.77, -0.47)	-2.01 (-3.52, -0.51)
PHYS		-0.18 (-1.79, 1.30)	-0.08 (-1.33, 1.05)	0.03 (-0.99, 0.93)
Mixed_PHYS		-0.19 (-1.95, 1.55)	-0.09 (-1.51, 1.35)	0.02 (-1.23, 1.27)
Health_MA				
PHYS+PHARM			0.10 (-0.88, 1.09)	0.22 (-1.41, 1.82)
PHARM		-0.10 (-1.09, 0.88)		0.11 (-1.16, 1.39)
NUTR		-0.22 (-1.82, 1.41)	-0.11 (-1.39, 1.16)	

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis

Table 3. Bayesian Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)				
Grip strength (kg)	PHYS_PSYCH	PLAC_STD	PHYS_NUTR	PHYS	Mixed_PHYS
PHYS+PSYCH		-3.14 (-8.01, 1.62)	-1.75 (-7.07, 3.30)	-2.60 (-7.51, 2.23)	-1.82 (-6.89, 3.02)
PLAC/STD	3.14 (-1.62, 8.01)		1.33 (-0.38, 3.07)	0.45 (0.12, 1.33)	1.38 (-0.12, 2.21)
PHYS+NUTR	1.75 (-3.30, 7.07)	-1.33 (-3.07, 0.38)		-0.80 (-2.57, 1.03)	0.01 (-2.19, 1.89)
PHYS	2.60 (-2.20, 7.51)	-0.45 (-1.33, -0.12)	0.80 (-1.03, 2.57)		0.89 (-1.04, 1.76)
Mixed_PHYS	1.82 (-3.02, 6.89)	-1.38 (-2.21, 0.13)	-0.01 (-1.89, 2.19)	-0.89 (-1.76, 1.04)	
Health_MA	2.89 (-1.99, 7.86)	-0.18 (-1.52, 0.73)	1.12 (-0.98, 3.06)	0.26 (-0.91, 1.61)	1.20 (-1.02, 2.28)
PHYS+PHARM					
PHARM	3.43 (-1.57, 8.50)	0.29 (-1.05, 1.66)	1.64 (-0.55, 3.81)	0.79 (-0.49, 2.51)	1.66 (-0.45, 3.12)
NUTR	2.20 (-3.05, 7.37)	-0.94 (-3.22, 1.27)	0.39 (-2.36, 3.11)	-0.40 (-2.71, 1.94)	0.38 (-2.25, 2.75)
Gait speed (m/s)					
PHYS+PSYCH		-3.21 (-7.87, 1.74)	-1.88 (-6.78, 3.32)	-2.67 (-7.36, 2.34)	-1.86 (-6.71, 3.11)
PLAC/STD	3.21 (-1.74, 7.87)		1.36 (-0.35, 3.04)	0.45 (0.13, 1.33)	1.40 (-0.13, 2.22)
PHYS+NUTR	1.88 (-3.32, 6.78)	-1.36 (-3.04, 0.35)		-0.83 (-2.56, 1.04)	-0.01 (-2.16, 1.90)
PHYS	2.67 (-2.34, 7.36)	-0.45 (-1.33, -0.13)	0.83 (-1.04, 2.56)		0.92 (-1.04, 1.75)
Mixed_PHYS	1.86 (-3.11, 6.71)	-1.40 (-2.22, 0.13)	0.01 (-1.90, 2.16)	-0.92 (-1.75, 1.04)	

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)			
Grip strength (kg)	Health_MA	PHYS_PHARM	PHARM	NUTR
PHYS+PSYCH	-2.89 (-7.86, 1.99)		-3.43 (-8.50, 1.57)	-2.20 (-7.37, 3.08)
PLAC/STD	0.18 (-0.73, 1.52)		-0.29 (-1.66, 1.05)	0.94 (-1.27, 3.22)
PHYS+NUTR	-1.12 (-3.06, 0.98)		-1.64 (-3.81, 0.55)	-0.39 (-3.11, 2.36)
PHYS	-0.26 (-1.61, 0.91)		-0.79 (-2.51, 0.49)	0.40 (-1.94, 2.71)
Mixed_PHYS	-1.20 (-2.28, 1.02)		-1.66 (-3.12, 0.45)	-0.38 (-2.75, 2.25)
Health_MA			-0.49 (-2.42, 1.08)	0.72 (-1.81, 3.17)
PHYS+PHARM				1.24 (-1.36, 3.89)
PHARM	0.49 (-1.08, 2.42)			
NUTR	-0.72 (-3.17, 1.81)		-1.24 (-3.89, 1.36)	
Gait speed (m/s)				
PHYS+PSYCH	-2.99 (-7.72, 2.10)		-3.51 (-8.32, 1.59)	-2.27 (-7.43, 3.13)
PLAC/STD	0.18 (-0.77, 1.53)		-0.32 (-1.65, 1.05)	0.93 (-1.25, 3.16)
PHYS+NUTR	-1.15 (-3.03, 0.97)		-1.67 (-3.79, 0.55)	-0.41 (-3.06, 2.24)
PHYS	-0.25 (-1.65, 0.89)		-0.81 (-2.53, 0.47)	0.40 (-1.94, 2.64)
Mixed_PHYS	-1.22 (-2.29, 1.02)		-1.71 (-3.13, 0.45)	-0.41 (-2.74, 2.20)

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis

Table 3. Bayesian Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)				
Gait speed (m/s)	PHYS_PSYCH	PLAC_STD	PHYS_NUTR	PHYS	Mixed_PHYS
Health_MA	2.99 (-2.10, 7.72)	-0.18 (-1.53, 0.77)	1.15 (-0.97, 3.03)	0.25 (-0.89, 1.65)	1.22 (-1.02, 2.29)
PHYS+PHARM					
PHARM	3.51 (-1.59, 8.33)	0.32 (-1.05, 1.65)	1.67 (-0.55, 3.79)	0.81 (-0.47, 2.53)	1.71 (-0.45, 3.13)
NUTR	2.27 (-3.13, 7.43)	-0.93 (-3.16, 1.25)	0.41 (-2.24, 3.06)	-0.40 (-2.64, 1.94)	0.41 (-2.20, 2.74)
Chair stand in 30 s, reps					
PHYS+PSYCH		-3.89 (-9.98, 2.24)	-3.12 (-10.54, 4.46)	-4.05 (-10.79, 2.72)	-3.32 (-10.80, 4.35)
PLAC/STD	3.89 (-2.24, 9.98)		0.77 (-3.55, 5.19)	-0.16 (-3.04, 2.79)	0.55 (-3.84, 5.08)
PHYS+NUTR	3.12 (-4.46, 10.54)	-0.78 (-5.19, 3.55)		-0.92 (-5.41, 3.52)	-0.20 (-6.36, 6.11)
PHYS	4.05 (-2.72, 10.79)	0.16 (-2.79, 3.04)	0.92 (-3.51, 5.41)		0.72 (-4.49, 6.05)
Mixed_PHYS	3.32 (-4.35, 10.80)	-0.55 (-5.08, 3.84)	0.20 (-6.11, 6.36)	-0.72 (-6.05, 4.49)	
Health_MA					
PHYS+PHARM					
PHARM	3.87 (-4.74, 12.54)	0.01 (-6.05, 6.15)	0.77 (-6.64, 8.27)	-0.16 (-6.84 6.64)	0.56 (-6.85, 8.19)
NUTR	4.01 (-4.37, 12.36)	0.14 (-5.57, 5.82)	0.90 (-4.88, 6.75)	-0.01 (-6.14, 6.08)	0.69 (-6.48, 7.96)

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)			
Gait speed (m/s)	Health_MA	PHYS_PHARM	PHARM	NUTR
Health_MA			-0.53 (-2.42, 1.09)	0.71 (-1.79, 3.07)
PHYS+PHARM				
PHARM	0.527 (-1.09, 2.42)			1.25 (-1.39, 3.80)
NUTR	-0.71 (-3.07, 1.79)		-1.25 (-3.80, 1.39)	
Chair stand in 30 s, reps				
PHYS+PSYCH			-3.87 (-12.54, 4.74)	-4.01 (-12.36, 4.37)
PLAC/STD			-0.01 (-6.15, 6.05)	-0.14 (-5.82 5.57)
PHYS+NUTR			-0.77 (-8.27, 6.64)	-0.91 (-6.75, 4.88)
PHYS			0.156 (-6.64, 6.84)	0.01 (-6.08, 6.14)
Mixed_PHYS			-0.56 (-8.19, 6.85)	-0.69 (-7.96, 6.48)
Health_MA				
PHYS+PHARM				
PHARM				-0.16 (-8.41, 8.17)
NUTR			0.16 (-8.17, 8.41)	

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis

Table 3. Bayesian Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)				
Five-time up and Go (s)	PHYS_PSYCH	PLAC_STD	PHYS_NUTR	PHYS	Mixed_PHYS
PHYS+PSYCH		0.93 (-4.16, 6.01)		0.39 (-5.39, 5.80)	0.45 (-5.29, 6.25)
PLAC/STD	-0.93 (-6.01, 4.16)			-0.54 (-3.08, 1.67)	-0.47 (-3.15, 2.32)
PHYS+NUTR					
PHYS	-0.39 (-5.80, 5.39)	0.54 (-1.67, 3.08)			0.07 (-2.88, 3.49)
Mixed_PHYS	-0.45 (-6.25, 5.29)	0.47 (-2.32, 3.15)		-0.07 (-3.49, 2.88)	
Health_MA					
PHYS+PHARM					
PHARM					
NUTR					

Outcomes	Effect of intervention in each column compared with intervention in each row Mean difference (95% confidence intervals)			
Five-time up and Go (s)	Health_MA	PHYS_PHARM	PHARM	NUTR
PHYS+PSYCH				
PLAC/STD				
PHYS+NUTR				
PHYS				
Mixed_PHYS				
Health_MA				
PHYS+PHARM				
PHARM				
NUTR				

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis

Table 4. Ranking of interventions in order that relate to effect on glucose control and physical performance improvement

Outcomes	Bayesian NMA		Bayesian meta regression		Frequentist NMA	
	SUCRA score	Rank	SUCRA score	Rank	P score†‡	Rank
HbAc1 (%)						
Health_MA	0.89	1	0.84	1	0.95	1
PHARM	0.68	2	0.58	3	0.74	2
PHYS+PHARM	0.65	3	0.56	4	0.71	3
PHYS_NUTR	0.63	4	0.68	2	0.66	4
PHYS+PSYCH	0.49	5	0.55	5	0.49	5
Mixed_PHYS	0.45	6	0.46	6	0.39	6
PHYS	0.39	7	0.40	7	0.35	7
NUTR	0.19	8	0.31	8	0.12	8
PLAC/STD	0.12	9	0.11	9	0.08	9
FBG(mmol/L)						
PHYS	0.8	1	0.81	1	0.71	1
Health_MA	0.79	2	0.8	2	0.65	3
PHYS+NUTR	50	3	0.55	3	0.38	5
Mixed_PHYS	0.47	4	0.46	4	0.66	2
NUTR	0.25	5	0.23	5	0.46	4
PLAC_STD	0.17	6	0.15	6	0.14	6
Muscle mass (kg/m^2)						
PHYS+NUTR	0.99	1	0.98	1	1	1
NUTR	0.49	2	0.30	7	0.57	2
Mixed_PHYS	0.46	3	0.29	6	0.51	3
PHYS	0.45	4	0.5	3	0.37	6
PLAC/STD	0.44	5	0.45	4	0.5	4
PHARM	0.38	6	0.55	2	0.38	5
PHYS+PHARM	0.28	7	0.43	5	0.18	7
Grip strength (kg)						
PHYS+PSYCH	0.83	1	0.87	1	0.85	1
Mixed_PHYS	0.72	2	0.54	5	0.79	2
PHYS+NUTR	0.7	3	0.72	2	0.68	3
NUTR	0.57	4	0.57	3	0.6	4
PHYS	0.51	5	0.56	4	0.5	5
Health_MA	0.34	6	0.40	6	0.33	6
PLAC/STD	0.19	7	0.12	7	0.16	7
PHARM	0.14	8	0.20	8	0.09	8
Gait speed (m/s)						
PHYS+PSYCH	0.88	1	0.93	1	0.97	1
PHYS+NUTR	0.64	2	0.48	4	0.61	3
Mixed_PHYS	0.47	4	0.21	6	0.64	2
PHYS	0.44	5	0.5	3	0.32	5
Health_MA	0.36	6	0.62	2	0.34	4
PLAC_STD	0.21	7	0.27	5	0.11	6
Chair stand in 30 s, reps						
PHYS+PSYCH	0.85	1	0.82	1	0.95	1
PHYS+NUTR	0.54	2	0.52	2	0.52	2
Mixed_PHYS	0.5	3	0.57	4	0.49	3
PHARM	0.42	4	0.51	3	0.42	5
NUTR	0.41	5	0.39	6	0.41	6
PLAC/STD	0.4	6	0.41	5	0.43	4
PHYS	0.37	7	0.38	7	0.27	7
Five-time up and go test, s						
PHYS+PSYCH	0.60	1	0.80	1	0.68	1
PHYS	0.55	2	0.33	3	0.54	2
Mixed_PHYS	0.52	3	0.57	2	0.46	3
PLAC/STD	0.32	4	0.29	4	0.33	4

SUCRA, Surface Under the Cumulative Ranking score
†P score for muscle mass and grip strength, the fixed model was used to produce the ranking because of the $I^2 < 50\%$, and the P scores of other measurements were estimated using random model.
‡P score and SUCRA score ranges from 0 to 1, where 1 indicates best intervention with no uncertainty and 0 tends to be worst intervention with no uncertainty.

dynamic balance than the control based on frequentist NMA with random model (Table 5), ranking first in Baysian NMA, Baysian meta regression, and frequentist NMA (Table 4). The publication bias for gait speed, lower muscle strength, and dynamic balance were assessed with all *p* values > 0.05.

Table 5. Frequentist Network meta-analysis matrix of results

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)				
HbAc1 (%)	Health_MA	Mixed_PHYS	NUTR	PHARM	PHYS
Health_MA					
Mixed_PHYS	-0.67 (-1.15, -0.19)				-0.08 (-0.45, 0.29)
NUTR	-0.89 (-1.36, -0.43)	-0.22 (-0.62, 0.17)			
PHARM	-0.33 (-0.90, 0.24)	0.34 (-0.17, 0.85)	0.56 (0.07, 1.06)		
PHYS	-0.70 (-1.11, -0.29)	-0.03 (-0.33, 0.27)	0.20 (-0.11, 0.50)	-0.37 (-0.81, 0.08)	
PHYS+NUTR	-0.44 (-0.91, 0.03)	0.23 (-0.15, 0.62)	0.45 (0.09, 0.82)	-0.11 (-0.61, 0.39)	0.26 (0.00, 0.52)
PHYS+PHARM	-0.33 (-1.05, 0.39)	0.34 (-0.34, 1.02)	0.56 (-0.10, 1.23)	-0.00 (-0.44, 0.44)	0.37 (-0.26, 1.00)
PHYS+PSYCH	-0.58 (-1.14, -0.03)	0.09 (-0.41, 0.58)	0.31 (-0.17, 0.79)	-0.25 (-0.84, 0.33)	0.11 (-0.31, 0.54)
PLAC/STD	-0.90 (-1.28, -0.52)	-0.23 (-0.52, 0.06)	-0.01 (-0.27, 0.26)	-0.57 (-0.99, -0.15)	-0.20 (-0.34, -0.06)
FBG (mmol/l)					
Health_MA					
Mixed_PHYS	-1.08 (-3.69, 1.52)				
NUTR	-1.78 (-4.15, 0.59)	-0.69 (-3.12, 1.73)			
PHARM					
PHYS	-0.13 (-2.17, 1.91)	0.96 (-1.15, 3.06)	1.65 (-0.15, 3.45)		

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)			
HbAc1 (%)	PHYS+NUTR	PHYS+PHARM	PHYS+PSYCH	PLAC/STD
Health_MA	.			-0.90 (-1.28, -0.52)
Mixed_PHYS	.			-0.17 (-0.49, 0.16)
NUTR	0.00 (-0.97, 0.97)			0.02 (-0.25, 0.29)
PHARM	.	0.00 (-0.44, 0.44)		-0.57 (-0.99, -0.15)
PHYS	0.11 (-0.21, 0.42)			-0.16 (-0.31, -0.02)
PHYS+NUTR				-0.56 (-0.93, -0.19)
PHYS+PHARM	0.11 (-0.56, 0.78)			
PHYS+PSYCH	-0.14 (-0.62, 0.34)	-0.25 (-0.98, 0.48)		-0.32 (-0.72, 0.08)
PLAC/STD	-0.46 (-0.73, -0.19)	-0.57 (-1.18, 0.04)	-0.32 (-0.72, 0.08)	
FBG (mmol/l)				
Health_MA				-1.89 (-3.70, -0.08)
Mixed_PHYS				-0.81 (-2.68, 1.07)
NUTR				-0.11 (-1.65, 1.42)
PHARM				
PHYS	-0.36 (-2.06, 1.35)			-1.87 (-2.87, -0.87)

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis.
Direct comparisons are represented above the grey rectangle whereas indirect comparisons are reported below the grey rectangle.

Table 5. Frequentist Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)				
FBG (mmol/l)	Health_MA	Mixed_PHYS	NUTR	PHARM	PHYS
PHYS+NUTR	-0.79 (-3.13, 1.55)	0.29 (-2.10, 2.69)	0.99 (-1.14, 3.12)		-0.66 (-2.06, 0.74)
PHYS+PHARM					
PHYS+PSYCH					
PLAC/STD	-1.89 (-3.70, -0.08)	-0.81 (-2.68, 1.07)	-0.11 (-1.65, 1.42)		-1.76 (-2.71, -0.82)
Muscle mass (kg/m^2)					
Health_MA					
Mixed_PHYS					
NUTR		-0.03 (-0.34, 0.28)			
PHARM		0.09 (-0.34, 0.52)	0.12 (-0.32, 0.55)		
PHYS		0.06 (-0.25, 0.38)	0.09 (-0.23, 0.41)	-0.03 (-0.47, 0.41)	
PHYS+NUTR		-2.03 (-3.00, -1.06)	-2.00 (-2.97, -1.04)	-2.12 (-3.13, -1.11)	-2.09 (-3.06, -1.12)
PHYS+PHARM		0.19 (-0.28, 0.66)	0.22 (-0.26, 0.69)	0.10 (-0.10, 0.30)	0.13 (-0.35, 0.61)
PHYS+PSYCH					
PLAC/STD		0.01 (-0.21, 0.23)	0.04 (-0.19, 0.26)	-0.08 (-0.45, 0.29)	-0.05 (-0.28, 0.18)

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)			
FBG (mmol/l)	PHYS+NUTR	PHYS+PHARM	PHYS+PSYCH	PLAC/STD
PHYS+NUTR				-0.57 (-2.81, 1.67)
PHYS+PHARM				
PHYS+PSYCH				
PLAC/STD	-1.10 (-2.58, 0.38)			
Muscle mass (kg/m^2)				
Health_MA				
Mixed_PHYS				0.01 (-0.21, 0.23)
NUTR				0.04 (-0.19, 0.26)
PHARM		0.10 (-0.10, 0.30)		-0.08 (-0.45, 0.29)
PHYS				-0.05 (-0.28, 0.18)
PHYS+NUTR				2.04 (1.10, 2.98)
PHYS+PHARM	2.22 (1.19, 3.25)			
PHYS+PSYCH				
PLAC/STD	2.04 (1.10, 2.98)	-0.18 (-0.60, 0.24)		

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis.
Direct comparisons are represented above the grey rectangle whereas indirect comparisons are reported below the grey rectangle.

Table 5. Frequentist Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)				
Grip strength (kg)	Health_MA	Mixed_PHYS	NUTR	PHARM	PHYS
Health_MA					
Mixed_PHYS	-1.34 (-1.93, -0.75)				
NUTR	-0.87 (-3.04, 1.31)	0.47 (-1.78, 2.72)			
PHARM	0.47 (-0.34, 1.28)	1.81 (0.81, 2.80)	1.34 (-0.98, 3.65)		
PHYS	-0.23 (-0.32, -0.14)	1.11 (0.52, 1.70)	0.64 (-1.53, 2.81)	-0.70 (-1.50, 0.11)	
PHYS+NUTR	-1.05 (-2.73, 0.62)	0.28 (-1.49,2.06)	-0.19 (-2.88, 2.51)	-1.52 (-3.38, 0.33)	-0.83 (-2.50, 0.85)
PHYS+PHARM					
PHYS+PSYCH	-2.97 (-7.60, 1.66)	-1.63 (-6.29, 3.03)	-2.10 (-7.21, 3.01)	-3.44 (-8.13, 1.25)	-2.74 (-7.37, 1.88)
PLAC/STD	0.17 (0.09, 0.25)	1.51 (0.92, 2.10)	1.04 (-1.14, 3.21)	-0.30 (-1.10, 0.50)	0.40 (0.36, 0.44)
Gait speed (m/s)					
Health_MA					
Mixed_PHYS	-0.05 (-0.21, 0.11)				
NUTR					
PHARM					
PHYS	0.00 (-0.15, 0.16)	0.05 (0.01, 0.10)			

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)			
Grip strength (kg)	PHYS+NUTR	PHYS+PHARM	PHYS+PSYCH	PLAC/STD
Health_MA				0.17 (0.09, 0.25)
Mixed_PHYS				1.51 (0.92, 2.10)
NUTR	0.00 (-7.10, 7.10)			0.96 (-1.23, 3.15)
PHARM				-0.30 (-1.10, 0.50)
PHYS	1.32 (-2.75, 5.38)			0.40 (0.36, 0.44)
PHYS+NUTR				1.58 (-0.19, 3.34)
PHYS+PHARM				
PHYS+PSYCH	-1.92 (-6.84, 3.00)			3.14 (-1.49, 7.77)
PLAC/STD	1.22 (-0.45, 2.90)		3.14 (-1.49, 7.77)	
Gait speed (m/s)				
Health_MA				0.01 (-0.15, 0.17)
Mixed_PHYS				0.06 (0.01, 0.11)
NUTR				
PHARM				
PHYS	-0.03 (-0.15, 0.09)			0.01 (0.00, 0.01)

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis.
Direct comparisons are represented above the grey rectangle whereas indirect comparisons are reported below the grey rectangle.

Table 5. Frequentist Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)				
Gait speed (m/s)	Health_MA	Mixed_PHYS	NUTR	PHARM	PHYS
PHYS+NUTR	-0.05 (-0.24, 0.13)	-0.00 (-0.11, 0.11)			-0.06 (-0.16, 0.04)
PHYS+PHARM					
PHYS+PSYCH	-0.15 (-0.33, 0.03)	-0.10 (-0.19, -0.01)			-0.15 (-0.23, -0.08)
PLAC/STD	0.01 (-0.15, 0.17)	0.06 (0.01, 0.11)			0.01 (0.00, 0.01)
Chair stand in 30 s, reps					
Health_MA					
Mixed_PHYS		0.46 (-5.31, 6.23)			
NUTR		0.30 (-3.85, 4.45)	-0.16 (-6.28, 5.97)		
PHARM		0.84 (-2.14, 3.81)	0.38 (-4.94, 5.69)	0.54 (-3.08, 4.16)	
PHYS		-0.12 (-3.93, 3.68)	-0.58 (-6.09, 4.93)	-0.42 (-4.75, 3.91)	-0.96 (-3.62, 1.70)
PHYS+NUTR					
PHYS+PHARM		-3.60 (-7.88, 0.68)	-4.06 (-10.27, 2.15)	-3.90 (-8.65, 0.85)	-4.44 (-8.20, -0.67)
PHYS+PSYCH		0.30 (-2.25, 2.85)	-0.16 (-5.33, 5.02)	0.00 (-3.28, 3.28)	-0.54 (-2.07, 1.00)
PLAC/STD					

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)			
Gait speed (m/s)	PHYS+NUTR	PHYS+PHARM	PHYS+PSYCH	PLAC/STD
PHYS+NUTR				0.09 (-0.03, 0.21)
PHYS+PHARM				
PHYS+PSYCH	-0.10 (-0.23, 0.03)			0.16 (0.08, 0.24)
PLAC/STD	0.06 (-0.04, 0.16)		0.16 (0.08, 0.24)	
Chair stand in 30 s, reps				
Health_MA				0.30 (-2.25, 2.85)
Mixed_PHYS	-1.00 (-7.16, 5.16)			0.00 (-5.28, 5.28)
NUTR				0.00 (-3.28, 3.28)
PHARM	-0.70 (-3.85, 2.45)			-0.60 (-2.20, 0.99)
PHYS				1.00 (-3.72, 5.72)
PHYS+NUTR				
PHYS+PHARM	-3.48 (-7.93, 0.97)			3.90 (0.46, 7.34)
PHYS+PSYCH	0.42 (-2.41, 3.25)		3.90 (0.46, 7.34)	
PLAC/STD				

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis.
Direct comparisons are represented above the grey rectangle whereas indirect comparisons are reported below the grey rectangle.

Table 5. Frequentist Network meta-analysis matrix of results (cont.)

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)				
Five-time up and go test, s	Health_MA	Mixed_PHYS	NUTR	PHARM	PHYS
Health_MA					
Mixed_PHYS					-0.97 (-3.85, 1.91)
NUTR					
PHARM					
PHYS		0.15 (-1.96, 2.27)			
PHYS+NUTR					
PHYS+PHARM					
PHYS+PSYCH		0.69 (-2.62, 4.00)			0.54 (-2.64, 3.72)
PLAC/STD		-0.23 (-2.02, 1.57)			-0.38 (-1.94, 1.17)

Outcomes	Effect of intervention in each row compared with intervention in each column Mean difference (95% confidence intervals)			
Five-time up and go test, s	PHYS+NUTR	PHYS+PHARM	PHYS+PSYCH	PLAC/STD
Health_MA				
Mixed_PHYS				-0.14 (-2.01, 1.72)
NUTR				
PHARM				
PHYS				-0.65 (-2.24, 0.94)
PHYS+NUTR				
PHYS+PHARM				
PHYS+PSYCH				-0.92 (-3.70, 1.86)
PLAC/STD			-0.92 (-3.70, 1.86)	

PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM, Pharmacotherapy; NUTR, Nutrition supplementation only. Cells without value represented no corresponding comparisons that existed and were included into the network meta-analysis.
Direct comparisons are represented above the grey rectangle whereas indirect comparisons are reported below the grey rectangle.

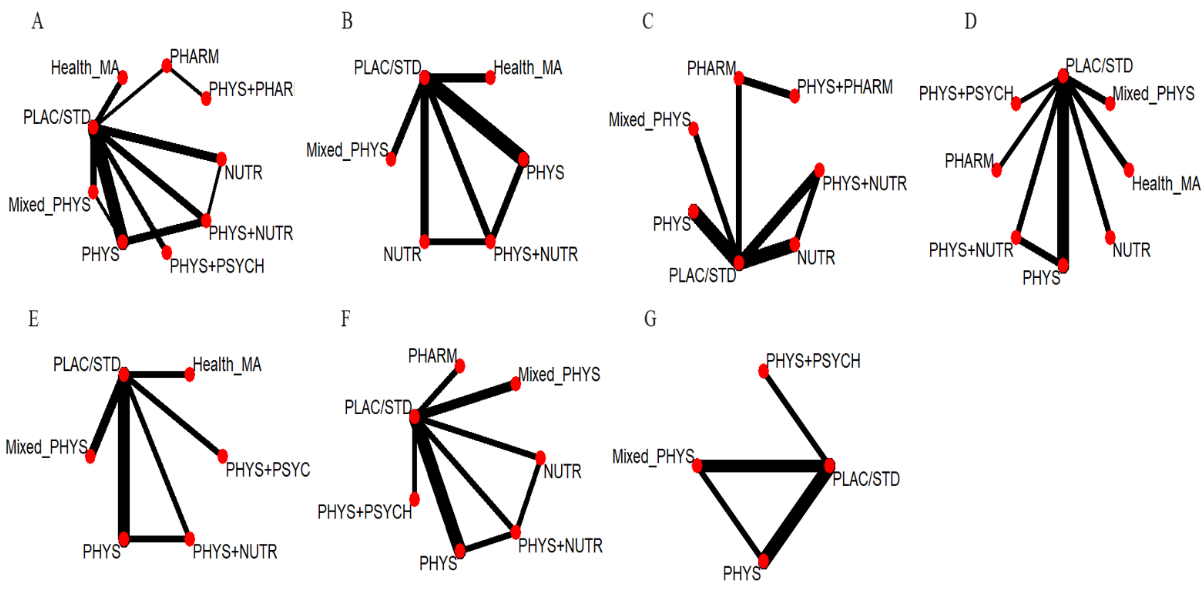

Figure 2. Network geometry for the outcomes of blood glucose level and physical performance. Each intervention node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects. (A) HbAc1. (B) Fasting blood glucose. (C) muscle mass. (D) grip strength. (E) gait speed. (F) lower muscle strength measured by chair stand test. (G) dynamic balance measured by five-time up and go test. PHYS+PSYCH, Physical activity + Psycho-social or cognitive training; PLAC/STD, Placebo or standard care; PHYS+NUTR, Physical activity +nutrition supplementation; PHYS, Physical activity only; Mixed_PHYS, Mixed Physical activity; Health_MA, Health management; PHYS+PHARM, Physical activity + Pharmacotherapy; PHARM,Pharmacotherapy; NUTR, Nutrition supplementation only.

DISCUSSION

Our NMA results indicated that health management provided by health providerslis is most promising for reducing HbAc1, better than pharmacotherapy, but showed less satisfactory effect in grip strength and gait speed. The intervention of PHYS+NUTR was the most effective in increasing muscle mass and also represented a good improvement in grip strength and gait speed. Moreover, thePHYS+PSYCH intervention was more powerful in increasing grip strength, gait speed, lower body muscle strength, and dynamic balance than the remaining interventions.

Our study recommended those who expected to decline HbA1c could engage in the individualized health management provided and supervised by health providers. The individualized precision diabetes medicine is recommended to older adults with T2DM.[44,45] A new published guideline for the management of diabetes mellitus in the elderly recommends the stratified and individualized management strategy to the diabetic elderly for improving prognostic effect such as decreasing the risk of sarcopenia and fall.[46] According to the healthy and nutritional status of the elderly, individualized nutrition and lifestyle intervention and degraded pharmacotherapy should be provided with supervision for the diabetic elderly combined with high risk of frailty and sarcopenia.46 Health management tends to be the multiple personalized lifestyle management supervised by health workers or digital devices, which proved more effective than routine care.[10,20,22,47] Although there are no RCTs to compare the individualized health management with exercise, nutrition therapy, or any other interventions, health management, always consisting of weight loss management, diet advice, or medication adherence supervision, is dynamically adjusted according to blood glucose level during the intervention period, leading to achieving great HbAc1 reduction than other interventions. However, personalized health management represented less satisfactory effects on physical performance. Evidence from two NMAs showed physical activity combined with or without nutritional supplements are the most beneficial to improve muscle mass and muscle strength than medication management, pharmacotherapy, psychosocial cognitive training, and nutrition supplement only for managing sarcopenia or frailty.[48,49] Thus, older adults with T2DM who received supervised and personalized health management are suggested to reinforce the exercise intensity and nutritional supplements for avoiding injury falls and muscle aches because of muscle weakness.

Exercise combined with cognitive training or nutritional supplements induced at best in improving physical performance, but shows less promising in glycemic control, in accordance with one umbrella review that compared the effect of nutritional interventions combined with or without physical activity on muscle mass and muscle strength in older people.[50] Another NMA of RCTs found that simultaneous combined physical and cognitive training was the most efficacious intervention for improving physical function compared to exercise only or nutrition only.[51] With our limited knowledge, there is no RCT aimed to compare the effect of exercise combined with cognitive training versus exercise combined with nutritional supplements on blood glucose control and improving physical function in older adults with T2DM. Just one RCT was conducted in older people to compare combined interventions of nutritional, physical, and cognitive training with nutrition only, exercise only, and cognitive training only on muscle strength, and physical activity level, of which combined intervention of three components achieved the best physical performance.[52] Moreover, one systematic review indicates that older individuals, always accompanied by chronic diseases such as T2DM, could focus more on muscle strength than muscle mass when evaluating physical performance.[53] Hence, combined intervention of exercise and cognitive training is important to improve physical performance and individualized health management should be combined with simultaneous exercise and cognitive training to optimize its effectiveness for both controlling blood glucose and improving physical function.

Our NMA study had several strengths. Firstly, a large sample size (n = 2889) of older adults with T2DM was included, so producing the power to test statistically significant mean differences. Secondly, our study only included RCTs, as a gold standard, which is the best way to evaluate the relative effectiveness of comparative interventions. Thirdly, we employed three NMA approaches to assess the relative effect of included interventions, which ensured our results were relatively stable and robust. Fourthly, we both assessed the glycemic control and physical function among the interventions received by older people with T2DM using NMA, as we know, this is the first systematic review to combine the direct and indirect evidence of 9 interventions available and compare their effects.

This review shared some limitations. Firstly, most RCTs included a sample size fewer than 100 participants, which may induce the higher risk of analytic bias. Secondly, there was inconsistency within the same head-to-head comparisons such as PHYS versus PHYS+NUTR and PHYS versus usual care. Although we used Bayesian NMA with a random model to decrease the potential heterogeneity, the considerable variability cannot be neglected. Thirdly, we did not further perform NMA adjusted for covariations such as duration of T2DM and follow-up weeks, because the number of RCTs is not enough for subgroup NMA analysis. But we did meta regression by adjusting the bias score assessed by Cochrane Collaboration's tool, and the most of NMA results using the meta regression method were similar to primary NMA results.

Based on the most up-to-date and evidence available, our review suggests individualized health management combined with physical and cognitive training is the optimal intervention to achieve glycemic control and improvement of physical function. To minimize muscle weakness when older adults receive individualized health management or pharmacotherapy to control blood glucose, simultaneously or sequentially exercise and cognitivetraining is required. The effect of individualized health management versus exercise combined with psychological training on glycemic control and improving physical performance needs further robust RCTs to directly assess and validate.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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