The effect comparisons of different exercise interventions on blood glucose and insulin resistance relative indicators for prediabetes: a network meta-analysis

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Research article

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Abstract

Background: In order to recommend the optimum type of exercise for type 2 diabetes prevention, the effect of different exercise interventions on glycaemic control and insulin resistance relative indicators were compared. Methods: The studies involving the curative effect of aerobic exercise trailing (AET) or resistance trailing (RT) for prediabetes were searched with pre-established strategy . The Body Mass Index (BMI), fasting blood glucose (FBG), glycated haemoglobin (HbA1c), Insulin and homeostasis model assessment-insulin resistance index (HOMAIR) were used as outcomes indictors. Q statistic was calculated to evaluate the heterogeneity within studies. A fixed effects model was chosen for pooling data with $p > 0.05$, otherwise, a random effects model was chosen. The consistency test in this network meta-analysis was conducted by Node-splitting analysis. Results: A total of 12 eligible studies were included into this network meta-analysis. According to p score values, prediabetes individuals in AET group had better curative effect in BMI (p score = 0.7525), Insulin (p score = 0.6411) and HOMAIR (p score = 0.6411) value controls than in other groups, while the curative effect of RT on FBG (p score = 0.8465) and HbA1c (p score = 0.8550) values were optimum. The rank of P-scores for each indicator under above two effect models was basically consistent, indicating that our results of network meta-analysis were stable. Conclusions: AET might be a better intervene method for improving insulin resistance to prediabetes, while RT was more effective than AET, AET+RT or CT for glycaemic control in prediabetes.

Background

Pre-diabetes, also defined as impaired glucose regulation (IGR), including increased glycated haemoglobin (HbA1c), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or combined IFG and IGT, is an intermediate state between normal glycometabolism and diabetes and presents with a poor glucose regulation function [1]. People with IFG is diagnosed with obvious enhanced blood glucose [Fasting blood glucose (FBG): 6.1-6.9 mmol/L] at morning before an overnight fast based on WTO definitions [2], while individuals with IGT have increased postprandial blood glucose [3]. Insulin resistance and pancreatic β-cell dysfunction are considered as two main causes for IFG and IGT development [4, 5].

Reportedly, individuals with prediabetes have a 30%-70% chance for developing type 2 diabetes over the next 4-30 years [6]. In China, the overall prevalence of diabetes is estimated to be 10.9%, while prediabetes is estimated to be 35.7% [7]. In addition, prediabetes and type 2 diabetes are involved in cardiovascular complications, which may contribute to elevated risk of mortality [8]. With the increasing prevalence of prediabetes and type 2 diabetes in China, prediabetes prevention may be an important strategy for delaying the onset of type 2 diabetes and many its complications.

Several factors such as smoking, harmful drinking, obesity, abnormal cholesterol and triglycerides may lead to increased risk of pre-diabetes [9]. It is suggested that lifestyle intervention involving increased physical activity, dietary changes for lower energy intake may prevent type 2 diabetes [10]. Interesting, exercise-induced weight reduction is superior to dieting for improving insulin resistance in obese person [11]. The underlying mechanism may be that exercise-induced weight reduction could lead to activated mitochondrial oxidative capacity and decreased endogenous glucose production to suppress unnecessary gluconeogenesis [12]. So far, several exercise interventions including aerobic exercise trailing (AET), resistance trailing (RT) or combined AET+RT are used for diabetes prevention in prediabetes individuals [13-15]. However, the comparative effectiveness of these interventions is unclear. Thus, in order to investigate the optimum type of exercise trailing for prediabetes individuals, the direct and network meta-analyses were both conducted to evaluate the effects of these different exercise trailings on Body Mass Index (BMI) changes, levels of fasting blood glucose (FBG), HbA1c, Insulin and homeostasis model assessment-insulin resistance index (HOMAIR) in the present study.

Methods

Search strategy

The studies involving the curative effect of aerobic exercise or resistance exercise for prediabetes were searched from PubMed, Embase, and Cochrane Library databases up to February 20, 2019. The searching terms were set as (pre-diabetes OR prediabetic OR “impaired glucose regulation” OR IGR OR “impaired fasting glucose” OR IFG OR “impaired glucose tolerace” OR IGT OR “glucose metabolism disorders”) AND (exercise OR sport). The language was limited in English.

Inclusion and exclusion criteria

The included studies must meet the criteria as follows: 1) the study published in English with the attempt to evaluate the curative effect of aerobic exercise or resistance exercise for prediabetes; 2) at least one of following main outcomes were reported, including BMI, FBG, the change values of HbA1c, Insulin and HOMAIR.

The study may be excluded if they met one of following situations: 1) the data provided in study was incomplete, which can't be used for following statistical analysis; 2) the study was review, comment or letter; 3) the study was repeatedly published or used for multiple studies by the same population, and only newest study or study with more information was included.

Data extraction and quality assessment

The following information were independently extracted from two investigators, including study characteristics (the first author of study, study region, publication year, the follow-up time, patient type of prediabetes, type of exercise and the total number of participants), and participants characteristics (age, gender ratio and BMI). In addition, the quality of studies was evaluated using 'Risk of bias' tool of Cochrane Collaboration [16], which assessed the issues of selection, performance, detection, attrition and reporting bias. During the course of data extraction and quality assessment, the disagreements were consulted via discussion with the third investigator.

Statistical analysis

In this study, direct and network (or indirect) meta-analyses were both performed for comparing the pooled data among groups. The "meta" package in R 3.4.3 software was used to merge data for direct comparisons. The effect size for variables was indicated as standardized mean difference (SMD) and its 95% CI (confidence interval). I^2 statistics was calculated to assess the heterogeneity within studies. If there was statistical difference in heterogeneity test statistics (I^2>50%), a random effects model was applied to calculate the pooled value, otherwise, a fixed effects model was used [17].

For network meta-analysis, the "netmeta" package in R 3.4.3 software was utilized. The Cochran's Q statistic was calculated to evaluate the heterogeneity within studies. A fixed effects model was chosen for calculating the pooled data under the p value of Q statistic lager than 0.05, otherwise, a random effects model was chosen [18]. In network meta-analysis, all treatments or interventions were ranked based on P-scores, and the higher P-score of intervention, the better curative effect [19].

Sensitivity analysis and consistency test

Fixed and random effects models were both used to perform the sensitivity analysis of P-score. The consistency test was conducted by Node-splitting analysis and the p value of Node-splitting analysis was used to compare the results from direct and indirect comparisons. If there was no significant difference between direct and indirect comparisons results (p>0.05), a consistency model was applied to pool the data, or an inconsistency model might be adopted.

Results

Eligible studies

The process of the study screening is presented in Figure 1. In total, 3979 relevant articles were searched from PubMed (1776), Embase (1851), and Cochrane Library (352) databases based on the preliminary search strategy. After removing 1524 duplicates, 2455 articles were subsequently analyzed, and 2328 irrelevant articles were further excluded by title and abstract reviewing. Next, the reminded 125 articles were future filtered through full text reviewing, and 103 articles that didn't accord with the inclusive criteria were eliminated, including 25 case series/report, 23 letter/ comment, 29 reviews/meta-analysis, 7 studies with duplicated populations and 31 articles without available data. As result, a total of 12 eligible studies were used to conduct following meta-analysis [13-15, 20-28].

Characteristics of eligible studies

The characteristics of 12 included studies are presented in Table 1. These studies were published between 1998 and 2017. The study regions were involved in Chile, Austria, Belgium, Netherlands, United States, Canada, Germany, Finland and Sweden. AET, control trailing (CT), RT and AET+RT were main types of exercise interventions. In total, 462 participants were recruited, of which 123 undergone AET, 214 undergone CT, 54 undergone RT and 71 undergone AET+RT. Majority of participants were obesity based on BMI values, and most of studies designed a 12-week of follow-up. The pre-diabetes subjects in included studies were mainly comprised of of IFG and IGT individuals.

Quality assessment

The results of quality assessment showed that all the included studies demonstrated a high risk of performance bias, and most of studies presented an unclear risk of Detection bias, allocation concealment and other bias. However, most of studies had a low risk of random sequence generation, attrition and reporting bias. Overall, the quality of included studies was moderate (Figure 2).

Direct meta-analysis

Before pooling the data, heterogeneity test was performed among studies reporting BMI, FBG, HbA1c, Insulin, and HOMAIR indicators, respectively. The results showed a significant heterogeneity was found among studies involving comparisons of AET vs. CT (I^2=56.0%) for BMI, AET vs. CT (I^2= 83.4%) and AET+RT vs. CT (I^2= 80.4%) for FBG, AET vs. CT (I^2=96.0%) and RT vs. CT (I^2=83.5%) for Insulin, and AET vs. CT (I^2=91.9%) and RT vs. CT (I^2=75.9%) for HOMAIR, thus the random effect model was used to pool data. Whereas, the other comparisons for each indicator were calculated using fix effect model. The results showed that the HbA1c value in prediabetes individuals undergone AET was significantly reduced than individuals undergone CT (SMD = -0.7179, 95%CI = -1.0421; -0.3937). In addition, the prediabetes in RT group had a lower HOMAIR value than in CT group (SMD =-1.4826, 95%CI = -2.5750; -0.3902) (Table 2). However, there was no statistical significance in other comparisons for each indicator (Table 2). Notably, the comparisons results obtained from only one included studies were unconsidered in our study.

Network meta-analysis

The network construction diagram showed that four comparisons between groups (RT vs. CT, RT vs. AET, AET+RT vs. CT, and AET vs. CT) were only found in included studies (Figure 3). Based on the Q statistic, the random effects model was used for the network meta-analysis. The results of P-scores for network meta-analysis showed there were no statistical difference between four comparisons for BMI, FBG, HbA1c, Insulin and HOMAIR. However, the greater decreases in BMI values could be seen in AET (p score = 0.7525) and AET+RT (p score = 0.5750) groups, while prediabetes individuals in RT groups had better curative effect on FBG (p score = 0.5750) and HbA1c (p score = 0.8550) values. In addition, the HOMA-IR and insulin values were better changed in AET (both p score = 0.6411) than in other groups (Tables 3 and 4).

Sensitivity analysis and consistency test

In order to evaluate whether the results of network meta-analysis was stable, the fixed and random effects models were both used to pool the data. Notably, the results showed the rank of P-scores for each indicator under above two effect models was basically consistent, indicating that our results of network meta-analysis were stable (Table 4). In addition, the result of Node-splitting analysis demonstrated that and the results from direct and indirect comparisons were consistent with all P>0.05 (Table 5).

Discussion

In present study, a total of 12 studies were included to compare the effect of RT, AET and AET+RT on BMI, FBG, HbA1c, Insulin, and HOMAIR in prediabetes individuals via performing direct and network meta-analysis. The results of network meta-analysis revealed that the prediabetes individuals in AET group had better curative effect in BMI, Insulin and HOMAIR value controls than in other groups, while the curative effect of AET on FBG and HbA1c values ranked second only to RT.

The BMI, insulin and HOMAIR as insulin resistance relative indicators are commonly used for evaluating diabetes and different exercise intervention modes have different effect on the BMI, insulin, and HOMAIR. Reportedly, the sensitivity to insulin are increased in both healthy individuals and diabetes patient after intense or moderate exercise [29]. In addition, HOMAIR values in prediabetes subjects are significantly reduced following exercise, and insulin secretion adjusts in an exercise intensity dependent manner is relative to the level of insulin resistance [30]. Moreover, it is revealed aerobic exercise improves insulin sensitivity in obese adolescents with lower HOMAIR level and the enhanced insulin sensitivity is positively correlated with reduced BMI [31]. Furthermore, the insulin and HOMA score are significantly lower in coronary artery patients with prediabetes after aerobic exercise compared with control group [21]. Notably, our results showed a greater reduction of BMI, insulin, and HOMAIR in AET than in other groups. Similarly, small but not statistically significant decreases of insulin and HOMA-IR are found in AET than RT [28]. Collectively, AET might be a better intervene method for improving insulin resistance to prediabetes with greater changes of BMI, insulin, and HOMAIR.

Reportedly, the glucose uptake and utilization are increased with AET via activating AMPK, while RT can enhance glucose uptake and reduce blood glucose via RE-induced GLUT4 translocation [32]. Thus, RT and AET can improve the glycemic control via different mechanisms [33, 34]. FBG and HbA1c as two glucose relative indicators for monitoring blood glycaemic control, the changes of which are associated with RT and AET intervenes. The study of Luo *et al* has showed that both RT and AET interventions can remarkably reduce the FBG levels in prediabetic participants compared with CT intervention, but no significantly different is found between RT and AET groups [35]. In addition, RT or AET alone can significantly decrease HbA1c levels in type 2 diabetes than CT, respectively, while the FBG value is only significantly reduced after RT [36]. It has suggested that AET has greater reduction of HbA1c in type 2 diabetics than RT [37]. On the contrary, Bweir S *et al* have found a significant decrease of HbA1c in RT group than in AET group [38]. In consistent with our study, it was demonstrated RT was more effective than AET, AET+RT or CT for glycaemic control with lower FBG and HbA1c in prediabetes. The difference of these two opposite results may be caused by different aerobic and resistance exercise programs, or intervention time.

With the purpose of providing some useful clues for diabetes prevention in the present study, it was first one to compare the effect of AET, AET+RT and RT on prediabetes. However, several limitations should be mentioned. Firstly, significant heterogeneity probably from different subjects with IFG or IGT and different study regions were found, which might be potential confounders to influence the results of present meta-analysis. Secondly, majority of included studies were studied in European and American area, which might lead to selection bias. Thirdly, the results of P-scores ranked under fix and random effect models were not all the same. Fourthly, the overall quality of present study was moderate, while all the included presented the high risk of blinding of participants and personnel (performance bias). Finally, most comparisons for each indicator were only reported in one included study and there was no combined power. Therefore, a great number of high quality randomized controlled studies with more comparisons for each indicator were needed in an updated investigation.

Conclusions

AET might be a better intervene method for improving insulin resistance to prediabetes with greater changes of BMI, insulin, and HOMAIR. RT was more effective than AET, AET+RT or CT for glycaemic control with lower FBG and HbA1c in prediabetes.

Abbreviations

AET, aerobic exercise trailing; BMI, Body Mass Index; CT, control trailing; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HOMAIR, homeostasis model assessment-insulin resistance index; IFG, impaired fasting glucose ; IGR, impaired glucose regulation; IGT, impaired glucose tolerance; RT, resistance trailing; SMD, standardized mean difference

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Conception and design: Jianchun Yin; Collection and assembly of data: Lijun Tang; Data analysis and interpretation: Yingjie Fang; Article writing: All authors; Final approval of article: All authors.

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Tables

Table 1. The results of direct meta-analysis

Variable	Group	k	SMD(95%CI)	Q	I^2 (%)	P	Model
BMI	AET vs. CT	4	-0.1976 [-0.7859; 0.3908]	6.80	56.0	0.08	Random
	AET+RT vs. CT	1	-0.2653 [-0.6478; 0.1172]	0.00	-	-	-
	RT vs. CT	1	0.0200 [-0.9922; 1.0321]	0.00	-	-	-
FBG	AET vs. CT	6	0.5217 [-0.2227; 1.2662]	30.75	83.7	<0.01	Random
	AET+RT vs. CT	2	-0.7787 [-1.9115; 0.3540]	5.10	80.4	0.02	Random
	RT vs. AET	1	-0.8907 [-1.3668; -0.4146]	0.00	-	-	-
	RT vs. CT	2	0.8762 [0.4429; 1.3095]	1.21	17.1	0.27	Fixed
HbA1c	AET vs. CT	4	-0.7179 [-1.0421; -0.3937]	5.94	49.5	0.11	Fixed
	AET+RT vs. CT	1	0.0245 [-0.3563; 0.4053]	0.00	-	-	-
	RT vs. AET	1	0.0000 [-0.4530; 0.4530]	0.00	-	-	-
	RT vs. CT	1	-1.8807 [-2.4257; -1.3357]	0.00	-	-	-
Insulin	AET vs. CT	5	-0.1425 [-2.0375; 1.7525]	100.54	96.0	<0.01	Random
	AET+RT vs. CT	1	-0.8934 [-1.9362; 0.1494]	0.00	-	-	-
	RT vs. AET	1	0.8907 [0.4146; 1.3668]	0.00	-	-	-
	RT vs. CT	3	-0.9305 [-2.0838; 0.2228]	12.11	83.5	<0.01	Random
HOMAIR	AET vs. CT	3	-1.3831 [-2.8158; 0.0495]	24.82	91.9	<0.01	Random
	AET+RT vs. CT	1	-0.5054 [-0.8925; -0.1183]	0.00	-	-	-
	RT vs. AET	1	0.6598 [0.1940; 1.1256]	0.00	-	-	-
	RT vs. CT	2	-1.4826 [-2.5750; -0.3902]	4.15	75.9	<0.01	Random

BMI: Body Mass Index; FBG: fasting blood glucose; HbA1c: glycated haemoglobin; HOMAIR: Insulin and homeostasis model assessment-insulin resistance index; AET: aerobic exercise trailing; RT: resistance trailing; CT: control trailing; SMD: Standard mean difference.

Table 2. The results of network meta-analysis

	AET			
BMI	-0.14 [-2.12; 1.83]	AET+RT		
	-0.41 [-1.11; 0.29]	-0.27 [-2.11; 1.58]	CT	
	-0.65 [-2.02; 0.71]	-0.51 [-2.76; 1.74]	-0.24 [-1.54; 1.05]	RT
	AET			
FBG	1.56 [-0.01; 3.13]	AET+RT		
	0.76 [-0.01; 1.51]	-0.80 [-2.17; 0.57]	CT	
	-0.24 [-1.62; 1.13]	-1.81 [-3.70; 0.08]	-1.00 [-2.31; 0.30]	RT
	AET			
HbA1c	-0.77 [-2.72; 1.18]	AET+RT		
	-0.75 [-1.66; 0.17]	0.02 [-1.69; 1.74]	CT	
	0.55 [-1.03; 2.13]	1.32 [-1.02; 3.66]	1.30 [-0.29; 2.88]	RT
	AET			
Insulin	1.10 [-3.24; 5.44]	AET+RT		
	0.21 [-1.43; 1.84]	-0.89 [-4.92; 3.13]	CT	
	0.57 [-2.69; 3.84]	-0.53 [-5.44; 4.39]	0.37 [-2.46; 3.20]	RT
	AET			
HOMAIR	1.10 [-3.24; 5.44]	AET+RT		
	0.21 [-1.43; 1.84]	-0.89 [-4.92; 3.13]	CT	
	0.57 [-2.69; 3.84]	-0.53 [-5.44; 4.39]	0.37 [-2.46; 3.20]	RT

Table 3. The P-score distributions for each indicator

BMI			FBG			HbA1c			Insulina			HOMAIR		
Variable	Fixed	Random	Variable	Fixed	Random	Variable	Fixed	Random	Variable	Fixed	Random	Variable	Fixed	Random
AET	0.8561	0.7525	RT	0.9751	0.8465	RT	0.9729	0.8550	AET	0.9410	0.6411	AET	0.4805	0.6411
AET+RT	0.7758	0.5750	AET	0.6916	0.7719	AET	0.6938	0.6579	CT	0.4200	0.5569	CT	0.4410	0.5569
CT	0.3526	0.3867	CT	0.3310	0.3215	AET+RT	0.1500	0.2805	RT	0.4805	0.4492	RT	0.4200	0.4492
RT	0.0155	0.2857	AET+RT	0.0024	0.0601	CT	0.1834	0.2066	AET+RT	0.1585	0.3528	AET+RT	0.1585	0.3528

Table 4. The results of consistency test

Variable	comparison	k	prop	Nma(95%CI)	direct(95%CI)	indir. (95%CI)	Diff(95%CI)	z	p-value
BMI	AET:CT	4	0.98	-0.41[-1.11;0.29]	-0.40[-1.11;0.31]	-1.14[-6.43;4.15]	0.74[-4.60;6.08]	0.27	0.7856
	AET:RT	1	0.53	-0.65[-2.02;0.71]	-0.91[-2.78;0.95]	-0.36[-2.35;1.63]	-0.55[-3.29;2.18]	-0.4	0.6909
	CT:RT	2	0.87	-0.24[-1.54;1.05]	-0.15[-1.54;1.23]	-0.86[-4.46;2.74]	0.71[-3.15;4.57]	0.36	0.7183
FBG	AET:CT	6	0.98	0.76[0.01;1.51]	0.81[0.04;1.57]	-1.26[-6.37;3.85]	2.07[-3.10;7.23]	0.78	0.4336
	AET:RT	1	0.55	-0.24[-1.62;1.13]	0.00[-1.86;1.86]	-0.54[-2.58;1.51]	0.54[-2.23;3.31]	0.38	0.7039
	CT:RT	2	0.87	-1.00[-2.31;0.30]	-1.30[-2.70;0.10]	0.88[-2.67;4.43]	-2.18[-5.99;1.64]	-1.12	0.2631
HbA1c	AET:RT	1	0.82	0.55[-1.03;2.13]	0.00[-1.74;1.74]	3.12[-0.63;6.86]	-3.12[-7.25;1.02]	-1.48	0.1394
	CT:RT	1	0.81	1.30[-0.29;2.88]	1.88[0.12;3.64]	-1.14[-4.75;2.46]	3.03[-0.99;7.04]	1.48	0.1394

k: Number of studies providing direct evidence; prop: Direct evidence proportion; nma: Estimated treatment effect (SMD) in network meta-analysis; direct: Estimated treatment effect (SMD) derived from direct evidence; indir.: Estimated treatment effect (SMD) derived from indirect evidence; Diff: Difference between direct and indirect treatment estimates; z: z-value of test for disagreement (direct versus indirect); p-value: p-value of test for disagreement (direct versus indirect).

Figures

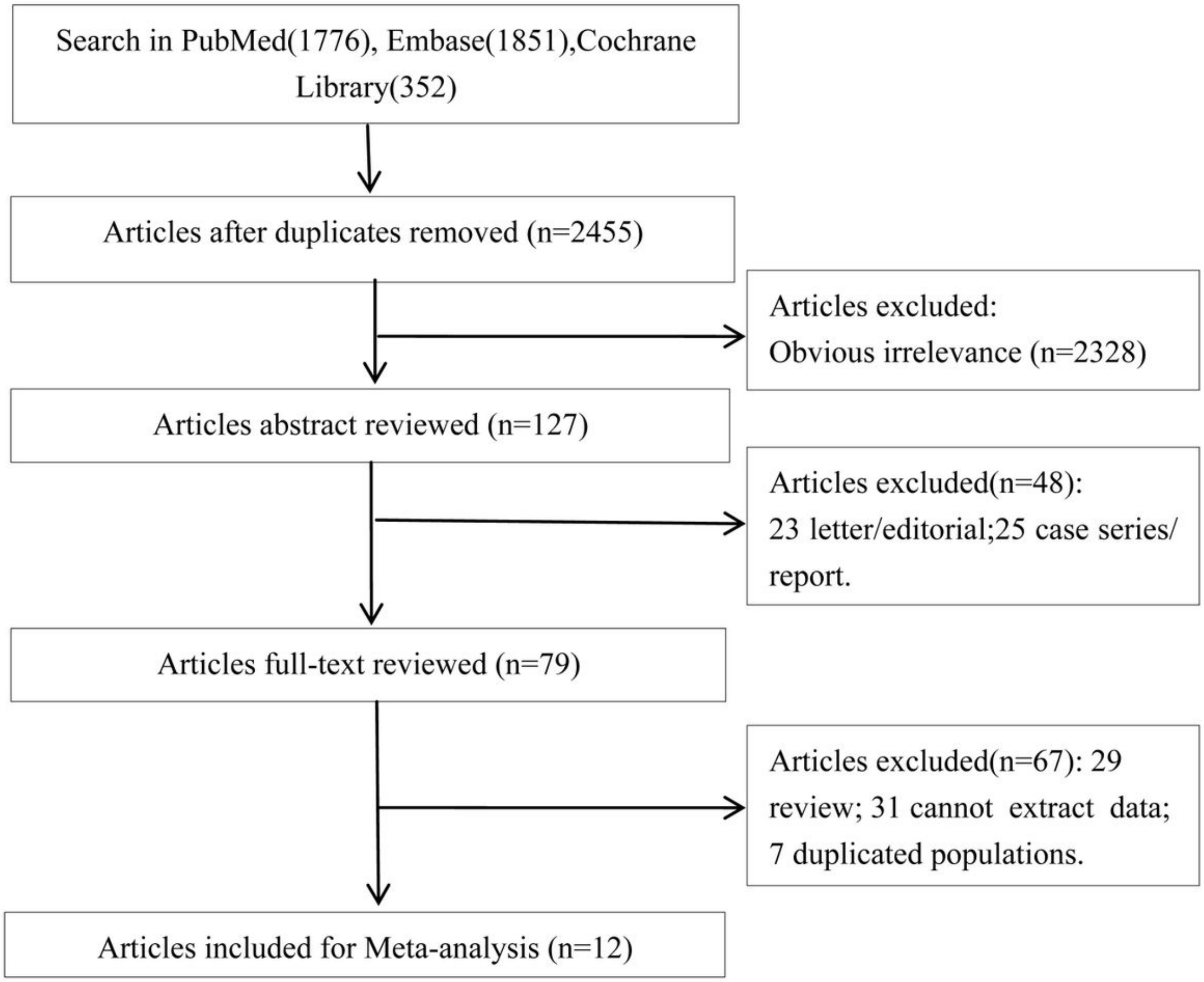

Figure 1

Literature search and study selection.

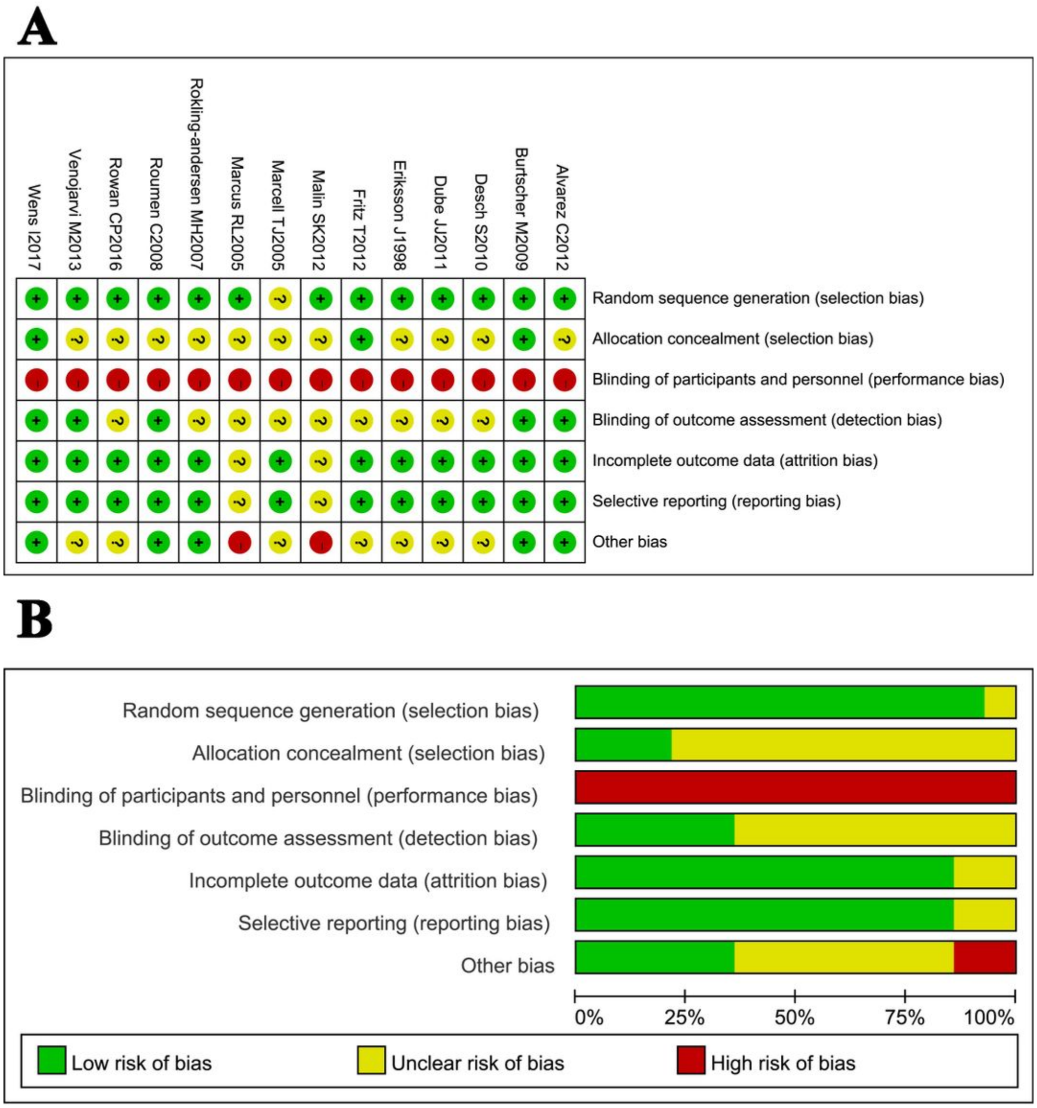

Figure 2

Quality assessments of the included studies. A: The risk of bias for each included studies; B: The summary of bias risk. “+” represents low risk of bias; “−” represents high risk of bias; “?” represents unclear risk of bias.

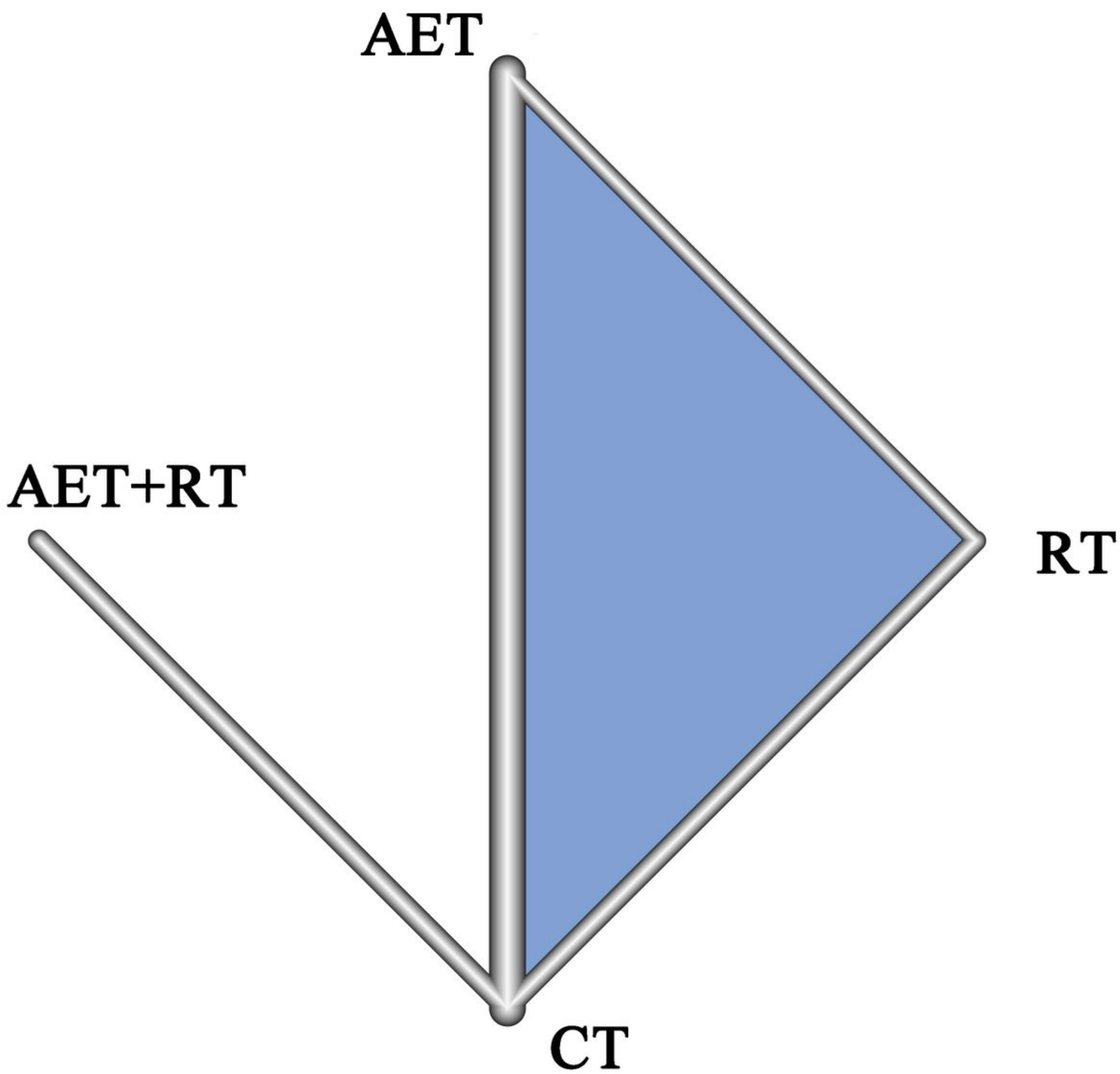

Figure 3

The network construction diagram.