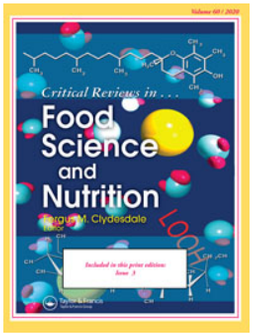

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REVIEW

The effects of resveratrol intake on weight loss: a systematic review and meta-analysis of randomized controlled trials

Reza Tabrizi[a], Omid Reza Tamtaji[b,c], Kamran B. Lankarani[d], Maryam Akbari[a], Ehsan Dadgostar[c], Mohammad Hossein Dabbaghmanesh[e], Fariba Kolahdooz[f], Amir Shamshirian[g], Mansooreh Momen-Heravi[h,i], and Zatollah Asemi[j]

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ABSTRACT

This systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to summarize the effect of resveratrol intake on weight loss. We searched the following databases until July 2018: MEDLINE, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials. Data were pooled using the inverse variance method and expressed as standardized mean difference (SMD) with 95% confidence intervals (95% CI). Out of 831 reports, 36 RCTs were eligible for including to our meta-analysis. The pooled results, using random-effects model showed that resveratrol supplementation significantly decreased body weight (SMD = −0.17; 95% CI, −0.33, −0.01; $P = 0.03$; I^2: 62.6), body mass index (BMI) (SMD = −0.20; 95% CI, −0.35, −0.05; $P = 0.01$; I^2: 60.6), fat mass (SMD = −0.32; 95% CI, −0.62, −0.03; $P = 0.03$; I^2: 77.9) and waist circumference (WC) (SMD = −0.42; 95% CI, −0.68, −0.16; $P = 0.001$; I^2: 75.2), and significantly increased lean mass (SMD = 1.21; 95% CI, 0.75, 1.67; $P < 0.001$; I^2: 87.6). We found no significant effect of resveratrol administration on leptin (SMD = −0.20; 95% CI, −0.68, 0.27; $P = 0.40$; I^2: 85.3) and adiponectin levels (SMD = 0.08; 95% CI, −0.39, 0.55; $P = 0.74$; I^2: 91.0). Resveratrol supplementation significantly decreased body weight in obese patients (SMD −0.43; 95% CI, −0.60, −0.26) compared with other diseases (SMD 0.02; 95% CI, −0.29, 0.33), and type 2 diabetes mellitus (SMD −0.17; 95% CI, −0.37, 0.02). Overall, the current meta-analysis demonstrated that resveratrol intake significantly reduced weight, BMI, WC and fat mass, and significantly increased lean mass, but did not affect leptin and adiponectin levels.

KEYWORDS
Resveratrol; weight loss; overweight; meta-analysis

Introduction

Obesity is a complex chronic status with multifactorial causes such as lifestyle, nutritional, behavior, environment and genetics (Manna and Jain 2015). Globally, obesity has reached epidemic proportions, with >1.6 billion people estimated to be overweight and >600 million of these estimated to be obese (Martins, Robertson, and Morgan 2008). It is causally correlated with several comorbidities that have serious impacts on quality of life as well as on parameters of mental health (Busutil et al. 2017). The increased risks related to obesity include developing type 2 diabetes mellitus (T2DM), hyperinsulinemia, metabolic syndrome, dyslipidemia (Gurka, Filipp, and DeBoer 2018; Singh et al. 2014), cardiovascular disease, hypertension and other chronic diseases, and various cancers (Vucenik and Stains 2012).

Common treatments for managing obesity in obese subjects include lifestyle changes such as weight loss, appropriate diet, and exercise (Villareal et al. 2011). Resveratrol is a phytoestrogen with antioxidant, anti-inflammatory effects that found in a diverse plant species (Szkudelska and Szkudelski 2010). In animal models, it was documented that resveratrol increases longevity, improves motor function, and exerts favorable weight-lowering effects (Alberdi et al. 2011; Wang et al. 2014), such as reduced total body fat and diminished deposits of white adipose tissue (Alberdi et al. 2011). In addition, inhibiting preadipocyte differentiation, decreasing adipocyte proliferation and inducing adipocyte apoptosis by resveratrol may be explained its anti-obesity effects (Wang et al. 2014). A review conducted by Wang et al.(2014), it was observed that the anti-obesity effects of resveratrol may be correlated with it playing a role in

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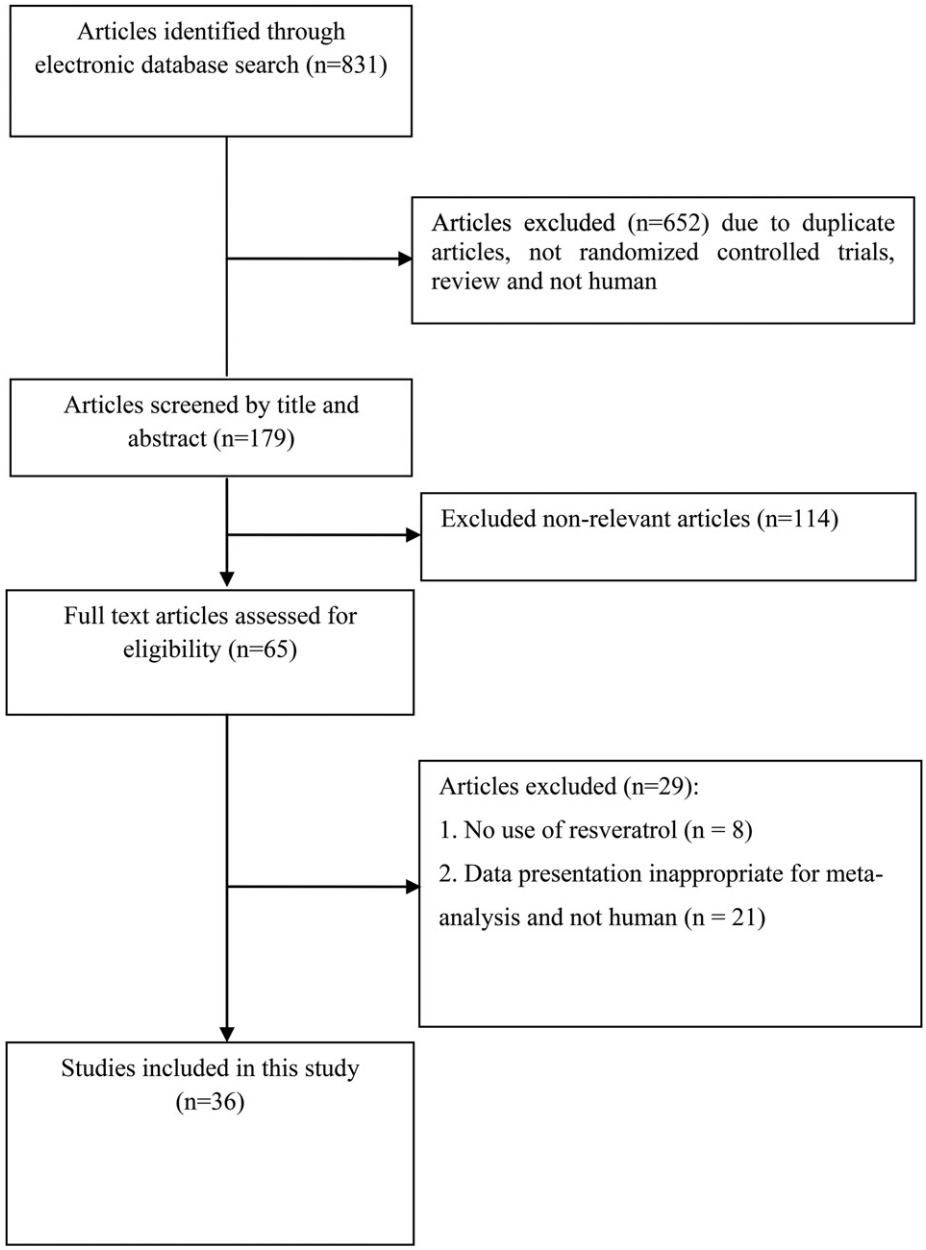


Figure 1. Literature search and review flowchart for selection of studies.

inhibiting preadipocyte differentiation, reducing adipocyte proliferation, inducing adipocyte apoptosis and decreasing de novo lipogenesis. In addition, resveratrol appears to mimic the effects of calorie restriction (Barger et al. 2008). The effects of resveratrol supplementation on weight loss have already been investigated in human models, though the current findings are controversial. In a study conducted by Faghihzadeh et al.(2014), taking 500 mg/day resveratrol by overweight nonalcoholic fatty liver disease (NAFLD) people for 12 weeks improved weight, body mass index (BMI), waist circumference (WC) and hepatic steatosis. However, high-dose resveratrol supplementation to obese men for 4 weeks had no effect on resting energy expenditure, oxidation rates of lipid and ectopic or visceral fat content (Poulsen et al. 2013).

Discrepancies among existing evidence might be associated with the differences existing in study design, characteristics of study populations, comorbid conditions, duration of administration, and the formulations and dosages of resveratrol used. Despite several randomized controlled trials (RCTs), we are aware of no systematic review and meta-analysis of RCTs about the effect of resveratrol on weight loss. This meta-analysis was performed to summarize the available evidence of RCTs to establish the effect of resveratrol on weight loss.

Methods

Search strategy and selection studies

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline were conformed to design, analysis, and reporting of this study. We conducted a systematic search for relevant RCTs through July 2018 by using of Cochrane Library, Embase, Medline, and Web of Science

Table 1. Characteristics of included studies.

Authors (Ref)	Publication year	Sample size (control/ intervention)	Population/Country	Intervention (name and daily dose)	Duration	Presented data	Age (y) (control, intervention)
Anton $SD_{(a,b)}$ et al. (Anton et al. 2014)	2014	10/12	Older adults/USA	Resveratrlol 300 mg	12 weeks	BW, WC	73.17 ± 2.08, 73.3 ± 2.06
Arzola-Paniagua et al. $_{(a,b,c,d,e,f,g,h,l,m,n,p)}$ (Arzola-Paniagua et al. 2016)	2016	24/15	Obesity/Mexico	Resveratrlol 100 mg	4 weeks	BW, BMI, FM, LM,WC	33.7 ± 11.9, 38.8 ± 9.59
Bhatt JK et al. (Bhatt, Thomas, and Nanjan 2012)	2012	28/29	T2DM/India	Resveratrlol 250 mg	12 weeks	BW, BMI	56.67 ± 8.91, 57.75 ± 8.71
Biesinger S et al. (Biesinger et al. 2016)	2015	18/18	Hypertension/USA	Resveratrol 60 mg	4 weeks	BW, BMI,	44 ± 3
Bo $S_{(a,b)}$ et al. (Bo et al. 2016)	2016	62/65	T2DM/ Italy	Resveratrlol 40 mg	24 weeks	BW, BMI, FM, WC, Adiponectin	64.9 ± 8.6, 65.4 ± 8.8
Chachay VS et al. (Chachay et al. 2014)	2014	10/10	NAFLD/Australia	Resveratrlol 3000 mg	8 weeks	BW, BMI	48.8 ± 12.2, 47.5 ± 11.2
Chen S et al. (Chen et al. 2015)	2015	30/30	NAFLD/China	Resveratrlol 600 mg	12 weeks	BW, BMI, WC	overall 20–60
Faghihzadeh F et al. (Faghihzadeh et al. 2014)	2015	25/25	NAFLD/Iran	Resveratrlol 500 mg	12 weeks	BW, BMI, LM	44.04 ± 10.10, 46.28 ± 9.52
Fujitaka $K_{(a,b)}$ et al. (Fujitaka et al. 2011)	2011	17/17	MetS/ Japan	Trans resveratrol 100 mg (Longevinex)	12 weeks	BW, BMI, WC	63 ± 9, 62 ± 14
Ghanim $H_{(a,b,c)}$ et al. (Ghanim et al. 2010)	2010	10/10	Healthy/ USA	Resveratrol 40 mg (from Polygonum Cuspidatum Extract 200 mg)	1 week	Leptin	36 ± 5
Gliemann L et al. (Gliemann et al. 2013)	2013	13/14	Aged men/Denmark	Resveratrlol 250 mg	8 weeks	BW, BMI	65 ± 1, 65 ± 1
Goh KP et al. (Goh et al. 2014)	2014	5/5	T2DM/Singapore	Resveratrlol 500 mg	12 weeks	BW, BMI, Adiponectin	55.8 ± 7.3, 56.8 ± 5.3
Heebøll S et al. (Heebøll et al. 2016)	2016	13/13	NAFLD/Denmark	Resveratrlol 1500 mg	24 weeks	BW, BMI	No
Huhn S et al. (Huhn et al. 2018)	2018	26/27	older adults/Germany	Resveratrol 200 mg	26 weeks	BW, BMI, Leptin	68.60 ± 4.92, 67.54 ± 5.07
Imamura H et al. (Imamura et al. 2017)	2017	25/25	T2DM/Japan	Resveratrlol 100 mg	12 weeks	BW, BMI	57.4 ± 10.6, 58.2 ± 10.1
Kantartzis K et al. (Kantartzis et al. 2018)	2018	52/53	Overweight/ Germany	Resveratrol 150 mg	12 weeks	Adiponectin	Overall 18–70
Khodabandehloo H et al. (Khodabandehloo et al. 2018)	2018	20/25	T2DM/Iran	Resveratrol 800 mg	8 weeks	BW, BMI, WC	56.48 ± 6.72, 61.1 ± 5.61
Kjær TN et al. $_{(a,\ b)}$(Kjaer et al. 2017)	2017	24/21	MetS/Denmark	Resveratrlol 150 mg	16 weeks	BW, BMI, FM, LM, Leptin, Adiponectin	49.1 ± 1.46, 47.8 ± 1.3
Konno $H_{(a,b)}$ et al. (Konno et al. 2013)	2013	15/14	Healthy/Japan	Resveratrol 750 mg from Melinjo (Gnetum gnemon L.) Seed Extract	4 weeks	BW, BMI	overall 35–70
Korsholm AS et al. (Korsholm et al. 2017)	2017	24/21	MetS/Denmark	Resveratrlol 1000 mg	16 weeks	BMI	51.9 ± 1.3, 47.8 ± 1.3
Kumar BJ et al. (Kumar and Joghee,2013)	2013	29/28	T2DM/India	Resveratrlol 250 mg	24 weeks	BW, BMI	56.67 ± 8.91, 57.75 ± 8.71
Mansur AP et al. (Mansur et al. 2017)	2017	24/24	Overweight/Brazil	Resveratrlol 500 mg	4 weeks	BW, BMI,LM,	58.46 ± 3.44, 58.63 ± 3.65
Most J et al. (Most et al. 2016)	2016	20/18	Obesity/Netherlands	Resveratrlol 80 mg +282 mg epigallocatechin-3-gallate	12 weeks	LM, Leptin, Adiponectin	36.1 ± 2.2, 38.7 ± 2.2
Most J et al. (Most et al. 2018)	2018	14/11	Obesity/Netherlands	Resveratrol 80 mg + epigallocatechin-3-gallate 282 mg	12 weeks	Leptin, Adiponectin	36 ± 3, 40 ± 3
Movahed A et al. (Movahed et al. 2013)	2013	31/33	T2DM/Iran	Resveratrlol 1000 mg	6 weeks	BW, BMI	52.45 ± 6.18, 51.81 ± 6.99
Méndez-del Villar M et al. (Méndez-del Villar et al. 2014)	2014	10/11	MetS/Mexico	Resveratrlol 1500 mg	12 weeks	BW, BMI, FM, WC	39.8 ± 5.4, 40.3 ± 5.4
Poulsen MM et al. (Poulsen et al. 2012)	2013	12/12	Obesity/Denmark	Trans-resveratrol 500 mg	4 weeks	Leptin	44.7 ± 3.5, 31.9 ± 2.9
	2018	23/23	T2DM/Iran	Resveratrlol 800 mg	8 weeks	BW, BMI, WC	

(*continued*)

Table 1. Continued.

Authors (Ref)	Publication year	Sample size (control/ intervention)	Population/Country	Intervention (name and daily dose)	Duration	Presented data	Age (y) (control, intervention)
Seyyedebrahimi S et al. (Seyyedebrahimi et al. 2018)							54.96 ± 6.37, 58.72 ± 6.06
Tome-Carneiro $J_{(a,b)}$ et al. (Tomé-Carneiro et al. 2012)	2012	25/25	CVD/ Spain	Resveratrlol-rich grape supplement (resveratrol 8 mg)	24 weeks	Adiponectin	62 ± 9, 63 ± 9
Tome-Carneiro $J_{(a,b)}$ et al. (Tomé-Carneiro et al.2013)	2013	25/25	CAD/Spain	Resveratrol 8 mg plus grape phenolics	24 weeks	Adiponectin	60 ± 12, 58 ± 9
Tome-Carneiro J et al. (João Tomé-Carneiro et al. 2013)	2013	9/13	Hypertension with T2DM/Spain	Resveratrol enriched 8 mg grape extract	48 weeks	Adiponectin	63 ± 12, 57 ± 10
Van der Made SM et al. (van der Made, Plat, and Mensink 2015)	2015	45/45	Obesity/Netherlands	Resveratrol 150 mg	4 weeks	BMI	61 ± 7
Witte AV et al. (Witte et al. 2014)	2014	23/23	Overweight/ Germany	Resveratrlol 200 mg	24 weeks	BW, BMI, Leptin	64.8 ± 6.8, 63.7 ± 5.3
Wong RH et al. (Wong et al. 2013)	2013	15/16	Obesity/Australia	Trans-resveratrol 75 mg	6 weeks	BMI	61
Yoshino J et al. (Yoshino et al. 2012)	2012	14/15	Healthy/USA	Resveratrlol 75 mg	12 weeks	BMI, FM, Leptin, Adiponectin	Overall 58 ± 4
Zortea K et al. (Zortea et al. 2016)	2016	9/10	Schizophrenia/Brazil	Resveratrlol 200 mg	4 weeks	BW, BMI, WC	46.4 ± 11.18, 41 ± 7.87

BW, body weight; BMI, body index mass; CAD, coronary artery disease; FM, fat mass; LM, lean mass; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NR, not reported; T2DM, type 2 diabetes mellitus; WC, waist circumference.

databases. Databases of International Standard Randomized Controlled Trial Number Register and Meta-register for RCTs were searched for all ongoing trials. Studies retrieved that examined the association between resveratrol intake and anthropometric measurements. Searches performed using the following MeSH and text keywords: intervention ("resveratrols" OR "resveratrol" AND "intake" OR "supplementation" OR "use"), and outcomes ["body weight (BW)" OR "BMI" OR "fat mass (FM)" OR "lean mass (LM)" OR "WC" OR "leptin" OR "adiponectin"]. The search strategy was restricted to human RCTs in English language.

Selection criteria

Studies were selected that met the following criteria: study was a human RCT performed either with parallel or crossover design, received resveratrol-containing supplements in the intervention group, whereas the control group received placebo, reported mean changes of anthropometric measurements including body weight, BMI, fat mass, lean mass and WC, and leptin, and adiponectin levels, along with standard deviation (SD), standard error of the mean (SEMs), or related 95% confidence intervals (CIs) for the intervention and placebo groups at baseline and end of intervention. RCTs were not placebo controlled or abstracts without full texts were excluded from current meta-analysis.

Quality assessment and data extraction

Two investigators have independently assessed the methodological quality and have extracted data of included RCTs using the Cochrane Collaboration risk of bias tool and a standard Excel forms, respectively. Any disagreement was resolved by consensus between the authors or discussion with a third author (ZA). The following domains were used for assessing the quality of included RCTs: "randomization generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data and selective outcome reporting, and the other sources of bias". The following items were extracted: the name of first author, the year of publication, country where study was conducted, age, study design, sample size (intervention/placebo groups), type and dose of intervention, duration of intervention, underling diseases, the mean (SD) changes in both treatment and placebo groups for body weight, BMI, fat mass, lean mass and WC, and leptin, and adiponectin levels. If outcomes were estimated by varying type and dose of intervention or with various follow-up of the included RCTs, the authors treated with each one having this situation as a separate trial in present meta-analysis and these studies were shown as alphabet letters.

Statistical analysis

The authors estimated the effects of resveratrol supplementation on anthropometric measurements including: (1) body weight, (2) BMI, (3) fat mass, (4) lean mass, (5) WC, (6) leptin, and (7) adiponectin levels. The pooled effect sizes

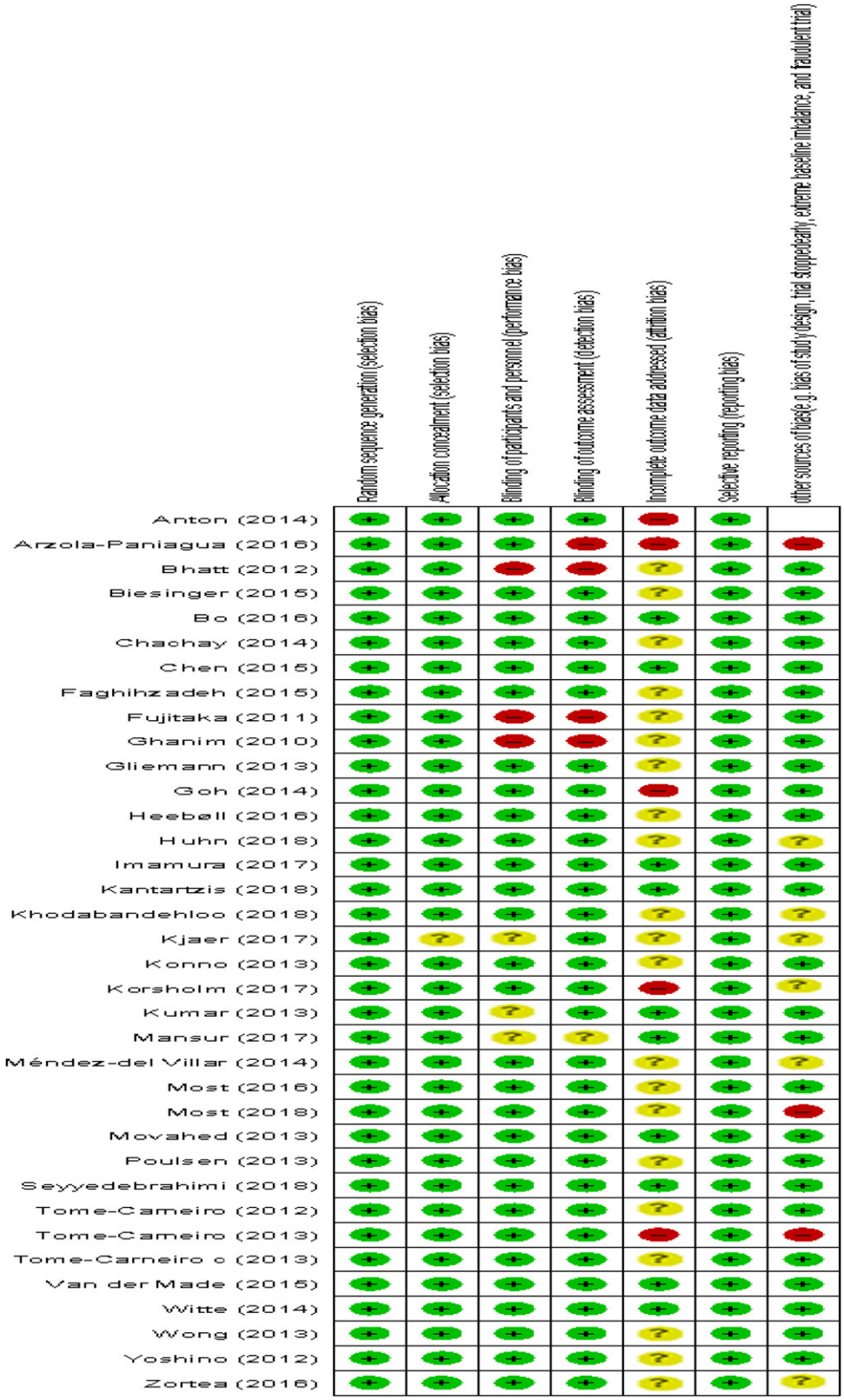


Figure 2. The methodological quality of included studies (risk of bias).

were considered as standardized mean differences (SMDs) and 95% CI. All related statistical analyses was performed using STATA software version 12.0 (Stata Corp., College Station, TX) and RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK). Cochrane's Q test and the I^2 statistic were used to evaluate heterogeneity. $I^2>50\%$ with $P<0.05$ showed significant heterogeneity across included RCTs, and the authors applied the DerSimonian and Laird random effects model to pool the SMDs; otherwise, the inverse variance fixed-effect model was used. Additional analyses as sensitivity and subgroup analyses were performed in current meta-analysis. Sensitivity analyses were

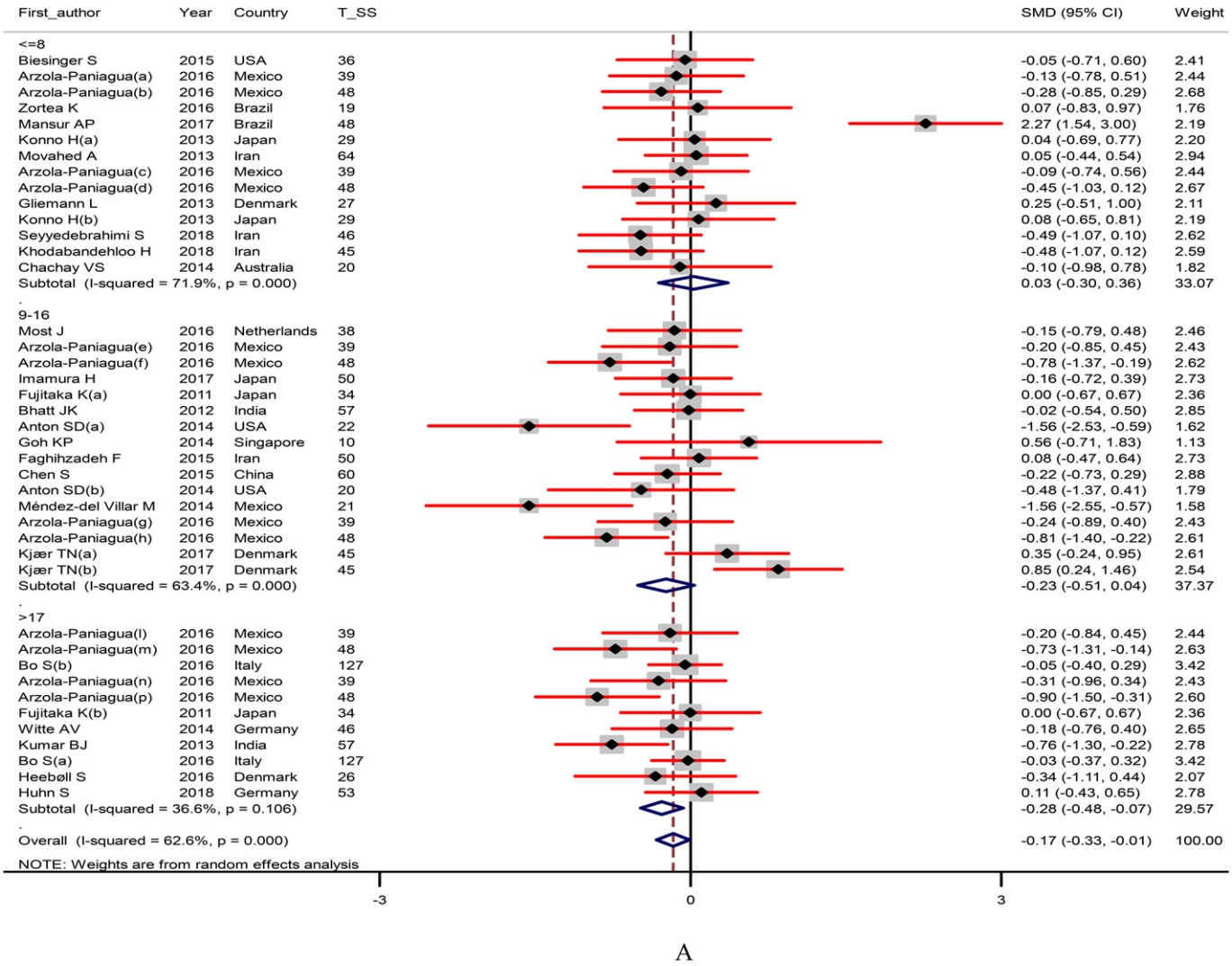


Figure 3. Meta-analysis anthropometric measurements standardized mean differences estimates for (A) body weight (B) for body mass index, (C) for fat mass, (D) for lean mass, (E) for waist circumference, (F) for adiponectin, and (G) for leptin levels in resveratrol and control groups (CI = 95%).

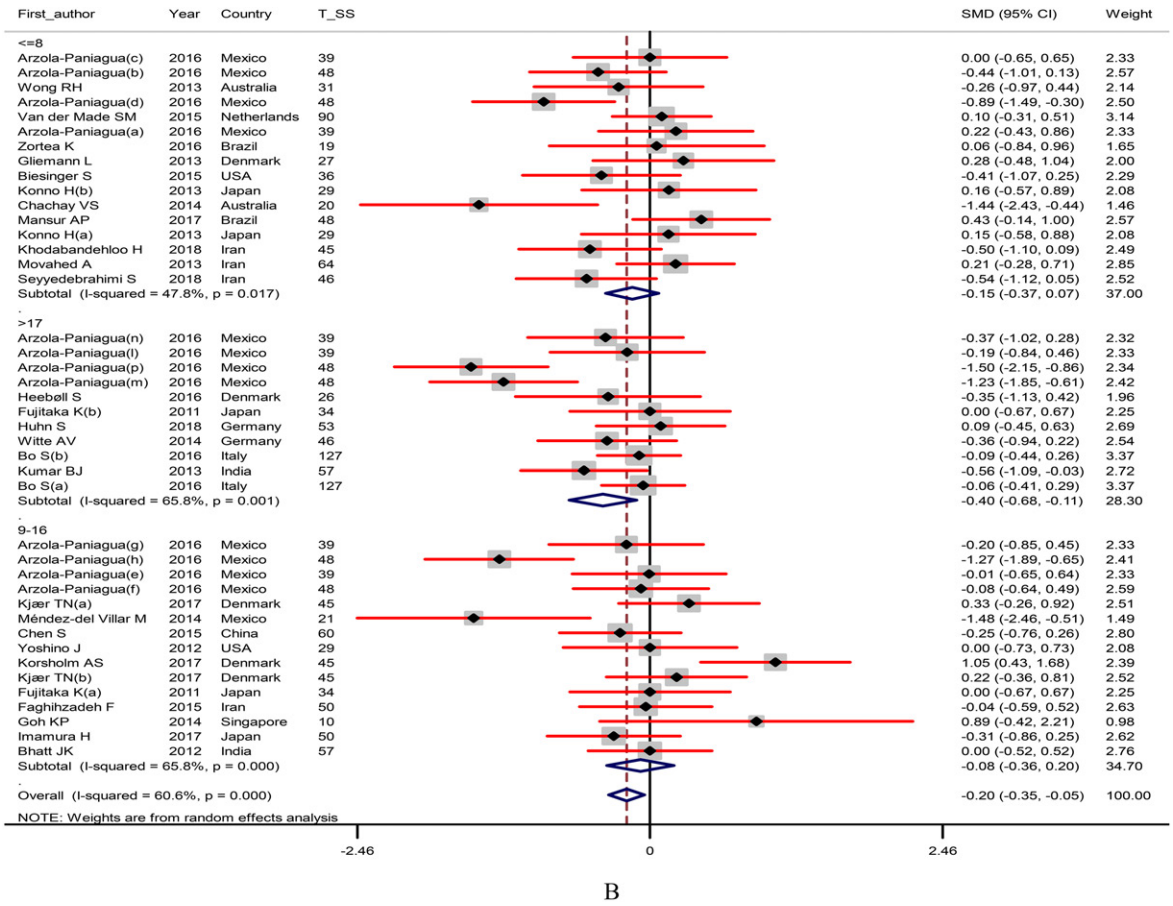
conducted using leave-one-out method to examine the influence one by one RCT on the validity of the pooled SMDs. Subgroup analyses were used to assess possible source of heterogeneity based on the following potential moderator variables; type of diseases (obesity vs. T2DM vs. other diseases), type of intervention (resveratrol vs. resveratrol plus other nutrients), dosage of resveratrol (<200 vs. 200–500 vs. >500 mg/day) and duration of intervention (≤8 weeks vs. 9–16 weeks vs. >17 weeks). The possible publication bias was assessed using Egger's- and Begg's-statists between included primary RCTs. *P*-value <0.05 were considered as statistically significant.

Results

Search results

In electronic database searches, 831 citations were initially identified. After excluding duplicates reports by checking titles and abstracts and removing the irrelevant trials, 36 articles were finally included in the current meta-analysis. **Fig. 1** illustrates the step by step process of identification and selection of relevant RCTs with more detail. All 36 articles were randomized, placebo-controlled trial. Thirty-two articles were performed using parallel and four articles had cross-over design. The total number of subjects was 1560 which were 781 and 779 participants in the intervention and placebo groups, respectively. Number of participants in each group varied from 10 to 127. Forty-one studies calculated the effects of resveratrol supplementation on body weight, forty-two on BMI, eighteen on fat mass, seventeen on lean mass, twenty-three on WC, fifteen on leptin, and eighteen studies on adiponectin levels. The included articles had been published between 2010 and 2018 in our meta-analysis. Dosage of intervention with resveratrol supplements varied from 8 to 3,000 mg/day, and duration of intervention ranged from one to 48 weeks. The characteristics of selected RCTs were summarized **Table 1**.

The methodological quality of included trials using the Cochrane Collaboration risk of bias tool base on the authors' Judgment on each risk of bias item is presented in **Fig. 2**. The findings of risk of bias assessment indicated that



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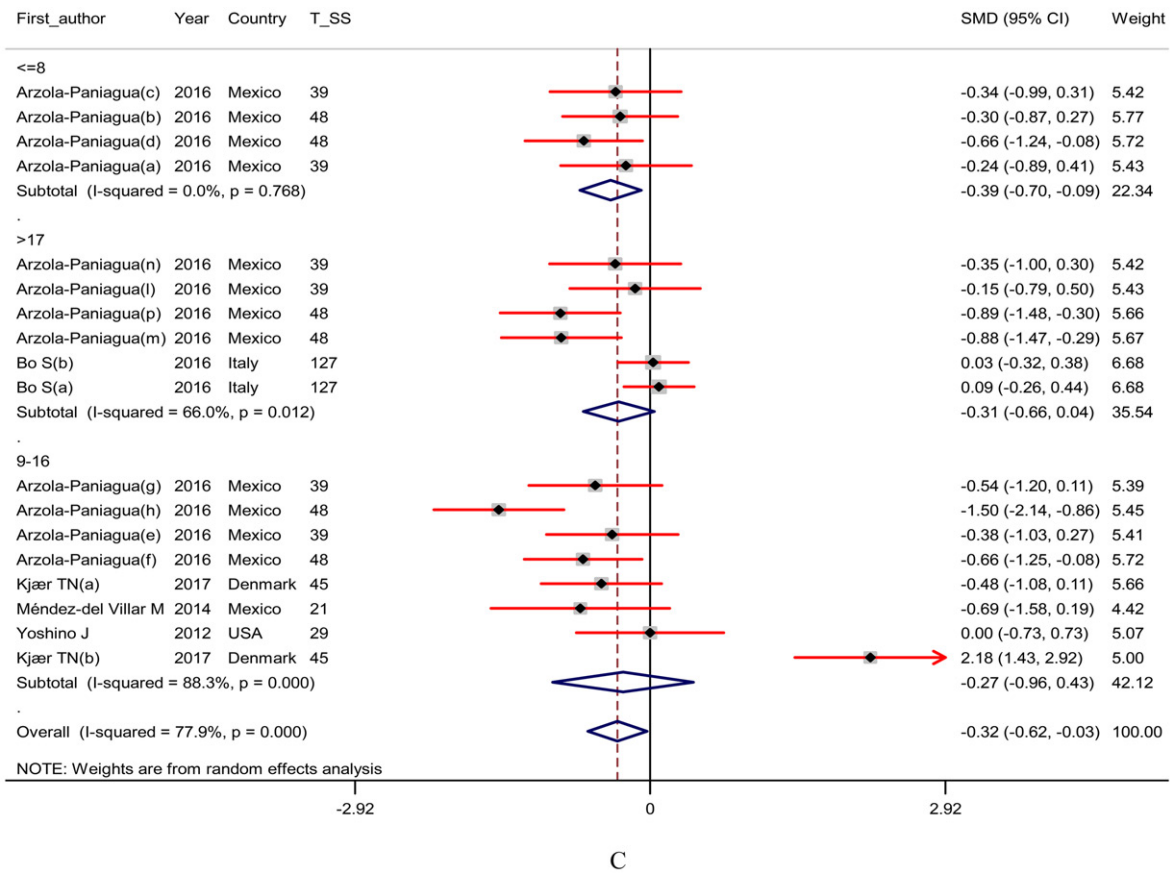

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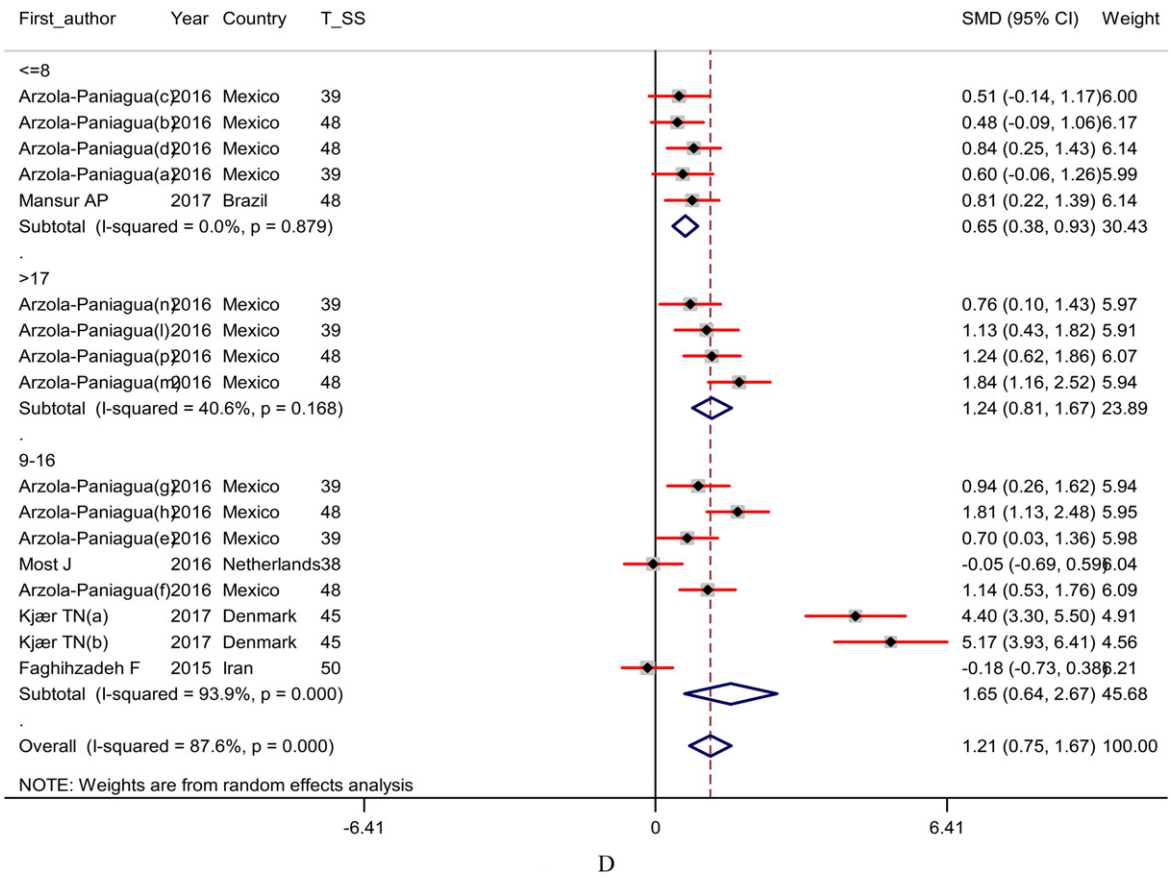

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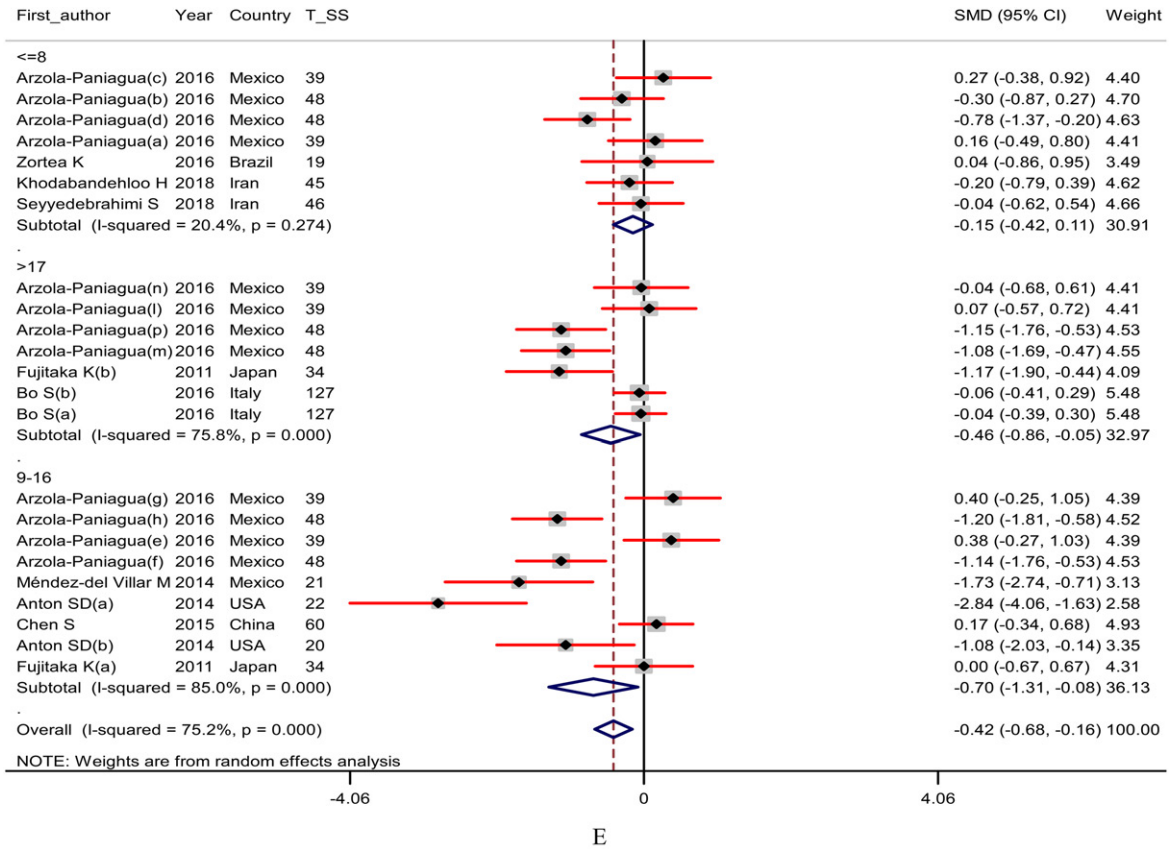

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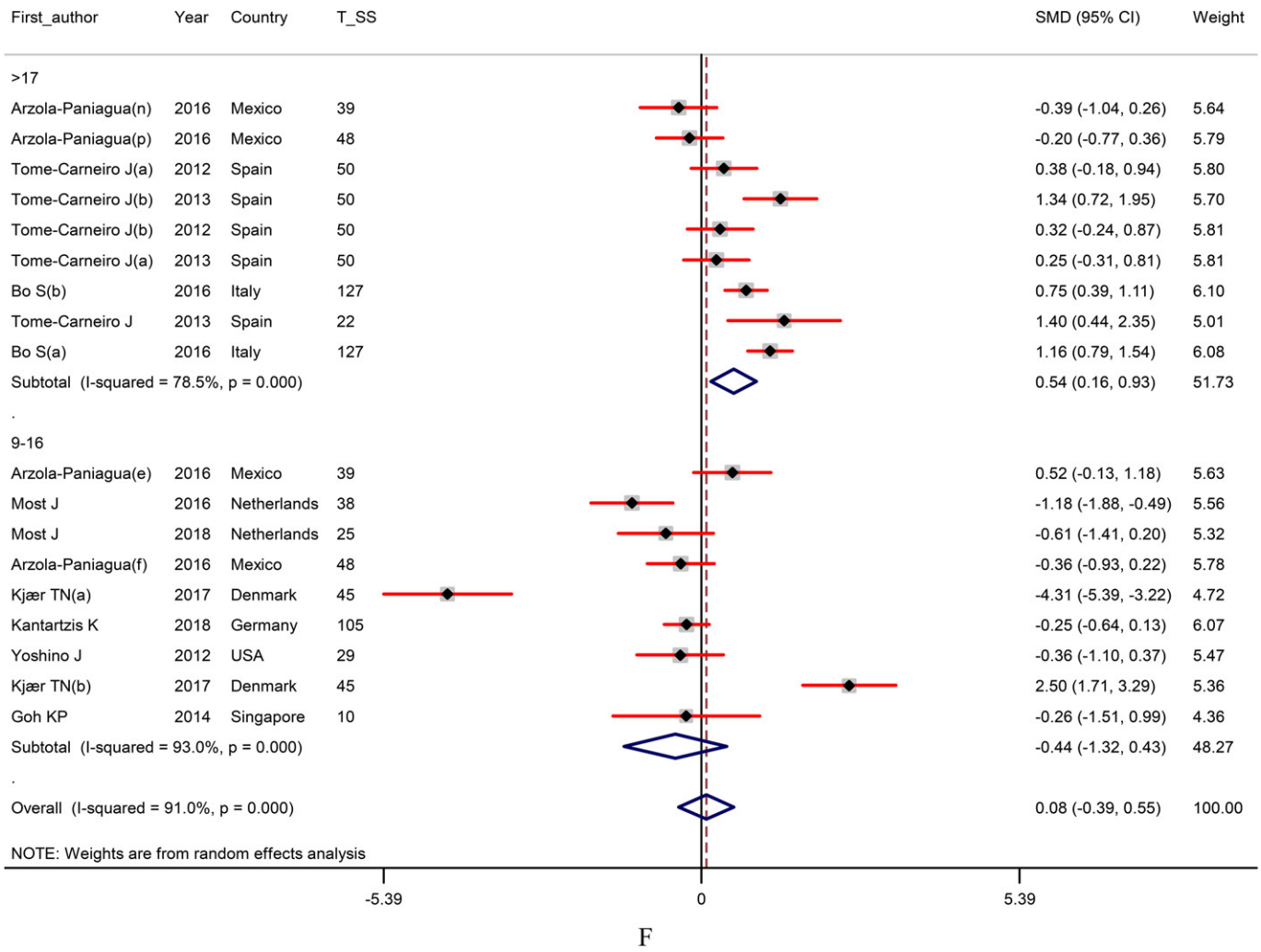

Figure 3. Continued.

8 studies were rated at low risk of bias, 19 studies were at unclear risk of bias, and 9 studies were at high risk bias based on the judgments of author.

Main outcomes

Effects of resveratrol supplementation on body composition

The effects of resveratrol supplementation on body composition are shown in **Fig. 3**. The pooled results, using random-effects model showed that resveratrol supplementation significantly decreased body weight (SMD = −0.17; 95% CI, −0.33, −0.01; $P = 0.03$; I^2: 62.6), BMI (SMD = −0.20; 95% CI, −0.35, −0.05; $P = 0.01$; I^2: 60.6), fat mass (SMD = −0.32; 95% CI, −0.62, −0.03; $P = 0.03$; I^2: 77.9) and WC (SMD = −0.42; 95% CI, −0.68, −0.16; $P = 0.001$; I^2: 75.2), and significantly increased lean mass (SMD = 1.21; 95% CI, 0.75, 1.67; $P < 0.001$; I^2: 87.6). We found no significant effect of resveratrol administration on leptin (SMD = −0.20; 95% CI, −0.68, 0.27; $P = 0.40$; I^2: 85.3) and adiponectin levels (SMD = 0.08; 95% CI, −0.39, 0.55; $P = 0.74$; I^2: 91.0). The association of between resveratrol intake and anthropometric measurements at baseline and endpoint of intervention for intervention and placebo groups (SMD) are presented in **Table 2**.

Subgroup analyses and sensitivity analyses

Resveratrol supplementation significantly decreased body weight in obese patients (SMD −0.43; 95% CI, −0.60, −0.26) compared with other diseases (SMD 0.02; 95% CI, −0.29, 0.33), and T2DM (SMD −0.17; 95% CI, −0.37, 0.02) (**Table 3**). There was a significant reduction in body weight; using studies used resveratrol plus other nutrients (SMD −0.59; 95% CI, −0.81, −0.37) vs. studies with only resveratrol (SMD −0.07; 95% CI, −0.24, 0.10). Considering different dosage of resveratrol used, our results showed a higher significant reduction in body weight when dose of <200 mg/day (SMD −0.27; 95% CI, −0.42, −0.12) compared with doses of 200–500 mg/day (SMD 0.07; 95% CI, −0.38, 0.51) and >500 mg/day (SMD −0.19; 95% CI, −0.49, 0.12). According to duration of intervention, our findings indicated that resveratrol supplementation significantly decreased body weight in trials with duration of intervention >17 weeks (SMD −0.28; 95% CI, −0.48, −0.07) vs. trails with duration ≤8 weeks (SMD 0.03; 95% CI, −0.30, 0.36) and 9–16 weeks (SMD −0.23; 95% CI, −0.51, 0.04).

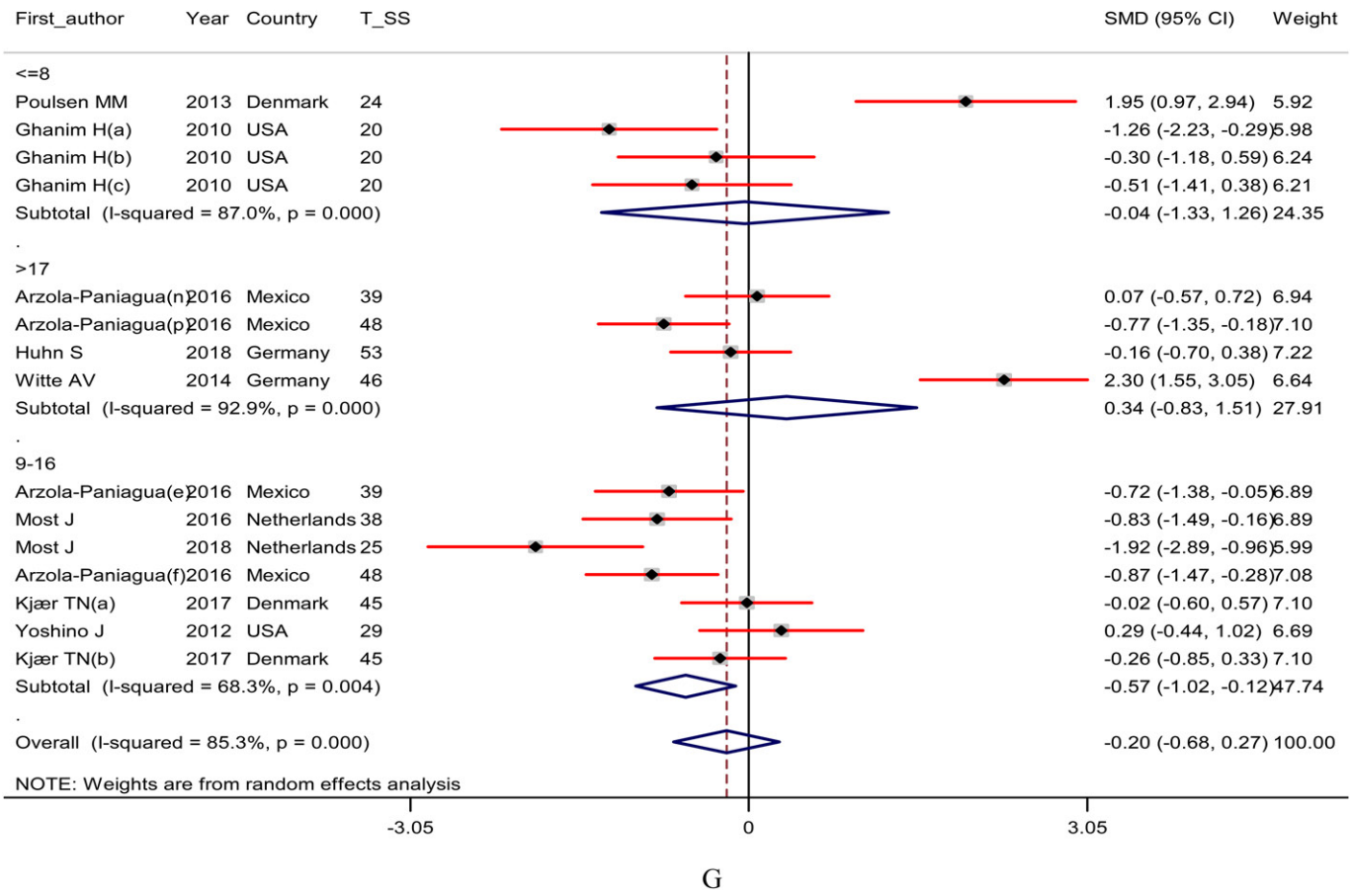

Figure 3. Continued.

Approximately similar findings were found for BMI, fat mass and WC based on potential moderator variables. Also regarding BMI groups, we found that resveratrol supplementation significantly decreased BW, BMI, fat mass, lean mass, and WC in trials with BMI $\geq$30 kg/m^2 vs. trails with BMI $<$30 kg/m^2.

For leptin levels, there was a significant reduction in the resveratrol plus other nutrients group (SMD −0.98; 95% CI, −1.40, −0.57) compared with only resveratrol (SMD 0.12; 95% CI, −0.43, 0.67) (**Table 3**). Our findings also indicated a higher significant reduction in leptin levels when doses $<$200 mg/day resveratrol applied (SMD −0.58; 95% CI, −0.92, −0.24) vs. doses of 200–500 (SMD 1.34; 95% CI, −0.39, 3.06) and $>$500 mg/day (SMD −0.26; 95% CI, −0.85, 0.33). Resveratrol administration significantly decreased leptin levels in studies with duration of intervention 9–16 weeks (SMD −0.57; 95% CI, −1.02, −0.12) compared with trials with the duration $\leq$8 (SMD −0.04; 95% CI, −1.33, 1.26) and $>$17 weeks (SMD 0.34; 95% CI, −0.83, 1.51).

The findings of subgroup analyses indicated that there were no significant differences between the before and after subgroup analyses pooled SMDs based on moderator's variables for lean mass and adiponectin levels. The subgroup analyses findings with more detail are presented in **Table 3**.

Sensitivity analyses indicated no significant changes between the before and after sensitivity pooled SMDs for BMI, lean mass, WC and adiponectin levels. However, the higher and lower pooled SMD for BMI in the sensitivity analysis were −0.16 (95% CI: −0.30, −0.02) after excluding Arzola-Paniagua et al. (2016)$_{(p)}$ study and −0.22 (95% CI: −0.36, −0.08) after removing Korsholm et al. (2017). The higher pooled SMD was 1.29 (95% CI: 0.83, 1.75) after removing Faghihzadeh et al. (2014) study and the lower pooled SMD for lean mass in the sensitivity analysis was 0.99 (95% CI: 0.61, 1.38) after excluding Kjaer et al. (2017)$_{(b)}$ study. For WC, the higher and lower pooled SMD in the sensitivity analysis were −0.35 (95% CI: −0.59, −0.11) after excluding Anton et al. (2014)$_{(a)}$ study and −0.45 (95% CI: −0.72, −0.19) after removing Arzola-Paniagua et al. (2016)$_{(g)}$ study. The lower pooled SMD for adiponectin levels was −0.05 (95% CI: −0.49, −0.39) after excluding Kjaer et al. (2017)$_{(b)}$ study and the higher for adiponectin levels in the sensitivity analysis was 0.29 (95% CI: −0.08, 0.68) after removing Kjaer et al. (2017)$_{(a)}$. Also, we found that there were significant effect between pre- and post-sensitivity pooled SMD for body weight after removing Arzola-Paniagua et al. (2016)$_{(p)}$ (SMD −0.14; 95% CI, −0.30, 0.01), Méndez-del Villar et al. (2014) (SMD −0.14; 95% CI, −0.29, 0.01), Anton$_{(a)}$ et al.(2014) (SMD −0.14; 95% CI, −0.29, 0.01), Khodabandehloo et al. (2018) (SMD −0.15; 95% CI, −0.32, 0.00), Kumar and Joghee (2013) (SMD −0.14; 95% CI, −0.30, 0.00), and Seyyedebrahimi et al. (2018) (SMD −0.15; 95% CI, −0.32, 0.00) studies, for fat mass after removing Arzola-Paniagua et al. (2016)$_{(p)}$

Table 2. The estimation of effects between resveratrol intake and anthropometric measurements in both intervention and placebo groups.

Variables		Number of study	Standardized mean difference	CI 95%	*P*-value	Heterogeneity		
						I^2 (%)	Q	*P*-value heterogeneity
BW	Intervention group (after vs. before)	37	−0.14	−0.23, −0.04	0.006	0.0	28.64	0.80
	Placebo group (after vs. before)	37	−0.11	−0.20, −0.01	0.026	0.0	14.69	0.99
	Change intervention group vs. placebo group	41	−0.17	−0.33, −0.01	0.039	62.6	106.81	<0.001
BMI	Intervention group (after vs. before)	40	−0.21	−0.30, −0.12	<0.001	0.0	30.40	0.83
	Placebo group (after vs. before)	40	−0.14	−0.23, −0.05	0.002	0.0	21.07	0.99
	Change intervention group vs. placebo group	42	−0.20	−0.35, −0.05	0.010	60.6	103.94	<0.001
FM	Intervention group (after vs. before)	18	−0.077	−0.27, 0.12	0.436	47.3	32.27	0.01
	Placebo group (after vs. before)	18	−0.03	−0.15, 0.10	0.679	0.0	13.29	0.71
	Change intervention group vs. placebo group	18	−0.32	−0.62, −0.03	0.031	77.9	77.02	<0.001
LM	Intervention group (after vs. before)	17	0.43	0.17, 0.70	<0.01	65.0	45.77	<0.001
	Placebo group (after vs. before)	17	−0.30	−0.58, −0.01	0.043	75.6	65.58	<0.001
	Change intervention group vs. placebo group	17	1.21	0.75, 1.67	<0.001	87.6	128.58	<0.001
WC	Intervention group (after vs. before)	20	−0.26	−0.39, −0.13	<0.001	6.8	20.39	0.37
	Placebo group (after vs. before)	20	−0.13	−0.25, −0.00	0.046	0.0	3.78	<0.001
	Change intervention group vs. placebo group	23	−0.42	−0.68, −0.16	0.001	75.2	88.84	<0.001
Leptin	Intervention group (after vs. before)	15	0.02	−0.22, 0.26	0.873	45.0	25.47	0.03
	Placebo group (after vs. before)	15	0.02	−0.15, 0.20	0.802	45.0	25.47	0.03
	Change intervention group vs. placebo group	15	−0.20	−0.68, 0.27	0.402	85.3	95.07	<0.001
Adiponectin	Intervention group (after vs. before)	17	0.13	−0.13, 0.40	0.325	73.7	60.83	<0.001
	Placebo group (after vs. before)	17	0.09	−0.04, 0.21	0.190	0.0	13.26	0.65
	Change intervention group vs. placebo group	18	0.08	−0.39, 0.55	0.741	91.0	188.87	<0.001

BW, body weight; BMI, body index mass; FM, fat mass; LM, lean mass; WC, waist circumference.

(SMD −0.28; 95% CI, −0.59, 0.01) study, and for leptin after removing Witte et al. (2014) (SMD −0.38; 95% CI, −0.74, −0.01) study.

Publication bias and quality assessment

Egger and Begg's tests showed no significant publication bias for meta-analyses estimating the effect of resveratrol supplementation on body weight (P Begg's test = 0.97, P Egger's test = 0.73), BMI (P_{Bg}=0.50, P_{Ee}=0.32), fat mass (P_{Bg}=0.97, P_{Ee}=0.42), adiponectin (P_{Bg}=0.34, P_{Ee}=0.17) and leptin levels (P_{Bg}=0.96, P_{Ee}=0.73). We found that there was a significant the possible of publication bias for lean mass (P_{Bg}=0.00, P_{Ee}=0.00) and for WC (P_{Eg}=0.17, P_{Be}=0.02). The authors used non-parametric method (Duval and Tweedie) to compute the results of censored articles for two outcomes; however, pooled SMDs for lean mass and WC did not significantly change after Duval and Tweedie test.

Discussion

This systematic review and meta-analysis is the first report of the effect of resveratrol supplementation on weight, BMI, WC, and fat and lean mass. The current meta-analysis demonstrated that resveratrol intake significantly reduced weight, BMI, WC and fat mass, and significantly increased lean mass, but did not affect leptin and adiponectin levels.

Obesity and diabetes constitute risk factors for morbidity and premature mortality (van Greevenbroek, Schalkwijk, and Stehouwer 2013). The current meta-analysis of RCTs demonstrated that resveratrol supplementation resulted in a significant decrease in weight, BMI, WC and fat mass, and a significant increase in lean mass, but did not affect leptin and adiponectin levels. However, several studies have reported the effects of resveratrol on weigh and BMI loss, the current findings are controversial. Few meta-analysis studies have reported the beneficial effects of resveratrol on metabolic profiles. In a meta-analysis conducted by Mohammadi-Sartang et al.(2017), resveratrol administration significantly improved adiponectin, but did not affect leptin levels. In another meta-analysis, resveratrol administration significantly reduced tumor necrosis factor-α and high-sensitivity C-reactive protein, but did not affect interleukin 6 concentrations (Koushki, Dashatan, and Meshkani 2018). Administration of resveratrol at a dosage of 500 mg three times per day for 90 days to patients with MetS significantly reduced weight, BMI, fat mass, WC and total insulin secretion (Méndez-del Villar et al. 2014). Also, 30 days of resveratrol administration to obese people induced metabolic changes mimicking the effects of calorie restriction (Timmers et al. 2011). In addition, Faghihzadeh et al. (2014) demonstrated that taking 500 mg/day resveratrol by overweight NAFLD people for 12 weeks improved weight, BMI, WC and hepatic steatosis. Improved metabolic profiles the following of resveratrol supplementation to patients with T2DM were also reported (Brasnyo et al. 2011). However, eight-week administration of resveratrol (3,000 mg/day) to patients with NAFLD did not decrease insulin resistance,

Table 3. The association between resveratrol intake on anthropometric measurements using subgroup analysis.

Variables		Number of SMD included	Subgroups	Pooled SMD (random effect)	95% CI	I^2 (%)	Overall I^2 (%)
BW	Type of disease	13	Obesity	−0.43	−0.60, −0.26	0.0	62.6
		19	Other	0.02	−0.29, 0.33	73.6	
		9	T2DM	−0.17	−0.37, 0.02	21.9	
	Type of intervention	34	Resveratrol	−0.07	−0.24, 0.10	60.7	
		7	Resveratrol plus other nutrients	−0.59	−0.81, −0.37	0.0	
	BMI groups	19	BMI ≥30 kg/m2	−0.32	−0.54, −0.11	52.7	
		22	BMI <30 kg/m2	−0.03	−0.25, 0.19	65.6	
	Dosage of resveratrol (mg/day)	19	<200 mg resveratrol	−0.27	−0.42, −0.12	16.2	
		11	200-500	0.07	−0.38, 0.51	82.3	
		11	>500 mg resveratrol	−0.19	−0.49, 0.12	55.7	
	Duration of study (week)	14	≤8 weeks	0.03	−0.30, 0.36	71.9	
		12	9–16 weeks	−0.23	−0.51, 0.04	63.4	
			>17 weeks	−0.28	−0.48, −0.07	36.6	
BMI	Type of disease	14	Obesity	−0.43	−0.73, −0.14	69.5	60.6
		19	Other	−0.02	−0.24, 0.20	51.8	
		9	T2DM	−0.16	−0.36, 0.03	26.0	
	Type of intervention	36	Resveratrol	−0.07	−0.20, 0.05	34.1	
		6	Resveratrol plus other nutrients	−0.89	−1.33, −0.44	69.4	
	BMI groups	21	BMI ≥30 kg/m2	−0.39	−0.67, -0.11	73.8	
		21	BMI <30 kg/m2	−0.04	−0.16, 0.07	0.0	
	Dosage of resveratrol (mg/day)	21	<200 mg resveratrol	−0.31	−0.52, −0.10	61.5	
		10	200–500	−0.02	−0.22, 0.17	12.9	
		11	>500mg resveratrol	−0.19	−0.58, 0.19	72.2	
	Duration of study (week)	16	≤8 weeks	−0.15	−0.37, 0.07	47.8	
		11	9–16 weeks	−0.08	−00.36, 0.20	65.8	
		15	>17 weeks	−0.40	−0.68, −0.11	65.8	
FM	Type of disease	12	Obesity	−0.58	−0.79, −0.37	27.3	77.9
		4	Other	0.25	−1.01, 1.52	91.8	
		2	T2DM	0.06	−0.19, 0.30	0.0	
	Type of intervention	12	Resveratrol	−0.07	−0.41, 0.27	75.2	
		6	Resveratrol plus other nutrients	−0.80	−1.11, −0.49	38.3	
	BMI groups	15	BMI ≥30 kg/m2	−0.40	−0.76, −0.05	78.6	
		3	BMI <30 kg/m2	0.05	−0.18, 0.29	0.0	
	Dosage of resveratrol (mg/day)	15	<200 mg resveratrol	−0.48	−0.69, −0.27	46.0	
		1	200–500	0.09	−0.26, 0.44	–	
		2	>500mg resveratrol	0.75	−2.06, 3.57	95.8	
	Duration of study (week)	4	≤8 weeks	−0.39	−0.70, −0.09	0.0	
		8	9–16 weeks	−0.27	−0.96, 0.43	88.3	
		6	>17 weeks	−0.31	−0.66, 0.04	66.0	
LM	Type of disease	13	Obesity	0.91	0.63, 1.19	59.7	87.6
		4	Other	2.49	0.27, 4.71	96.9	
		–	T2DM	–	–	–	
	Type of intervention	10	Resveratrol	1.38	0.63, 2.13	91.2	
		7	Resveratrol plus other nutrients	1.03	0.54, 1.52	77.0	
	BMI groups	14	BMI ≥30 kg/m2	1.43	0.93, 1.94	86.7	
		3	BMI <30 kg/m2	0.19	−0.42, 0.81	69.0	
	Dosage of resveratrol (mg/day)	14	<200 mg resveratrol	1.10	0.70, 1.51	80.8	
		2	200–500	0.31	−0.66, 1.27	82.4	
		1	>500 mg resveratrol	5.17	3.93, 6.41	–	
	Duration of study (week)	5	≤8 weeks	0.65	0.38, 0.93	0.0	
		4	9–16 weeks	1.65	0.64, 2.67	93.9	
		8	>17 weeks	1.24	0.81, 1.67	40.6	

(*continued*)

Table 3. Continued.

Variables		Number of SMD included	Subgroups	Pooled SMD (random effect)	95% CI	I^2 (%)	Overall I^2 (%)
WC	Type of disease	12	Obesity	−0.38	−0.74, −0.01	76.0	75.2
		7	Other	−0.86	−1.59, −0.13	82.7	
		4	T2DM	−0.07	−0.28, 0.14	0.0	
	Type of intervention	17	Resveratrol	−0.21	−0.47, 0.06	67.9	
		6	Resveratrol plus other nutrients	−0.93	−1.21, −0.64	26.4	
	BMI groups	14	BMI ≥30 kg/m2	−0.43	−0.78, −0.09	75.4	
		9	BMI <30 kg/m2	−0.40	−0.80, 0.00	75.4	
	Dosage of resveratrol (mg/day)	15	<200 mg resveratrol	−0.38	−0.68, −0.07	74.4	
		3	200–500	−0.85	−2.26, 0.57	89.6	
		5	>500 mg resveratrol	−0.45	−1.03, 0.12	71.9	
	Duration of study (week)	7	≤8 weeks	−0.15	−0.42, 0.11	20.4	
		7	9–16 weeks	−0.46	−0.86, −0.05	75.8	
		9	>17 weeks	−0.70	−1.31, −0.08	85.0	
Leptin	Type of disease	7	Obesity	−0.46	−1.14, 0.21	84.5	85.3
		8	Other	0.03	−0.61, 0.67	84.7	
		–	T2DM	–	–	–	
	Type of intervention	11	Resveratrol	0.12	−0.43, 0.67	84.6	
		4	Resveratrol plus other nutrients	−0.98	−1.40, −0.57	32.8	
	BMI groups	8	BMI ≥30 kg/m2	−0.34	−0.91, 0.23	82.6	
		7	BMI <30 kg/m2	−0.05	−0.88, 0.77	88.2	
	Dosage of resveratrol (mg/day)	11	<200 mg resveratrol	−0.58	−0.92, −0.24	59.3	
		3	200–500	1.34	−0.39, 3.06	93.9	
		1	>500mg resveratrol	−0.26	−0.85, 0.33	–	
	Duration of study (week)	4	≤8 weeks	−0.04	−1.33, 1.26	87.0	
		4	9-16 weeks	−0.57	−1.02, −0.12	68.3	
		7	>17 weeks	0.34	−0.83, 1.51	92.9	
adiponectin	Type of disease	6	Obesity	−0.35	−0.78, 0.07	61.5	91.0
		8	Other	0.03	−0.85, 0.92	94.2	
		4	T2DM	0.90	0.46, 1.34	55.9	
	Type of intervention	12	Resveratrol	0.17	−0.44, 0.79	92.5	
		6	Resveratrol plus other nutrients	−0.11	−0.78, 0.55	85.3	
	BMI groups	13	BMI ≥30 kg/m^2	0.08	−0.51, 0.66	91.2	
		5	BMI <30 kg/m^2	0.08	−0.75, 0.91	90.7	
	Dosage of resveratrol (mg/day)	15	<200 mg resveratrol	−0.13	−0.59, 0.34	89.1	
		2	200–500	0.58	−0.79, 1.95	78.2	
		1	>500 mg resveratrol	2.50	1.71, 3.29	–	
	Duration of study (week)	–	≤8 weeks	–	–	–	
		9	9–16 weeks	−0.44	−1.32, 0.43	93.0	
		9	>17 weeks	0.54	0.16, 0.93	78.5	

BW, body weight; BMI, body index mass; FM, fat mass; LM, lean mass; WC, waist circumference.

steatosis, or abdominal fat distribution (Chachay et al. 2014). Furthermore, resveratrol supplementation at a dosage 1 g/day for 45 days to patients with T2DM could not influence body weight and BMI (Movahed et al. 2013). Conflicting data from the published studies might be attributed to the differences existing in study design, characteristics of study populations, comorbid conditions, duration of administration, and the formulations and dosages of resveratrol used. Therefore, long-term studies with larger sample sizes are needed to provide definitive answers as to whether, and more importantly how, resveratrol intake might affect energy expenditure, body weight and BMI in humans.

Few mechanisms are proposed for weight-lowering effects of resveratrol. Animal studies have demonstrated that the reduction in weight gain in response to resveratrol intake in animals fed high-fat diets may be due to an increase in energy expenditure (Dal-Pan, Blanc, and Aujard 2010; Lagouge et al. 2006). In addition, resveratrol administration results in activating myocellular AMP-activated protein kinase (AMPK) and increased sirtuin 1 (SIRT1) and Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) protein concentrations, effectively leading to a considerable improvement in mitochondrial activity, as suggested by a simultaneous elevation in citrate synthase activity (Timmers et al. 2011). Goh et al.(2014) found that resting metabolic rate through increased gene expression of skeletal muscle SIRT1and AMPK was significantly increased after 12 weeks of resveratrol supplementation at a dosage of 3 g/day to patients with T2DM. Increased gene expression of skeletal muscle SIRT1and AMPK suggesting potential beneficial exercisemimetic effects (Goh et al. 2014). Moreover, inhibiting preadipocyte differentiation, decreasing adipocyte proliferation and inducing adipocyte apoptosis by resveratrol may be explained its anti-obesity effects (Wang et al. 2014).

The current study had a few limitations. Various doses of resveratrol used were administered for intervention in the included studies. We were unable to evaluate the dose-response association between supplementation and anthropometric measurements. One of the major limitations of the study was the inclusion of studies with relatively small sample size that could influence type-2 statistical error.

Conclusions

Overall, the current meta-analysis demonstrated that resveratrol intake significantly reduced weight, BMI, WC and fat mass, and significantly increased lean mass, but did not affect leptin and adiponectin levels.

Acknowledgments

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Abbreviations

BW	body weight
BMI	body index mass
FM	fat mass
LM	lean mass
WC	waist circumference

Disclosure statement

The authors declare no conflict of interest.

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