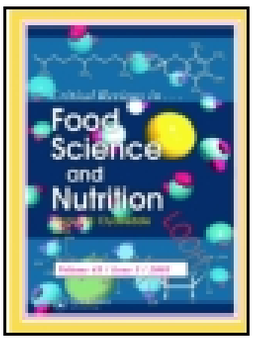

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Xiao-Fei Guo, Jiao-Mei Li, Jun Tang & Duo Li (2017): Effects of resveratrol supplementation on risk factors of non-communicable diseases: A meta-analysis of randomized controlled trials, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1349076

To link to this article: http://dx.doi.org/10.1080/10408398.2017.1349076

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https://doi.org/10.1080/10408398.2017.1349076

Effects of resveratrol supplementation on risk factors of non-communicable diseases: A meta-analysis of randomized controlled trials

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ABSTRACT

The results of randomized controlled trials (RCTs) investigating resveratrol supplementation on risk factors of non-communicable diseases (NCDs) have been inconsistent. The present meta-analysis aimed to quantitatively evaluate the effects of resveratrol intervention on risk factors of NCDs. PubMed and Scopus databases were searched up to June 2017. Weighted mean differences were calculated for net changes in risk factors of NCDs by using a random-effects model. Pre-specified subgroup and univariate meta-regression analyses were carried out to explore the sources of heterogeneity. Twenty-nine studies (30 treatment arms) with 1069 participants were identified. Resveratrol supplementation significantly reduced the concentrations of fasting glucose (−4.77 mg/dL; 95% CI: −9.33 to −0.21 mg/dL; $P = 0.040$), total cholesterol (TC) (−9.75 mg/dL; 95% CI: −17.04 to −2.46 mg/dL; $P = 0.009$), and C-reactive protein (CRP) (−0.81 mg/L; 95% CI: −1.42 to −0.21 mg/L; $P = 0.009$). Resveratrol intervention exerted significant reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in subjects with type 2 diabetes mellitus (T2DM). Subgroup analysis also showed that the trials with resveratrol intervention ≥3 months significantly reduced the low-density lipoprotein cholesterol (LDL-C), DBP, and glycated hemoglobin (HbA1c) values. The results did not support that resveratrol intervention had favorable effects in altering high-density lipoprotein cholesterol (HDL-C), triglyceride (TAG), and homeostasis model assessment of insulin resistance (HOMA-IR). The present study provides substantial evidence that resveratrol supplementation has favorable effects on several risk factors of NCDs.

KEYWORDS

Resveratrol; non-communicable diseases; risk factors; randomized controlled trial; meta-analysis

Introduction

Non-communicable diseases (NCDs), also known as chronic diseases, are generally slow-progressing and long-duration diseases (Li, 2015). Based on the definition of World Health Organization (WHO), there are four major NCDs, including cardiovascular diseases (CVD), cancers, diabetes, and chronic respiratory diseases (World Health Organization, 2013). It has been estimated that NCDs rank the leading cause of death worldwide (World Health Organization, 2013). In recent decades, the prevalence of NCDs has unprecedentedly increased and imposed a serious economic impact on healthcare. Nutrient sensing signaling pathways, such as AMP-activated protein kinase (AMPK) and Silent Information Regulator1 (SIRT1), have been paid close attention, and emerged as key targets for novel treatment of NCDs, such as metabolic dysfunction and type 2 diabetes mellitus (T2DM) (Hausenblas et al., 2015). Given the side-effect of pharmacotherapy, it is therefore necessary to explore novel NCDs chemopreventive drugs with acceptable efficacy and toxicity limits.

During the last decades, phytochemicals have received increasing attention and research to prevent or reverse NCDs (Knekt et al., 2002; Quiñones et al., 2013; Guo et al., 2016). Among them, resveratrol, which is mainly found in the skin of grapes and related products, has been studied intensively due to the "French paradox." It has been demonstrated that SIRT1 can be a target to be activated by resveratrol treatment, thus widespread studies have explored its biological benefits on human health (Howitz et al., 2003). Extensive investigations, no matter in vitro or in vivo models, have demonstrated that resveratrol treatment is associated with decreased risk of NCDs, including T2DM (Su et al., 2006; Fiori et al., 2013), CVD (Raj et al., 2014), and cancers (Singh et al., 2015). However, the conclusions from randomized controlled trials (RCTs) have been inconsistent. For example, 5 studies (6 treatment arms) reported that resveratrol intervention has a favorable effect on concentration of fasting glucose (Bhatt et al., 2012; Kumar and Joghee, 2013; Movahed et al., 2013; Anton et al., 2014; Chen et al., 2015), but not the remaining 15 studies (Ghanim et al., 2010; Fujitaka et al., 2011; Tome-Carneiro et al., 2012b; .Yoshino et al., 2012; Gliemann et al., 2013; Konno et al., 2013; Poulsen et al., 2013; Bashmakov et al., 2014; Chachay et al., 2014; Goh et al., 2014; Witte et al., 2014; Macedo et al., 2015; Heebøll et al., 2016; Thazhath et al., 2016; Zortea et al., 2016). Similarly, the conclusions of RCTs that have

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assessed resveratrol intervention on other risk factors of NCDs are controversial, including glycated hemoglobin (HbA1c), insulin, homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TAG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), diastolic blood pressure (DBP), systolic blood pressure (SBP), C-reactive protein (CRP), and tumor necrosis factor (TNF)-α.

Several meta-analyses have explored resveratrol intervention on risk factors of NCDs. Sahebkar first reported the pooled estimates of resveratrol supplementation on plasma lipid profiles with 7 RCTs; however, no beneficial effect was found (Sahebkar, 2013). A meta-analysis of 11 RCTs has investigated the effects of resveratrol on glucose control and insulin sensitivity. Only two trials have reported the changes of fasting glucose, HbA1c, and HOMA-IR in subjects with T2DM, thus the favorable effects of resveratrol intervention on glucose control and insulin sensitivity should be explained with caution (Liu et al., 2014). Besides, a meta-analysis of 4 RCTs has shown that SBP, HbA1c, and creatinine values were significantly reduced with resveratrol intervention in subjects with T2DM (Hausenblas et al., 2015). Resveratrol treatment might be as an adjunct of pharmacological management in subjects with T2DM. A recent meta-analysis of 10 RCTs did not support the effects of resveratrol intervention in improving CVD risk factors such as CRP, serum lipid profiles, SBP, and DBP (Sahebkar et al., 2015). However, another meta-analysis of 6 RCTs showed that a higher dose of resveratrol supplementation (>150 mg per day) significantly reduced SBP, but not DBP (Liu et al., 2015).

Recently, a number of RCTs regarding resveratrol supplementation on risk factors of NCDs have been published; however, the results are still inconsistent (Anton et al., 2014; Bashmakov et al., 2014; Chachay et al., 2014; Faghihzadeh et al., 2014; Goh et al., 2014; Mendez-del Villar et al., 2014; Witte et al., 2014; Chen et al., 2015; Faghihzadeh et al., 2015; Macedo et al., 2015; Samsami-Kor et al., 2015; Heebøll et al., 2016; Thazhath et al., 2016; Zortea et al., 2016). Therefore, to provide a more comprehensive, up-to-date assessment of resveratrol supplementation and NCDs risk factors, we conducted a systematic review and meta-analysis of resveratrol supplementation on risk factors of NCDs, including fasting glucose, HbA1c, insulin, HOMA-IR, TC, LDL-C, HDL-C, TAG, ALT, AST, DBP, SBP, CRP, and TNF-α.

Methods

The present systematic review and meta-analysis were based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Literature search

A systematic literature search was conducted in PubMed and Scopus databases up to June 2017. We used resveratrol or resveratrols as search terms. Additionally, reference lists of original studies, recent reviews, and meta-analyses were also scrutinized. Clinical trials with resveratrol as intervention were included. The health status of the enrolled volunteers were heterogeneous, including metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), T2DM, CVD, and healthy subjects. Accordingly, the risk factors of these NCDs were chosen for the present meta-analysis, namely fasting glucose, HbA1c, insulin, HOMA-IR, TC, LDL-C, HDL-C, TAG, ALT, AST, DBP, SBP, CRP, and TNF-α. A study that met the following criteria was included in the meta-analysis: (1) RCTs of either parallel or cross-over design; (2) the study assessed the impact of purified resveratrol or standardized resveratrol-enriched extracts on risk factors of NCDs; (3) the study had an appropriate controlled design, e.g., if resveratrol was administrated as an adjunct to another drug/supplement, the control group received that drug/supplement; and (4) the study provided available data to calculate the differences between baseline and endpoint for risk factors of NCDs.

Data extraction and quality assessment

Data extraction was independently carried out by two researchers, and any discrepancy was resolved via discussion. The characteristics of each identified articles were extracted, including first author, publication year, region, sample-size, gender, mean age, health status, duration of intervention, study design, dose of resveratrol intake per day, dietary data, and medication. Besides, the means and standard deviations (SDs) of the NCDs risk factors at baseline and endpoint in both intervention and control groups were extracted, respectively. If the outcomes had reported multiple times at different stages, the final outcome was extracted for data synthesis. Toward the trial that did not provide SDs directly, we calculated them from standard error of the mean (SEM) or 95% confidence interval (CI) using the equation listed in the Cochrane handbook (Higgins, 2011). The Jadad score criteria were used for quality assessment, including the following items: (1) random sequence generation, (2) randomization, (3) allocation concealment, (4) blinding, and (5) reporting the reason of dropout (Moher et al., 1998). The trial scored one point for each aspect reported, and the Jadad score $\geq$4 was regarded as high quality. The units were converted to mg/dL for fasting glucose, TC, LDL-C, HDL-C, and TAG, to mU/L for insulin, to mg/L for CRP, and to μg/L for TNF-α, respectively.

Data synthesis

A random-effects model developed by DerSimonian and Laird was employed to calculate the pooled estimates (DerSimonian and Laird, 1986). Heterogeneity between the studies was evaluated by I^2 statistic. The I^2 value of 25%, 50%, and 75% was classified as low, moderate, and high degrees of heterogeneity, respectively (Higgins, 2011). To identify the source of heterogeneity, subgroup and meta-regression analyses were performed to focus on information of the subjects: health status, various NCDs, mean age, dose of resveratrol supplementation, and duration of intervention. To determine whether the pooled effect was steady, sensitivity analysis was conducted by omitting one trial at a time, and the summary estimate was re-calculated. Furthermore, publication bias was conducted with Begg's rank correlation test (significant level at $P < 0.1$). Statistical analysis was performed with STATA 11.0 for Windows (Stata CORP, College station, TX). Except as otherwise specified, P-value less than 0.05 was considered as statistically significant.

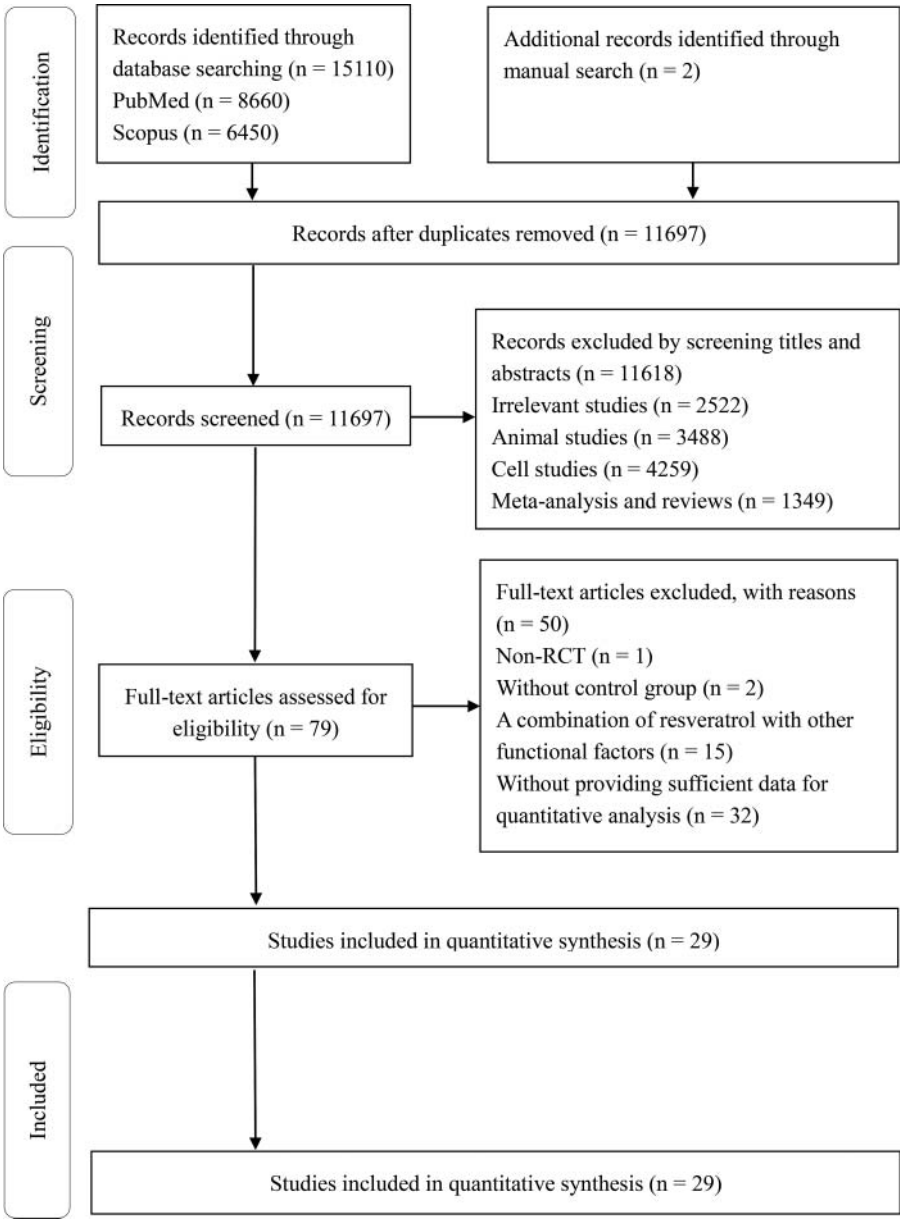

Figure 1. PRISMA flow diagram of the study selection procedure.

Results

Results of study selection

The PRISMA flow diagram of literature search is shown in Figure 1. After removal of 3413 duplicates, 11,697 unique articles were retrieved from PubMed, Scopus, and hand searching. Of these, 11,618 articles were deleted by screening the titles and abstracts, leaving 79 articles for full-text examination. After checking full-text, 50 articles were excluded because they did not meet the inclusive criteria (e.g., without providing available data, multi-component intervention, and study design). Ultimately, 29 articles were selected for inclusion and quantitative synthesis.

Study characteristics

The characteristics of the 29 articles are shown in Table 1. Among them, 3 studies were conducted in the North America (Ghanim et al., 2010; Yoshino et al., 2012; Anton et al., 2014), 9 in Europe (Magyar et al., 2012; Tome-Carneiro et al., 2012a; Tome-Carneiro et al., 2012b;. Gliemann et al., 2013; Militaru et al., 2013; Poulsen, et al., 2013; Tome-Carneiro et al., 2013; Witte et al., 2014; Heebøll et al., 2016), 3 in Oceania (Timmers et al., 2011; Chachay et al., 2014; Thazhath et al., 2016), 10 in Asia (Fujitaka et al., 2011; Bhatt et al., 2012; Konno et al., 2013; Kumar and Joghee, 2013; Movahed et al., 2013; Faghihzadeh et al., 2014; Goh et al., 2014; Chen et al., 2015; Faghihzadeh et al., 2015; Samsami-Kor et al., 2015), 3 in South America (Mendez-del Villar et al., 2014; Macedo et al., 2015; Zortea et al., 2016), and 1 in Africa (Bashmakov et al., 2014). The sample-size of the subjects ranged from 10 to 64, with a total of 1069 participants. The dose of resveratrol supplementation ranged from 10 to 3000 mg, and the duration of intervention lasted from 4 weeks to 12 months. One study has reported the effects of moderate dose (300 mg per day), and high dose (1000 mg per day) of resveratrol supplementation on risk factors of NCDs(Anton et al., 2014). Nine studies were conducted in healthy subjects, while the rest of

Table 1. Characteristics of the 29 eligible RCTs.

Author, year	Country	No. (control/ intervention)	Gender (F/M); mean age, year	Health status	Duration	Study design	Dose of RES intake per day (purity of RES, %)	Control	Diet change	Medication	Jadad score
Anton, 2014	U.S	20 (10/10)	(10/10) 73 ± 72	Overweight	3 months	Parallel	1,000 mg of RES from grapes and knotweed (7%)	Placebo	NR	NR	3
Bashmakov, 2014	Egypt	24 (10/14)	(9/15); 56.4 ± 9.1	T2DM	2 months	Parallel	50 mg (NR)	Placebo	NR	NR	3
Bhatt, 2012	India	57 (29/28)	(36/21); 57.2 ± 8.7	T2DM	3 months	Parallel	250 mg (NR)	Placebo	NR	Hypoglycemic agents	3
Chachay, 2014	Australia	20 (10/10)	(0/20); 65 ± 1	NAFLD	8 weeks	parallel	3,000 mg (NR)	Placebo (MC)	NR	NR	3
Chen, 2015	China	60 (30/30)	(18/42); 44.3 ± 10.5	NAFLD	3 months	parallel	300 mg (≥98%)	Placebo (PU and MD)	NR	NR	4
Faghihzadeh, 2014	Iran	50 (25/25)	(15/35); 45.2 ± 9.8	NAFLD	12 weeks	Parallel	500 mg (NR)	Placebo (MCT)	Usual diet	NR	4
Faghihzadeh, 2015	Iran	50 (25/25)	(15/35); 45.2 ± 9.8	NAFLD	12 weeks	Parallel	500 mg (NR)	Placebo (paraffin)	Advised diet	NR	4
Fujitaka, 2011	Japan	34 (17/17)	(9/25); 62.5 ± 11.6	Met	3 months	Parallel	100 mg (NR)	Placebo	NR	Taking medications	2
Ghanim, 2010	U.S	20 (10/10)	(24/32); 36 ± 5	Healthy	6 months	Parallel	200 mg of RES from PCE (20%)	Placebo	NR	NR	1
Gliemann, 2013	Denmark	27 (13/14)	(0/27); 65 ± 1	Aged male	8 weeks	Parallel	250 mg (NR)	Placebo	NR	Two subjects taking medications	3
Goh, 2014	Singapore	10 (5/5)	(0/10); 56.3 ± 6.0	T2DM	12 weeks	Parallel	3,000 mg (NR)	Placebo	NR	Hypoglycemic medications	3
Heebøll, 2016	Denmark	26 (13/13)	(NR); 18-70	NAFLD	6 months	Parallel	1,500 mg (NR)	Placebo	NR	NR	3
Konno, 2013	Japan	29 (15/14)	(0/29); 32-49	Healthy	8 weeks	Parallel	750mg of RES from MSE (>20%)	Placebo (DE and CE)	NR	NR	2
Kumar, 2013	India	57 (29/28)	(36/21); 57.2 ± 8.7	T2DM	6 months	Parallel	250 mg (NR)	Placebo	NR	Hypoglycemic agents	2
Macedo, 2015	Brazil	60 (30/30)	(0/60); 21.9 ± 9.7	Healthy	3 months	Parallel	100 mg (≥98%)	Placebo (MD)	Usual diet	None	2
Magyar, 2012	Hungary	40 (20/20)	(14/23); 66.4 ± 8.7	CVD	3 months	Parallel	10 mg (NR)	Placebo	NR	Medical therapy	3
Mendez-del Villar, 2014	Mexico	21 (10/11)	(15/6); 40.0 ± 5.3	Met	3 months	Parallel	1,500 g (NR)	Placebo	NR	Medical/nutritional therapy	2
Militaru, 2012	Romania	58 (29/29)	(23/35); 64.6 ± 6.4	CVD	2 months	Parallel	20 mg (50%)	None	NR	Medical therapy	2
Movahed, 2013	Iran	64 (31/33)	(34/30); 52.11 ± 6.54	T2DM	1.5 months	Parallel	1,000 mg (99%)	Placebo (MC)	NR	Antidiabetic medications	4
Poulsen, 2013	Denmark	24 (12/12)	(0/24); 38.3 ± 7.3	Obese	4 weeks	Parallel	1,500 mg (NR)	Placebo (MD)	Usual diet	None	4
Samsami-Kor , 2015	Iran	49 (24/25)	(NR); 38.3 ± 14.1	UC	6 weeks	Parallel	500 mg (NR)	Placebo (MCT)	Usual diet	NR	2
Thazhath, 2016	Australia	14 (14/14)	(4/10); 67.5 ± 1.6	T2DM	5 weeks	Cross-over	500 mg (NR)	Placebo (MC)	NR	NR	3
Timmers, 2011	Netherlands	11 (11/11)	(0/11); 52.5 ± 2.1	Obese	1 month	Cross-over	150 mg (99.9%)	Placebo	Standard lunch	NR	2
Tome-Carneiro, 2012	Spain	50 (25/25)	(30/20); 62.5 ± 8.29	CVD risk	6 months	Parallel	350 mg of GE-RES, (6.57%)	Placebo (MD)	Usual diet	Statins	3
Tome-Carneiro, 2012	Spain	49 (24/25)	(29/20) 62.5 ± 8.9	CVD risk	12 months	Parallel	350 mg of GE-RES (2.31%)	Placebo (MD)	NR	Statins	4
Tome-Carneiro, 2013	Spain	50 (25/25)	(5/45); 59 ± 11	CVD	12 months	Parallel	350 mg of GE-RES (0-6 months) 700 mg of GE-RES (6-12 months) (2.31%)	Placebo (MD)	Usual diet	Statins	4
Witte, 2014	Germany	46 (23/23)	(18/28); 64.3 ± 6.1	Healthy subjects	26 weeks	Parallel	200 mg (NR)	Placebo (SO)	NR	NR	1
Yoshino, 2012	U.S	29 (14/15)	(29/0); 59.0 ± 4.2	Healthy female	12 weeks	Parallel	75 mg (≥99.7%)	Placebo	NR	NR	2
Zortea, 2016	Brazil	19 (9/10)	(0/19); 43.8 ± 9.9	SZ Patients	4 weeks	Parallel	200 mg (98%)	Placebo	Advised diet	Clozapine	3

Abbreviations: CE, cellulose; CVD, cardiovascular diseases; DE, dextrin; GE-RES, resveratrol-enriched grape extract; MC, microcellulose; MCT, medium-chain triglycerides; MD, maltodextrin; Met, metabolic syndrome; MSE, Melinjo seed extract; NAFLD, non-alcoholic fatty liver disease; NR, not reported; PCE, polygonum cuspidatum extract; SO, sunflower oil; PU, pullulan; RCT, randomized controlled trial; RES, resveratrol; SZ, schizophrenia; T2DM, type 2 diabetes mellitus; UC, ulcerative colitis;

the studies were conducted in subjects with NCDs, including metabolic syndrome, T2DM, CVD, and ulcerative colitis. Two studies used cross-over design and the other studies used parallel design. According to Jadad score criteria, 7 studies were regarded as high quality (Tome-Carneiro et al., 2012b;. Movahed et al., 2013; Poulsen et al., 2013; Tome-Carneiro et al., 2013; Faghihzadeh et al., 2014; Chen et al., 2015; Faghihzadeh et al., 2015), and the remaining studies were regarded as low quality studies (Ghanim et al., 2010; Timmers et al., 2011; Fujitaka et al., 2011; Bhatt et al., 2012; Magyar et al., 2012; Tome-Carneiro et al., 2012a;. Yoshino et al., 2012; Gliemann et al., 2013; Konno et al., 2013; Kumar and Joghee, 2013; Militaru et al., 2013; Anton et al., 2014; Bashmakov et al., 2014; Chachay et al., 2014; Goh et al., 2014; Mendez-del Villar et al., 2014; Witte et al., 2014; Macedo et al., 2015; Samsami-Kor et al., 2015; Heebøll et al., 2016; Thazhath et al., 2016; Zortea et al., 2016).

Effect of resveratrol supplementation on risk factors of NCDs

Twenty-one trials provided available data on fasting glucose concentrations (Ghanim et al., 2010; Fujitaka et al., 2011; Bhatt et al., 2012; Tome-Carneiro et al., 2012a; . Yoshino et al., 2012; Gliemann et al., 2013; Konno et al., 2013; Kumar and Joghee, 2013; Movahed et al., 2013; Poulsen et al., 2013; Anton et al., 2014; Bashmakov et al., 2014; Chachay et al., 2014; Goh et al., 2014; Witte et al., 2014; Chen et al., 2015; Macedo et al., 2015; Heebøll et al., 2016; Thazhath et al., 2016; Zortea et al., 2016). The pooled effect showed that resveratrol supplementation significantly reduced the fasting glucose concentrations (−4.77 mg/dL; 95% CI: −9.33 to −0.21 mg/dL; $P = 0.040$), with a high between-study heterogeneity ($I^2 = 93.3\%$, $P_{\text{for heterogeneity}} < 0.001$) (Figure 2). Ten trials reported the effect of resveratrol supplementation on HbA1c values, and the pooled effect showed a marginally significant reduction in HbA1c values (−0.23%; 95% CI: −0.49%–0.03%; $P = 0.079$; $I^2 = 94.7\%$, $P_{\text{for heterogeneity}} < 0.001$) (Supplementary Figure 1) (Fujitaka et al., 2011; Bhatt et al., 2012; Magyar et al., 2012; Konno et al., 2013; Kumar and Joghee, 2013; Movahed et al., 2013; Poulsen et al., 2013; Goh et al., 2014; Witte et al., 2014; Thazhath et al., 2016). Eleven trials reported resveratrol intervention on insulin concentrations, and the pooled effect was not significant (−0.37 mU/L; 95% CI: −1.63–0.89 mU/L; $P = 0.565$; $I^2 = 58.5\%$, $P_{\text{for heterogeneity}} = 0.007$) (Supplementary Figure 2) (Ghanim et al., 2010; Fujitaka

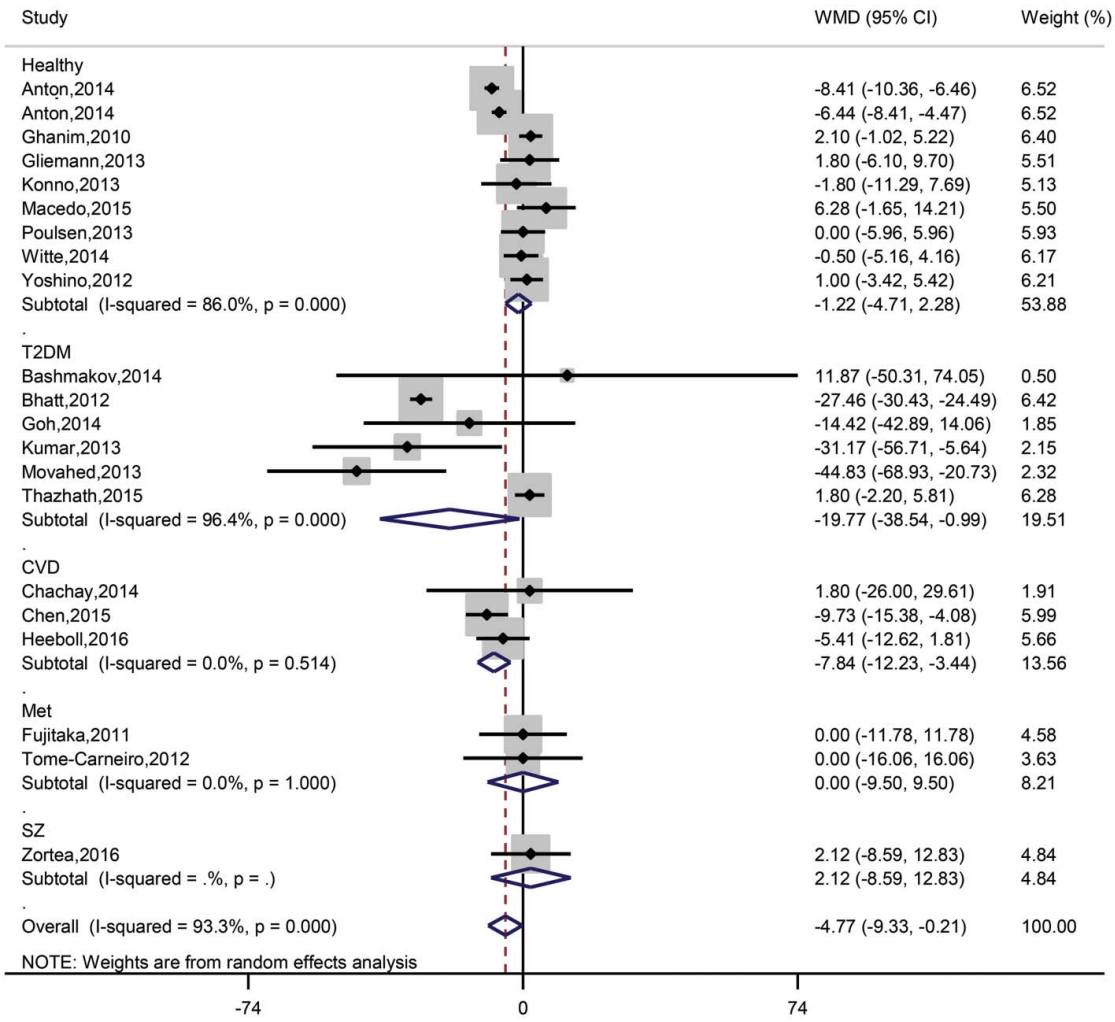

Figure 2. Effect of resveratrol intervention on fasting glucose concentrations. The pooled effect was calculated by using a random-effects model. The diamond represents the overall estimated effect, and the horizontal lines denote 95% CI. Abbreviations: CVD, cardiovascular diseases; Healthy: healthy subjects; Met, metabolic syndrome; SZ, schizophrenia; T2DM, type 2 diabetes mellitus.

et al., 2011; Yoshino et al., 2012; Movahed et al., 2013; Poulsen et al., 2013; Bashmakov et al., 2014; Chachay et al., 2014; Goh et al., 2014; Witte et al., 2014; Chen et al., 2015; Heebøll et al., 2016). Meanwhile, resveratrol supplementation did not impose a significant reduction in HOMA-IR values (−0.33; 95% CI: −0.75–0.10; $P = 0.132$; $I^2 = 71.3\%$, $P_{\text{for heterogeneity}} < 0.001$) (Supplementary Figure 3) (Ghanim et al., 2010; Fujitaka et al., 2011; Yoshino et al., 2012; Konno et al., 2013; Movahed et al., 2013; Poulsen et al., 2013; Chachay et al., 2014; Goh et al., 2014; Chen et al., 2015; Heebøll et al., 2016). For TC, 18 trials were included, and resveratrol supplementation imposed a significant reduction in TC concentrations (−9.75 mg/dL; 95% CI: −17.04 to −2.46 mg/dL, $P = 0.009$; $I^2 = 67.1\%$, $P_{\text{for heterogeneity}} < 0.001$) (Figure 3) (Ghanim et al., 2010; Bhatt et al., 2012; Magyar et al., 2012; Tome-Carneiro et al., 2012a; Tome-Carneiro et al., 2012b; . Yoshino et al., 2012; Gliemann et al., 2013; Konno et al., 2013; Kumar and Joghee, 2013; Militaru et al., 2013; Movahed et al., 2013; Poulsen et al., 2013; Bashmakov et al., 2014; Chachay et al., 2014; Witte et al., 2014; Chen et al., 2015; Faghihzadeh et al., 2015; Macedo et al., 2015; Zortea et al., 2016). Twenty trials provided sufficient data on concentrations of HDL-C and LDL-C (Ghanim et al., 2010; Fujitaka et al., 2011; Bhatt et al., 2012; Magyar et al., 2012; Tome-Carneiro et al., 2012a; . Yoshino et al., 2012; Gliemann et al., 2013; Konno et al., 2013; Kumar and Joghee, 2013; Militaru et al., 2013; Movahed et al., 2013; Poulsen et al., 2013; Bashmakov et al., 2014; Chachay et al., 2014; Goh et al., 2014; Chen et al., 2015; Faghihzadeh et al., 2015; Macedo et al., 2015; Heebøll et al., 2016; Zortea et al., 2016). Resveratrol supplementation did not impose significant effects in concentrations of HDL-C (−0.11 mg/dL; 95% CI: −1.29–1.08 mg/dL, $P = 0.858$; $I^2 = 13.3\%$, $P_{\text{for heterogeneity}} = 0.288$) and LDL-C (−4.47 mg/dL; 95% CI: −11.63–2.69 mg/dL, $P = 0.221$; $I^2 = 78.9\%$, $P_{\text{for heterogeneity}} < 0.001$) (Supplementary Figures 4, 5). Twenty trials provided available data on TAG concentrations, and the pooled effect was not significant (1.38 mg/dL; 95% CI: −8.86–11.61 mg/dL; $I^2 = 75.0\%$, $P_{\text{for heterogeneity}} < 0.001$) (Supplementary Figure 6) (Ghanim et al., 2010; Fujitaka et al., 2011; Bhatt et al., 2012; Magyar et al., 2012; Tome-Carneiro et al., 2012a; . Yoshino et al., 2012; Gliemann et al., 2013; Konno et al., 2013; Kumar and Joghee, 2013; Movahed et al., 2013; Militaru et al., 2013; Poulsen et al., 2013; Chachay et al., 2014; Goh et al., 2014; Witte et al., 2014; Chen et al., 2015; Faghihzadeh et al., 2015; Macedo et al., 2015; Heebøll et al., 2016; Zortea et al., 2016). Thirteen trials reported resveratrol

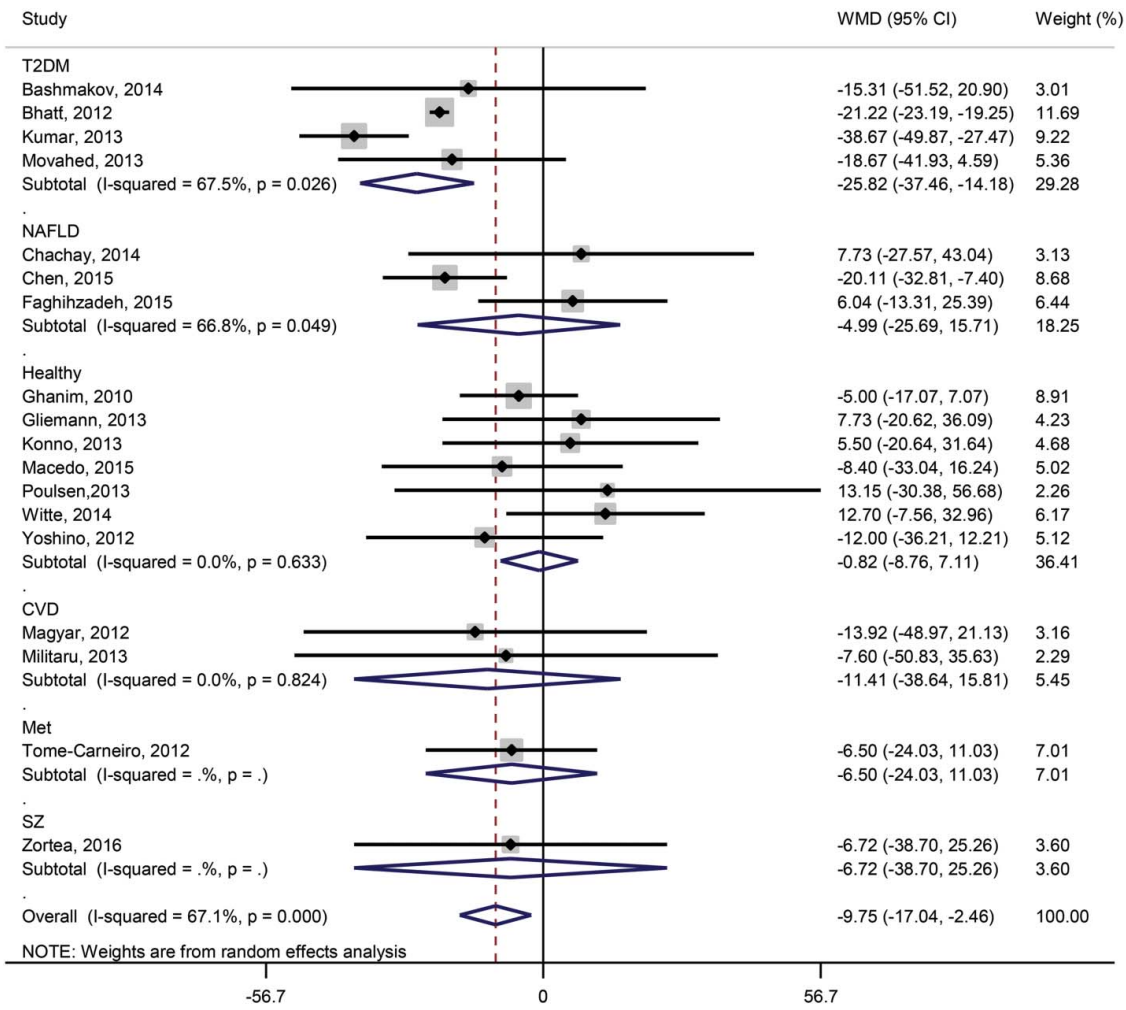

Figure 3. Effect of resveratrol intervention on TC concentrations. The pooled effect was calculated by using a random-effects model. The diamond represents the overall estimated effect, and the horizontal lines denote 95% CI. Abbreviations: TC, total cholesterol; CVD, cardiovascular diseases; Healthy: healthy subjects; Met, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; SZ, schizophrenia; T2DM, type 2 diabetes mellitus.

supplementation on SBP and DBP (Fujitaka et al., 2011; Timmers et al., 2011; Yoshino et al., 2012; Konno et al., 2013; Kumar and Joghee, 2013; Movahed et al., 2013; Anton et al., 2014; Bhatt et al., 2014; Witte et al., 2014; Chen et al., 2015; Heebøll et al., 2016). The pooled estimated mean changes in SBP (−4.23 mmHg; 95% CI: −11.43–2.96 mmHg, $P = 0.249$; $I^2 = 96.5\%$, $P_{\text{for heterogeneity}} < 0.001$) and DBP (−2.82 mmHg; 95% CI: −5.70–0.05 mmHg, $P = 0.055$; $I^2 = 84.7$, $P_{\text{for heterogeneity}} < 0.001$) were lowered(Supplementary Figures 7, 8); however, the pooled effects did not reach statistically significant difference. Twelve trials reported resveratrol supplementation on concentrations of ALT (Tome-Carneiro et al., 2012a; . Konno et al., 2013; Macedo et al., 2013; Poulsen et al., 2013; Anton et al., 2014; Chachay et al., 2014; Faghihzadeh et al., 2014; Goh et al., 2014; Chen et al., 2015; Heebøll et al., 2016), and 10 trials on AST (Tome-Carneiro et al., 2012a; . Konno et al., 2013; Movahed et al., 2013; Anton et al., 2014; Chachay et al., 2014; Chen et al., 2015; Faghihzadeh et al., 2015; Macedo et al., 2015; Heebøll et al., 2016). Although the concentrations of ALT (−1.73 IU/L; 95% Cl: −4.36–0.91 IU/L, $P = 0.199$; $I^2 = 82.2\%$, $P_{\text{for heterogeneity}} < 0.001$) and AST (−2.52 IU/L; 95% CI: −5.38–0.34 IU/L; $P = 0.084$; $I^2 = 93.4\%$, $P_{\text{for heterogeneity}} < 0.001$) were lowered with resveratrol supplementation, these effects were not significant (Supplementary Figures 9, 10). The mean change in CRP concentrations was calculated in 12 trials (Fujitaka et al., 2011; Magyar et al., 2012; Tome-Carneiro et al., 2012b; . Yoshino et al., 2012; Militaru et al., 2013; Poulsen et al., 2013; Tome-Carneiro et al., 2013; Bashmakov et al., 2014; Chachay et al., 2014; Faghihzadeh et al., 2014; Witte et al., 2014; Zortea et al., 2016), and the pooled effect showed that resveratrol supplementation significantly reduced the CRP concentrations (−0.81 mg/L; 95% CI: −1.42 to −0.21 mg/L, $P = 0.009$; $I^2 = 69.6\%$, $P_{\text{for heterogeneity}} < 0.001$) (Figure 4). The pooled effect of 10 studies showed that resveratrol supplementation imposed a marginally significant reduction in TNF-α concentrations (−0.35μg/L; 95% CI: −0.73–0.04 μg/L, $P = 0.079$; $I^2 = 9.2\%$, $P_{\text{for heterogeneity}} = 0.358$) (Supplementary Figure 11) (Tome-Carneiro et al., 2012b; . Magyar et al., 2012; Poulsen et al., 2013; Tome-Carneiro et al., 2013; Chachay et al., 2014; Faghihzadeh et al., 2014; Witte et al., 2014; Chen et al., 2015; Samsami-Kor et al., 2015; Heebøll et al., 2016).

Subgroup and meta-regression analyses

Supplemental resveratrol significantly reduced the concentrations of fasting glucose in subjects with T2DM (−19.77 mg/dL; 95% CI: −38.54 to −0.99 mg/dL) or CVD (−7.84 mg/dL;

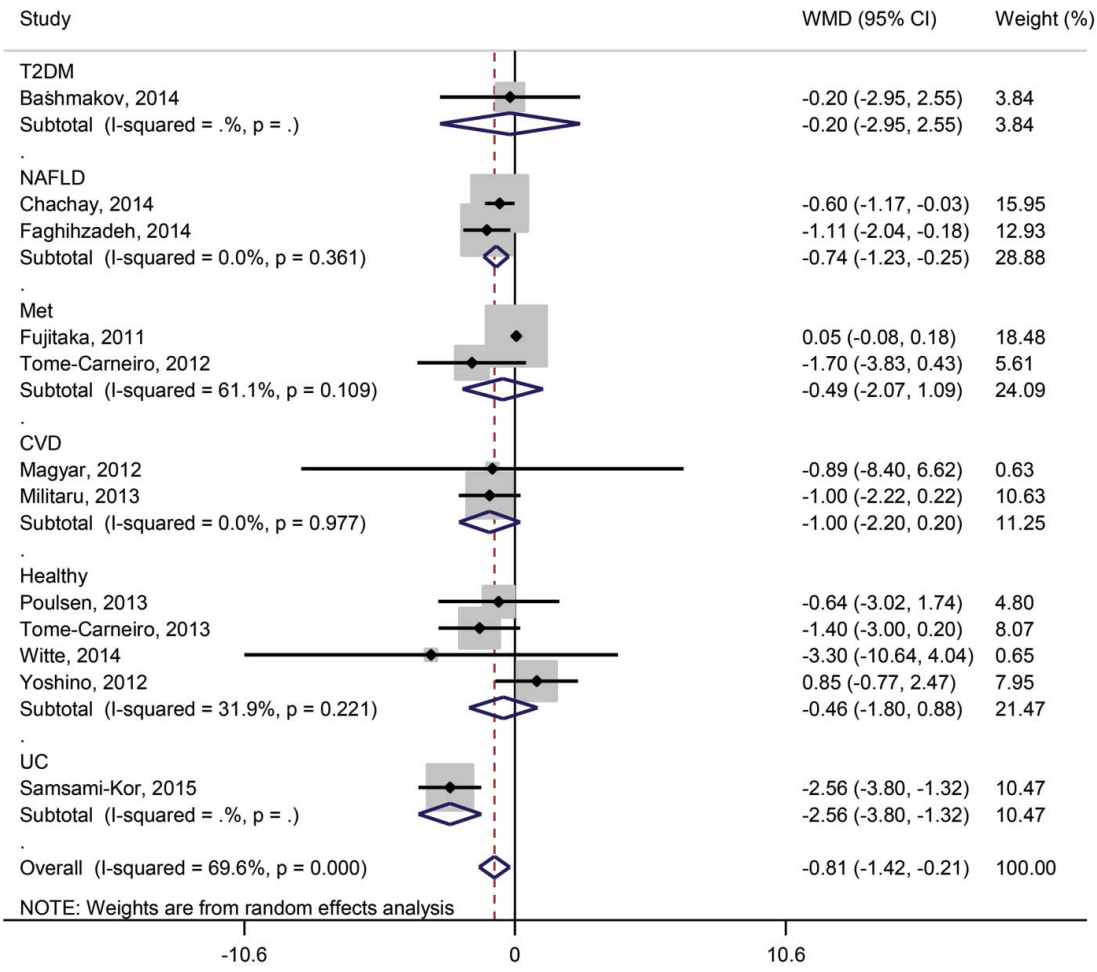

Figure 4. Effect of resveratrol intervention on CRP concentrations. The pooled effect was calculated by using a random-effects model. The diamond represents the overall estimated effect, and the horizontal lines denote 95% CI. Abbreviations: CRP, C-reactive protein; CVD, cardiovascular diseases; Healthy: healthy subjects; Met, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; UC, ulcerative colitis.

95% CI: −12.23 to −3.44 mg/dL) (Table 2). The trials stratified by duration of resveratrol supplementation indicated that the pooled effect with intervention ≥3 months significantly reduced the fasting glucose concentrations (−7.01 mg/dL; 95% CI: −13.37 to −0.64 mg/dL) (Table 2). Similarly, resveratrol supplementation showed a greater Hb1Ac lowering effect in subjects with NCDs (−0.34%; 95% CI: −0.72%–0.03%) than healthy subjects (−0.07%; 95% CI: −0.25%–0.10%), and exerted a marginally significant reduction in HbA1c values (−0.49%; 95% CI: −0.99%–0.01%) in subjects with T2DM (Table 2). Meanwhile, the pooled effect showed that resveratrol supplementation imposed a significant reduction in Hb1Ac values in trials with a period of intervention ≥3 months (−0.27%; 95% CI: −0.54% to −0.01%) (Table 2). The pooled effect of the trials stratified by health status showed a significant reduction in concentrations of insulin in subjects with NCDs (−1.75 mU/L; 95% CI: −3.49 to −0.01 mU/L), and a significant heterogeneity was observed between subgroups, with meta-regression analysis ($P = 0.045$) (Supplementary Table 1). Regarding blood lipid profiles, resveratrol supplementation imposed a significant reduction in TC concentrations (−25.82 mg/dL; 95% CI: −37.46 to −14.18 mg/dL) in subjects with T2DM (Table 2). The trials stratified by health status manifested that resveratrol supplementation showed a significant reduction in TC concentrations in subjects with NCDs (−16.54 mg/dL; 95% CI: −24.48 to −8.60 mg/dL), and a significant heterogeneity was discerned between subgroups with meta-regression analysis ($P = 0.034$) (Table 2). Meanwhile, the trials with a period of intervention ≥3 months (−14.55 mg/dL; 95% CI: −19.88 to −9.21 mg/dL) or resveratrol intervention <500 mg per day (−11.27 mg/dL; 95% CI: −16.78 to −5.76 mg/dL) imposed a significant reduction in LDL-C concentrations (Table 3). Meta-regression analyses for LDL-C concentrations were significant in trials stratified by dose ($P = 0.01$) and duration of resveratrol intervention ($P < 0.001$) (Table 3). Resveratrol supplementation also exerted significant reductions in SBP (−14.41 mmHg; 95% CI: −21.81 to −7.01 mmHg) (Supplementary Table 1) and DBP (−6.47 mmHg; 95% CI: −10.83 to −2.11 mmHg) (Table 3) in subjects with T2DM. Meanwhile, the pooled effects showed that DBP values were significantly reduced in trials with resveratrol supplementation ≥500 mg per day (−4.08 mmHg; 95% CI: −6.24 to −1.93 mmHg) and intervention ≥3 months (−4.77 mmHg; 95% CI: −7.73 to −1.81 mmHg), respectively. Meta-regression analysis for DBP was significant in trials stratified by duration of resveratrol supplementation ($P = 0.030$) (Table 3). For CRP, resveratrol supplementation exerted a significant reduction in CRP concentrations in subjects with NAFLD (−0.74 mg/L; 95% CI: −1.23 to −0.25 mg/L) or NCDs (−0.92 mg/L; 95% CI: −1.63 to −0.21 mg/L), and the pooled effect showed a greater lowering effect in subjects with resveratrol supplementation ≥500 mg per day (−1.21 mg/L; 95% CI: −2.10 to −0.33 mg/L) (Table 3). Besides, the pooled effects of resveratrol supplementation <500 mg per day imposed significant reductions in ALT and AST concentrations (Supplementary Table 3). Meta-regression analyses for dose of resveratrol supplementation (meta-regression for ALT ($P < 0.001$) and AST ($P = 0.020$)) were significant (Supplementary Table 3).

Sensitivity analysis and publication bias

Sensitivity analysis showed that the pooled estimates of resveratrol intervention on risk factors of NCDs were not substantially driven after deleting any 1 trial at a time (Supplementary Figures 12–25). Begg's rank correlation showed that no obvious publication bias was observed in relation to fasting glucose ($P = 0.165$), HbA1c ($P = 0.128$), insulin ($P = 0.392$), HOMA-IR ($P = 0.107$), TC ($P = 0.622$), HDL-C ($P = 0.746$), LDL-C ($P = 0.516$), TAG ($P = 0.846$), ALT ($P = 0.146$), AST ($P = 0.145$), SBP ($P = 0.625$), DBP ($P = 0.393$), CRP ($P = 0.324$), and TNF-α ($P = 0.524$).

Discussion

In this meta-analysis based on 29 RCTs (30 treatment arms), resveratrol supplementation showed a significant reduction in fasting glucose concentrations, especially in subjects with T2DM or CVD. Resveratrol supplementation also imposed a significant reduction in TC concentrations, and a greater lowering effect was observed in subjects with T2DM. Besides, the mean difference in CRP concentrations was also significantly reduced, especially in subjects with NAFLD. Meanwhile, supplemental resveratrol significantly reduced the values of SBP and DBP in subjects with T2DM. Additionally, the trials with resveratrol intervention ≥3 months exerted significant reductions in values of HbA1c, LDL-C, and DBP.

The biological functions of resveratrol supplementation on risk factors of NCDs have been investigated extensively in clinical trials, however, the conclusions of RCTs have been inconsistent. A meta-analysis of 11 RCTs has reported resveratrol intervention on fasting glucose and HbA1c values (Liu et al., 2014). The pooled estimates of 2 RCTs showed that resveratrol supplementation significantly reduced the fasting glucose and HbA1c values in subjects with T2DM; however, the summary effects were not significant in healthy subjects (Liu et al., 2014). Another meta-analysis of 4 RCTs reported that supplemental resveratrol significantly reduced the HbA1c values in subjects with T2DM, but not for fasting glucose concentrations (Hausenblas et al., 2015). Twenty-one trials were included in the present meta-analysis, and supplemental resveratrol exerted a significant reduction in fasting glucose concentrations, especially in subjects with T2DM (6 treatment arms) or CVD (3 treatment arms), but not in healthy subjects. The present meta-analysis provided substantial evidence of resveratrol supplementation on glucose control. Meanwhile, resveratrol intervention marginally reduced the HbA1c values in subjects with T2DM or metabolic syndrome. The reason why healthy subjects showed no significant changes in fasting glucose and HbA1c levels following resveratrol supplementation is unclear. One possible reason was that healthy subjects had a healthy diet pattern and normal baseline fasting glucose and HbA1c levels, whose levels could fluctuate in a certain range under normal physiological conditions; therefore, supplementation with resveratrol might not affect glucose control in these subjects.

The data from International Diabetes Federation (IDF) have shown that the individuals, who suffered from diabetes over

Table 2. Subgroup and meta-regression analyses for fasting glucose, HbA1c and TC levels.

	Fasting glucose mg/dL					HbA1c %					TC mg/dL				
			Heterogeneity					Heterogeneity					Heterogeneity		
Factors stratified	No.	Pooled effect (95% CI)	I^2 (%)	P^a	P^b	No.	Pooled effect (95% CI)	I^2 (%)	P^a	P^b	No.	Pooled effect (95% CI)	I^2 (%)	P^a	P^b
Mean age, year					0.289					0.256					0.092
< 60	12	−8.15 (−17.0, 0.69)	95.7%	< 0.001		6	−0.41 (−0.80, −0.02)	94.4%	< 0.001		12	−14.00 (−21.86, −6.15)	66.1%	< 0.001	
≥ 60	9	−2.70 (−6.21, 0.81)	74.7%	< 0.001		4	−0.06 (−0.25, 0.13)	66.8%	0.029		6	1.13 (−9.37, 11.62)	0.00	0.671	
Health status					0.075					0.956					0.034
Healthy	9	−1.22 (−4.71, 2.28)	86.0%	< 0.001		3	−0.07 (−0.25, 0.10)	62.2%	0.056		7	−0.82 (−8.76, 7.11)	0.00	0.633	
NCDs	12	−9.91 (−20.0, 0.19)	93.7%	< 0.001		7	−0.34 (−0.72, 0.03)	93.5	< 0.001		11	−16.54 (−24.48, −8.60)	57.9%	0.008	
Various NCDs					0.098					0.475					0.183
Met	2	0.00 (−9.50, 9.50)	1.00	0.00		1	−0.20 (−0.49, 0.09)	0.00	1.00		1	−6.50 (−24.03, 11.03)	0.00	1.00	
CVD	3	−7.84 (−12.23, −3.44)	0.0	0.514		1	0.00 (−0.60, 0.60)	0.00	1.00		2	−11.41 (−38.64, 15.81)	0.00	0.824	
T2DM	6	−19.77 (−38.54, −0.99)	96.4%	0.00		5	−0.49 (−0.99, 0.01)	95.5%	< 0.001		4	−25.82 (−37.46, −14.18)	67.5%	0.026	
NAFLD	0					0					3	−4.99 (−25.69, 15.71)	66.8%	0.049	
Dose of resveratrol intake					0.344					0.420					0.290
< 500 mg	14	−3.31 (−10.89, 4.26)	95.3%	< 0.001		6	−0.26 (−0.50, −0.03)	83.3%	< 0.001		14	−11.88 (−19.63, −4.13)	67.5%	< 0.001	
≥ 500 mg	7	−6.56 (−10.09, −3.02)	66.4%	0.007		4	−0.05 (−0.29, 0.20)	73.6%	0.010		4	−0.83 (−15.04, 13.37)	10.9%	0.338	
Duration					0.300					0.506					0.123
< 3 mon	11	−0.19 (−3.66, 3.27)	96.2%	< 0.001		5	−0.07 (−0.29, 0.14)	69.8%	0.010		10	−2.42 (−11.35, 6.51)	0.00	0.791	
≥ 3 mon	10	−7.01 (−13.37, −0.64)	36.3%	0.109		5	−0.27 (−0.54, −0.01)	85.6%	< 0.001		8	−14.71 (−24.00, −5.42)	77.2%	< 0.001	

Abbreviations: CI, confidential interval; HbA1c, glycated hemoglobin; NCDs, non-communicable diseases; No., number of included studies; TC, total cholesterol; Met, metabolic syndrome; CVD, cardiovascular diseases; T2DM; type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; P^a for heterogeneity; P^b for meta-regression analysis.

Table 3. Subgroup and meta-regression analyses for LDL-C, DBP and CRP levels.

	LDL-C mg/dL					DBP mmHg					CRP mg/L				
			Heterogeneity					Heterogeneity					Heterogeneity		
Factors stratified	No.	Pooled effect (95% CI)	I^2 (%)	P^a	P^b	No.	Pooled effect (95% CI)	I^2 (%)	P^a	P^b	No.	Pooled effect (95% CI)	I^2 (%)	P^a	P^b
Mean age, year					0.694					0.670					0.746
< 60	13	−5.27 (−14.29, 3.76)	84.3%	< 0.001		8	−3.13 (−7.36, 1.10)	83.2%	< 0.001		5	−0.88 (−2.09, 0.32)	65.0%	0.022	
≥ 60	7	−2.59 (−10.52, 5.35)	0.0	0.827		5	−2.90 (−5.46, −0.34)	39.2%	0.160		7	−0.58 (−1.18, 0.01)	55.6%	0.035	
Health status					0.755					0.426					0.849
Healthy	6	−3.86 (−12.42, 4.70)	28.5%	0.221		6	−2.17 (−5.18, 0.84)	54.5%	0.052		4	−0.46 (−1.80, 0.88)	31.9%	0.221	
NCDs	14	−5.08 (−14.22, 4.07)	82.1%	< 0.001		7	−3.73 (−7.88, 0.43)	81.9%	< 0.001		8	−0.92 (−1.63, −0.21)	77.6%	< 0.001	
Various NCDs					0.942					0.088					0.991
Met	2	−4.28 (−14.73, 6.18)	0.00	0.808		1	4.00 (−3.49, 11.49)	0.00	1.00		2	−0.49 (−2.07, 1.09)	61.1%	0.109	
CVD	2	−9.31 (−29.20, 10.58)	0.00	0.604		0					2	−1.00 (−2.20, 0.20)	0.00	0.977	
T2DM	5	−9.38 (−25.14, 6.38)	87.5%	< 0.001		3	−6.47 (−10.83, −2.11)	69.3%	0.038		1	−0.20 (−2.95, 2.55)	0.00	1.00	
NAFLD	4	2.45 (−22.58, 27.49)	85.1%	< 0.001		3	−3.33 (−8.42, 1.76)	51.9%	0.125		2	−0.74 (−1.23, −0.25)	0.00	0.361	
Dose of resveratrol intake					0.010					0.574					0.235
< 500 mg	14	−11.27 (−16.78, −5.76)	51.7%	0.013		8	−1.84 (−6.44, 2.77)	86.4%	< 0.001		8	−0.39 (−1.03, 0.25)	31.8%	0.174	
≥ 500 mg	6	9.08 (−8.18, 26.34)	75.8%	0.001		5	−4.08 (−6.24, −1.93)	19.5%	0.291		4	−1.21 (−2.10, −0.33)	62.9%	0.044	
Duration					< 0.001					0.030					0.827
< 3 mon	10	8.76 (−0.05, 17.58)	33.6%	0.139		5	0.78 (−2.32, 3.89)	6.0%	0.402		7	−0.88 (−1.58, −0.19)	53.4%	0.045	
≥ 3 mon	10	−14.55 (−19.88, −9.21)	48.7%	0.041		8	−4.77 (−7.73, −1.81)	82.6%	< 0.001		5	−0.68 (−1.72, 0.37)	38.5%	0.164	

Abbreviations: CI, confidential interval; CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NCDs, non-communicable diseases; No., number of included studies; Met, metabolic syndrome; CVD, cardiovascular diseases; T2DM; type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; P^a for heterogeneity; P^b for meta-regression analysis.

382 million in 2012, have increased by 13-fold, as compared with 1980 (Kokil et al., 2015). To curb this trend, it is important and necessary to search nutraceuticals with acceptable efficacy in glucose control. As an adjunct of pharmacotherapy, resveratrol treatment has a beneficial effect in glucose control among patients with T2DM (Liu et al., 2014; Hausenblas et al., 2015). The dose of resveratrol intake greater than 500 mg per day, with a period of intervention ≥3 months, will be effective.

The beneficial effect of resveratrol administration on glucose control in subjects with NCDs might be attributed to the two following aspects: (1) SIRT1 expression could be activated via resveratrol supplementation (Tanno and Ayano, 2010). As transcription factor of sirtuin family, SIRT1, which is a key modulator responsible for downstream of calorie restriction pathways, plays beneficial roles in glucose homeostasis and insulin sensitivity (Jiang, 2008). (2) Resveratrol administration is also associated with increased glucose transporter (GLUT-4) translocation through AMPK/Akt/endothelial nitric oxide synthase (eNOS) signaling pathway to stimulate glucose uptake (Penumathsa et al., 2010).

For cardio-biomarkers, a meta-analysis of RCTs has reported that a 38.6 mg/dL (1 mmol/L) reduction of TC and LDL-C concentrations results in a 24.5%–28% decrease for CVD-related mortality, and 26.6%–29.5% decrease for CVD-related events (Gould et al., 2007). Additionally, a 1 mg/dL reduction of LDL-C concentration is associated with coronary artery disease risk deceased by 1% (Lei et al., 2010). The pooled estimates of the trials with resveratrol intervention ≥3 months showed significant lowering effects on TC and LDL-C concentrations, so supplemental resveratrol for a long-duration will have important clinical implications in reducing CVD risk. However, the outcomes are inconsistent with previous meta-analyses, which have shown that resveratrol intervention had no favorable effects on concentrations of TC and LDL-C (Sahebkar, 2013; Sahebkar et al., 2015). The completely different results could be explained as follows: first, the literature search of the previous meta-analysis was updated to August 2014, so limited related data were available in relation to supplemental resveratrol on blood lipid profiles. Recently, supplemental resveratrol has been received considerable interest on blood lipid profiles, and several RCTs with resveratrol as intervention have published. Thus, 20 trials were included in the present meta-analysis compared with 11 (Sahebkar et al., 2015) or 7 (Sahebkar, 2013) trials in the previous meta-analysis. Therefore, the statistical power of our outcomes was stronger, and results were more authentic. Second, we performed subgroup analysis exploring the effects of dose and duration of resveratrol intervention on TC and LDL-C concentrations. Third, Fujitaka et al. provided the concentrations of CRP in 3 and 6 months after resveratrol intervention(Fujitaka et al., 2011). The present study only included the data in 6 months, while the previous meta-analysis included the outcomes of CRP concentrations both in 3 and 6 months (Sahebkar et al., 2015). Additionally, one study was excluded in the present meta-analysis as it used multi-component nutraceuticals as intervention (Bakker et al., 2010); however, the previous meta-analysis included the study (Sahebkar et al., 2015). Finally, the present meta-analysis found that resveratrol intervention was effective in reducing TC and LDL-C concentrations with a period of intervention ≥3 months.

High blood pressure has been demonstrated to be a major risk factor of CVD. It has been estimated that each increment of blood pressure by 20/10 mmHg above 115/75 mmHg is associated with two-fold CVD risk for people aged 40–70 years (Fournier and Safar, 2003). The pooled effects showed that SBP and DBP levels were significantly reduced in subjects with T2DM after resveratrol intervention. Moreover, the trials with resveratrol intervention ≥500 mg per day or ≥3 months had a favorable effect on DBP, but not SBP. The results were partially inconsistent with a previous meta-analysis, which showed that resveratrol supplementation higher than 150 mg per day exerted a significant reduction in SBP, but not DBP (Liu et al., 2015). The literature search of the previous meta-analysis was updated to January 2014. Up to now, a growing number of RCTs in relation to resveratrol supplementation on blood pressure have been published. There were 13 trials in the present meta-analysis compared with 6 trials in the previous meta-analysis, so our outcomes had a stronger statistical power and larger sample-size, and thus were steadies. Meanwhile, subgroup and meta-regression analyses have been conducted and identified that the duration of resveratrol supplementation might be the source of heterogeneity. Due to limited available data, the previous study had not focused on subgroup and meta-regression analyses with respect to duration of resveratrol intervention (Liu et al., 2015). Therefore, the present study found that resveratrol intervention showed a significant reduction in DBP value (resveratrol intervention ≥500 mg per day or ≥3 months). Besides, the pooled estimates of the trials with resveratrol intervention <500 mg per day had favorable effects on concentrations of ASL and ALT, which are surrogate biomarkers of NAFLD in clinical settings. Since limited trials reported resveratrol supplementation on ASL and ALT concentrations, the results should be explained with caution. Added trials are warranted to focus on the relationship between resveratrol supplementation and risk factors of liver damage.

As the leading cause of death worldwide, it has been estimated that 17.5 million people have died of CVD events, accounting for 31% of all global deaths (World Health Organization, 2015). Dyslipidemias are the primary risk factors associated with the initiation, propagation, and development of CVD (Okamura, 2010). In clinical practice, statin medications have been widely proven to be well tolerated and effective in the prevention and treatment of CVD (Patel et al., 2016). Although they have been generally accepted in the primary and secondary prevention of CVD events, accumulating evidence has shown that adverse effects of statin therapy, such as statin-associated muscle symptoms (SAMS), lead to intolerability and cessation (Banach et al., 2015; Patel et al., 2016). Statin intolerance and non-adherence in clinical practice might be the pivotal reasons of inadequate lowering of LDL-C in patients with CVD risk (Banach et al., 2016). In recent years, plant-origin nutraceuticals have been paid close attention, and those nutraceuticals have shown a valuable reservoir of novel drugs in terms of improving blood lipid profiles and reducing CVD risk (Sahebkar et al., 2016). Interesting findings of the present meta-analysis showed that TC and LDL-C concentrations were significantly reduced with resveratrol intervention ≥3 months.

In consideration of statin intolerance and poor therapy adherence, supplemental resveratrol can be partly substituted for statins in the prevention and treatment of CVD (Banach et al., 2016; Patel et al., 2016). Recently, cardiovascular polypills, which consist of statin, aspirin, and one or more anti-hypertensive medications, have received considerable interest, and are effective in lowering blood pressure and LDL-C values in patients at risk of CVD (Kolte et al., 2016). Since supplemental resveratrol has shown not only significant reductions in TC and LDL-C concentrations, but also DBP with a period of intervention ≥3 months, its treatment might be recommended as a part of the combination therapy/polypills to pharmacological management. Although the optimal dose of resveratrol intake cannot be obtained in the present study, 500 mg per day intake will be beneficial in individuals at risk of CVD as well as patients with CVD. Additionally, resveratrol should be supplemented with a period of intervention ≥3 months.

Chronic and low-grade inflammation plays an important role in the initiation and development of NCDs (Li et al., 2014). It has been suggested that elevated CRP and TNF-α concentrations are associated with increased insulin resistance, CVD, and T2DM risk (Furuta et al., 1995; Ridker et al., 1998; Ferrari, 1999; Freeman et al., 2002). A previous meta-analysis of RCTs reported that resveratrol intervention has no effect on CRP concentrations (Sahebkar et al., 2015); however, our outcome supported a significant reduction in CRP concentrations. The inconsistent outcomes might be attributed to the different inclusive criteria. First, an included study by Fujitaka et al. reported concentrations of CRP in 3 and 6 months after resveratrol intervention(Fujitaka et al., 2011). Our meta-analysis only included the data in 6 months, while the previous meta-analysis included the outcomes of CRP concentrations in 3 and 6 months (Sahebkar et al., 2015). Second, one study included in the previous meta-analysis was excluded in the present meta-analysis as it did not use purified resveratrol or standardized resveratrol-enriched extracts as only intervention (Bakker et al., 2010). Third, our study included recent studies that reported resveratrol intervention on CRP concentrations (Chachay et al., 2014; Faghihzadeh et al., 2014; Witte et al., 2014; Samsami-Kor et al., 2015). Finally, the pooled estimate supported a favorable effect of resveratrol supplementation in reducing CRP concentrations. Furthermore, our outcome supported that resveratrol intervention marginally reduced the TNF-α concentrations in subjects with NCDs or duration of intervention ≥3 months.

The possible mechanisms through which resveratrol supplementation improves risk factors of NCDs have been summarized as follows: (1) Supplemental resveratrol has special targets at nitric oxide (NO), AMPK, and SIRT1. NO is an endogenous cardio-protective molecule, and its concentration will reduce in people with cardiovascular risk (Förstermann and Sessa, 2011). Resveratrol administration could reverse NO concentrations in rats with CVD (Liu et al., 2005). Besides, AMPK, which is a pivotal factor associated with generation of NO, will be activated after resveratrol administration (Raj et al., 2014). Additionally, elevated SIRT1, activated by resveratrol treatment, will increase the expression of SERCA 2A (Sulaiman et al., 2010), which plays an important target for systolic and diastolic function through mediating uptake and release of calcium. Accordingly, the risk factors of CVD have been improved. (2) NCDs-protective properties of resveratrol intervention are also relative to its antioxidant and anti-inflammatory abilities. Cell lines and animal models have shown that resveratrol supplementation results in increased generation of antioxidant enzymes, such as superoxide dismutase (Tanno and Ayano, 2010), catalase (Movahed et al., 2012), and glutathione peroxidase (Ning et al., 2010). Meanwhile, resveratrol treatment can inhibit nuclear factor kappa B (NF-κB) activation through inhibition of inhibitor of κB (IκB) degradation to show anti-inflammatory activity (Schubert et al., 2011). Accordingly, the concentrations of inflammatory factors, such as CRP and TNF-α, have been downregulated.

The limitations of the present study should be acknowledged. First, although 29 studies included in the study provided a strong statistical power, the health status of the subjects were heterogeneous, including healthy subjects, CVD, T2DM, NAFLD, and metabolic syndrome. So when it came to single health status, the number of trials was rather limited. Second, significant heterogeneities were observed in relation to these risk factors. Subgroup and meta-regression analyses were performed, suggesting that health status, dose, and duration of resveratrol intervention were partial sources of heterogeneity. Third, the dose of resveratrol supplementation ranged from 8 to 3000 mg, and the duration of intervention ranged from 4 weeks to 12 months. It was difficult to estimate the optimal dose and duration of resveratrol intervention aimed at risk factors of NCDs. However, our outcomes suggested that resveratrol intervention ≥3 months at a dose of 500 mg per day would be beneficial for subjects with NCDs.

Pharmacokinetics and toxicity of resveratrol intervention in clinical trials have been investigated, and the results have shown that resveratrol supplementation appears to be well-tolerated and no marked toxicity (Cottart et al., 2010). Resveratrol intervention is associated with abdomen-related side effect at a high dose for a long period, but the side effect is modest and reversible (Cottart et al., 2014). Safety evaluation in clinical trials supports the use of resveratrol as a pharmacological drug for treatment of NCDs. Due to the rapid and extensive hepatic first-pass metabolism (Walle et al., 2004; Boocock et al., 2007), resveratrol is quickly and substantially metabolized to resveratrol glucuronides and resveratrol sulfates, leading to a relatively low bioavailability (Andreadi et al., 2014). Therefore, it is not surprising that resveratrol supplementation shows no effect on risk factors in several studies. In order to enhance its benefits on health status, future studies need to improve the bioavailability of resveratrol metabolism, such as modification of chemical structure and physical strategies (Sahebkar et al., 2015).

Conclusion

The present systematic review and meta-analysis provides further evidence for the beneficial effects of resveratrol supplementation on concentrations of fasting glucose, TC, and CRP, especially for subjects with NCDs. When the intervention is longer than 3 months, resveratrol effectively reduces the values of HbA1c, LDL-C, and DBP. Given the favorable benefits identified through the meta-analysis, further insights into this topic require additional long-term RCTs to obtain the optimal dose and duration of resveratrol intervention on risk factors of NCDs.

Conflicts of interest

None.

Funding

This study was funded by the National Basic Research Program of China (973 Program: 2015CB553604); by National Natural Science Foundation of China (NSFC, No. 81273054); and by the PhD Programs Foundation of Ministry of Education of China (20120101110107).

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