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Obesity Comorbidity/Treatment

The effects of resveratrol intervention on risk markers of cardiovascular health in overweight and obese subjects: a pooled analysis of randomized controlled trials

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Abstract

Background: Potential effects of resveratrol consumption on cardiovascular disease risk factors and body weight in overweight/obese adults have not been fully elucidated. Our present analysis was to evaluate the effects of resveratrol consumption on risk markers related to cardiovascular health in overweight/obese Individuals.

Methods: Multiple literature databases were systematically searched, and 21 studies were included. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI), and heterogeneity was assessed with the I2 test. Publication bias and subgroup analyses were also performed.

Results: There were variations in reporting quality of included studies. Resveratrol intervention significantly lowered total cholesterol (WMD, –0.19 mmol/L; 95% CI, –0.32 to –0.06; P = 0.004), systolic blood pressure (WMD, –2.26 mmHg; 95% CI, –4.82 to –0.49; P = 0.02), and fasting glucose (WMD, –0.22 mmol/L; 95% CI, –0.42 to –0.03; P = 0.03). Heterogeneity was noted for these outcomes (35.6%, 38.7% and 71.4%, respectively). Our subgroup analysis showed significant reductions in total cholesterol, systolic blood pressure, diastolic blood pressure, glucose, and insulin in subjects ingesting higher dose of resveratrol (≥300 mg/day).

Conclusion: Our finding provides evidence that daily resveratrol consumption might be a candidate as an adjunct to pharmacological management to better prevent and control cardiovascular disease in overweight/obese individuals.

Keywords: Cardiovascular risk factors, obesity, overweight, resveratrol.

Abbreviations: AEs, adverse events, BMI, body mass index, CI, confidence interval, CVD, cardiovascular disease, DBP, diastolic blood pressure, HbA1c, haemoglobin A1c, HDL-C, high-density lipoprotein cholesterol, HOMA-IR, homeostatic model assessment of insulin resistance, IL-6, interleukin-6, LDL-C, low-density lipoprotein cholesterol, NAFLD, non-alcoholic fatty liver disease, RCTs, randomized controlled trials, RCVR, residual cardiovascular risk, SBP, systolic blood pressure, SD, standard deviation, SEs, standard errors, T2DM, type 2 diabetes mellitus, TBARS, thiobarbituric acid reactive substances, TC, total cholesterol, TG, triglycerides, TNF-α, tumour necrosis factor-α, WMD, weighted mean difference.

Introduction

The prevalence of obesity has dramatically increased globally and has become a major public health challenge. According to the World Health Organization, over 1.9 billion adults were overweight, including 600 million obese in 2014 (1). Observational epidemiologic studies have shown that overweight and obesity are independent risk factors for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (2). Persistence of excess adiposity in children and adults can lead to metabolic abnormality (i.e. dyslipidemia, insulin resistance, hypertension and procoagulant state) (3). The increasing rate of CVD in the developed world has created an urgent need for effective strategies to reduce the obesity-related health risk and progression of CVD. A large body of evidence now shows that interventions utilizing dietary nutraceuticals or functional foods can help people achieve and maintain cardiovascular health and reduce CVD risk throughout all stages of the lifespan (4,5). The effect of healthy dietary habits is mediated not only by variations in plasma lipid levels but also by their possible effects on altered insulin sensitivity, blood pressure (BP) control, postprandial glucose levels, oxidative stress and inflammatory state (6).

Resveratrol (*trans* −3,4',5-trihydroxystilbene), a polyphenol phytoalexin compound, is mainly identified as a major component in several plants species and various foods such as grapes, berries, white hellebore (*Veratrum grandiflorum O. Loes*), red wine and nuts (7). A growing body of research indicates that resveratrol exerts several health benefits especially in CVD, hypertension, ischemic disorders, heart failure, T2DM, obesity and ageing (8,9). However, to our knowledge, the precise effects of resveratrol on cardiovascular risk factors in obesity and overweight population groups are inconsistent and have not been fully evaluated. We therefore performed a comprehensive review of the literature and carried out a meta-analysis of randomized controlled trials (RCTs) to quantitatively evaluate the overall effects of resveratrol on plasma lipids, blood pressure, glucose control, insulin sensitivity, inflammatory markers and body weight in overweight/obese individuals. The results of our analysis provide new insight that could be incorporated into dietary guidelines to impair atherosclerosis development and improve cardiovascular health in obese and overweight individuals while also highlighting directions for future clinical research.

Methods

Search strategy and study selection

Based on the guidelines for the Quality of Reporting of Meta-analyses (QUORUM), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (http://www.embase.com) and the Cochrane Library (http://www.cochrane.org) databases were systematically searched for RCTs that estimated the effects of resveratrol consumption in overweight or obese individuals without language and age restrictions from the earliest available online indexing year to January 2016. Our search strategy used the following Medical Subject Headings (MeSH) and corresponding key words: 'resveratrol' OR 'resveratrols' OR '*trans*-resveratrol' OR '3,5,4-trihydroxystilbene' OR '3,4,5-stilbenetriol' OR 'resveratrol*'. The search was restricted to clinical trials in humans. Details of the search strategy are shown in Appendix S1. The title and abstract of the studies identified were scanned to exclude any studies that were clearly irrelevant. If the potential relevant reports were non-English language publications, we entrusted an international medical editing company to translate the articles for further information. The reference list associated with all of the studies retrieved in the search was used to identify other potentially relevant publications. Review articles were also scanned to find additional eligible studies. Two authors (D. L. and H. H.) first independently and manually checked the reference lists of the eligible articles or relevant review papers and then crosschecked and reached a consensus on all potentially relevant studies. Details of the study selection for inclusion in this meta-analysis are shown in Table S1.

Quality assessment

A risk-of-bias assessment was systematically performed by two investigators (H. H. and D. L.) using instructions described in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1.0) (10). The items used for the assessment of each study were as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. For all of the eligible studies, a judgment of 'Yes' indicated a low risk of bias, while 'No' indicated a high risk of bias. Labelling an item as 'Unclear' indicated an unclear or unknown risk of bias. Any disagreements were adjudicated by a third author. There were no disagreements among the reviewers on the quality assessment.

Data extraction and outcome measures

Data extraction and data synthesis were conducted according to the preferred reporting items for systematic reviews and meta-analyses statement (11). For studies that met our inclusion criteria, the data were extracted for parameters related to the following: first author's

name, publication year, number of subjects enrolled, types of study design, patient characteristics (including the mean age, sex, mean body mass index [BMI] and health status), type of intervention, dose, duration of treatment, location, outcome measures and type of diet. For studies that reported multiple time points for the same subjects, the data from the longest period were used.

Predefined primary outcomes were the differences in the total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, insulin sensitivity, haemoglobin A1c (HbA1c) and homeostatic model assessment of insulin resistance (HOMA-IR). Secondary outcomes included BMI, body weight, interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). For continuous outcomes, all of the data were captured as the means ± SD. When the SDs were not directly available, they were imputed from SEs, 95% confidence intervals (CIs) or *P* values using correlation coefficient methods referenced in the *Cochrane Handbook for Systematic Reviews of Interventions* (10).

Data synthesis and analysis

In the present study, the effect sizes were expressed as the weighted mean differences (WMDs) and 95% CIs between the intervention and control groups. Statistical heterogeneity between the trials included in this meta-analysis was quantified using the I^2 statistic. I^2 values $<50\%$ and $\geq 50\%$ corresponded to the use of the fixed-effects and random-effects model, respectively (12). To explore the influence of various factors on the cardiovascular risk factors of resveratrol intervention, we further performed a priori subgroup analysis according to the baseline BMI, study design, resveratrol dose, medication duration and health status. Additionally, a sensitivity analysis was also performed using the leave-one-out method (i.e. removing one study each time and repeating the analysis) to evaluate the stability of the results. Furthermore, we evaluated the potential publication bias of the studies included with funnel plots, and Egger's regression asymmetry test ($P < 0.05$ was considered representative of a statistically significant publication bias) (13). A *P* value less than 0.05 was considered significant, and all of the tests were two sided. Two investigators (G. C. and D. L.) independently performed the statistical analyses with STATA (version 12; StataCorp, College Station, TX), crosschecked and reached a consensus on all of the items. Any discrepancy was resolved by discussion and consensus.

Results

Identification of relevant studies

The flow of articles from the initial search to the final inclusion in this systematic review is shown in Fig. S1. Cross-checking of the reference lists by two authors from the collected articles and reviews did not identify any additional articles. A total of 275 citations were obtained by the initial database search. After the removal of duplicates, 113 titles and abstracts were screened; of these, 37 abstracts appeared to be potentially relevant and were collected as full-text articles to be assessed for eligibility. A total of 17 articles were subsequently excluded for the reasons listed in Fig. S1, which left 21 articles that were finally included in the present analysis (14–33).

Study characteristics and validity assessment

A summary of the key details of these included studies are found in Table 1. These studies were published between 2002 and 2016. The population sizes varied from 8 to 66, including a total of 681 subjects. Among the included studies, the mean baseline BMI of overweight/obese adults varied from 25.4 to 34.6 $kg\,m^{-2}$. The dosage of resveratrol used in the included studies ranged from 8 to 3,000 $mg\,d^{-1}$, with a median of 300 $mg\,d^{-1}$; the duration of the resveratrol intervention varied from 2 weeks to 6 months (median: 3 months). The mean age of the participants in each trial ranged from 38.3 to 73.4 years. Participants in one study displayed mild hypertriglyceridemia, two trials selected subjects with metabolic syndrome and three trials included patients with T2DM. Of the remaining 15 trials, three were conducted in patients with CVD, four were conducted in participants with non-alcoholic fatty liver disease (NAFLD) and eight studies were performed in obese or overweight but otherwise healthy subjects. Nineteen of the 21 studies suggested that the subjects maintain a usual diet, whereas two studies imposed restrictions on resveratrol intake. Most of the trials (16 trials) adopted a parallel study design (the control groups received placebo or grape extract with a similar polyphenolic content but lacking resveratrol), and five trials used a crossover study design.

Risk of bias in individual studies

Overall, 10 trials were judged to be at a low risk of bias, eight at an unclear risk and three at a high risk of bias. All of the included trials sufficiently addressed the criteria of complete outcome data, selective reporting and other biases. An adequate randomized sequence was generated in 10 trials (16,17,19,20,22,24,25,29,31,33); eight selected studies did not provide sufficient data about random

Table 1 Characteristics of the included studies[†]

Source	Sample size[‡]	Study design	Population characteristics	Gender (M/F)	Mean age[§]	BMI[§] ($kg\,m^{-2}$)	Intervention		Locations	Duration	Outcomes of measures	Type of diet
							Treatment group	Control group				
Fujitaka *et al.* (2011)	34	R, P	Overweight patients with metabolic syndrome	25/9	62.5	27.0	Trans-resveratrol capsules, 100 mg d^{-1}	No intervention	Japan	3 months	SBP, DBP, HbA1c, HOMA-IR, BMI, TG, LDL, HDL, BMI, IL-6 and weight	Usual diet
Timmers *et al.* (2011)	11	R, DB, C	Obese volunteers but otherwise healthy adults	11/0	52.5	31.5	Resveratrol capsule, 150 m d^{-1}	Placebo	the Netherlands	30 d	SBP, DBP, glucose, insulin and TG	Usual diet, resveratrol-free
Tome-Carneiro *et al.* 2012	50	R, DB, P	Obese patients with CVD	21/29	59.0	31.5	GE-RES capsules, 16 mg d^{-1}	GE capsules (without RES)	Spain	6 months	SBP, DBP, glucose, BMI, TC, TG, LDL, HDL, IL-6 and TNF-α	Usual diet
Tome-Carneiro *et al.* 2012a	50	R, DB, P	Obese volunteers with CVD	21/29	59.0	31.5	GE-RES capsules, 8 mg d^{-1}	GE capsules (without RES)	Spain	6 months	Glucose, TC, TG, LDL and HDL	Usual diet
Magyar *et al.* 2012	40	R, DB, P	Overweight patients with CVD	26/14	66.3	28.7	Resveratrol capsule, 10 mg d^{-1}	Placebo capsule	Europe	3 months	TC, TG, LDL and HDL	Usual diet
Wong *et al.* (2013)	28	R, DB, C	Obese but otherwise healthy adults	12/16	61.0	33.3	Trans-resveratrol capsule, 75 mg d^{-1}	Placebo	Australia	6 weeks	SBP, DBP and BMI	Usual diet
Movahed *et al.* (2013)	66	R, DB, P	Overweight patients with T2DM	33/33	52.4	27.1	Resveratrol tablets, 1,000 mg d^{-1}	Placebo tablets	Iran	45 d	SBP, DBP, Glucose, Insulin, HOMA-IR, HbA1c, BMI, TC, TG, LDL, HDL and weight	Usual diet, resveratrol-free
Dash *et al.* (2013)	8	R, DB, C	Overweight or obese individuals with mild hypertriglyceridemia	8/0	45.8	31.1	Resveratrol capsule, 1,000 mg d^{-1}	Placebo	Italy	2 weeks	Glucose, insulin, HOMA-IR and TG	Usual diet
Poulsen *et al.* (2013)	24	R, DB, P	Obese subjects but otherwise healthy men	24/0	38.3	32.5	Resceratrol capsule, 500 mg d^{-1}	Placebo	Denmark	4 weeks	Glucose, insulin, HOMA-IR, HbA1c, TC, TG, LDL, HDL, IL-6 and TNF-α	Usual diet
Villar *et al.* 2014	24	R, DB, P	Obese patients with metabolic syndrome	NA	39.8	34.6	Trans-resveratrol capsules, 1500 mg d^{-1}	Placebo capsules	Mexico	90 d	SBP, DBP, glucose, BMI, TC, TG, LDL, HDL and weight	Usual diet
Chachay *et al.* (2014)	20	R, DB, P	Overweight or obese men diagnosed with NAFLD	20/0	48.1	31.5	Resveratrol capsule, 3,000 mg d^{-1}	Placebo	Australia	8 weeks	SBP, DBP, glucose, insulin, BMI, TC, TG, LDL, HDL, HOMA-IR, IL-6, TNF-α, and weight	Usual diet
Witte *et al.* (2014)	46	R, DB, P	Healthy overweight older individuals	28/18	64.2	27.5	Resveratrol capsule, 200 mg d^{-1}	Placebo	Germany	26 weeks	SBP, DBP, glucose, insulin, BMI, TG, TC, LDL, HDL, HbA1C, IL-6, TNF-α and weight	Usual diet
Anto *et al.* (2014a)	17	R, DB, P		11/11	73.2	29.8	Resveratrol capsule, 300 mg d^{-1}	Placebo	USA	12 weeks	SBP, DBP, glucose and weight	Usual diet

(*Continues*)

Table 1 (Continued)

Source	Sample size‡	Study design	Population characteristics	Gender (M/F)	Mean age§	BMI§ (kg m^{-2})	Intervention		Locations	Duration	Outcomes of measures	Type of diet
							Treatment group	Control group				
			Overweight but otherwise healthy adult									
Anto *et al.* (2014b)	15	R, DB, P	Overweight but otherwise healthy adult	10/10	73.4	29.4	Resveratrol capsule, 1,000 mg d^{-1}	Placebo	USA	12 weeks	SBP, DBP, glucose and weight	Usual diet
Bashmakov *et al.* (2014)	24	R, DB, P	Overweight patients with T2DM	15/9	56.9	28.5	Trans -resveratrol, 50 mg d^{-1}	Placebo	UK	60 d	Glucose, insulin, TC, LDL and HDL	Usual diet
Faghihzadeh *et al.* 2015	50	R, DB, P	Overweight patients with NAFLD	35/15	45.2	28.5	Resveratrol capsule, 500 mg d^{-1}	Placebo capsule	Iran	12 weeks	SBP, DBP, glucose, insulin, HOMA-IR, BMI, TC, TG, LDL, HDL, IL-6, TNF-α and weight	Usual diet
Chen *et al.* (2015)	60	R, DB, P	Overweight subjects with NAFLD	42/18	44.3	25.7	Resveratrol capsules, 300 mg d^{-1}	Placebo capsules	China	3 months	SBP, DBP, glucose, insulin, HOMA-IR, BMI, TC, TG, LDL, HDL, TNF-α and weight	Usual diet
Gliemann *et al.* (2015)	27	R, DB, P	Overweight but otherwise healthy aged men	27/0	65.0	25.4	Trans-resveratrol, 250 mg/d	Placebo capsules	Denmark	8 weeks	Glucose, BMI, TC, TG, LDL, HDL and weight	Usual diet
Made *et al.* (2015)	45	R, DB, C	Overweight and slightly obese subjects	25/20	60.0	28.8	Resveratrol capsule, 150 mg d^{-1}	Placebo	the Netherlands	4 weeks	SBP, DBP, glucose, BMI, TC and HDL	Usual diet
Heebøll *et al.* (2016)	28	R, DB, P	Overweight patients with NAFLD	18/10	43.3	32	Resveratrol, 1500 mg d^{-1}	Placebo	Denmark	6 months	SBP, DBP, glucose, insulin, HOMA-IR, BMI, TG, LDL, HDL and weight	Usual diet
Thazhath *et al.* (2016)	14	R, DB, C	Overweight patients with T2DM	10/4	67.5	27.7	Resveratrol capsules, 1,000 mg d^{-1}	Placebo	Australia	5 weeks	Glucose, HbA1c and weight	Usual diet

†BMI, body mass index; C, crossover; CVD, cardiovascular disease; DB, double-blind; DBP, diastolic blood pressure; F, female; GE, grape extract; GE-RES, grape extract containing resveratrol; HDL, high-density lipoprotein cholesterol; HbA1c, haemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; IL-6, interleukin-6; LDL, low-density lipoprotein cholesterol; M, male; NA, not available; NAFLD, non-alcoholic fatty liver disease; P, parallel; R, randomized; ; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TNF-α, tumour necrosis factor-α; T2DM, type 2 diabetes mellitus.
‡For parallel design, sample size is the sum of treatment group and control group.
§Values are provided as mean.

sequence generation (15,18,21,23,26,27,32). The details of the risk-of-bias analysis are shown in Table S2.

Pooled effects of resveratrol administration on lipid concentrations and blood pressure in overweight and obese subjects

The plasma levels of TC, LDL-C, HDL-C and TG were evaluated in 13, 14 and 15 studies, respectively. As shown in Fig. 1 a-d, the use of resveratrol appeared to significantly lower TC (WMD, $-0.19\,mmol\,L^{-1}$; 95% CI, −0.32 to −0.06; $P = 0.004$), without significant heterogeneity ($I^2 = 39\%$); however, no significant change was detected in the LDL-C (WMD, $-0.06\,mmol\,L^{-1}$; 95% CI, −0.26 to 0.14; $P = 0.54$; $I^2 = 56\%$), HDL-C (WMD, $0.01\,mmol\,L^{-1}$; 95% CI, −0.03 to 0.05; $P = 0.67$; $I^2 = 33\%$) and TG (WMD, $-0.04\,mmol\,L^{-1}$; 95% CI, −0.15 to 0.08; $P = 0.55$; $I^2 = 0\%$) values in overweight and obese participants.

The results for BP were reported in 14 RCTs representing 577 participants. Compared with the control group, overweight and obese subject consumption of resveratrol significantly reduced the SBP level (WMD, −2.26 mmHg; 95% CI, −4.82 to −0.49; $P = 0.02$; $I^2 = 36\%$; Fig. 1e). However, the pooled result showed that resveratrol intervention did not significantly reduce the DBP level compared with that of the control (WMD, −0.30 mmHg; 95% CI, −1.78 to 1.19; $P = 0.70$; Fig. 1f), without significant heterogeneity ($I^2 = 36\%$).

Effects of resveratrol on glucose control and insulin sensitivity in overweight and obese subjects

Compared with the control group, resveratrol intervention did not significantly influence the levels or concentrations of fasting blood glucose (18 RCTs; WMD, $-0.23\,mmol\,L^{-1}$; 95% CI, −0.42 to −0.03; $P = 0.03$; $I^2 = 72\%$), insulin (10 trials; WMD, −0.47 μIU/mL; 95% CI, −2.21 to 1.27; $P = 0.60$; $I^2 = 61\%$), HbA1c (5 trials; WMD, −0.12%; 95% CI, −0.31 to 0.07; $P = 0.21$; $I^2 = 68\%$) and HOMA-IR (8 trials; WMD, −0.48; 95% CI, −1.14 to 0.19; $P = 0.16$; $I^2 = 72\%$) in overweight and obese subjects. Forest plots summarizing the meta-analysis of trials for each measured parameter are shown in Fig. 2.

Effects of resveratrol consumption on inflammation markers and body weight in overweight and obese subjects

Other identified risk factors, such as BMI, body weight, IL-6 and TNF-α, were also pooled in our systematic analysis after resveratrol ingestion. The pooled results of these studies showed that resveratrol consumption was not associated with an influence on IL-6 (WMD, −0.13 ρg/mL; 95% CI, −0.9 to 0.64; $P = 0.74$; $I^2 = 16\%$), TNF-α (WMD, $-0.37\,\rho g\,mL^{-1}$; 95% CI, −0.93 to 0.19; $P = 0.20$; $I^2 = 17\%$), BMI (WMD, $-0.20\,kg\,m^{-2}$; 95% CI, −0.50 to 0.10; $P = 0.19$; $I^2 = 0\%$) and body weight (WMD, −0.57 kg; 95% CI, −1.39 to 0.26, $P = 0.18$; $I^2 = 0\%$) in overweight and obese subjects (Table 2).

Additional analysis

We further conducted a subgroup analysis to explore the effects of baseline BMI, resveratrol dose, health status, mean age and intervention duration on the overall effects of resveratrol on CVD risk factors in overweight and obese individuals.

In a subgroup analysis stratified by baseline BMI, the supplementation of resveratrol significantly affected the level of SBP (WMD, −3.27 mmHg; 95% CI, −6.08 to −0.45; $P = 0.02$), TC (WMD, $-0.24\,mmol\,L^{-1}$; 95% CI, −0.39 to −0.10; $P = 0.001$) and HbA1c (WMD, −0.17%; 95% CI, −0.29 to −0.06; $P = 0.003$) in subjects with BMI $\geq 30\,kg\,m^{-2}$. In the subgroup analysis by resveratrol dose, resveratrol supplementation resulted in significant improvement compared with the control condition for SBP (WMD, −4.91 mmHg; 95% CI, −8.02 to −1.80; $P = 0.002$), DBP (WMD, −2.98 mmHg; 95% CI, −5.26 to −0.69; $P = 0.01$), glucose (WMD, $-0.37\,mmol\,L^{-1}$; 95% CI, −0.67 to −0.08; $P = 0.01$), insulin (WMD, −1.73 μIU/mL; 95% CI, −2.91 to −0.55; $P = 0.004$), and TC (WMD, $-0.28\,mmol\,L^{-1}$; 95% CI, −0.50 to −0.06; $P = 0.01$) in the high-dose resveratrol group ($\geq 300\,mg\,d^{-1}$). However, a significant reduction in HbA1c was observed in subjects who consumed consumption <300 mg of resveratrol daily. Regarding the subgroup analysis by metabolic-related comorbidities, significant reductions in SBP and TC were shown in overweight and obese subjects with metabolic-related comorbidities (for SBP, −4.00 mmHg [−6.85, −1.15], $P = 0.006$; for TC, $-0.29\,mmol\,L^{-1}$ [−0.44, −0.14], $P = 0.0001$). However, in overweight and obese subjects without metabolic-related comorbidities, we found a significant reduction in the levels of glucose (WMD, $-0.15\,mmol\,L^{-1}$; 95% CI, −0.27 to −0.03; $P = 0.01$) and HbA1c (WMD, −0.15%; 95% CI, −0.29 to −0.01; $P = 0.04$). We also stratified the studies according to the intervention duration (<3 or ≥3 months), and a significant change in SBP (WMD, −3.42 mmHg; 95% CI, −6.37 to −0.47; $P = 0.02$), glucose (WMD, $-0.4\,mmol\,L^{-1}$; 95% CI, −0.68 to −0.11; $P = 0.006$) and HbA1c (WMD, 0.17%; 95% CI, −0.29 to −0.05; $P = 0.004$) were observed in overweight and obese subjects with the consumption of resveratrol for ≥3 months; whereas a significant change in insulin (WMD, −2.23 μIU/mL; 95% CI, −3.56 to −0.90; $P = 0.001$) and TC (WMD, $-0.25\,mmol\,L^{-1}$; 95% CI, −0.42 to −0.07; $P = 0.007$) were observed in overweight and obese subjects with the consumption of resveratrol for

<3 months. The summary of the subgroup analysis results is shown in Table S3.

In the sensitivity analysis, the pooled effects of resveratrol on study endpoints did not change after systematically eliminating each trial. Furthermore, we also omitted the studies with a high risk of bias and excluded the study that did not use a placebo as a control. The aggregated results were similar to the overall analysis (Table S4). All of the

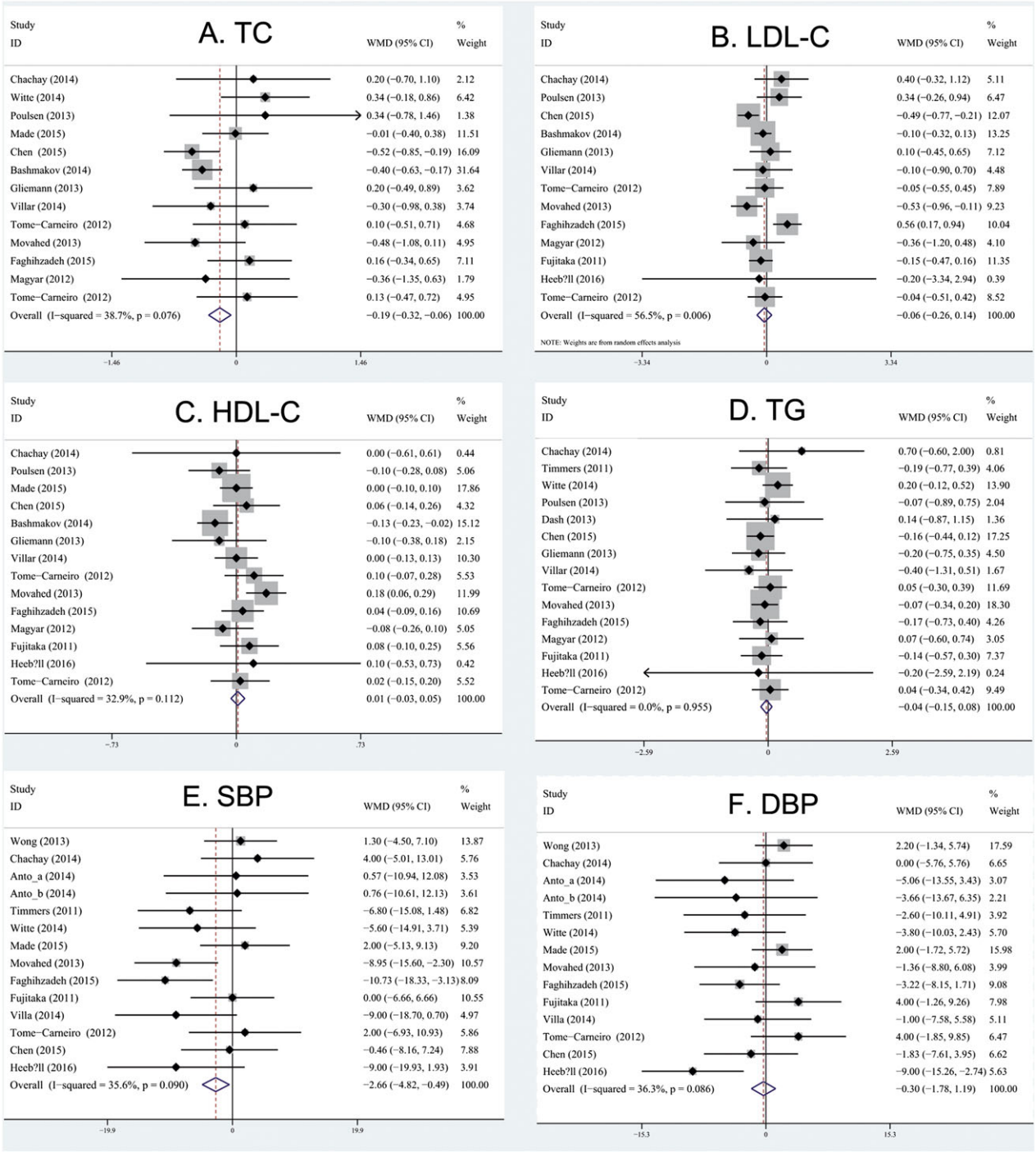

Figure 1 Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of resveratrol supplementation on plasma lipids and statement (BP) in overweight/obese subjects. Horizontal lines of each study correspond to the 95% confidence interval (CI). Areas of shadow rectangles reflect weight.

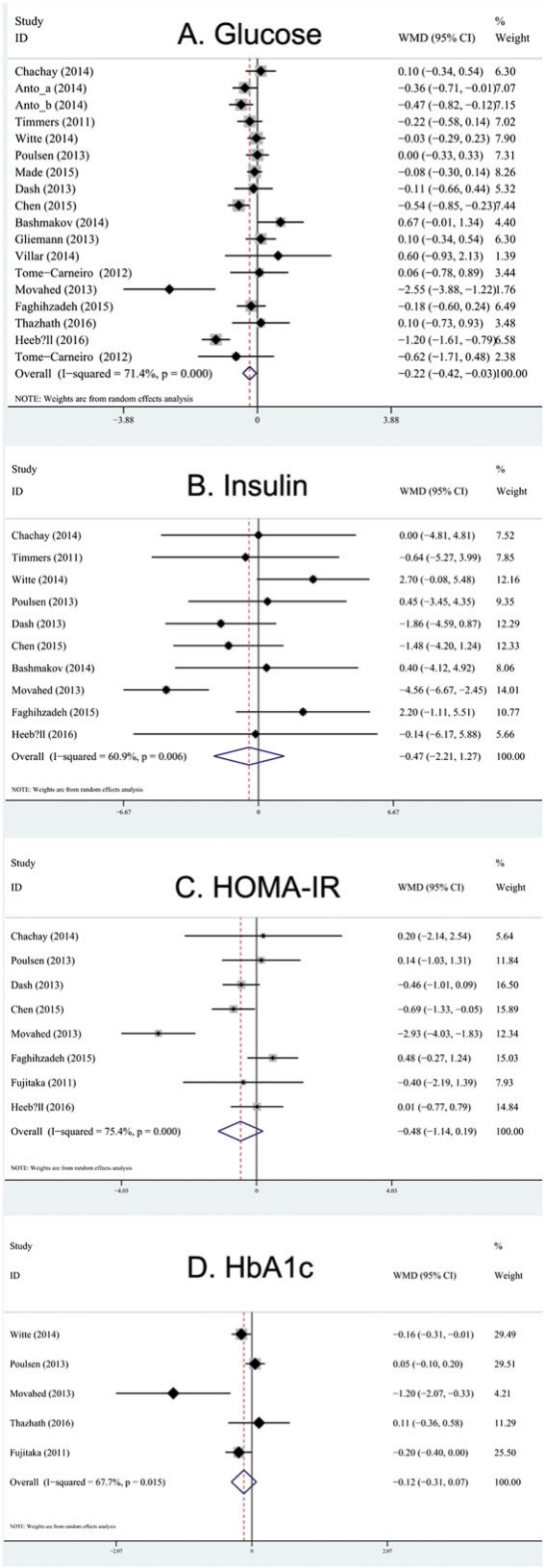

Figure 2 Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of resveratrol supplementation on glucose, insulin, HOMA-IR and HbA1c in overweight/obese subjects. Horizontal lines of each study correspond to the 95% confidence interval (CI). Areas of shadow rectangles reflect weight.

results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and robust.

Tolerability and safety of resveratrol consumption

Resveratrol was well tolerated, and no serious adverse events (AEs) occurred among most of the eligible trials during the study period. Only three RCTs reported AEs (24,26,32). The investigators in one of these reported mild gastrointestinal side-effects described as an increased frequency of bowel movements and loose stools (24). A serious case of febrile leukopenia and thrombocytopenia after 10 days of resveratrol treatment was reported in one study (32). The study conducted by Anton *et al.* reported that participants receiving a higher dose of resveratrol ($\geq$300 mg d^{-1}) had slightly lower haemoglobin levels, lower mean corpuscular haemoglobin concentration levels and higher alkaline phosphatase levels than baseline (26).

Publication bias

No evidence of publication bias was detected in the meta-analysis of the effects of resveratrol consumption on the study endpoints by Egger's regression tests (for TC, $P = 0.951$; for LDL, $P = 0.760$; for HDL, $P = 1.000$; for TG, $P = 0.921$; for SBP, $P = 0.661$; for DBP, $P = 0.063$; for glucose, $P = 1.000$). Funnel plots regarding these study outcomes are shown in Fig. 3 and Fig. S2.

Discussion

Main findings

In our present study, we comprehensively and systematically reviewed the current available literature that investigates the effects of resveratrol on CVD-related-risk biomarkers in overweight/obese subjects. The findings from the current study demonstrate that overweight or obese participants receiving resveratrol had statistically significantly lower SBP, fasting glucose and TC after treatment than control individuals. However, the use of resveratrol did not appear to alter DBP, insulin, HOMA-IR, HbA1c, TG, LDL-C, HDL-C, BMI and body weight values. We also found that a statistically significant beneficial effect of resveratrol supplement on SBP and TC was observed in subjects with a BMI $\geq$30 kg m^{-2}, a parallel study design and overweight or obese subjects with metabolic-related comorbidities. In addition, findings from the subgroup analysis clearly showed that resveratrol consumption significantly decreased the levels of SBP, DBP, glucose, insulin and TC in subjects that ingested a higher dose of resveratrol ($\geq$300 mg d^{-1}).

Table 2 Effect of resveratrol consumption on inflammation markers and body weight in overweight/obese subjects

Markers outcomes	Number of trials	Number of. patients	WMD (95% CI)†	*P* Value	I^2 (%)
Body weight (kg)	12	461	−0.57 (−1.39, 0.26)	0.18	0
BMI (kg m^{-2})	12	585	−0.20 (−0.50, 0.10)	0.19	0
IL-6 (ρg mL^{-1})	6	258	−0.13 (−0.90, 0.64)	0.74	16
TNF-α (ρg mL^{-1})	6	250	−0.37 (−0.93, 0.19)	0.20	17

†WMD, weighted mean differences; CI, confidence interval.
BMI, body mass index; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α.

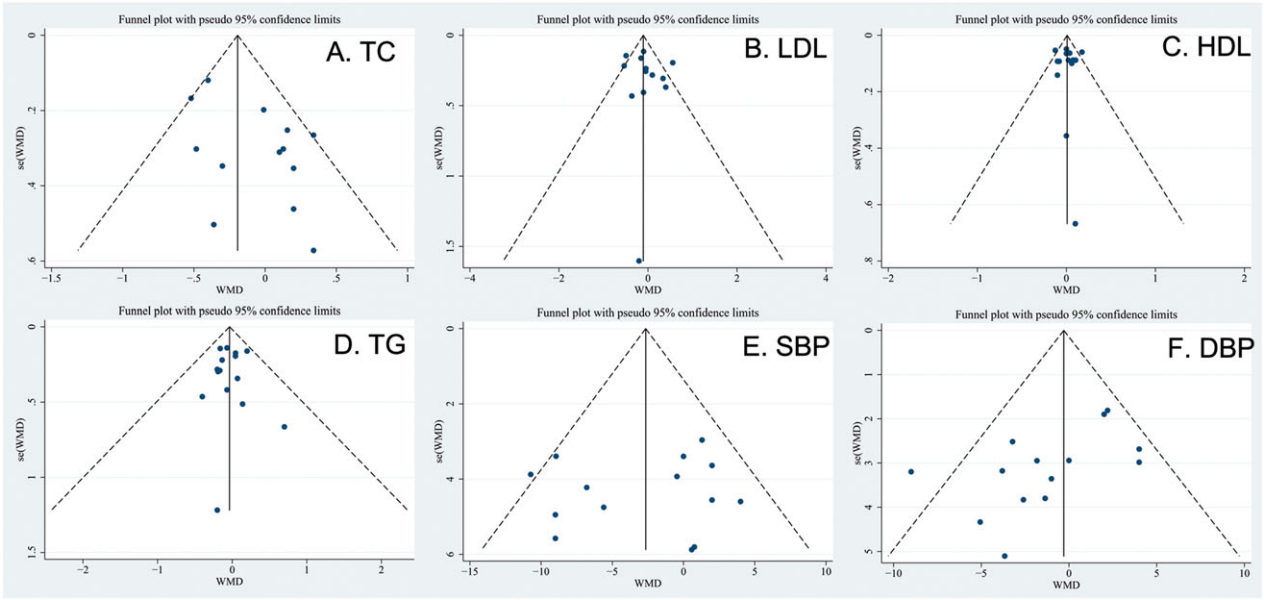

Figure 3 Funnel plot detailing publication bias in the studies reporting the impact of resveratrol on lipid and blood pressure.

Comparison with previous studies

Several meta-analyses quantifying the effects of resveratrol on lipids, BP, glucose or insulin in healthy populations or subjects with T2DM (34–36) have been published. However, the effects of resveratrol on body weight and cardiovascular related-risk factors in overweight/obese patient groups remain inconsistent and have not been systematically examined. Herein, this is the first meta-analysis to identify and quantify the effects of resveratrol on the markers of lipid and lipoprotein metabolism, glucose metabolism, inflammation and body weight in overweight/obese populations within RCTs because overweightness and obesity are independent risk factors of non-communicable disease development, especially CVD. A previous meta-analysis conducted by Liu *et al.* (34) implied that resveratrol consumption significantly improved glucose control and insulin sensitivity in patients with T2DM but did not show a similar effect on nondiabetic participants. A further pooled analysis has demonstrated that the beneficial effects of resveratrol supplementation were identified for SBP, HbA1c and creatinine but not for fasting glucose, HOMA-IR, DBP, insulin, TG, LDL or HDL-C in T2DM (35). Compared with the previous study, we consider our study to be important for several reasons as follows: first, obesity is a high-risk factor for CVD development, and the high incidence of obesity and overweightness calls for novel preventive and therapeutic modalities. The results of our analysis will provide clinicians with an unbiased consensus of the current human clinical trial data, which can be directly applied to practice while also highlighting directions for future clinical research. Second, this meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses guidelines and recommendations of the Cochrane Collaboration. To investigate the impact of resveratrol on various parameters among these studies, previously defined subgroup analyses (baseline BMI, study design, resveratrol dose, intervention duration and health status) were also performed. Third, the quality assessment suggested that the overall study quality was fair, and no significant publication bias was detected. Finally, a sensitivity analysis was conducted by omitting any single trial or based on various exclusion criteria. Overall, the main findings were robust in the sensitivity analysis.

Implications for clinical practice and further research

Despite substantial progress in the pharmacological treatment of CVD risk factors, the residual cardiovascular risk (RCVR) is still a challenge for effective primary and secondary CVD prevention (37). Recent trials and current international guidelines have suggested that the initial first step to reduce overall cardiovascular risk is implemented by pharmacological approaches that are well established as highly effective and safe across gender, age and CVD risk groups (38,39). Once the target levels of the main risk factors are achieved, the patients who remain at a high RCVR should be identified as early as possible. In these specific subgroups with RCVR, individualized approaches, effective combination lipid-lowering therapy or a more aggressive glucose or blood pressure-lowering strategy should be used. In our present meta-analysis of available RCTs, the pooled result revealed that resveratrol intervention may significantly reduce the levels of SBP, DBP, glucose, insulin and TC in overweight/obese subjects ingesting a higher dose of resveratrol ($\geq$300 mg d^{-1}) without obvious AEs, suggesting that resveratrol may be considered an adjunct to the pharmacological management of CVD and reduction of residual vascular risk in overweight and obese populations. In the Heart Outcomes Prevention Evaluation (HOPE) study, the use of the angiotensin-converting-enzyme inhibitor ramipril was associated with a 22% relative risk reduction in cardiovascular death, myocardial infarction or stroke, despite only a modest reduction in SBP (3.3 mmHg) (40). Thus, the 2.26 mmHg reduction in SBP observed in our meta-analysis with resveratrol is not only statistically significant but likely also clinically significant. The exact mechanisms responsible for the glucose-lowering, lipid-lowering and BP-lowering effects of resveratrol are not completely understood. Several studies have demonstrated that the antihypertensive effect of resveratrol can be explained by the following hypotheses: resveratrol restores mesenteric and cardiac endothelial nitric oxide synthase activities or reduces the increase in the levels of thiobarbituric acid reactive substances and possibly modulates the production of endothelin-1, angiotensin II and nitric oxide (41,42). Moreover, resveratrol is beneficial in controlling the BP levels in obese humans by decreasing the sleeping and resting metabolic rates (15). Similarly, the observed effects of resveratrol intake on glucose are also supported by several *in vivo* mechanistic study findings, in which resveratrol has been shown to activate sirtuin 1 expression *in vivo* (15) or stimulate glucose uptake by increasing glucose transporter type 4 expression (43) and activating glucose uptake in the absence of insulin (44).

We also assessed the effects of resveratrol consumption on the inflammatory markers of CVD in overweight or obese individuals. Recently, inflammation has been believed to play a central role in the pathogenesis of obesity and chronic disease (45,46). A low-grade inflammatory status provides additional information for cardiovascular risk stratification and prediction, which have also been regarded as useful biomarkers for assessing cardiovascular events in populations with various disease settings (47). A reduction in the inflammatory status may prevent the occurrence of disorders and diseases related to overweightness. In the present study, however, we failed to find any statistically significant differences between the resveratrol products and control groups. Most notably, these results are inconclusive because of the limited eligible RCTs included in these outcomes; further adequately powered studies are needed.

Based on our main findings, some suggestions for future research should be highlighted. First, there is a need to standardize a resveratrol intervention protocol for overweight or obese populations (including the consistency of dosage, timing, duration of administration and designed rigorously with large sample sizes) because great variability and methodological problems exist in the present trials. In addition, although certain beneficial effects were observed after resveratrol intervention, further studies evaluating the effects of resveratrol consumption on all primary clinical endpoints, such as cardiovascular morbidity and all-cause mortality, are required. Finally, although evidence from the current study indicated that resveratrol is generally considered effective and well tolerated, the side effects of resveratrol should be given much attention.

Limitations

In interpreting the current results, some limitations of this meta-analysis should be noted. First, although extensive searches and clear inclusion criteria were made, it cannot be entirely guaranteed that all relevant articles were selected because the measures of lipid profiles, BP or glucose control were not the primary outcomes in most of the trials selected for this meta-analysis and the null findings of the secondary outcomes may not have always been published. Second, several trials lacked adequate methodological information, such as the method of randomization, allocation concealment, blinding, funding and dropouts, which may result in clinical heterogeneity.

Conclusions

In conclusion, our findings provide evidence that a daily higher dose of resveratrol ($\geq$300 mg d^{-1}) consumption might be a candidate as an adjunct to pharmacological management to better prevent and control CVD in overweight and obese individuals.

Conflict of interest statement

The authors state that they have no conflicts of interest.

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12458

Appendix 1: Search strategy
Appendix 2: Supplemental Table S1 Inclusion criteria to select studies for the present meta-analysis.
Appendix 3: Supplemental Table S2 Quality assessment of the included studies 1.
Appendix 4: Supplemental Table S3 Subgroup analyses of the effects of resveratrol consumption on CVD risk markers in overweight and obese subjects.
Appendix 5: Supplemental Table S4 Additional Analyses-Sensitivity Analyses.
Appendix 6: Supplemental Figure S1 Flow chart of data base searches and articles included in the present meta-analysis.
Appendix 7: Supplemental Figure S2 Funnel plot detailing publication bias in the studies reporting the impact of resveratrol on other outcomes.

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