Systemic review/Meta-analysis

Usefulness of resveratrol supplementation in decreasing cardiometabolic risk factors comparing subjects with metabolic syndrome and healthy subjects with or without obesity: meta-analysis using multinational, randomised, controlled trials

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Abstract

Introduction: Resveratrol (RES), a natural polyphenolic compound, has been linked to some beneficial effects against cardiovascular disease (CVD).
Material and methods: We conducted a systematic search to conduct a meta-analysis on cardiometabolic risk factors modulated by RES targeting patients with metabolic syndrome (Met-S) and Obese/Healthy (O/H) subjects. The PICO (Patient, Intervention, Comparison, Outcome) research question was: Does RES among patients with Met-S and O/H subjects reduce the cardiometabolic risk? The first group was affected with MetS, which is defined as a clustering of abdominal obesity, dyslipidaemia, hyperglycaemia, and hypertension in a single individual. The second group was composed of 'obese/healthy' individuals, i.e. healthy subjects with or without obesity. We performed a literature search of MEDLINE/ PubMed, Scopus, and Google Scholar for randomised, controlled trials (RCT) that estimated the effects of RES on cardiometabolic risk factors.
Results: We found 780 articles, of which 63 original articles and reviews were identified. Data from 17 well-conducted RCT studies, comprising 651 subjects, were extracted for analysis. Overall, RES had a significant influence on Homeostatic Model Assessment-Insulin Resistance (HOMA-IR), resulting in a mean difference of –0.520665 (95% CI: –1.12791; –0.01439; p = 0.00113). In Met-S, RES significantly reduced glucose, low-density lipoprotein-cholesterol (LDL-C), and total cholesterol (T-Chol) as detected by the mean difference of –1.069 (95% CI: –2.107, –0.032; p = 0.043), –0.924 (95% CI: –1.804, –0.043; p = 0.040), and –1.246 (95% CI: –2.314, –0.178; p = 0.022), respectively.
Conclusions: Despite some heterogeneity in the populations, RES supplementation seems to improve cardiometabolic health, decreasing some risk factors (HOMA-IR, LDL-C, and T-Chol) associated with CVD.

Key words: heart, metabolic syndrome, resveratrol, meta-analysis, randomised, controlled trial.

Introduction

There is a growing interest in using natural compounds as potential therapeutics for chronic diseases or cancer preventive agents [1]. Polyphenols belong to a category of chemical compounds that are classified into several classes according to their chemical type, such as phenolic acids, flavonoids, stilbenes, and lignans. The beneficial effects of flavonoids in atherosclerosis progression and cardiovascular disease has been reported recently because dietary flavonoids reduce oxidative stress, exert anti-inflammatory actions, are anti-thrombogenic, strengthen endothelial function, modify lipid levels, and adjust glucose metabolism.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, with an increasing environmental burden hitting especially middle-income countries [2–5]. Atherosclerosis, the leading cause of ischaemic heart disease (IHD), cerebrovascular, and peripheral vascular diseases, is a progressive and complicated disease process often associated with recognised risk factors such as hypertension, hypercholesterolaemia, type 2 diabetes mellitus (T2DM), and tobacco smoking [3, 6, 7]. The association of glucose intolerance with insulin resistance, hypertension, dyslipidaemia, and central obesity predisposing individuals to the development of T2DM and CVD has been described as 'metabolic syndrome' (Met-S) [8–21]. More than a third of American adults with body mass index (BMI) higher of 30 kg/m^2 may have a higher risk of developing conditions like T2DM, CVD, and stroke than the general population. However, a proportion of obese adults defy the odds, maintaining metabolic health despite the excess weight, and they have been labelled Obese/Healthy (O/H) [22, 23].

Resveratrol (3,4′,5-trihydroxy-trans-stilbene, $C_{14}H_{12}O_3$, RES), a natural polyphenolic compound that exists in a large variety of plant species, including grapes, peanuts, and berries, has long been used as a herbal remedy and dietary supplement. The concept of the "French paradox" may suggest that the French nutritional style is quite healthy [24]. French people have a relatively low incidence of CVD despite having a diet rich in saturated fats, and red wine consumption may be responsible for lowering of the serum lipids [25]. Since 1992, there has been a rise of studies investigating the health benefits of RES in cardiovascular health [26–28]. RES is known for its antioxidant and anti-inflammatory properties and for its ability to upregulate endothelial NO synthase (eNOS). Its ability to scavenge $^{\bullet}OH/O_2^{\bullet-}$ and peroxyl radicals may be crucial in limiting the lipid peroxidation processes in CVD [29, 30]. Several preclinical studies on animal models have indeed highlighted beneficial effects of RES on CVD. These studies are underpinned by the identification of numerous molecular targets, including silent information regulator 2/sirtuin 1 (SIRT-1), AMP-activated protein kinase (AMPK), nuclear factor-like 2 (Nrf2), and nuclear factor-κB (NF-κB), among others [31–37]. RES is also beginning to be the target of social and ideological debates in some cultures [38–44]. On the other hand, some systematic reviews of randomised, controlled trials (RCTs) seem to have failed to indicate specific beneficial effects of RES supplementation for selected risk factors for CVD [45, 46]. The prevalence of MetS is rapidly increasing worldwide. In fact, MetS is not only increasing in industrialised countries but also in developing countries associated with a lifestyle change, including some Asian and African countries. MetS is impacting the global incidence of life-threatening CVD such as stroke and myocardial infarction. Effective treatment for cardiovascular risk factors in MetS often requires pharmacological intervention. To the best of our knowledge, the available pharmacological tools are usually not sufficiently effective, and additional protocols may be needed to prevent the development of major cardiovascular complications in MetS.

Considering recent RCTs [47, 48], and T2DM systematic reviews [49], we hypothesised that RES could reduce the cardiometabolic risk factors for CVD. In this paper, we report our results from an investigation using a comprehensive meta-analysis of published RCTs to quantitatively assess the effects of RES on reducing CVD risk factors comparing subjects with Met-S and subjects labelled O/H.

Material and methods

Search strategy

We performed a literature search in MEDLINE/PubMed (up to October 31, 2016; http://www.ncbi.nlm.nih.gov/pubmed/), Scopus, and Google Scholar (up to October 31, 2016) using the following search terms in the title and abstract: 'Resveratrol' or 'Resveratrols' (plural). We searched the key terms alongside the following limitations: English-language, human studies, and clinical trials. To qualify for inclusion ("inclusion criteria") the studies had to be randomised, controlled trials comparing interventions that differed only in resveratrol condition. If other interventions were given, they had to be the same in all treatment groups. Only articles that were published in English-language, peer-reviewed journals were included. Reference lists and reviews were further handsearched to identify RCTs examining the effects of RES on two groups of subjects. The first group was affected with MetS with or without coronary artery disease (CAD). Met-S is defined as a clustering of

key cardiovascular risk factors; namely, abdominal obesity, dyslipidaemia, hyperglycaemia, and hypertension in a single individual. Interestingly, some names, such as syndrome X, dysmetabolic syndrome, insulin resistance syndrome, and the "deadly quartet" have also been used. CVD may have a broad definition, but usually subjects with CVD present with CAD, MetS, and/or hypertension. The second group that we considered in our meta-analysis is labelled 'obese/healthy' (O/H), i.e. healthy with or without obesity. The justification is that during the past 15 years numerous studies have shown an 'obesity paradox'. In fact, despite the adverse effects that obesity may have on the risk factors associated with CVD and other chronic diseases, patients with overweight or obesity, who show a 'healthy habit', often astoundingly harbour a better prognosis than leaner patients. Our investigative research group aims to perform accurately systematic reviews adhering strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and relative statements at the University of Alberta, Edmonton, Canada [1, 10, 50–59]. The PICOS criteria (Patient/Problem, Intervention, Comparison groups, Outcome, and Setting) were used for both research question and title.

Data extraction

All published papers were reviewed by four of the authors (BoC, JF, BrC, and CS). An initial qualitative assessment was performed double-blind, and notes were discussed to identify flaws and determine a quality coefficient for each paper. In the initial data extraction phase, baseline characteristics from each of the selected papers were extracted and tabulated in a spreadsheet. These components included: author, year, study design, and participant information. Pre- and post-treatment values of selected parameters and their respective standard deviations (SD) were extracted for the interventional and control groups of each study. Mean differences and SD differences were obtained directly from the retrieved scientific literature. If these values were not provided, they were calculated using the formulas mean difference = (post-treatment value – pre-treatment value) and $SD_{diff} = \sqrt{SD_{pre\text{-}treatment}^2/n + sd_{post\text{-}treatment}^2/n}$ [60]. We found that these formulas gave values to compare the RCT uniformly. Not all papers used the same units. Consequently, unit conversions were carried out using conversion formulas (Table I).

HOMA-IR stands for Homeostatic Model Assessment of Insulin Resistance, which evaluates both the presence and extent of any insulin resistance that may be encountered in a patient. The healthy range is 1.0 (0.5–1.4). If the HOMA-IR score is less than 1.0, there is a status of insulin-sensitivity that is optimal, while a value above 1.9 indicates early insulin resistance, and above 2.9 indicates significant insulin resistance. HOMA-IR is calculated by multiplying insulin rate (uIU/ml or mU/l) and the glycemia (mg/dl). The HOMA-IR calculation requires U.S. standard units and the use of specific conversions. With regard to insulin, we used pmol/l to uIU/ml by dividing by (÷) 6.945, while for glucose we used mmol/l to mg/dl by multiplying by (×) 18.

We classified the studies into two groups: (1) Metabolic Syndrome (Met-S)/T2DM with and without CAD and (2) Obese/Healthy (O/H) (no metabolic syndrome/T2DM or CAD) [61]. In the final stage of data extraction, the most relevant data from the initial phase were narrowed down and tabulated for inputting into the Comprehensive Meta-Analysis (CMA) program (Biostat, Englewood, NJ, USA). Information about the studies included: study name and year, duration, classification, gender, the number of the subjects treated, and the number of those who were referred as controls. Information about the factors included: units, intervention mean difference, and intervention difference SD, control mean difference, control difference SD,

Table I. Conversion formulas

Factor	Conversion		Conversion formula
	From	To	
Glucose	mmol/l	mg/dl	(mmol/l) × 18
Serum Insulin	mU/l	µIU/ml	(mU/l)/6.945
LDL-C	mmol/l	mg/dl	(mmol/l) × 38.6
HDL-C	mmol/l	mg/dl	(mmol/l) × 38.6
T-Chol	mmol/l	mg/dl	(mmol/l) × 38.6
TG	mmol/l	mg/dl	(mmol/l) × 88.5
CRP	g/l	mg/l	(g/l) × 1000

LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, T-Chol – total cholesterol, TG – triglycerides, CRP – C-reactive protein.

and pre/post correlation. If data were available, we performed pre-/post-correlation calculations by finding the relationship between all treatment and control pre-treatment values and all treatment and control post-treatment values. We used the correlation function of Excel (CORREL) (Windows 10 Pro, Microsoft Corporation, Silicon Valley, CA, USA).

Statistical analysis

We performed the meta-analysis using the Comprehensive Meta-Analysis (CMA) software (Biostat, 14 North Dean Street, Englewood, NJ 07631 USA) [62]. A mixed-effects analysis was assigned to investigate the influence of RES on the cardiometabolic risk factors. Mixed effects models are useful when data are available that contain more than one source of random variability. In fact, an outcome may be measured more than once on the same person, i.e. repeated measures taken over time. In this scenario, we have to account for both within-person and across-person variability [63–66]. A comparison between interventional and control groups was made. To calculate the standardised mean difference between treatment and control groups, we used the mean difference of the control group minus the mean difference of the treatment group, divided by the SD of the change score. Moreover, we conducted an analysis across the Met-S and O/H groups and a gender-specific analysis.

One of the significant aspects in our meta-analysis was to ensure that point estimates were not computed from a biased collection of studies. The benefit is that exaggeration of the actual effect size of treatment can be avoided. Hence, we assessed how many biases could be present in our meta-analysis and examined their potential impact on our findings. We used the Egger's method of bias assessment, which recommends the use of the inverse of the SE, i.e. precision, to predict the standardised effect size. All statistical analysis was carefully perused three times by three of the authors (BoC, JF, BrC) and verified by the senior author (CS).

Results

Data sources and literature search

A flow diagram outlining the process of study selection is shown in Figure 1. A total of 8821 articles were initially identified, and studies that did not involve humans were excluded, with 780 items remaining. Of these reports, there were 63 that were RCT and reviews involving RES. In the final stage of study selection following exclusion of duplicated, overlapping, and non-relevant studies, 17 articles of well-conducted RCTs were selected for inclusion [47, 67–84]. Exclusion criteria included studies that were duplicated, showed overlapping, or, according to the authors, were considered non-relevant. All studies were evaluated singly and scored by three authors (BoC, JF, BrC), and any inclusion or exclusion needed to have full consensus. These reports were then split into two groups (Met-S and O/H). In particular, Bhatt *et al.* (2012) [85] and Kumar *et al.* (2013) [73] had the same study, disguised as different studies with different authors. In examining the methods and results for those studies, it is apparent that they are the same study (same sample size with accurate same baseline values), just with two different durations. Thus, we decided to use Kumar's review because it was a more extended study. Fujitaka's 2011 study [86] has Dr. Das as a senior author, and Dr. Das was found guilty of research fraud. Some of his work has been retracted from the scientific literature. Thus, the results from that paper cannot be fully trusted, and all authors agreed and decided to exclude it. Unfortunately, Dr. Das, a prominent cardiovascular researcher with early research on catalase, glutathione, and superoxide dismutase, who had 19 papers retracted following findings of misconduct by the University of Connecticut (USA), died at the age of 67 on Sep 19, 2017. Dr. Das suffered a stroke because of the stress, although he defended himself and filed a lawsuit against the university.

Study characteristics

Table II summarises the characteristics of studies included in our meta-analysis. The 17 eligible studies comprised 651 subjects. Most of the studies (16 out of 17) used parallel design, with three studies using cross-over design. The total number

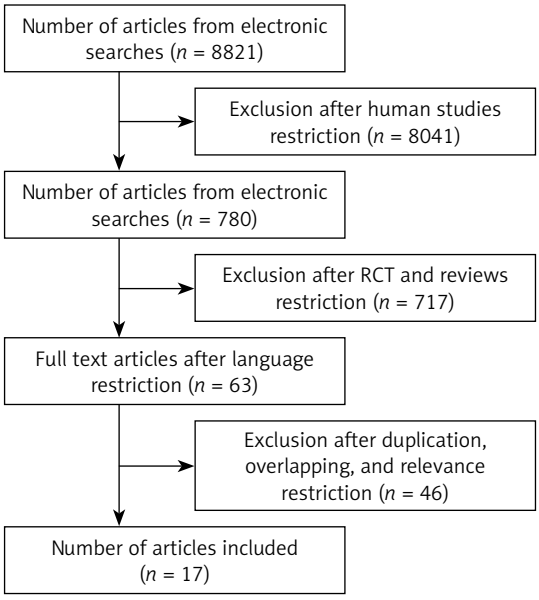


Figure 1. PRISMA-based flow-chart showing the selection process for articles of resveratrol included in the systematic review

Table II. Eligible studies in alphabetical order (n = 17)

1st author [ref.]# (year), country	CSD	DUR	RES	*N*	T-P and age	RES Group	Controls	BMI
Agarwal [67] (2013), USA	P	30	400	41	Healthy ≥ 18	*N* = 20[1]	*N* = 21 (PBO)	–
Bashmakov [47] (2014), Sweden	P	60	100	24	T2DM 54.0 ±10.1	*N* = 14 (c)	*N* = 10 (PBO)	–
Brasnyo [68] (2011), Hungary	P	30	10	19	T2DM 57.9 ±7.9	*N* = 10 (c)	*N* = 9 (PBO)	–
Chachay [69] (2014), Australia	P	56	3000	20	Obese 48.8 ±12.2	*N* = 10 (c)	*N* = 10 (PBO)	31.8
Dash [70] (2013), Canada	C-O	14	2000[2]	16	Obese 45.8 ±8.8	*N* = 8 (p[2])	*N* = 8 (PBO)	31.1 ±4.8
Faghihzadeh [71] (2015), Iran	P	84	500	50	NAFLD 44.4 ±10.1	*N* = 25 (c)	*N* = 25 (PBO)	28.3 ±3.5
Ghanim [72] (2010), USA	P	42	40	20	Healthy 36 ±5	*N* = 10 (c)	*N* = 10 (PBO)	21.8 ±0.5
Kumar [73] (2013), India	P	182	250	57	T2DM 57.7 ±8.9	*N* = 28 (c + OHAs)	*N* = 29 (OHAs only)	24.7 ±3.6
Magyar [74] (2012), Hungary	P	90	10	40	CAD (stable), 65.3 ±9.7	*N* = 20 (t)	*N* = 20 (PBO)	29.3 ±2.1
Mendez-del Villar [83] (2014), Mexico	P	90	1500	24	Met-S 30–50 years	*N* = 12 (c)	*N* = 12 (PBO)	–
Militaru [76] (2013), Romania	P	60	20	58	CAD (stable), 64.9 ±5.8	*N* = 29 (c)	*N* = 29 (Nil)	–
Movahed [77] (2013), Iran	P	45	1000	66	T2DM 52.4 ±6.1	*N* = 33 (c)	*N* = 33 (PBO)	27.1 ±3.1
Poulsen [78] (2013), Denmark	P	28	500	24	Obese 44.7 ±12.1	*N* = 12 (t)	*N* = 12 (PBO)	32.5 ±2.1
Timmers [79] (2011), Netherlands	C-O	30	150	22	Obese 52.5 ±2.1	*N* = 11 (c)	*N* = 11 (PBO)	31.5 ±2.7
Tome-Carneiro [80] (2013), Spain (*Cardiovasc Drugs Ther)*	P	365	350	50	CAD stable 60 ± 12	*N* = 25	*N* = 25	29.7 ±5.1
Van der Made [81] (2015), Netherlands	C-O	28	150	90	Obese 60 ±7	*N* = 45 (c)	*N* = 45 (PBO)	28.3 ±3.2
Yoshino [82] (2012), USA	P	84	75	30	Healthy 58.2 ±4.0	*N* = 15 (c)	*N* = 15 (PBO)	24.2 ±2.8

Age (baseline and in years), CSD – clinical study design, DUR – duration (days), RES – resveratrol (mg/dl), N – number of subjects, P – parallel, C-O – cross-over, T-P – target-population, BMI – body-mass index (kg/m²), [1]different formulation; [2]1 g/day for 1 week, then 2 g/day for 1 week, OHA – oral hypoglycaemic agents, PBO – placebo, c – capsules, p – pills, t – tablets. Faghihzadeh et al. presented data of all 50 subjects, but one patient (control group) discontinued the study because of disliking to continue and one patient (intervention group) may have been omitted from the final evaluation having body weight loss more than 10% of baseline.

of subjects in each study ranged from 16 to 90, and the concentration of RES ranged from 10 to 2000 mg/dl. The duration of RES treatment varied from 14 to 365 days. We noted some heterogeneity in the subjects recruited involving healthy subjects, obese subjects, subjects with a 'stable' CAD, individuals with T2DM, patients with non-alcoholic fatty liver disease (NAFLD), and patients with Met-S.

Statistical evaluation

The results of a mixed-effects analysis to investigate the influence of RES on the cardiometabolic risk factors are shown in Table III. Comparison of treatment with control groups revealed a positive influence of RES on the risk factors HOMA-IR (Homeostatic Model Assessment-Insulin Resistance), which resulted in a mean difference of –0.520 (95% CI: –1.127, –0.014; $p < 0.001$). The mean difference for LDL-C (mg/dl) was –0.569 (95% CI: –1.163, 0.026; $p = 0.061$), while that for T-Chol was –0.492 (95% CI: –1.073, –0.242; $p = 0.097$). The remaining cardio-metabolic risk factors did not show any significant influence of RES. Figure 2 shows the forest plots of the influence of RES on some of the studied risk factors for heart disease. The influence of RES on HOMA-IR was

Table III. Meta-analysis of resveratrol supplementation on cardiometabolic risk factors

Variable	*N*	Point estimate	Standard error	Lower limit	Upper limit	*P*-value	*Q*-value	d*f* (Q)	*P*-value (Q)	I^2
Overall:										
CRP [mg/l]	5	–0.208	0.490	–1.169	0.753	0.671	44.289	4	0.000	90.968
DBP [mm Hg]	7	–0.006	0.235	–0.466	0.454	0.980	20.879	6	0.002	71.263
Glucose [mg/dl]	13	–0.330	0.328	–0.973	0.313	0.315	126.431	12	0.000	90.509
HDL-C [mg/dl]	14	0.238	0.310	–0.370	0.846	0.443	145.031	13	0.000	91.036
HOMA-IR	8	–0.570	0.284	–1.127	–0.014	0.045	31.148	7	0.000	77.527
Insulin [µIU/ml]	10	–0.134	0.226	–0.576	0.309	0.554	33.846	9	0.000	73.409
LDL-C [mg/dl]	12	–0.653	0.354	–1.347	0.041	0.065	135.390	11	0.000	91.875
SBP [mm Hg]	8	–0.414	0.265	–0.932	0.105	0.118	31.818	7	0.000	78.000
T-chol [mg/dl]	14	–0.624	0.341	–1.291	0.044	0.067	171.272	13	0.000	92.410
TG [mg/dl]	12	–0.078	0.370	–0.804	0.648	0.834	136.418	11	0.000	91.937
Metabolic syndrome:										
CRP [mg/l]	4	–0.192	0.641	–1.448	1.063	0.764	44.289	3	0.000	93.226
DBP [mm Hg]	3	0.119	0.417	–0.698	0.936	0.775	10.274	2	0.006	80.533
Glucose [mg/dl]	4	–1.559	0.733	–2.996	–0.122	0.033	43.228	3	0.000	93.060
HDL-C [mg/dl]	7	1.235	0.585	0.088	2.382	0.035	114.981	6	0.000	94.782
HOMA-IR	2	–1.113	0.233	–1.570	–0.656	0.000	0.007	1	0.935	0.000
Insulin [µIU/ml]	2	–0.576	0.582	–1.716	0.565	0.323	5.642	1	0.018	82.277
LDL-C [mg/dl]	7	–1.175	0.583	–2.319	–0.031	0.044	118.830	6	0.000	94.951
SBP [mm Hg]	4	0.047	0.237	–0.417	0.510	0.844	5.704	3	0.127	47.404
T-chol [mg/dl]	7	–1.898	0.725	–3.318	–0.477	0.009	159.099	6	0.000	96.229
TG [mg/dl]	6	–0.744	0.771	–2.256	0.768	0.335	133.582	5	0.000	96.257
Obese healthy:										
CRP [mg/l]	1	–0.263	0.318	–0.885	0.360	0.408	0.000	0	1.000	0.000
DBP [mm Hg]	4	–0.100	0.320	–0.727	0.526	0.753	10.029	3	0.018	70.086
Glucose [mg/dl]	9	0.145	0.314	–0.470	0.761	0.643	52.751	8	0.000	84.835
HDL-C [mg/dl]	7	–0.289	0.284	–0.845	0.268	0.309	26.859	6	0.000	77.661
HOMA-IR	6	–0.381	0.337	–1.042	0.280	0.259	21.849	5	0.001	77.115
Insulin [µIU/ml]	8	–0.017	0.240	–0.488	0.454	0.944	22.113	7	0.002	68.344
LDL-C [mg/dl]	5	0.027	0.235	–0.433	0.487	0.907	8.427	4	0.077	52.536
SBP [mm Hg]	4	–0.873	0.370	–1.598	–0.149	0.018	12.212	3	0.007	75.434
T-chol [mg/dl]	7	–0.018	0.165	–0.342	0.306	0.912	9.729	6	0.137	38.331
TG [mg/dl]	6	0.104	0.150	–0.189	0.398	0.486	2.800	5	0.731	0.000

SE – standard error, N – number of studies.

overall significant. HOMA-IR involved eight studies, which yielded a mean difference of –0.520, as mentioned above. More precisely, looking at Figure 2 A, i.e. that of HOMA-IR, most of the SDs in the means for each of the nine studies examined, where this data was available, were positioned on the left side of the zero-centre line. Five studies showed no difference, and the overall summary (mean) difference for all the nine studies included in HOMA-IR analysis was negative and significant.

Table III. Cont.

Variable	*N*	Point estimate	Standard error	Lower limit	Upper limit	*P*-value	*Q*-value	d*f* (Q)	*P*-value (Q)	I^2
Both male and female:										
CRP [mg/l]	4	–0.192	0.641	–1.448	1.063	0.764	44.289	3	0.000	93.226
DBP [mm Hg]	4	–0.055	0.327	–0.695	0.585	0.866	13.435	3	0.004	77.671
Glucose [mg/dl]	8	–0.748	0.400	–1.533	0.036	0.062	81.112	8	0.000	91.370
HDL-C [mg/dl]	10	0.608	0.375	–0.128	1.344	0.105	117.445	10	0.000	92.337
HOMA-IR	3	–0.668	0.265	–1.187	–0.149	0.012	4.055	2	0.132	50.677
Insulin [µIU/ml]	5	–0.634	0.186	–0.998	–0.270	0.001	6.137	4	0.189	34.822
LDL-C [mg/dl]	9	–0.876	0.453	–1.763	0.012	0.053	123.867	9	0.000	93.541
SBP [mm Hg]	4	–0.285	0.400	–1.069	0.499	0.476	19.639	3	0.000	84.724
T-chol [mg/dl]	10	–0.930	0.461	–1.832	–0.027	0.044	165.727	10	0.000	94.569
TG [mg/dl]	8	–0.388	0.554	–1.475	0.698	0.483	134.626	8	0.000	94.800
Male:										
CRP [mg/l]	1	–0.263	0.318	–0.885	0.360	0.408	0.000	0	1.000	0.000
DBP [mm Hg]	2	–0.269	0.331	–0.917	0.379	0.415	1.561	1	0.212	35.923
Glucose [mg/dl]	4	0.847	0.804	–0.730	2.424	0.293	33.894	3	0.000	91.149
HDL-C [mg/dl]	3	–0.909	0.920	–2.711	0.894	0.323	23.361	2	0.000	91.439
HOMA-IR	4	–0.629	0.643	–1.889	0.631	0.328	23.743	3	0.000	87.365
Insulin [µIU/ml]	4	0.507	0.407	–0.291	1.306	0.213	10.872	3	0.012	72.407
LDL-C [mg/dl]	2	0.418	0.253	–0.078	0.914	0.098	0.375	1	0.540	0.000
SBP [mm Hg]	3	–0.825	0.417	–1.642	–0.009	0.048	5.797	2	0.055	65.500
T-chol [mg/dl]	3	0.057	0.224	–0.382	0.495	0.801	0.092	2	0.955	0.000
TG [mg/dl]	3	0.243	0.225	–0.198	0.685	0.280	1.213	2	0.545	0.000

SE – standard error, N – number of studies.

None of the summaries of the differences of the means for the remaining examined risk factors were significant. The LDL-C was involved in 17 studies (Figure 2 B). The influence of RES on this risk factor was negative, with a summary mean difference of –0.569 (95% CI: –10.163, 0.026; p = 0.061). Similarly, T-Chol was included in 18 studies, which arrived at a summary mean difference of –0.492 (95% CI: –1.073, –0.242; p = 0.097) (Figure 2 C).

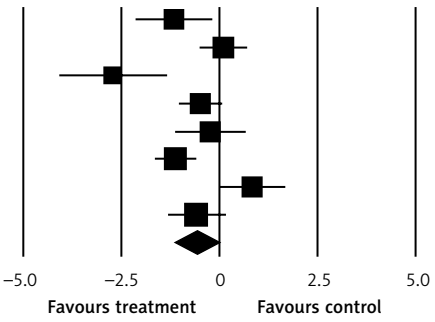
The last four columns in Table III describe the characteristics of heterogeneity in the studies. The *Q*-value for each risk factor is a sum that reflects total dispersion and depends on the number of reviews included. All the values of *Q* were highly significant. A significant amount of *Q* is evidence that the exact summated mean differences vary. In fact, for instance, the *Q*-value for HOMA-IR was 31.148 (p < 0.001). Overall, the risk factors returned moderate to high heterogeneity. The greatest heterogeneity was found among the 17 reviews of the T-Chol risk factor, yielding a *Q*-value of 171.272 (p < 0.001). The corresponding I-squared, i.e. the share of the observed variance reflecting real changes in the point estimate, was 92.4%. The lowest amount of heterogeneity resulted from the eight studies involved in DBP, with a *Q*-value of 20.879 (p = 0.002).

Comparison of the effect between Met-S with the group O/H

In the Met-S group, there was evidence of RES effect on glucose, LDL-C, and T-Chol, as detected by the mean difference of –1.069 (95% CI: –2.107, –0.032; p = 0.043), –0.924 (95% CI: –1.804, –0.043; p = 0.040), and –1.246 (95% CI: –2.314, –0.178; p = 0.022), respectively. Similarly, HOMAR-IR was significant, but the number of studies does not allow a reliable meta-analysis conclusion. The O/H group showed a significant decrease in systolic

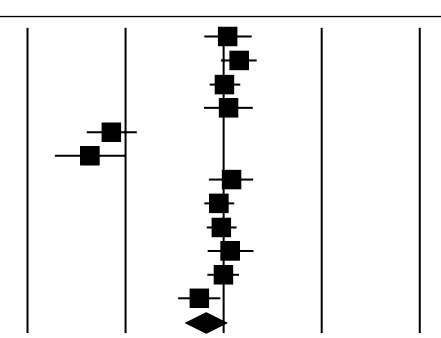
A

Study name	Statistics for each study			Sample size		Standard difference in means and 95% CI	Relative weight
	Standard difference in means	Variance	*P*-value	Treatment	Control		
Brasnyo (2011)	–1.149	0.246	0.020	10	9		11.16
Chachay (2014)	0.109	0.100	0.731	20	20		13.98
Dash (2013)	–2.706	0.479	< 0.001	8	8		8.44
Faghihzadeh (2015)	–0.476	0.082	0.097	25	25		14.43
Ghanim (2010)	–0.222	0.201	0.620	10	10		11.89
Movahed (2013)	–1.103	0.070	< 0.001	33	33		14.75
Poulsen (2013)	0.845	0.182	0.047	12	12		12.25
Yoshino (2012)	–0.571	0.139	0.125	15	15		12.25
	–0.570	0.081	0.045				



B

Study name	Statistics for each study			Sample size		Standard difference in means and 95% CI	Relative weight
	Standard difference in means	Variance	*P*-value	Treatment	Control		
Bashmakov (2014)	0.131	0.172	0.752	14	10		8.21
Chachay (2014)	0.540	0.104	0.093	20	20		8.59
Faghihzadeh (2015)	0.033	0.080	0.907	25	25		8.74
Ghanim (2010)	0.163	0.201	0.716	10	10		8.06
Kumar (2013)	–4.022	0.212	< 0.001	28	29		8.00
Magyar (2012)	–4.789	0.387	< 0.001	20	20		7.20
Mendez-del Villar (2014)	0.249	0.168	0.543	12	12		8.23
Militaru (2013)	–0.173	0.069	0.511	29	29		8.80
Movahed (2013)	–0.090	0.061	0.716	33	33		8.85
Poulsen (2013)	0.221	0.168	0.589	12	12		8.23
Tome-Carneiro (2013)	–0.022	0.080	0.938	25	25		8.74
Yoshino (2012)	–0.876	0.146	0.022	15	15		8.35
	–0.653	0.125	0.065				



C

Study name	Statistics for each study			Sample size		Standard difference in means and 95% CI	Relative weight
	Standard difference in means	Variance	*P*-value	Treatment	Control		
Bashmakov (2014)	0.464	0.176	0.269	14	10		7.34
Chachay (2014)	0.000	0.100	1.000	20	20		7.71
Dash (2013)	0.179	0.251	0.722	8	8		7.01
Faghihzadeh (2015)	0.083	0.080	0.769	25	25		7.81
Ghanim (2010)	0.813	0.217	0.081	10	10		7.15
Kumar (2013)	–21.023	3.947	< 0.001	28	29		2.17
Magyar (2012)	–3.335	0.239	< 0.001	20	20		7.06
Mendez-del Villar (2014)	0.856	0.182	0.045	12	12		7.31
Militaru (2013)	–0.139	0.069	0.598	29	29		7.87
Movahed (2013)	–0.122	0.061	0.621	33	33		7.91
Poulsen (2013)	0.070	0.167	0.864	12	12		7.38
Tome-Carneiro (2013)	–0.172	0.080	0.543	25	25		7.81
Van der Made (2015)	–0.051	0.044	0.810	45	45		8.00
Yoshino (2012)	–0.980	0.149	0.011	15	15		7.46
	–0.624	0.116	0.067				

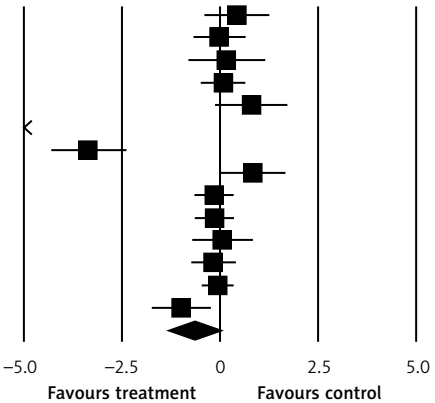


Figure 2. A – Forest plots of the of the influence of resveratrol (RES) on heart disease risk factors targeting the homeostatic model assessment-insulin resistance (HOMA-IR). **B** – Forest plots of the of the influence of resveratrol (RES) on heart diseases risk factors targeting the low-density lipoprotein-cholesterol (LDL-C) (mg/dl). **C** – Forest plots of the of the influence of resveratrol (RES) on heart diseases risk factors targeting the total cholesterol (T-chol) (mg/dl). The last row in the study name column refers to the overall evaluation

blood pressure (SBP) in the presence of RES by –0.873 (95% CI: –1.598, –0.149; $p = 0.018$). In the presence of RES, glucose insignificantly increased among the O/H group (mean difference = 0.145; 95% CI: –0.470, –0.761; $p = 0.643$), while it significantly decreased among the Met-S group. In fact, in the Met-S group, RES reduced the glucose level of –1.069 (95% CI: –2.107, –0.032; $p = 0.043$).

Comparison of RES effects across gender groups

The influence of RES on the risk factors for CVD was examined under female, male, and mixed-sex categories. The female group contained one female-only RCT study, which was insufficient to run a meta-analysis. Regarding the male group, none of the summaries of the mean differences were significant. Conversely, within the mixed-gender group, three risk factors showed significant effects of RES, including HOMA-IR, LDL-C, and insulin. The influence of RES on HOMA-IR involved three studies, which yielded a mean difference of –0.668 (95% CI: –1.187, –0.149; p = 0.012). The LDL-C (mg/dl) included 10 studies. The influence of RES on LDL-C was negative, with a summary mean of –0.827 (95% CI: –1.604, –0.049; p = 0.037). Insulin comprised five studies, with a summary mean of –0.634 (95% CI: –0.998, –0.270; p = 0.001). The insignificant and relatively low values of Q for HOMAR-IR and insulin could be attributed to lack of heterogeneity or low precision due to the small number of studies included.

Publication bias assessment

One of the major issues in our meta-analysis was to ensure that point estimates were not computed from a biased collection of studies. The benefit is that exaggeration of the true effect size of treatment can be avoided. Hence, we assessed how many biases could be present in our meta-analysis and examined their potential impact on our findings. We used Egger's method of bias assessment, which recommends the use of the inverse of the SE, i.e. precision, to predict the standardised effect size. We found that the intercept (B_0), which is used for capturing the bias, was not significant: 0.541 (95% CI: –3.367, 4.449; 1-tailed p-value = 0.386). We estimated the impact of the bias using Duval and Tweedie's method, which may suggest imputation of missing studies. Following the random effects model and without affecting any changes, the summary (mean) difference for the combined studies was –0.196 (95% CI: –0.341, –0.050). We applied the trim-and-fill method [87, 88], a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analyses (Figure 3). The summary (mean) difference was –0.240 (95% CI: –0.384, –0.097). Hence the absolute value of the difference between imputed and non-imputed was –0.054, which means that the corrected method arrived at a slightly lower mean difference compared to the original analysis. There may be a bias, but its impact would be minor regarding RES input difference in the context of our study. In other words, the inclusion of only relevant studies might shift the results probably without changing the key findings [79].

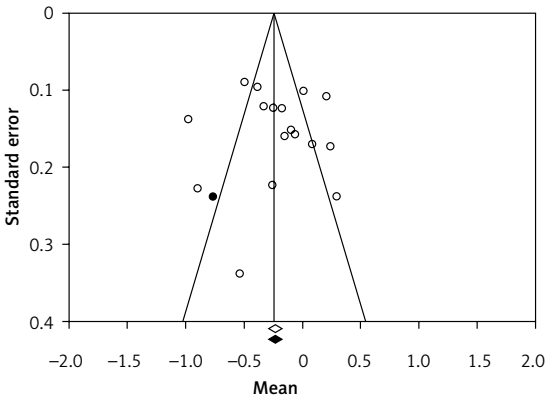


Figure 3. Publication bias plot

Discussion

Numerous studies have shown that RES may protect against CVD through several potential mechanisms. These studies, reviewed initially by Sahebkar [45] in 2013, include downregulation of proinflammatory cytokines, inhibition of LDL oxidation, improved insulin sensitivity, lowering of arterial blood pressure, inhibition of platelet aggregation, improvement of the endothelial function, as well as circumvention of cardiac hypertrophy/fibrosis. The molecular mechanisms of protective effects of RES may include the activations of SIRT-1 and AMPK, and inhibitions of cyclooxygenases and NF-κB in the downregulation of pro-inflammatory stimuli, as observed in Met-S and liver tumours [32, 35]. Despite the promising results of targeting complex array of signalling pathways in pre-clinical studies, conflicting results have been observed in some RCTs [89]. Sahebkar [45, 46] showed a lack of efficacy of RES antagonising CRP and on selected CVD risk factors, while Hausenblas *et al.* [49] showed positive effects on SBP and creatinine.

In this systematic search to conduct a meta-analysis, the effects of RES supplementation were evaluated through an analysis of 22 RCTs with 800 subjects. It seems plausible to suggest that RES supplementation positively influences HOMA-IR, LDL-C, and T-Chol. Our investigation may have several strengths. We conducted a comprehensive search, assessed inclusion and exclusion criteria, and with the scrutiny of careful perused available datasets, divided the studies into two groups. Exclusion criteria included studies that were duplicated, showed overlapping, and, according to the authors, were considered non-relevant. All studies were evaluated singly and scored by three authors (BoC, JF, BrC), and any inclusion or exclusion needed to have full consensus. It is conceivable that some studies used in other me-

ta-analyses were not included in this investigation. Despite these discordances, the choice to include a specific study was derived from the careful examination of the articles. It is also predictable that articles subsequent to our systematic search may add value to the meta-analysis. We would also be interested in including studies published after this research was concluded, but this would require more investigation and perusal of articles. It is not feasible because the three independent authors are currently located in different places, and changing the consensus would introduce some bias to the study. On the other hand, we would consider appropriate discussion of some of the most recent studies that are extremely relevant to our investigation.

It is useful to mention some of the most relevant studies. A meta-regression analysis based on 17 studies, which is a tool used in meta-analysis to examine the impact of moderator variables on study effect size using regression-based techniques, revealed a positive association between systolic BP-lowering RES activity BMI at baseline [90]. In this Italian study, Fogacci *et al.* found that RES was moderately well-tolerated without serious adverse events in most of the eligible trials [90]. These authors suggest that RES may promote cardiovascular health, mostly when used in high daily dose (≥ 300 mg/day) and in diabetic patients. Akbari *et al.* evaluated 28 RCTs and showed that RES intervention significantly increased the levels of flow-mediated dilatation among patients with MetS and related disorders, but RES supplements did not affect systolic blood pressure and diastolic blood pressure [91]. Using a variation on the inverse-variance method to incorporate an assumption that the different studies are evaluating different, but related, intervention effects, Asgary *et al.* found a significant impact of RES supplementation on glucose level and waist circumference compared with the control group. Also, these authors combined the results of studies on rat samples showing a net effect of RES on decreasing weight and systolic blood pressure. According to these authors, it can influence significantly the increasing HDL level but was not significantly effective on total cholesterol. The significative effect was seen at the dosage of greater than 500 mg and with long-term interventions equal to or more than 10 weeks [92]. Zhao *et al.* evaluated 10 randomised controlled trials, including eight randomised, parallel, controlled studies and two crossover-controlled studies [93]. The results on 363 patients with type 2 diabetes mellitus showed that longer RES supplementation (≥ 6 months) can reduce triglyceride levels, but there was an increase of total cholesterol in patients within obesity range undergoing RES supplementation. Mousavi *et al.* performed a meta-analysis including 28 trials, with data suggesting that there is an effect of RES on weighted mean differences, BMI, and waist circumference [94]. No significant effect of RES supplementation on fat mass was found. A significant reduction was detected for dosage of < 500 mg/day, long-term interventions (≥ 3 month), and on people with obesity. It may be part of a personalised therapy [95, 96]. Substantially, there are many nutraceuticals described in medical literature and Chinese traditional medicine with different levels of effectiveness and evidence on lowering the cardiometabolic risk in patients with metabolic syndrome [97], but RES is probably one of the most studied compounds. Nevertheless, RES seems to improve the lipid metabolic levels or other cardiometabolic risks only in some patients affected with metabolic syndrome, suggesting that personalised medicine and a personalised approach should be a line of action in these patients.

Our document is not a systematic review discussing the outcomes of the single studies, but we considered some biochemical values that have been evaluated and clinical definitions that are being updated. Our evaluation may help in supporting the use of RES in health policies in the second half of the 21st century. A meta-analysis is not a final study but has a temporary value according to the definitions used in the period of data collection. In the future, more uniformity would be advisable to perform a meta-analysis. However, our meta-analysis may show some beneficial influence of RES supplementation on cardiometabolic risk factors in subjects with Met-S with CVD, while RES supplementation to O/H individuals without cardiometabolic risk factors failed to demonstrate any significant change. Our results seem to be in contrast with some previous evidence [45], although a separation of the 10 RCTs of mixed cardiometabolic risks did not occur in previous studies. In line with our results, some positive effects of RES supplementation for SBP, and creatinine in T2DM, were found in another study [49]. Our investigation included more reviews than those involved in Hausenblas *et al.* [49]. Our study seems to provide some evidence for the benefits of RES supplementation in patients with cardiometabolic risk factors.

On the other hand, our investigation has some limitations, including the variable size of the groups in the single studies, ranging from 16 to 90 subjects, some heterogeneity of the target population, the variable study duration (14 through 365 days), and the exclusion of non-English language texts. Also, some of the most recent literature data were not included, but expanding the meta-analysis may not have made a difference, because we have seen in this literature different inclusion criteria with groups ranging quite vari-

ably. Moreover, RES supplementation was used in different formulations, including modified RES supplementation [86], grape extract RES [80, 84, 98], and purified extract of *Polygonum cuspidatum* containing RES [72], among others, with a dosage ranging from 10 to 2000 mg/day, therefore leaving the optimal choice of dose, duration, and even the RES preparation open to debate. While there are many individuals living healthy lives in North America despite an obese status, the metabolic/physiological responses to RES may be different between obese and non-obese individuals. Although it may be difficult to consider an overweight subject as healthy, there is some evidence that fat and non-obese are metabolically entirely equivalent. Currently, the category healthy/obese in some countries is an actual part of the general population. Overweight and obesity have reached epidemic proportions in some countries, not only in the USA, but increasing in Europe, Asia, and Africa. The very high prevalence of class III obesity (BMI $\geq$ 40 kg/m^2) is concerning, having reached 3% in the USA. Recently some controversy has encircled the idea that some obese subjects can be considered healthy regarding their metabolic and cardiorespiratory fitness, which has been termed the 'obesity paradox'. There is apparently a very favourable prognosis in patients with obesity, who have no identifiable metabolic abnormalities and who have preserved some of their fitness [99]. In our study, we did not consider HbA_{1c} because of the heterogeneity of the time frame identified in several studies. Because HbA_{1c} is a measure of average plasma glucose concentration over a 3-month period, we could not examine studies of at least 3-months duration accurately (at a minimum) to be evaluated in our meta-analysis. In the future, we would like to review studies with a uniform dosage of RES and a uniform duration of treatment. Both conditions may allow more uniformity in the evaluation of the role of RES in decreasing the risk of significant cardiovascular complications.

In conclusion, despite the limitations that we have mentioned above, we consider that RES supplementation may improve cardiometabolic health, decreasing some risk factors (HOMA-IR, LDL-C, and T-Chol) associated with CVD in some patients, and it should be part of personalised medicine.

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Conflict of interest

The authors declare no conflict of interest.

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