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The effect of grape products containing polyphenols on C-reactive protein levels: a systematic review and meta-analysis of randomised controlled trials

Sahar Sarkhosh-Khorasani[1,2] and Mahdieh Hosseinzadeh[1,2]*

[1]*Department of Nutrition, Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, 8915173160, Iran*

[2]*Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, 8915173160, Iran*

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Abstract

Although grape polyphenols can decrease chronic inflammations, their effect on C-reactive protein (CRP) levels is still controversial. So, this meta-analysis was conducted to investigate the effect of grape products containing polyphenols on CRP concentrations. In order to collect the relevant randomised controlled trials (RCT), the databases of PubMed, Scopus, Web of Science and Google Scholar were searched up to 30 March 2020. The random effects model, standardised mean difference (SMD) and 95 % CI were applied in data analysis. Meta-analysis was conducted over seventeen eligible RCT containing a total of 668 participants. The study registration number is CRD42018110169. Based on the results, grape products containing polyphenols decreased CRP levels significantly (SMD = −0·229; 95 % CI −0·41, −0·05; $P = 0·013$). Sensitivity analysis was performed by removing each individual study and the results did not change. According to the subgroup analysis, higher doses of grape polyphenols (>500 mg/d) and longer intervention periods (≥12 weeks) had significant effects on CRP levels. Furthermore, grape polyphenols significantly reduced the CRP levels in patients with a clinical condition. In the same vein, grape seed extract and other grape products, such as grape extract, juice and raisins, decreased CRP levels significantly. According to the meta-regression results, the CRP level depends on the dose and duration of the grape polyphenol supplementation. Based on the findings, grape products containing polyphenols had a significant effect on CRP levels. Further well-designed and long-term clinical trials are highly recommended to achieve more comprehensive and accurate results.

Key words: **Grape seed extract: Polyphenols: C-reactive protein: Systematic reviews: Meta-analyses**

Inflammation is a set of complex changing responses that protects the body against cell and tissue damages. It also eliminates or suppresses the harmful pathogens, such as bacteria, trauma, chemicals or other destructive substances[1,2]. Inflammation is a physiological response of the immune system that promotes the healing and regeneration processes[1,2]. The process of inflammation involves two phases: (1) the process of acute inflammation by oedema and emigration of leucocytes and (2) chronic patterns of inflammation in the presence of lymphocytes and macrophages along with proliferation of blood vessels, fibrosis and tissue necrosis[3]. Chronic and prolonged inflammation can be harmful and may lead to chronic diseases, such as CVD[4], type 2 diabetes, insulin resistance[4,5], the metabolic syndrome (MetS)[6] and different kinds of cancers[4,7,8].

Literature analysis showed that inflammation was usually characterised by regional vascular dilatation, increased blood flow, increased vascular penetration, release of fluid into the interstitial space, increased fibrinogen and coagulation, as well as migration of granulocytes and monocytes into the injured tissue[9–11]. In response to inflammation, different vessels and immune cells are involved in a series of cascading events[12]. C-reactive protein (CRP) is an acute-phase protein synthesised by the liver cells in response to inflammation[13] and a predictor of CVD[14]. The CRP is also one of the most important biomarkers because it is better suited to studying the relationship between inflammation and CVD[15,16] than cell adhesion molecules, specifically cytokines or fibrinogen, which may cause inflammatory situations[17]. Furthermore, findings showed the extra hepatic production of CRP in different cells, including peripheral mononuclear cells[18], human coronary artery smooth muscle cells[19], human neurons[20], kidney epithelial cells[21] and atherosclerotic lesions[22]. Based on some studies, CRP bond with bacterial ligands, damage tissues, prevent them from binding with FC receptors and improve inflammatory processes[23,24]. Furthermore, CRP is a systemic sensitive index for evaluating inflammation and a valid predictor biomarker in disorders with inflammatory-involved processes[25–29]. In several randomised controlled trials (RCT), grape and its products had positive effects

Abbreviations: CRP, C-reactive protein; GSE, grape seed extract; MetS, metabolic syndrome; RCT, randomised clinical trial; SMD, standardised mean difference.

* **Corresponding author:** Mahdieh Hosseinzadeh, email hoseinzade.mahdie@gmail.com

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on disorders with inflammatory process, such as CVD[30,31], type 2 diabetes, insulin resistance[32,33] and the MetS[34–36]. These beneficial effects are mainly due to the polyphenols contained in grape and its products[2]. Various phenolic compounds have been found in grape skin, flesh and seed[37], which mainly include anthocyanins, flavanols, stilbenes (resveratrol) and phenolic acids[38,39]. The phenolic compounds of the grape have anti-inflammatory properties[2]. Expression of CRP in the liver is related to TNF-α, IL-6 and IL-1, which are directly secreted from visceral fat tissues to the liver portal system[40]. Grape polyphenols, especially flavanols, inhibit the pro-inflammatory cytokines or endotoxin-mediated kinases and transcription factors involved in the metabolic diseases[41]. This process results in suppressing inflammatory cytokines[41–43] and ultimately reduces expression of the CRP gene[42,44].

Some animal studies showed positive effects of grape polyphenols on the reduction of CRP concentrations[44–46]. The results of RCT are contradictory with regard to the effects of different grape products containing polyphenols on the CRP levels. For example, in a crossover study, consumption of 600 mg of grape seed extract per d for 4 weeks significantly reduced high-sensitivity CRP in thirty-two participants with type 2 diabetes[47]. Moreover, in a study on 115 people with diabetes and a recent history of myocardial infarction, consumption of red wine decreased the CRP levels significantly[48]. Similarly, polyphenol compounds of grape products significantly decreased CRP levels in other studies[49–55]. However, some other studies indicated that consuming 60 g of grape powder rich in polyphenols for 10 weeks had no significant effect on healthy participants with obesity[56]. Furthermore, taking 90 g of raisins (containing 138·5–221·5 mg polyphenols) per d for 4 weeks had no significant effect on CRP levels[57]. Other studies also found no significant effect of grape polyphenols on CRP levels[58–74].

Although some clinical trials were carried out over the effect of grape polyphenol supplementation on CRP levels, no consistent evidences exist on the effectiveness of grape polyphenols. In addition, no systematic review and meta-analysis has ever been conducted in this area. Thus, the aim of this systematic review and meta-analysis was to summarise the overall effect of grape products containing polyphenols on CRP concentrations. In addition, we assessed the effects of different dosage and duration of supplementation. To hit this target, polyphenol-containing grape products were categorised into grape extract, grape seed extract (GSE), grape powder, juice, red wine and raisins. Moreover, participants were categorised into healthy individuals and patients with a clinical condition.

Materials and methods

Search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines[75].

The protocol of the present study was registered in PROSPERO, an International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO) with the registration number of CRD42018110169.

We searched online databases, including PubMed (http://www.pubmed.com), ISI Web of Science (http://www.webofknowledge.com), Scopus (http://www.scopus.com) and Google Scholar (http://www.scholar.google.com) up to 30 March 2020 without any restrictions. The comprehensive search strategy was conducted using following keywords and medical subject heading terms: 'Polyphenols', 'Grape', 'grape seed', 'grape seed extract', 'wine', 'C-Reactive Protein', 'CRP', 'Inflammation', 'inflammatory mediators', 'Anti-Inflammatory Agents', combined with 'Intervention Studies', 'intervention', 'controlled trial', 'randomized', 'randomised', 'random', 'randomly', 'placebo' and 'assignment'. We used Boolean operators (AND and OR) to connect the aforementioned terms (supporting information). To widen our search scope, the trial registries of Iranian Registry of Clinical Trials and Clinical Trials.gov were checked to identify unpublished trials in this context. Additionally, reference lists of the related original and review articles were carefully checked to obtain other eligible studies.

To ensure about comprehensiveness of the searches, we checked the references of all included studies manually for any possible further sources.

Eligibility criteria

The selected studies for this meta-analysis: (1) were original articles with an RCT design; (2) evaluated the effect of grape products containing polyphenols on CRP levels compared with the placebo or other interventions; (3) reported the dose of grape products; (4) did not administer grape product with other products or special diets; (5) used participants with 18 years of age or higher; (6) lasted 3 weeks or more; (7) reported the CRP level as the primary or secondary measure; and (8) were in English.

Study selection

Two authors (S. S.-K. H. and M. H.) separately performed the initial screening according to the articles' titles and abstracts to avoid missing articles. In the next step, the full texts of all related articles were investigated by researchers to select studies that investigated the effect of grape products containing polyphenols on CRP levels. Moreover, Hassan Mozaffari-Khosravi checked the findings and resolved the disagreements by discussion (Fig. 1).

Data extraction

At this stage, S. S.-K. H. and M. H. summarised the articles' data including author's family name, year of publication, sample size, dose and type of intervention, duration of study, type of study (crossover or parallel study design), participants' sex and age, healthy status of participants, as well as the mean and standard deviations of CRP concentration in the intervention and control groups at the baseline and end of the studies. The collected information was double checked by Hassan Mozaffari-Khosravi.

Quality assessment

Two researchers (S. S.-K. H. and M. H.) independently evaluated the methodological quality of the included articles according to the Cochrane risk of bias tool. Any disagreement was resolved through consensus or consultation with another researcher

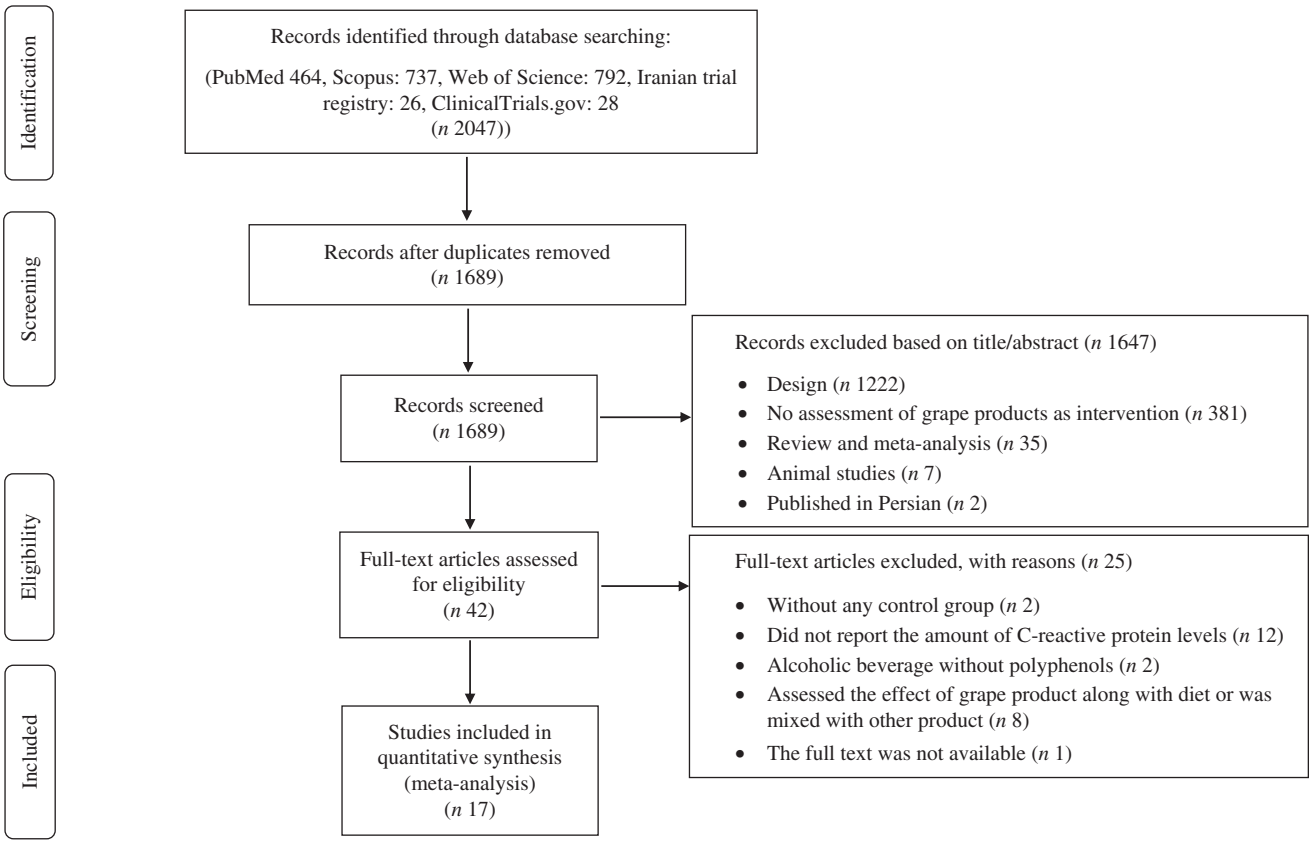

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) flow diagram of study selection process.

(Hassan Mozaffari-Khosravi). The risk of bias in the included RCT was assessed according to the Cochrane Collaboration's tool, including six domains of: (1) sequence generation; (2) allocation and concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; and (6) selective reporting. Each domain was classified into three categories: low risk of bias, high risk of bias and unclear risk of bias[76].

NutriGrade

The present meta-analysis examined the effect of grape products containing polyphenols on CRP levels. The overall quality of the present study was evaluated by the NutriGrade scoring system (maximum of ten points)[77]. The following items were considered for meta-analyses of the RCT: (a) risk of bias, (b) precision, (c) heterogeneity, (d) directness, (e) publication bias, (f) funding bias and (g) study design. The credibility of evidence was evaluated as (a) high (≥8 points), (b) moderate (6–7·99 points), (c) low (4–5·99) and (d) very low (0·3–3·99 points).

Data synthesis and analysis

To calculate the effect size for each parameter, the mean changes and standard deviations of the intervention and control groups/periods were extracted from each study. These rates were used to estimate the mean difference and its corresponding standard error. Standardised mean difference (SMD) was defined as the effect size. Later, SMD was calculated after dividing mean by standard deviation. In studies that reported the standard error value, SE was converted into SD as follows: $SD = SE \times \sqrt{n}$ (n = number of participants in each group). In order to incorporate between-study variation, a random effects model was used to calculate the SMD with 95 % CI for conducting the meta-analysis. Between-study heterogeneity was tested by Cochran's Q test and quantified by the I^2 statistic, where a significant Q test ($P < 0{\cdot}05$) and a value for $I^2 > 75$ % were considered to indicate considerable heterogeneity[78]. Subgroup analysis was conducted to explore the possible source of heterogeneity among the studies. Publication bias was also evaluated by examining the funnel plot and formal testing for 'funnel plot' asymmetry using Begg's test and Egger's test, respectively[79]. Sensitivity analysis was performed to identify the effect of an individual study or a particular group of studies on the findings[79]. If the results differ across sensitivity analyses, this is an indication that the result may need to be interpreted with caution[79]. Moreover, sensitivity analysis was conducted to explore the impact of excluding each study on the overall results. Statistical analyses were conducted using STATA version 11.2 (StataCorp.). The statistically significant level was set at P values < 0·05.

Meta-regression

Meta-regression was performed in order to evaluate the association of estimated effect size with grape polyphenol dose and duration of trial.

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Results

Study selection and characteristics

Our search throughout the databases of Google Scholar, PubMed, Web of Science, Scopus, Iranian trial registry and ClinicalTrials.gov resulted in a total of 2024 articles. The search strategy is shown in online Supplementary material. After removing the duplicate studies and screening the included articles' titles and abstracts, 1689 papers remained. Later, 1647 other studies were excluded since they had not RCT design (*n* 1222), did not evaluate the effect of grape products as interventions (*n* 381) and they were animal studies (*n* 7), review/meta-analysis studies (*n* 35), and in Persian (*n* 2). Full texts of the remaining articles were reviewed and twenty-five papers were excluded since: they did not have control group[80,81], did not report the amount of CRP levels[82–93], contained alcoholic beverage without polyphenols[94,95], assessed the effect of grape product along with a diet[96–98] or with other products[99–103], its full text was not available although an email that was sent to the corresponding author[104]. Therefore, seventeen studies were included in our systematic review and meta-analysis (Fig. 1).

Characteristics of all studies investigated in our systematic review and meta-analysis are indicated in Table 1. All studies were published from 2004 to 2018. A total of 668 participants were investigated in these studies: 469 individuals in the intervention and 429 people in the control groups. Regarding the place of studies, seven studies were conducted in Europe[51,57,61,62,64,71,72], three in Australia[58,63,69], five in America[56,65–67,70] and two studies were carried out in Asia[68] and Africa[59]. All studies were randomised controlled trials with parallel or crossover design. All studies were conducted within 4–24 weeks and the doses of grape polyphenols were from 22·4 mg/d to 2000 mg/d. In addition, grape products containing polyphenols were administered in several forms of GSE[58,59,61,65], grape powder[56,67,68,70], red wine[51,63,64,69,72], raisins[57], grape juice[66], grape extract[71] and grape polyphenols[62].

Quality assessment of studies

We assessed quality of our included studies according to the Cochrane risk of bias tool (Table 2). Six of our included studies described random sequencing generation[57,62,63,69] but a lack of information was found in this regard in the other studies. Allocation concealment was performed in four studies[57,62,63,69]. Moreover, most of the studies had a low risk for blinding of participants except four studies which had unclear risk because they did not mention about blinding procedure[58,63,69,72], and incomplete outcome data were addressed in all of the studies except one study[57]. Outcome assessors were unclear in most of the studies, while all the studies had a low risk for selective outcome reports. The details of the risk of bias assessment in individual studies are presented in Table 2.

NutriGrade

The overall quality of the present meta-analysis using the NutriGrade scoring system resulted in the total score of 5 for the meta-analysis of the effect on circulating CRP levels; accordingly, the quality of evidence for an effect of polyphenols on CRP is low. This score indicating low confidence in the effect estimate, which shows further research, will provide important evidence on the confidence and likely change the effect estimate.

The effect of grape products containing polyphenols on C-reactive protein levels

As a result, seventeen studies were included in the meta-analysis. Only one study indicated that grape products containing polyphenols had a significant reduction effect on CRP levels. Finally, our pooled analysis demonstrated that high intakes of grape products containing polyphenols were associated with lower concentrations of CRP (SMD = −0·229; 95 % CI −0·41, −0·05; $P = 0·013$) (Fig. 2). Moreover, in our study, overall result was not affected by the removal of any particular study. So, the results can be considered robust as even with different decisions they remain the same/similar (online Supplementary Fig. S1). A significant heterogeneity was observed between studies (Cochran's Q test, Q statistic = 397·07, $P < 0·001$, I^2 95·97).

Subgroup analysis

The results of subgroup analysis are shown in Table 3 and the forest plots are shown in Figs. 3–7.

Subgroup analysis based on health status. Higher concentrations of grape polyphenols could significantly decrease CRP levels in patients with a clinical condition (healthy subject: SMD = −0·166; 95 % CI −0·49, 0·16; $P = 0·315$, Cochran's Q test, Q statistic = 374·75, $P < 0·001$, I^2 98·13; patients with a clinical condition: SMD = −0·204; 95 % CI −0·31, −0·10; $P < 0·001$, Cochran's Q test, Q statistic = 18·39, $P = 0·018$, I^2 56·50) (Fig. 3).

Subgroup analysis based on study duration. Also, grape polyphenols could significantly decrease the concentration of CRP in studies with duration of above 12 weeks (<12 weeks: SMD = −0·037; 95 % CI −0·33, 0·26; $P = 0·804$, Cochran's Q test, Q statistic = 98·76, $P < 0·001$, I^2 93·92; ≥ 12 weeks: SMD = −0·333; 95 % CI −0·53, −0·13; $P = 0·001$, Cochran's Q test, Q statistic = 184·25, $P < 0·001$, I^2 95·11) (Fig. 4).

Subgroup analysis based on study design. In parallel studies, grape polyphenols have a significant decreasing effect on the CRP concentration (crossover: SMD = −0·176; 95 % CI −0·38, 0·03; $P = 0·098$, Cochran's Q test, Q statistic = 381·91, $P < 0·001$, I^2 97·64; parallel: SMD = −0·400; 95 % CI −0·80, −0·002; $P = 0·049$, Cochran's Q test, Q statistic = 12·51, $P = 0·05$, I^2 52·04) (Fig. 5).

Subgroup analysis based on doses of grape polyphenols. Besides, a significant lowering on the concentration of CRP was found in higher dose of grape polyphenols (≤500 mg/d: SMD = −0·160; 95 % CI −0·42, 0·10; $P = 0·224$, Cochran's Q test, Q statistic = 149·24, $P < 0·001$, I^2 94·64; >500 mg/d: SMD = −0·288; 95 % CI −0·53, −0·05; $P = 0·019$, Cochran's Q test, Q statistic = 177·94, $P < 0·001$, I^2 96·06) (Fig. 6).

Subgroup analysis based on type of grape products. Moreover, among different kinds of grape products, GSE and other kinds of grape products (raisins, grape polyphenols, grape extract and

Table 1. Study design and participants' characteristics included in the meta-analysis*
(Mean values and standard deviations)

Study	Intervention product	Country	RCT design	Health status of participants	Age of participants (years)	Sex of participants		BMI of participants (kg/m^2)	Control product	Dose of GPCP (g/d)	Total polyphenols (mg/d)	Period (week)	CRP levels (mg/l)
						M	F						
Bardagjy *et al.*[56]	Grape powder	USA	Crossover	Healthy obese	Total: 48·6 (SD 15·4)	4	16	Total: 37 (SD 9·9)	Placebo	60	297	10	INT pre: 5·4 (SD 5·5) INT post: 6·7 (SD 7·7) CON pre: 6·1 (SD 6·2) CON post: 6·7 (SD 6·5)
Barden *et al.*[69]	Red wine	Australia	Crossover	Healthy subjects	Total: 54·1 (SD 6·6)	22	0	Total: 27·5 (SD 2·9)	Water	375	891·75	12	INT pre: 1·36 (SD 0·3) INT post: 1·27 (SD 0·3) CON pre: 1·36 (SD 0·3) CON post: 1·14 (SD 0·3)
Kanellos *et al.*[57]	Raisins	Greece	Parallel	Healthy smokers	Intervention: 30·8 (SD 7·5)/control: 29·8 (SD 5·23)	27	9	Intervention: 24·4 (SD 2·81)/control: 24·4 (SD 2·99)	No raisins	90	178·75	4	INT pre: 1·9 (SD 1·41) INT post: 2·7 (SD 3·29) CON pre: 1·5 (SD 2·25) CON post: 2 (SD 3)
Turki *et al.*[59]	GSE	Tunisia	Parallel	CKD patients	Intervention: 62·3 (SD 9·10)/control: 62·7 (SD 7·58)	19	14	NR	Placebo	2	2000	24	INT pre: 1·8 (SD 2·4) INT post: 2·9 (SD 1·44) CON pre: 1·8 (SD 0·95) CON post: 3·3 (SD 0·63)
Mori *et al.*[63]	Red wine	Australia	Crossover	T2D men and postmenopausal women	Total: 59·3 (SD 5·6)	19	5	Total: 29·3 (SD 4·8)	Water	Men: 300 Women: 230	689	12	INT pre: 1·66 (SD 0·365) INT post: 1·388 (SD 0·278) CON pre: 1·66 (SD 0·365) CON post: 1·36 (SD 0·345)
Vaisman *et al.*[68]	Red grape cell powder	Israel	Parallel	Pre-/mild hypertension	Intervention: 57·6 (SD 7·2)/control: 56·4 (SD 7·0)	32	14	Intervention: 26·4 (SD 3·0)/control: 26·3 (SD 4·1)	Placebo	0·4	22·4	12	INT pre: 1·6 (SD 1·8) INT post: 1·8 (SD 2) CON pre: 2·2 (SD 2) CON post: 1·9 (SD 1·7)
Zunino *et al.*[67]	Grape powder	USA	Crossover	Healthy obese	M: 37·1 (SD 10·5) F: 34·7 (SD 13·9)	8	16	M: 36·6 (SD 4·4) F: 36·9 (SD 5·3)	Placebo powder	92	62·24	9	INT pre: 8·43 (SD 10·14) INT post: 11·12 (SD 15·07) CON pre: 8·43 (SD 10·14) CON post: 7·81 (SD 8·89)
Janiques *et al.*[70]	Grape powder	Brazil	Parallel	Non-diabetic HD patients	Intervention: 53·0 (SD 9·8)/control: 52·7 (SD 13·7)	18	14	Intervention: 22·0 (SD 2·1)/control: 22·6 (SD 3·6)	Placebo	12	500	5	INT pre: 26 (SD 3) INT post: 27 (SD 3) CON pre: 26 (SD 3) CON post: 28 (SD 2)
Hokayem *et al.*[62]	Grape polyphenols	France	Parallel	Healthy obese	Intervention: 49·7 (SD 8·49)/control: 48·4 (SD 7·74)	18	20	Intervention: 29·3 (SD 2·68)/control: 29·1 (SD 2·70)	Placebo	2	2000	9	INT pre: 2·5 (SD 1·79) INT post: 2·1 (SD 1·34) CON pre: 2·4 (SD 2·55) CON post: 2·3 (SD 2·55)
Tomé-Carneiro *et al.*[71]	Grape extract	Spain	Parallel	T2D and hypertensive	Total: 60 (SD 11)	35	0	Total: 31·3 (SD 4·7)	Placebo	0·35	350	24	INT pre: 3·3 (SD 1·2) INT post: 3 (SD 1·2) CON pre: 3·9 (SD 2·4) CON post: 4·5 (SD 1·8)
Chiva-Blanch *et al.*[64]	Red wine	Spain	Crossover	High risk of CVD men	Total: 60 (SD 8)	67	0	Total: 29·6 (SD 3·9)	Gin	272	318	12	INT pre: 2·18 (SD 0·31) INT post: 2·17 (SD 0·33) CON pre: 2·18 (SD 0·31) CON post: 2·15 (SD 0·28)
Weseler *et al.*[61]	GSE	Netherlands	Parallel	Non-obese smokers	Intervention: 45 (SD 8·10)/control: 46·5 (SD 8·70)	28	0	Intervention: 24 (SD 3·87)/control: 25 (SD 3·60)	Placebo	0·2	200	8	INT pre: 2·5 (SD 1·756) INT post: 2·5 (SD 1·756) CON pre: 1·75 (SD 1·507) CON post: 2 (SD 1·826)

Table 1. (*Continued*)

Study	Intervention product	Country	RCT design	Health status of participants	Age of participants (years)	Sex of participants		BMI of participants (kg/m^2)	Control product	Dose of GPCP (g/d)	Total polyphenols (mg/d)	Period (week)	CRP levels (mg/l)
						M	F						
Dohadwala *et al.*[66]	Concord grape juice	USA	Crossover	Mild/pre-hypertension	Intervention: 41 (SD 13)/control: 44 (SD 11)	44	20	Intervention: 28·0 (SD 3·8)/control: 28·0 (SD 3·9)	Placebo beverage	595	1172	12	INT pre: 1·1 (SD 0·525) INT post: 0·8 (SD 0·525) CON pre: 1·2 (SD 0·575) CON post: 1·4 (SD 0·85)
Mellen *et al.*[65]	GSE	USA	Crossover	Patients with CVD risk	Total: 52·1 (SD 8·1)	25	25	Total: 29·8 (SD 6·0)	Placebo	1·3	1300	14	INT pre: 15·4 (SD 8·5) INT post: 13·8 (SD 8·5) CON pre: 14·9 (SD 9·2) CON post: 12·8 (SD 8·5)
Retterstol *et al.*[72]	Red wine	Norway	Crossover	Healthy subjects	Total: 50·2 (SD 9·6)	30	57	Total: 25·9 (SD 9·7)	Abstention	150	390	6	INT pre: 0·86 (SD 1·19) INT post: 1·04 (SD 0·9) CON pre: 0·86 (SD 1·19) CON post: 0·91 (SD 1·07)
Estruch *et al.*[51]	Red wine	Spain	Crossover	Healthy subjects	Total: 37·6 (SD 7·4)	40	0	NR	Gin	320	832	12	INT pre: 1·63 (SD 0·97) INT post: 1·28 (SD 1·02) CON pre: 1·56 (SD 1·21) CON post: 1·32 (SD 1·15)
Clifton *et al.*[58]	GSE	Australia	Crossover	Patients with above-average vascular risk	Total: 58	24	11	Total: 28·4	Control yogurt	2	1000	12	INT pre: 3·63 (SD 5·01) INT post: 3·4 (SD 3·53) CON pre: 3·63 (SD 5·01) CON post: 3·73 (SD 4·64)

RCT, randomised controlled trial; M, male; F, female; GPCP, grape products containing polyphenols; CRP, C-reactive protein; INT, intervention; CON, control; GSE, grape seed extract; CKD, chronic kidney disease; NR, not reported; T2D, type 2 diabetes; HD, haemodialysis.

* Meta-analyses were conducted using the random effects model. Main analysis: all included studies were conducted on no-grape polyphenol controls and intervention group who consumed grape product containing polyphenols.

Table 2. Cochrane risk of bias assessment

Study (ref)	Bias due to random sequence generation (selection bias)	Bias due to allocation concealment (selection bias)	Bias due to blinding of participants and personnel (performance bias)	Bias due to blinding of outcome assessment (detection bias)	Bias due to incomplete outcome data (attrition bias)	Bias in selective reporting (reporting bias)
Bardagjy *et al.*[56]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Barden *et al.*[69]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Kanellos *et al.*[57]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Turki *et al.*[59]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Mori *et al.*[63]	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Vaisman *et al.*[68]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Zunino *et al.*[67]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Janiques *et al.*[70]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Hokayem *et al.*[61]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Tomé-Carneiro *et al.*[71]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Chiva-Blanch *et al.*[64]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Weseler *et al.*[61]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Dohadwala *et al.*[66]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Mellen *et al.*[65]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Retterstol *et al.*[72]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Estruch *et al.*[51]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Clifton *et al.*[58]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk

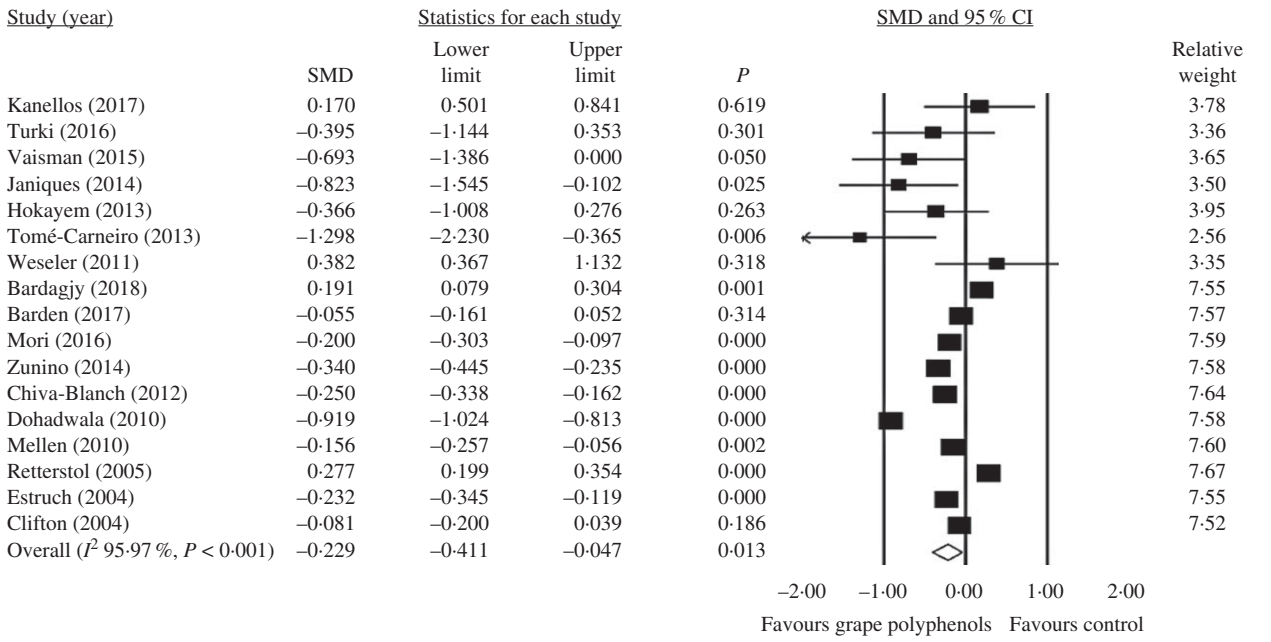

Fig. 2. Forest plot of the effect of grape products containing polyphenols on C-reactive protein levels. SMD, standardised mean difference.

juice) showed a significant decrease in CRP concentration (GSE: SMD = −0·121; 95 % CI −0·20, −0·04; P = 0·004, Cochran's Q test, Q statistic = 3·15, P = 0·36, I^2 4·96; Other: SMD = −0·598; 95 % CI −1·16, −0·03; P = 0·038, Cochran's Q test, Q statistic = 13·14, P = 0·004, I^2 77·17), but red wine and grape powder did not have any significant effect in this regard (red wine: SMD = −0·091; 95 % CI −0·31, 0·13; P = 0·422, Cochran's Q test, Q statistic = 106·84, P < 0·001, I^2 96·25; grape powder: SMD = −0·312; 95 % CI −0·74, 0·11; P = 0·152, Cochran's Q test, Q statistic = 52·36, P < 0·001, I^2 94·27) (Fig. 7).

Meta-regression

Random effect meta-regression was conducted to assess the association of estimated effect size with dose of grape polyphenols and duration of trial. The results showed that changes in CRP concentrations were dependent on the dose of grape polyphenol intake (slope −0·00031; 95 % CI −0·0003, −0·0002; P < 0·001) (Fig. 8) and duration of trial (slope −0·07793; 95 % CI −0·09, −0·06; P < 0·001) (Fig. 9). Based on the findings, an increase in the dose of administered grape polyphenols and duration of trial can significantly change the concentrations of CRP.

Table 3. Subgroup analysis of the effect of grape polyphenol supplementation on C-reactive protein (CRP) levels (Effect sizes and 95 % confidence intervals)

CRP	No.	Effect size	95 % CI	*P*	Heterogeneity	
					I^2 (%)	*P* heterogeneity
Health status						
Patients with a clinical condition	9	−0·204*	−0·306, −0·103	<0·001	56·50	0·018
Healthy	8	−0·166	−0·489, 0·158	0·315	98·13	<0·001
Type of study						
Parallel	7	−0·400*	−0·798, −0·002	0·049	52·04	0·051
Crossover	10	−0·176	−0·385, 0·032	0·098	97·64	<0·001
Duration of study						
12 weeks or more	10	−0·333*	−0·534, −0·132	0·001	95·11	<0·001
Lower than 12 weeks	7	−0·037	−0·333, 0·258	0·804	93·92	<0·001
Dose of grape polyphenols						
More than 500 mg/d	8	−0·288*	−0·529, −0·047	0·019	96·06	<0·001
500 mg/d or lower	9	−0·160	−0·419, 0·098	0·224	94·64	<0·001
Type of products						
Grape seed extract	4	−0·121*	−0·203, −0·040	0·004	4·96	0·368
Grape powder	4	−0·312	−0·739, 0·115	0·152	94·27	<0·001
Red wine	5	−0·091	−0·312, 0·131	0·422	96·25	<0·001
Other†	4	−0·598*	−1·163, −0·033	0·038	77·17	0·004

* Significant decrease in the outcome was observed.
† Raisins, grape extract and juice.

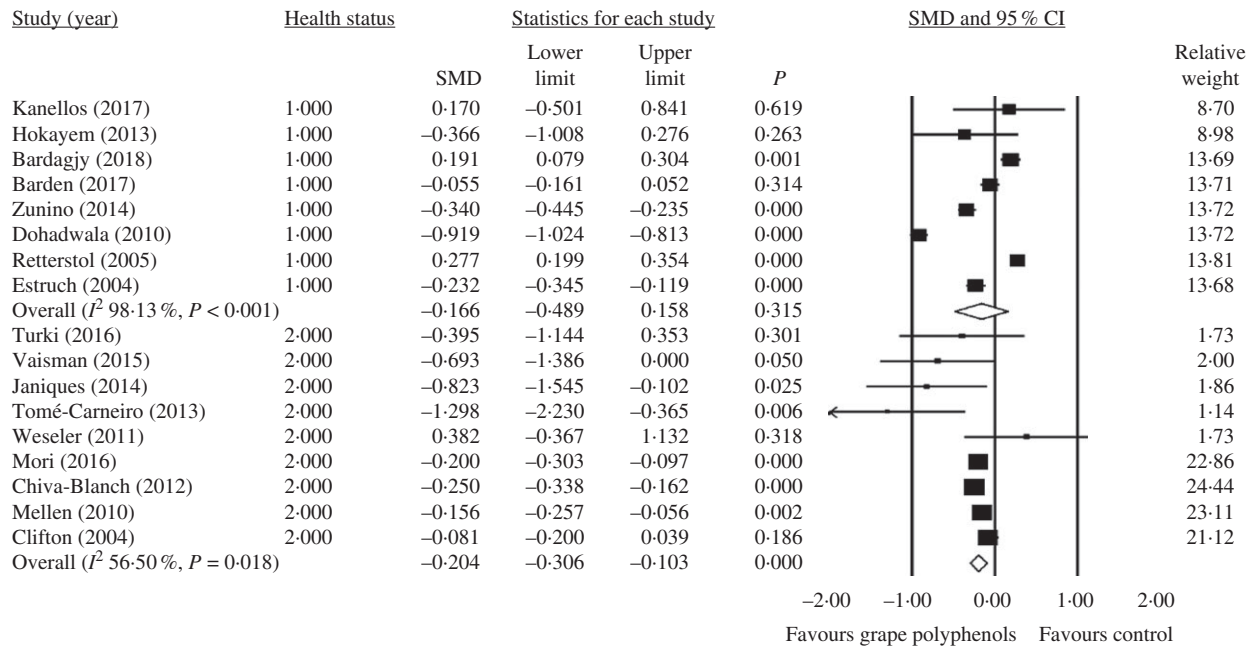

Fig. 3. Forest plot of the effect of grape polyphenol intake on C-reactive protein levels in healthy participants and patients with a clinical condition. SMD, standardised mean difference.

Publication bias

Funnel plots did not show any publication bias for the effect of grape products containing polyphenols on CRP levels (online Supplementary Fig. S2); asymmetry tests confirmed the same results (Begg's test, $P = 0·65$ and Egger's test, $P = 0·55$).

Discussion

The findings showed that grape products containing polyphenols decreased the CRP levels significantly. The results of subgroup analysis indicated that higher doses of grape polyphenols (>500 mg/d), longer intervention periods (≥12 weeks) and parallel study designs affected the CRP levels significantly. According to our findings, grape products such as GSE and other kinds of grape products (such as raisins, grape polyphenol, grape extract and juice) had significant effects on CRP levels. However, grape powder and red wine did not have any significant effect on the CRP levels. Moreover, the effect of grape polyphenols on CRP was significantly different between the healthy participants and patients with a clinical condition.

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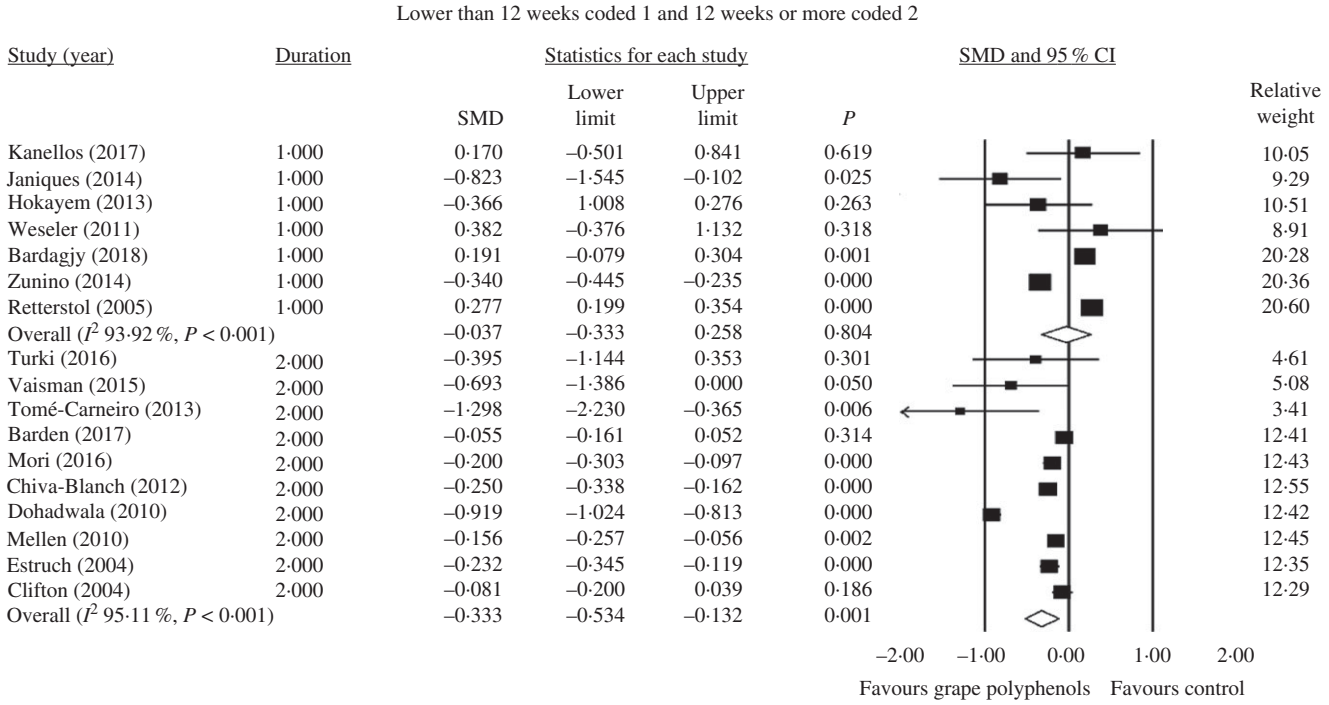

Fig. 4. Forest plot of the effect of grape polyphenol intake on C-reactive protein levels in studies with a duration of 12 weeks or more and lower than 12 weeks. SMD, standardised mean difference.

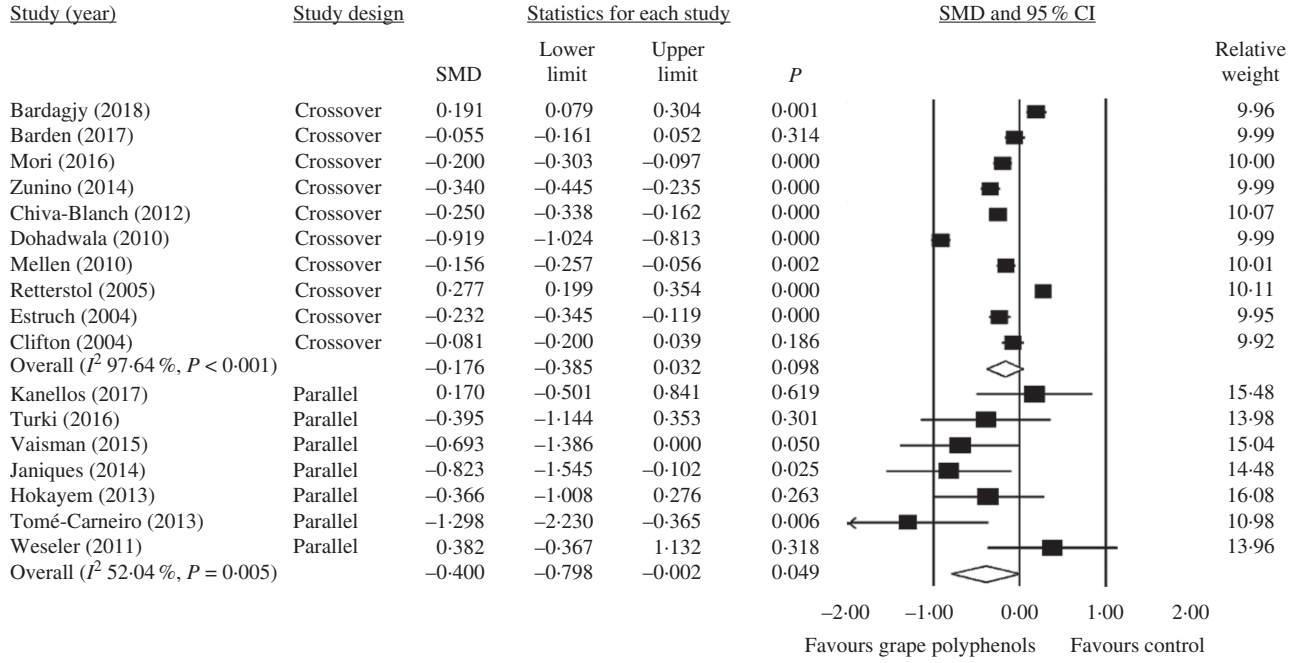

Fig. 5. Forest plot of the effect of grape polyphenol intake on C-reactive protein levels in studies with parallel and crossover designs. SMD, standardised mean difference.

To the best of our knowledge, the present study was the first meta-analysis investigating the effect of grape polyphenols on CRP concentrations.

In the same line with our results, other systematic reviews and meta-analyses showed significant effects of supplementation with grape polyphenols on decreasing systolic blood pressure[105] and increasing the endothelial function[106]. However, a systematic review indicated that grape polyphenols did not have any significant effect on glycaemia, blood pressure and lipid profile in the MetS patients[107]. In this regard, some limited evidences suggested a positive effect of grape polyphenols on insulin sensitivity[107]. Moreover, a meta-analysis showed that

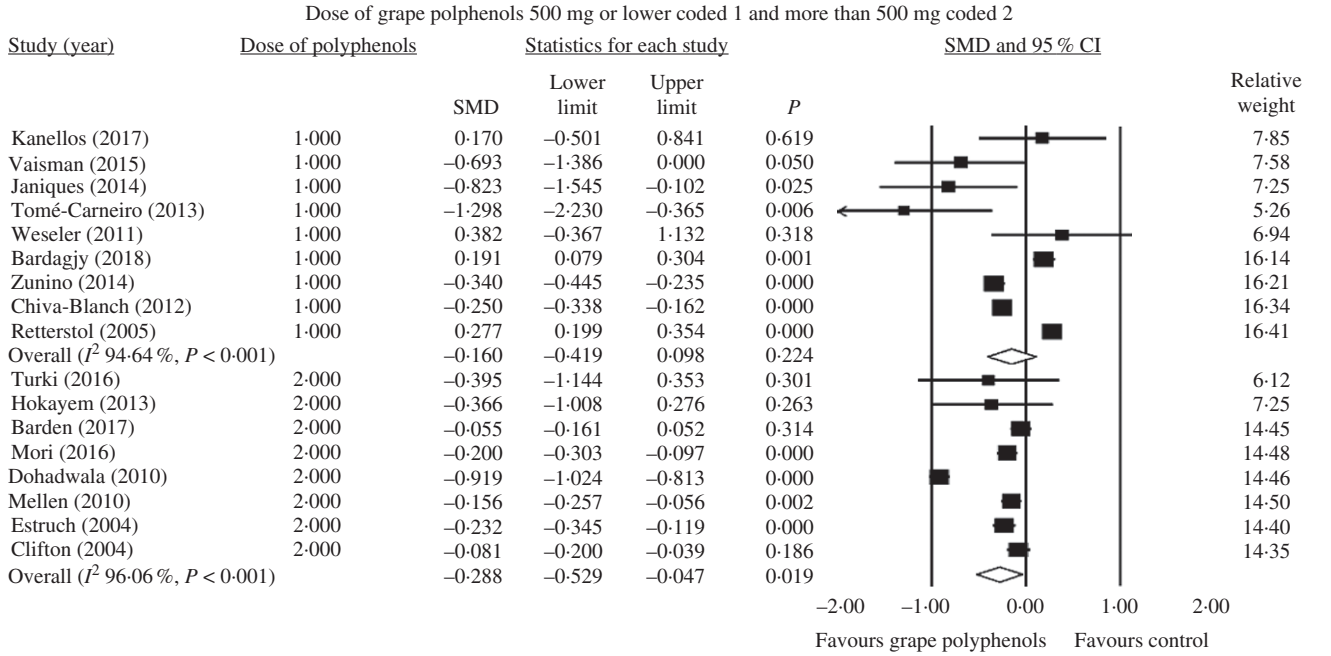

Fig. 6. Forest plot of the effect of grape polyphenol intake in doses of 500 mg/d or lower and more than 500 mg/d on C-reactive protein levels. SMD, standardised mean difference.

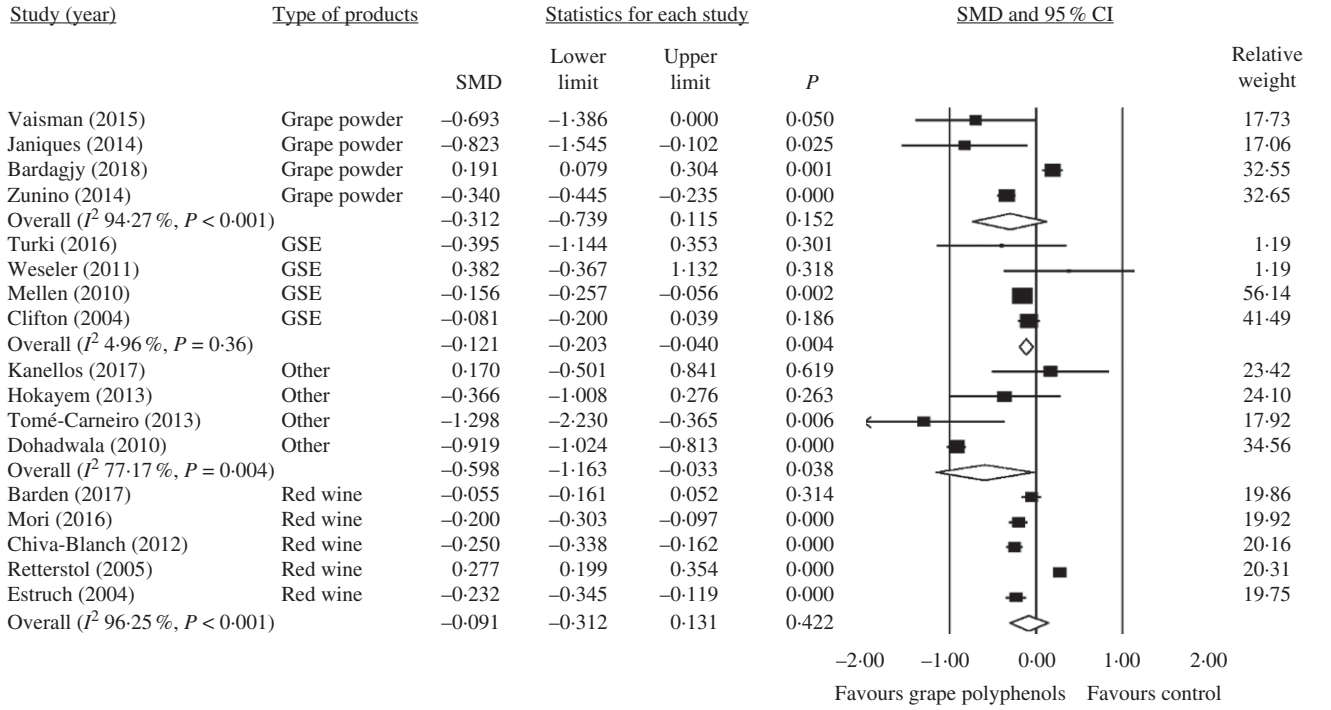

Fig. 7. Forest plot of the effect of grape polyphenol intake on C-reactive protein levels in different grape products contain polyphenols. SMD, standardised mean difference; GSE, grape seed extract.

supplementation with purified anthocyanin or anthocyanin-rich extract did not have any significant effect on the CRP levels. Although changes in CRP concentrations had no association with the trial duration, a significant relationship was found between anthocyanin dosage and CRP level[108]. Other meta-analyses over the effect of resveratrol on concentration of serum inflammatory mediators indicated that resveratrol might be able to reduce CRP secretion[109,110]. Significant improvement in inflammatory markers supported that resveratrol was an adjunct to pharmacological management of metabolic diseases.

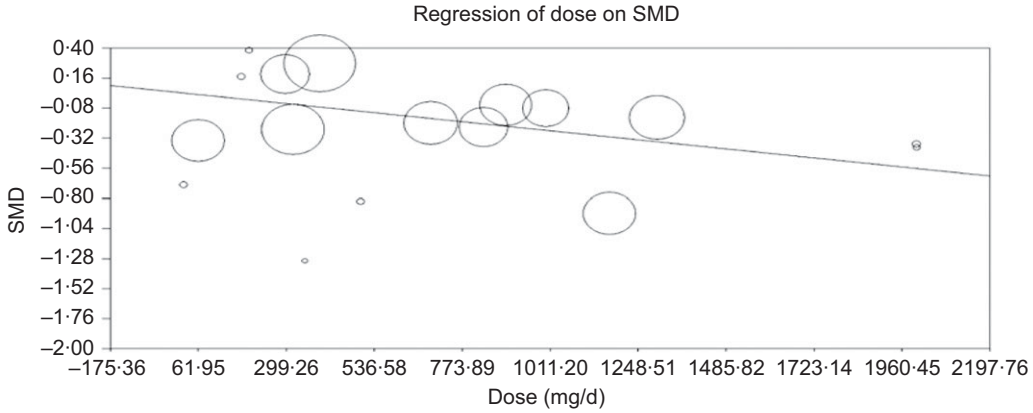

Fig. 8. Meta-regression plots of the association of standardised mean difference (SMD) in plasma C-reactive protein concentrations values and intake of grape products containing polyphenols with doses of grape polyphenols. The size of each circle is inversely proportional to the variance of change.

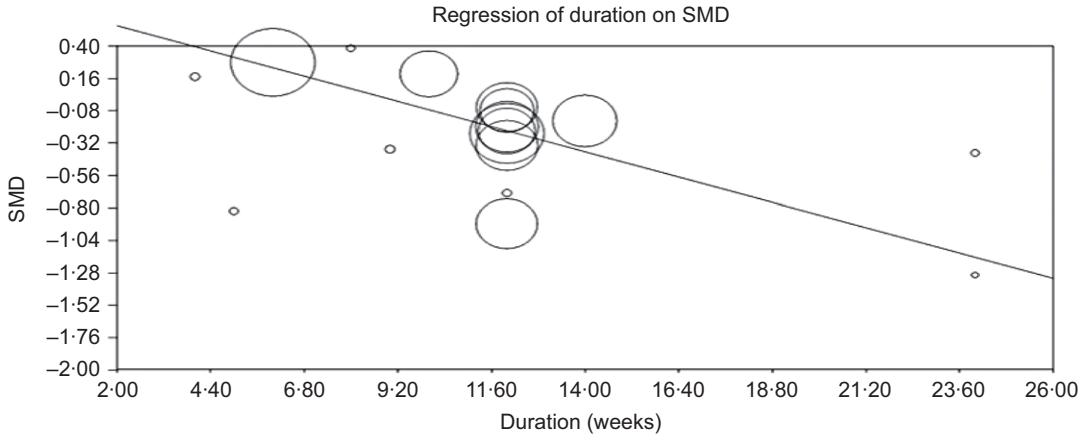

Fig. 9. Meta-regression plots of the association of standardised mean difference (SMD) in plasma C-reactive protein concentrations values and intake of grape products containing polyphenols with duration of trial. The size of each circle is inversely proportional to the variance of change.

In agreement with the results of this research, grape products containing polyphenols had a significant effect on the reduction of CRP concentrations in some animal[44,45,111] and trial[47–55,112] studies. The researchers concluded that supplementation with grape polyphenolic products decreased the CRP levels significantly not only in patients with diabetes[47,48], the MetS[50], and overweight or obesity[112] but also among healthy participants[49,51–55].

In contrast to the results of our study, grape products containing polyphenols had no significant effect on CRP either in people with type 2 diabetes[63,71,82], chronic kidney disease[59,113], haemodialysis[70,114,115], hypertension[66,68,116], obesity[62,67], overweight[117], the MetS[118], smoking habit[61], high risk for CVD[119] and CVD[65,120,121] or in healthy participants[30,57,60,64,69,72–74,122–130]. Some of these studies were only investigated in our systematic review and were not included in our meta-analysis because they did not meet our inclusion criteria[30,47–50,52–55,60,73,74,82,112–118,120–130]. These discrepancies were attributed to the amount of administered grape product, participants' primary CRP level, various dietary habits[72], type of diet[121,127], consumption of polyphenols containing products with food[51,131], poor compliance[63], participants' sex and small sample size of studies[72].

In patients with a clinical condition, the baseline CRP levels may be more influenced by grape polyphenol products[72]. In concordance with our results, Li *et al.* found that the effect of grape polyphenols was more pronounced on improvement of the endothelial function in people with cigarette smoking and coronary artery diseases[106]. Furthermore, grapes or their products were effective in lowering blood pressure in individuals with clinical conditions[132]. In addition, the results of subgroup analysis showed that higher doses of grape polyphenols (>500 mg/d) were associated with a significant decrease in CRP levels. In contrast to our results, a meta-analysis over the effects of grape polyphenols on blood pressure showed that lower doses of polyphenols reduced systolic blood pressure significantly[105]. Retterstol *et al.* indicated that consumption of red wine had a U-shaped association with systemic markers of inflammation (CRP)[72]. Another study over the association between different doses of red wine and blood pressure indicated that moderate drinkers had greater reductions of the systolic blood pressure than those who drank higher doses of wine[133]. This may be due to the threshold effect of the grape polyphenols on inflammatory factors such as CRP[72].

Grape polyphenols apply their anti-inflammatory effects through various mechanisms. One of these mechanisms is gene expression[134], such as reducing the expression of anti-inflammatory cytokines genes of TNF-α, IL-6[132] and CRP[42,45]. The production of CRP in liver cells is regulated by IL-6, IL-1 and TNF-α[40]. NF-κB is responsible for increasing the expression of inflammatory cytokines genes[135–137], including TNF-α, IL-6, IL-1β and IL-8[41]. Grape polyphenols inhibit NF-κB pathway signals[138,139], which can reduce CRP production. In addition, various grape products containing polyphenols have a beneficial effect on intestinal microbiota, such as increase of bifidobacteria[132], which is positively associated with reduction of CRP among consumers of these products[52]. Moreover, grape and its products reduce inflammation and decrease the production of reactive species by inhibiting enzymes, such as nucleotide adenine dinucleotide phosphate oxidase[2,115]. It was also clearly confirmed that grape phenols had chemoprophylaxis effects[140]. Modulation of chronic inflammation is affected by grape phenolics, since induction of inflammatory cells' apoptosis can cause resolution of inflammation[138].

The present study contained some strengths. The source of grape polyphenols was almost consistent among the investigated trials (five red wine studies, four grape powder studies, four GSE studies and four studies of other products). Moreover, subgroup analysis was conducted on the study type (parallel and crossover) and duration (<12 and ≥12 weeks), products' type (GSE, grape powder, red wine, etc.), dose of grape polyphenols (≤500 and >500 mg/d), as well as participants' health status (healthy participants and patients with a clinical condition). The conducted sensitivity analyses showed that the overall result was not affected by any particular study. So, the results can be considered robust as even with different decisions they remain the same. Moreover, studies that included other interventions or a special diet along with grape polyphenol supplementation were excluded since they might influence the net impact of grape polyphenols on CRP.

The present study had some limitations. First, CRP was evaluated as the 'secondary outcome' in most RCT. The subgroup analysis showed that the effect of grape products containing polyphenols on CRP levels was significant in higher doses of grape polyphenols and longer intervention periods. So, further clinical trials are needed over the effect of grape polyphenol on the CRP or other inflammatory factors as primary outcome using higher doses and longer duration. Most of the investigated studies did not evaluate the participants' physical activity, diet, genetic background and possible polymorphisms that might mediate the effect of grape polyphenol on CRP that are suggested for future studies. Some of the included studies did not report the doses of pure polyphenols in grape products and serum levels of polyphenols in study population; polyphenol contents in grape products are varied widely because many factors influence their contents, such as grape cultivars, season, processing, storage condition and duration. Future researchers are suggested to report the amount of grape polyphenol in their test products and serum levels of polyphenols in participants. Moreover, the standardised polyphenol extracts are recommended to control for the influence of non-polyphenol compounds. Although we performed a subgroup analysis based on pre-specified subgroup, we identified a heterogeneous group of studies and by subgrouping for health status of participants, type and doses of grape products, design and duration of studies, none of the plausible factors that might explain heterogeneity do so, with the exception of grape seed products. Moreover, NutriGrade score indicating low confidence in the effect estimate, which shows further research, will provide important evidence on the confidence and likely change the effect estimate. Therefore, the overall conclusions of the present study should be interpreted with caution and more studies are needed in this area.

Conclusion

The current systematic review and meta-analysis of RCT demonstrated the significant effect of grape polyphenols on CRP concentrations. However, this effect depends on the administered dosage and type of grape polyphenols, the study duration and the participants' health status. In this regard, to investigate the effectiveness of grape polyphenols on CRP levels, further well-designed RCT are required with larger sample sizes and longer durations.

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The authors' responsibilities were as follows: S. S.-K. H. and M. H. designed the study. S. S.-K. H. and M. H. performed systematic research and study selection; S. S.-K. H. and M. H. independently evaluated the methodological quality of the included articles according to Cochrane risk of bias tools. The data collected and extracted by S. S.-K. H. and M. H. S. S.-K. H. and M. H. performed the statistical analysis. S. S.-K. H. wrote the draft of the manuscript. M. H. critically revised the manuscript and approved the final version of manuscript to be submitted. All authors read and approved the final version of the article.

The authors declare no conflicts of interest to report regarding the present study.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114520003591

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