Effects of pomegranate juice on blood pressure: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Punica granatum L. (Pomegranate) has been claimed to provide several health benefits. Pomegranate juice is a polyphenol-rich fruit juice with high antioxidant capacity. Several studies suggested that pomegranate juice can exert antiatherogenic, antioxidant, antihypertensive, and anti-inflammatory effects. Nevertheless, the potential cardioprotective benefits of pomegranate juice deserve further clinical investigation. To systematically review and meta-analyze available evidence from randomized placebo controlled trials (RCTs) investigating the effects of pomegranate juice consumption and blood pressure (BP). A comprehensive literature search in Medline and Scopus was carried out to identify eligible RCTs. A meta-analysis of eligible studies was performed using a random-effects model. Quality assessment, sensitivity analysis and publication bias evaluations were conducted using standard methods. Quantitative data synthesis from 8 RCTs showed significant reductions in both systolic [weighed mean difference (WMD): −4.96 mmHg, 95% CI: −7.67 to −2.25, $p < 0.001$) and diastolic BP (WMD: −2.01 mmHg, 95% CI: −3.71 to −0.31, $p = 0.021$) after pomegranate juice consumption. Effects on SBP remained stable to sensitivity analyses. Pomegranate juice reduced SBP regardless of the duration (>12 wks: WMD = −4.36 mmHg, 95% CI: −7.89 to −0.82, $p = 0.016$) and 240 cc: WMD = −3.62 mmHg, 95% CI: −6.62 to −0.63, $p = 0.018$) and 240 cc provided a borderline significant effect in reducing DBP. The present meta-analysis suggests consistent benefits of pomegranate juice consumption on BP. This evidence suggests it may be prudent to include this fruit juice in a heart-healthy diet.

1.Introduction

Cardiovascular disease is the number one cause of mortality and morbidity worldwide. Hypertension is a leading risk factor for cardiovascular disease [1,2]. It has been demonstrated a linear relationship between blood pressure levels and the risk of cardiovascular disease and also the state of pre-hypertension (not clinically expressed hypertension) is considered a cardiovascular risk for a large part of the population [2]. Therefore, lowering blood pressure, even in the normal range,

through dietary modifications may decrease the risk of end-organ damage caused by hypertension [1,2]. Lifestyle modifications, including adherence to a heart-healthy diet, have substantial effects on cardiovascular risk factors such as hypertension [2]. Mounting evidence from epidemiological studies suggests that there is an association between diets rich in fruits and vegetables and a reduction in the incidence of cardiovascular disease [3]. Fruits and vegetables contain a wide range of potentially cardioprotective components including fibre, folate, anti-oxidants, vitamins and a large number of non-nutrient phytochemicals such as carotenoids and polyphenols [3–5]. Epidemiological evidence suggests that polyphenols, at least in part, might explain the cardiovascular benefits from increased fruit and vegetable intake [5]. A growing evidence suggests putative beneficial effects of various polyphenol subclasses on biological systems [5]. Accordingly, some clinical intervention studies support the hypothesis of cardiovascular benefits from polyphenol-rich beverages including tea, cocoa and red wine [5–8]. Furthermore, consumption flavonoidrich fruits and vegetables has been proposed to lower blood pressure and confer cardiovascular protection [3–5]. Punica granatum L. (Pomegranate) has been widely investigated in relation to its cardioproetctive and anti-hypertensive effects. Pomegranate has been claimed to provide several health benefits. Pomegranate juice is a polyphenol-rich fruit juice with a high antioxidant capacity. Pomegranate can help preventing or treating several cardiovascular risk factors including hypertension, hypercholesterolemia, oxidative stress, hyperglycemia, and inflammation [3,9]. Nevertheless, studies investigating the antihypertensive effects of pomegrnate juice have produced different results. An explanation for these discrepant results could be differences in the source and polyphenolic content of juice that was used, and also differences in demographic characteristics of the populations studied in clinical trials. Furthermore, extrapolation of experimental data to the human is fraught with problems, predominantly regarding the bioavailability and metabolism of the different classes of polyphenols [6–9]. Finally, individual studies assessing the anti-hypertensive effects of pomegranate juice have been mainly performed with limited number of participants, thereby making generalization of results difficult. The impact

of fruit polyphenols on cardiovascular mortality is of considerable public health importance and would help to inform policy on recommendations of the types of fruits to be consumed for cardiovascular protection. Thus, we aimed to perform an up-to-date systematic review and meta-analysis of randomized controlled trials (RCTs) investigating the effects of pomegranate juice consumption on blood pressure.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and metaanalysis (PRISMA) statement guidelines [10]. SCOPUS (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) and two Iranian bibliographic databases namely MagIran (www. magiran.com) and Scientific Information Database (www.SID.ir) were searched using the following search terms in titles and abstracts (also in combination with MESH terms): ("randomized controlled trial" OR randomized OR placebo) and ("blood pressure" OR hypertension OR anti-hypertensive OR hypotension OR hypotensive) and (pomegranate OR Punica). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature was searched from inception to December 12th, 2014.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (i) be a randomized clinical case-control or case cross-over trial, (ii) investigated the impact of pomegranate juice on blood pressure, (iii) presentation of sufficient information on baseline and at the end of study in both pomegranate and control groups, and (iv) administering pomegranate for a period of at least 2 weeks. Exclusion criteria were (i) non-clinical studies, (ii) uncontrolled trials, (iii) administering pomegranate preparations via non-oral routes e.g. topical application or mouth rinse, (iv) administering pomegranate preparations other than pomegranate juice (e.g. seed oil, vinegar, etc),

(v) lack of sufficient information on baseline or follow-up lipid concentrations, and (vi) administration of an active comparator in the control group e.g. grape juice, apple juice, etc.

2.3. Data extraction

Eligible studies were reviewed and the following data were extracted: 1) first author's name; 2) year of publication; 3) study location; 4) number of participants in the pomegranate and control groups; 5) dose and duration of supplementation with pomegranate products; 6) age, gender and body mass index (BMI) of study participants; 7) circulating concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and glucose; 8) systolic and diastolic blood pressure; and 9) fasting glucose concentrations.

2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [11]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

2.5. Quantitative data synthesis

Meta-analysis was conducted using the Comprehensive MetaAnalysis V2 software (Biostat, NJ) [12]. Systolic and diastolic blood pressure values were collated in mmHg. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [(SDpre-treatment)2 + (SDpost-treatment)2 − (2R × SDpre-treatment × SDpost-treatment)], assuming a correlation coefficient (R) = 0.5. In case of reporting SEM, SD was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects. Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at end of follow-up in the treatment group−measure at baseline in the treatment group) − (measure at end of follow-up in the control group−measure at baseline in the control group).

Selection offixed effects model was used for analyses unless in case of significant heterogeneity, where a random-effects model was applied. Interstudy heterogeneity was assessed using Cochrane Q statistic and quantified by I 2 statistic. Weighting of studies was done using generic inverse variance method. In case of multiple evaluations in a single study group, the values belonging to the longest time point were used for the analyses. Effect size was expressed as weighed mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach [13–15].

2.6. Meta-regression

Meta-regression was performed in order to evaluate the association between calculated WMD in blood pressure with dose and duration of supplementation of pomegranate juice in the included studies.

2.7. Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" method was used to adjustthe analysis for the effects of publication bias [16].

3. Results

3.1. Included studies

From the 986 published studies identified through systematic database search, 930 were excluded after evaluation of titles and abstracts because of not meeting inclusion criteria. From the remaining 56 studies, 48 articles were additionally excluded after careful evaluation (43 studies because of not measuring blood pressure, 4 studies for having uncontrolled design, and 1 study for being non-original). Therefore, 8 RCTs were finally included were included in the systematic review and meta-analysis [17–24]. The study selection process is shown in Table 1.

3.2. Characteristics of included studies

A total of 574 individuals were recruited from the 8 RCTs, including 322 and 252 subjects in the pomegranate and control groups (participants enrolled from the cross-over trial were considered in both groups), respectively. Included studies were recently published between 2004 and 2014. All RCTs used pomegranate juice as active treatment [17–24]. The intervention period with pomegranate ranged between 2 weeks [23] and 18 months [19]. Most of the included studies were randomized, double blind, placebo-controlled [17–19,22–24], two were single-blind, placebo-controlled double-arm parallel-group [20], and one had a single-arm cross-over design [21]. Selected trials enrolled subjects with hypertension [23], ischemic coronary heart disease [18], carotid artery stenosis [17], at least 1 cardiovascular risk factor and a high carotid intima-media tickness [19], type 2 diabetes [22], hemodialysis [24], and healthy volunteers [20,21]. Baseline and demographic characteristics of included studies are summarized in Fig. 1 [17–24].

3.3. Risk of bias assessment

3.3.1. Quality of bias assessment

Some of the included studies were characterized by lack of information about the random sequence generation and allocation concealment [17,19,21,23,24]. Most of the selected studies were double-blind, excepttwo single-blind studies [20,23], and one that did not provide sufficient information about blinding [17,21]. However, with respect to reporting bias due to selective outcome reporting, almost all studies had a low risk of bias. Details of the quality assessment are shown in Table 2 [17–24].

3.4. Quantitative data synthesis

Fixed-effect meta-analysis of data from 8 RCTs showed significant reductions in both SBP (WMD: −4.96 mmHg, 95% CI: −7.67 to −2.25, $p < 0.001$) and DBP (WMD: −2.01 mmHg, 95% CI: −3.71 to −0.31, $p = 0.021$) following supplementation with pomegranate juice (Fig. 2). The estimated effect size for the impact of pomegranate juice on SBP was robust in the leave-one-out sensitivity analysis whilst the DBP-lowering effect was sensitive to the study by Tsang et al. [21], yielding an effect size equivalent to −1.58 mmHg; 95% CI: −3.37 to +0.21 ($p = 0.083$) (Fig. 3). When the RCTs

were stratified according to their duration,there was a significant reducing effect of pomegranate juice on SBP in both subsets of studies with > 12 (WMD: −4.36 mmHg, 95% CI: −7.89 to −0.82, p = 0.016) and < 12 (WMD: −5.83 mmHg, 95% CI: −10.05 to −1.61, p = 0.007) week lengths (Fig. 4). As for DBP, a significant reduction was observed in trials with 12 weeks (WMD: −0.97 mmHg, 95% CI: −3.09 to +1.15, p = 0.370) (Fig. 5). Another subgroup analysis was performed to investigate the impact of pomegranate juice dose on the observed antihypertensive effects. Reduction of SBP remained significant at both subsets of studies administering >240 cc (WMD: −3.62 mmHg, 95% CI: −6.62 to −0.63, p = 0.018) and < 240 cc (WMD: −11.01 mmHg, 95% CI: (Fig. 6). With respect to DBP, there was no significant effect with doses 240 cc (WMD: −1.74 mmHg, 95% CI: −3.62 to +0.14, p = 0.070) (Fig. 7).

3.5. Meta-regression analysis

Fixed-effect meta-regression analyses were performed to evaluate the association between blood pressure-lowering effects of pomegranate juice and dose and duration of supplementation as potential moderator variables. Changes in SBP and DBP showed no association with either pomegranate juice dose ([SBP]: slope: +0.01; 95% CI: −0.02 to +0.04; p = 0.582; [DBP]: slope: −0.01; 95% CI: −0.03 to +0.01; p = 0.250) or duration of supplementation ([SBP]: slope: +0.02; 95% CI: −0.06 to +0.10; p = 0.610; [DBP]: slope: +0.03; 95% CI: −0.02 to +0.08; p = 0.248) (Figs. 8 and 9).

3.6. Publication bias

Visual inspection of the funnel plot of the study precision (inverse SEM) by effect size (mean difference) suggested asymmetry for the impact of pomegranate consumption on both SBP and DBP. Using trim-and-fill correction, 2 and 1 potentially missing studies were imputed for the analysis of SBP and DBP, respectively. The imputed effect sizes of pomegranate juice on SBP and DBP were −4.08 mmHg (95% CI: −6.71 to −1.45) and −1.58 mmHg (95% CI: −3.21 to +0.04), respectively (Fig. 10). In addition to visual inspection of funnel plots, presence of publication bias was explored using Begg's rank correlation test and Egger's linear regression test. None of these tests

indicated a significant evidence of publication bias for the impact of pomegranate juice on SBP and DBP (Table 3).

4. Discussion

Findings from this meta-analysis evaluating 8 RCTs showed that pomegranate juice is able to significantly decrease both SBP and DBP levels. Further, of particular interest. Pomegranate juice reduced SBP regardless of the duration of supplementation, and the administered dose, whereas doses >240 cc of pomegranate juice provided a borderline significant effect in reducing DBP. To the authors' knowledge, this is the first pooled estimate of the effects of pomegranate juice on blood pressure. The mean 5/2 mmHg BP-lowering effect we found might be relevant in term of cardiovascular (CV) risk reduction. Indeed, it is expected that a systolic BP reduction of about 3 mmHg lead to a reduction in relative risk (RRR) of both myocardial infarction (5.5%) and stroke (7%) [25]. Recently, a meta-analysis of individual participant data from RCTs showed that a mean BP difference of 5.4/3.1 mmHg produces significant RRR of CV diseases, similar across the various CV risk groups of patients, preventing 14 to 38 CV events, respectively from low- to high- CV risk individuals after a median of 4 years of follow-up [26]. Even in patients with grade 1 hypertension, an average BP reduction of 3.6/2.4 mmHg determined a significant reduction in strokes (OR = 0.72), CV deaths (OR = 0.75) and total deaths (OR = 0.78) as evaluated in another meta-analysis of individual-level data from RCTs [27]. Elsewhere, it has been shown that prolonged reduction of SBP by only 2 mmHg results in reduction in the incidence of death secondary to stroke (7%) and other vascular etiologies (10%) [28]. Moreover, another meta-regression analysis showed that the risk of stroke decreased by 13% for each 5-mmHg reduction in SBP and by 11.5% for each 2-mmHg reduction in DBP [29]. Finally, it is interesting to consider that the effects of BP lowering drugs in reducing the risk of CV diseases are shown to be largely due to BP reduction and independent by the drugs [30]. Therefore, the benefits of pomegranate may be considered clinically relevant. Possible mechanisms favoring a BP decrease after pomegranate intake may be related to beneficial vascular effects of flavonoids contained in pomegranate. In this regard, there is increasing evidence that

isolated phenolics as well as flavonoid-rich foods may exert beneficial effects on oxidative stress, endothelial function and the renin-angiotensin-aldosterone system [5,6]. Oxidative stress has been suggested to be deeply involved in the pathogenesis of hypertension [31]. Of note, endothelial cells may react with reactive oxygen species, particularly superoxide anion, resulting in endothelial dysfunction and arterial stiffening [32]. In addition, the oxidative stress is able to significantly impair the endothelial-dependent vasodilation reducing the nitric oxide (NO) bioavailability via by decreasing NO synthase (NOS) activity and/or enhancing NO breakdown [5,32]. In line with this, de Nigris et al. [33] showed that down-regulation of endothelial NOS induced by oxidized low-density lipoprotein was counteracted by pomegranate juice in human coronary endothelial cells. According with this, pomegranate juice might exert beneficial effects on the starting and progression of the atherosclerotic process by promoting NOS bioactivity. Moreover, pomegranate may positively affect arterial function by modulating some inflammatory pathways, also reducinc the activity of the well known NF-B pathway [34]. Different interventional studies indicated that flavonoid-rich foods intake (tea, red wine and cocoa) can improve NO-dependent vasodilation in patients with overt cardio-cerebrovascular diseases as well as in healthy volunteers with or without cardiovascular risk factors [6,8]. However, although with some contrasting results, Kelishadi et al. [35] reported significant improvement in both endothelium-dependent and −independent (nitroglycerininduced) dilation after 4 h of pomegranate juice consumption. Of note, the reported increase of vasodilation persisted until the end of supplementationperiod (1month)inadolescents withmetabolic syndrome [35]. Moreover, Sumner et al. [34] in a study including forty-five patients with stable coronary heart disease with confirmed stress-induced ischemia (documented by at least one reversible myocardial perfusion defect on computed tomography), reported that daily consumption of pomegranate juice was able to improve myocardial ischemia and by increasing myocardial perfusion. Moreover, beyond antioxidant effects, pomegranate juice has been suggested to lower BP through a direct interaction with the angiotensin-converting enzyme (ACE). Indeed, an experimental study showed that pomegranate juice consumption was able to attenuate angiotensin II-induced hypertension in diabetic rats, and also to

block the effects of different catecholamines on arterial BP and vasoreactivity, also counteracting the increased ACE activity in diabetic hypertensive rats after chronic administration [36]. Mohan and colleagues [37] reported that consumption of pomegranate juice reduced the serum ACE activity in hypertensive patients [37]. However, Lynn et al. [20] showed positive BP effects but failed to report any change in serum ACE concentration by pomegranate juice intake. Therefore, suggesting the ACE inhibitory effect of pomegranate juice needs to be furtherly explored. Moreover, a recent study by Kojadinovic et al. [38], aiming to evaluate the effects of PJ on lipid peroxidation and phospholipid fatty acid composition in patients with metabolic syndrome, reported that although not significantly (also due to a small study population) PJ consumption presented a tendency to decrease systolic blood pressure. There are some potential limitations to this meta-analysis. First, the number of analyzed studies and population size was relatively small, though the pooled population size was enough to allow detection of a statistically significant effect. Second, included RCTs were heterogeneous in design and characteristics of studied populations. We tried to address this heterogeneity by quantitative evaluation of heterogeneity and selection of a random-effects model, where I 2 value exceeded 50%. Besides, we performed subgroup and meta-regression analyses to control the effect size for potential confounders. Nevertheless, the possibility of confounded results due to heterogeneity still cannot be fully excluded. Finally, not all of the included RCTs were exclusively performed in hypertensive populations, and this calls for additional studies primarily aiming to assess the BP-lowering effects of pomegranate juice in hypertensive individuals. In conclusion, results of this meta-analysis, being the first of its kind, provided evidence for the benefit of pomegranate juice consumption in lowering BP. It appears that hypotensive effects of pomegranate juice might be more likely to be elicited in hypertensive patients. In light of these promising results, pomegranate juice might be considered as an effective tool to the anti-hypertensive medications and also as a constituent of daily diet for patients who are high risk for hypertension and cardiovascular disease. Hence, future studies are recommended to study the BP-lowering effects of pomegranate juice in hypertensive

populations, and also ascertain the long-term impact of pomegranate juice consumption on the complications of hypertension as well as cardiovascular events.

Conflict(s) of Interest/Disclosure(s) No conflicts to disclose

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Table 1. Characteristics of studies included in the meta-analysis.

Author	Study design	Target Population	Treatment duration	N	Study groups	Age, years	Female (n, %)	BMI, (kg/m²)	SBP (mmHg)	DBP (mmHg)	Fasting glucose (mg/dl)	Total cholesterol (mg/dl)	LDL cholesterol (mg/dl)	HDL cholesterol (mg/dl)	Triglycerides (mg/dl)
Aviram et al. (2004)	Randomized, placebo-controlled	Carotid artery stenosis (hypertension and hyperlipidemia)	1 year	10	PJ 50 ml/day	ND	ND	ND	174±8	81±3	123±9	184±7	113±6	47±4	118±16
								ND	160±7	88±4					
				9	Control	ND	ND				ND	ND	ND	ND	ND
Sumner et al. (2005)	Randomized, double-blind, placebo-controlled	Ischemic coronary heart disease	3 months	26	PJ 240 ml/day	69±11	4 (15.0)	28±6	130±15	72±12	116±31	170±42	91±33	48±11	149±107
				19	Control	69±9	1 (5.0)	29±5	126±25	72±11	121±63	157±32	80±35	46±12	155±102
Davidson et al. (2009)	Randomized, double-blind, placebo-controlled	At least 1 cardiovascular risk factor and high CIMT	18 months	146	PJ 240 ml/day	60.8±7.3	61 (42.0)	28.6±4.8	127.7±18.7	70.9±10.5	94.6±10.0	224.3±37.8	138.8±33.5	55.1±15.4	152.8±75.4
				143	Control	60.5±7.8	64 (45.0)	28.7±4.5	129.3±18.4	71.5±11.0	94.7±8.9	227.2±35.7	142.3±29.6	56.1±13.9	144.3±65.4
Lynn et al. (2012)	Randomized parallel single-blind, placebo-controlled	Healthy subjects	4 weeks	24	PJ 330 ml/day	39.0±1.24	16 (66.6)	24.99±1.26	115.2±2.4	72.1±1.7	ND	ND	ND	ND	ND
						36.1±0.92		24.99±1.06	111.7±2.1	69.6±1.6					
				24	Control		16 (66.6)				ND	ND	ND	ND	ND
Tsang et al. (2012)	Randomized, placebo-controlled, cross-over	Healthy volunteers	4 weeks	28		50.4±6.1	16 (57.1)	26.7±3.3							
					PJ 500 ml/day				128.9±5.1	76.2±4.8	86.7±9.5	210.8±38.7	128.0±28.2	58.8±17.0	101.6±34.5
					Control				133.8±16.3	80.9±10.9	85.4±4.9	174.4±19.7	98.2±30.5	56.5±21.7	101.0±45.2
Sohrab et al (2014)	randomized, double-blind, placebo-controlled	patients with type 2 diabetes	12 weeks			55±6.7	11 (50.0)	29.4±3.9	ND	ND	160.3±47.8	ND	ND	ND	ND
									ND	ND		ND	ND	ND	ND
				22	PJ 250 ml/day	56.9±3.2	10 (45.5)	28.6±4.2			148.7±42.1				
				22	control										
Asgary et al. (2014)	Single-blind, placebo-controlled	Hypertension	2 weeks	11	PJ 150 ml/day	58.9±5.0	8 (72.7)	26.7±3.4	124.5±15.7	76.3±6.7	90.6±7.0	218.7±42.8	127.2±24.2	49.2±8.0	171.1±78.9
				10	Control	46.9±12.3	7 (70.0)	27.9±4.1	128.0±13.1	85.0±8.0	89.1±11.3	187.0±30.2	109.4±25.8	40.4±6.9	165.6±124.3
Shema-Didi et al. (2014)	Randomized, double-blind, placebo-controlled	Hemodialysis patients	1 year	66	PJ 100 cc 3 times/week	ND	ND	ND	135.7±21.3	67.7±13.8	ND	167.3±43.5	100.0±33.1	36.8±10.8	167.3±86.3

Values are expressed as mean ± SD

Abbreviations: PJ, pomegranate juice; ND, no data; BMI, body mass index.

Table 2. Assessment of risk of bias in the studies included in the meta-analysis.

Study	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data
Asgary et al.	H	H	L	L	H	L	L
Aviram et al.	U	U	U	H	U	U	H
Davidson et al.	U	L	L	U	L	L	L
Lynn et al.	L	U	L	L	H	L	L
Shema-Didi et al.	U	U	L	L	L	L	L
Sohrab et al.	L	L	L	L	L	U	H
Sumner et al.	L	L	L	L	L	L	L
Tsang et al.	U	U	L	U	H	U	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

Table 3. Assessment of publication bias in the impact of pomegranate juice consumption on blood pressure.

	Begg's rank correlation test,			Egger's linear regression test					Fail safe N test
	Kendall's Tau[a]	***z*-value**	***p*-value**	**Intercept**	**95% CI**	***t***	**df**	***p*-value**	***n*[b]**
SBP (mmHg)	-0.46	1.61	0.108	-1.58	-3.28 to 0.11	2.29	6	0.062	28
DBP (mmHg)	-0.18	0.62	0.536	-0.39	-2.16 to 1.37	0.54	6	0.606	3

[a]With continuity correction; [b]Number of theoritically missing studies. SBP: systolic blood pressure; DBP: diastolic blood pressure.

Figure legends

Figure 1. Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of the impact of pomegranate consumption on plasma lipid concentrations.

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pomegranate juice consumption on blood pressure.

Figure 3. Leave-one-out sensitivity analysis for the impact of pomegranate juice consumption on blood pressure.

Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pomegranate juice consumption on systolic blood pressure in the subsets of trials with > 12 weeks and < 12 weeks lengths.

Figure 5. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pomegranate juice consumption on diastolic blood pressure in the subsets of trials with > 12 weeks and < 12 weeks lengths.

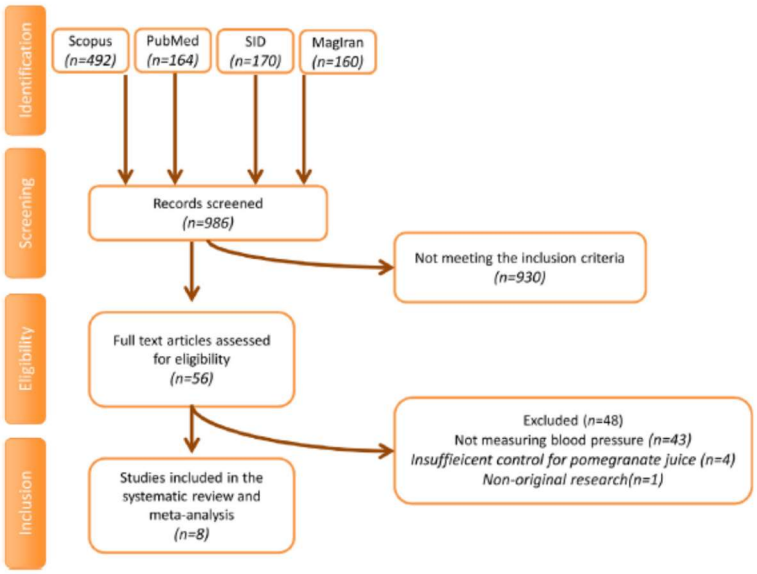
Figure 6. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pomegranate juice consumption on systolic blood pressure in the subsets of trials with > 240 cc < 240 cc doses.

Figure 7. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of pomegranate juice consumption on diastolic blood pressure in the subsets of trials with > 240 cc < 240 cc doses.

Figure 8. Meta-regression plots of the association between mean changes in systolic blood pressure with dose and duration of supplementation with pomegranate juice. The size of each circle is inversely proportional to the variance of change.

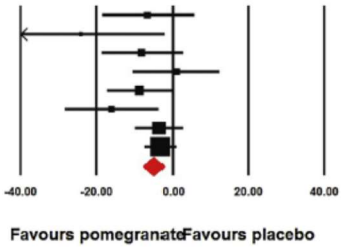
Figure 9. Meta-regression plots of the association between mean changes in diastolic blood pressure with dose and duration of supplementation with pomegranate juice. The size of each circle is inversely proportional to the variance of change.

Figure 10. Funnel plots detailing publication bias in the studies selected for analysis. Trim and fill method was used to impute for potentially missing studies. Open circles represent observed published studies; closed circles represent imputed unpublished studies.


Identification
Screening
Eligibility
Inclusion
Scopus (n=492)
PubMed (n=164)
SID (n=170)
Magiran (n=160)
Records screened (n=986)
Not meeting the inclusion criteria (n=930)
Full text articles assessed for eligibility (n=56)
Excluded (n=48)
Not measuring blood pressure (n=43)
Insuffieicent control for pomegranate juice (n=4)
Non-original research(n=1)
Studies included in the systematic review and meta-analysis (n=8)

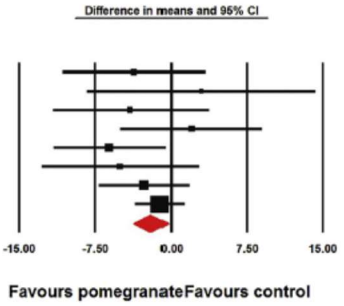
SBP

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Asgary et al., 2013	-6.360	6.080	36.962	-18.276	5.556	-1.046	0.296
Aviram et al., 2004	-24.000	11.119	123.626	-45.792	-2.208	-2.159	0.031
Sohrab et al., 2008	-8.000	5.396	29.121	-18.577	2.577	-1.482	0.138
Sumner et al., 2005	1.000	5.718	32.690	-10.206	12.206	0.175	0.861
Tsang et al., 2012	-8.500	4.307	18.553	-16.942	-0.058	-1.973	0.048
Shema-Didi et al., 2014	-15.900	6.265	39.246	-28.179	-3.621	-2.538	0.011
Lynn et al., 2012	-3.510	3.156	9.961	-9.696	2.676	-1.112	0.266
Davidson et al., 2009	-3.170	2.027	4.108	-7.143	0.803	-1.564	0.118
	-4.964	1.382	1.911	-7.674	-2.255	-3.591	0.000



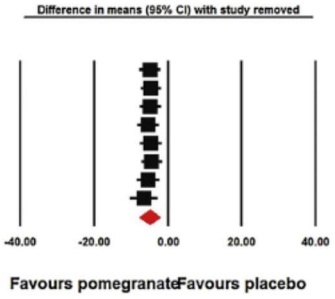
DBP

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Asgary et al., 2013	-3.640	3.570	12.747	-10.638	3.358	-1.020	0.308
Aviram et al., 2004	3.000	5.733	32.862	-8.236	14.236	0.523	0.601
Sohrab et al., 2008	-4.000	3.910	15.291	-11.664	3.664	-1.023	0.306
Sumner et al., 2005	2.000	3.547	12.583	-4.952	8.952	0.564	0.573
Tsang et al., 2012	-6.070	2.812	7.909	-11.582	-0.558	-2.158	0.031
Shema-Didi et al., 2014	-5.000	3.934	15.476	-12.710	2.710	-1.271	0.204
Lynn et al., 2012	-2.640	2.256	5.091	-7.062	1.782	-1.170	0.242
Davidson et al., 2009	-1.110	1.210	1.464	-3.482	1.262	-0.917	0.359
	-2.012	0.869	0.755	-3.715	-0.309	-2.315	0.021



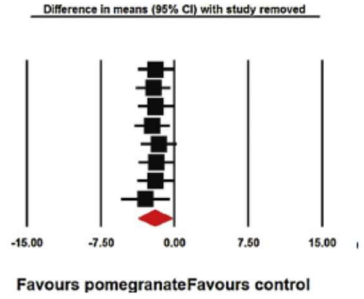
SBP

Study name	Point	Standard error	Statistics with study removed: Variance	Lower limit	Upper limit	Z-Value	p-Value
Asgary et al., 2013	-4.888	1.420	2.015	-7.671	-2.106	-3.443	0.001
Aviram et al., 2004	-4.665	1.393	1.941	-7.396	-1.935	-3.349	0.001
Sohrab et al., 2008	-4.751	1.430	2.045	-7.554	-1.948	-3.322	0.001
Sumner et al., 2005	-5.335	1.425	2.030	-8.127	-2.542	-3.744	0.000
Tsang et al., 2012	-4.558	1.460	2.131	-7.419	-1.697	-3.123	0.002
Shema-Didi et al., 2014	-4.405	1.417	2.009	-7.183	-1.627	-3.108	0.002
Lynn et al., 2012	-5.310	1.538	2.365	-8.324	-2.296	-3.453	0.001
Davidson et al., 2009	-6.525	1.890	3.573	-10.230	-2.820	-3.452	0.001
	-4.964	1.382	1.911	-7.674	-2.255	-3.591	0.000



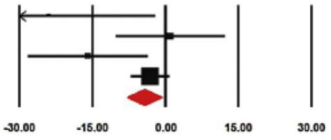
DBP

Study name	Point	Standard error	Statistics with study removed: Variance	Lower limit	Upper limit	Z-Value	p-Value
Asgary et al., 2013	-1.909	0.896	0.803	-3.665	-0.153	-2.131	0.033
Aviram et al., 2004	-2.130	0.879	0.773	-3.853	-0.407	-2.422	0.015
Sohrab et al., 2008	-1.909	0.891	0.794	-3.655	-0.162	-2.141	0.032
Sumner et al., 2005	-2.268	0.896	0.803	-4.025	-0.511	-2.530	0.011
Tsang et al., 2012	-1.583	0.914	0.835	-3.374	0.207	-1.733	0.083
Shema-Didi et al., 2014	-1.859	0.891	0.794	-3.605	-0.112	-2.086	0.037
Lynn et al., 2012	-1.902	0.942	0.887	-3.748	-0.057	-2.020	0.043
Davidson et al., 2009	-2.972	1.249	1.560	-5.420	-0.525	-2.380	0.017
	-2.012	0.869	0.755	-3.715	-0.309	-2.315	0.021



> 12 weeks

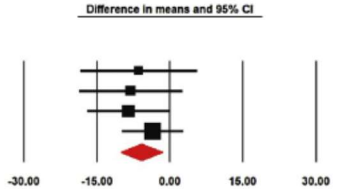
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aviram et al., 2004	-24.000	11.119	123.626	-45.792	-2.208	-2.159	0.031
Sumner et al., 2005	1.000	5.718	32.690	-10.206	12.206	0.175	0.861
Shema-Didi et al., 2014	-15.900	6.265	39.246	-28.179	-3.621	-2.538	0.011
Davidson et al., 2009	-3.170	2.027	4.108	-7.143	0.803	-1.564	0.118
	-4.358	1.803	3.251	-7.892	-0.824	-2.417	0.016



Favours pomegranateFavours control

< 12 weeks

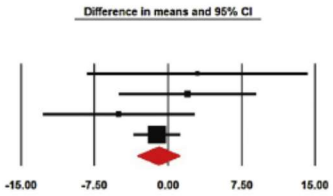
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Asgary et al., 2013	-6.360	6.080	36.962	-18.276	5.556	-1.046	0.296
Sohrab et al., 2008	-8.000	5.396	29.121	-18.577	2.577	-1.482	0.138
Tsang et al., 2012	-8.500	4.307	18.553	-16.942	-0.058	-1.973	0.048
Lynn et al., 2012	-3.510	3.156	9.961	-9.696	2.676	-1.112	0.266
	-5.829	2.153	4.636	-10.050	-1.609	-2.707	0.007



Favours pomegranateFavours control

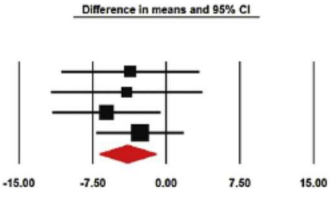
> 12 weeks

Study name	Difference in means	Standard error	Statistics for each study: Variance	Lower limit	Upper limit	Z-Value	p-Value
Aviram et al., 2004	3.000	5.733	32.862	-8.236	14.236	0.523	0.601
Sumner et al., 2005	2.000	3.547	12.583	-4.952	8.952	0.564	0.573
Shema-Didi et al., 2014	-5.000	3.934	15.476	-12.710	2.710	-1.271	0.204
Davidson et al., 2009	-1.110	1.210	1.464	-3.482	1.262	-0.917	0.359
	-0.969	1.080	1.166	-3.086	1.147	-0.897	0.370



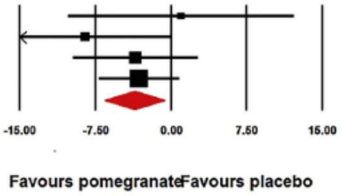
< 12 weeks

Study name	Difference in means	Standard error	Statistics for each study: Variance	Lower limit	Upper limit	Z-Value	p-Value
Asgary et al., 2013	-3.640	3.570	12.747	-10.638	3.358	-1.020	0.308
Sohrab et al., 2008	-4.000	3.910	15.291	-11.664	3.664	-1.023	0.306
Tsang et al., 2012	-6.070	2.812	7.909	-11.582	-0.558	-2.158	0.031
Lynn et al., 2012	-2.640	2.256	5.091	-7.062	1.782	-1.170	0.242
	-3.928	1.464	2.143	-6.797	-1.059	-2.683	0.007



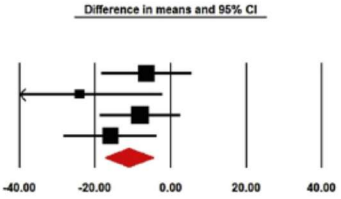
> 240 cc/day

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Sumner et al., 2005	1.000	5.718	32.690	-10.206	12.206	0.175	0.861
Tsang et al., 2012	-8.500	4.307	18.553	-16.942	-0.058	-1.973	0.048
Lynn et al., 2012	-3.510	3.156	9.961	-9.696	2.676	-1.112	0.266
Davidson et al., 2009	-3.170	2.027	4.108	-7.143	0.803	-1.564	0.118
	-3.623	1.528	2.335	-6.618	-0.628	-2.371	0.018



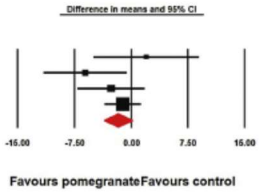
< 240 cc/day

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Asgary et al., 2013	-6.300	6.080	36.962	-18.276	5.556	-1.046	0.296
Aviram et al., 2004	-24.000	11.119	123.626	-45.792	-2.208	-2.159	0.031
Sohrab et al., 2008	-8.000	5.396	29.121	-18.577	2.577	-1.482	0.138
Shema-Didi et al., 2014	-15.900	6.265	39.246	-28.179	-3.621	-2.538	0.011
	-11.015	3.245	10.530	-17.376	-4.655	-3.394	0.001



> 240 cc/day

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Sumner et al., 2005	2.000	3.547	12.583	-4.952	8.952	0.564	0.573
Tsang et al., 2012	-6.070	2.812	7.909	-11.582	-0.558	-2.158	0.031
Lynn et al., 2012	-2.640	2.256	5.091	-7.062	1.782	-1.170	0.242
Davidson et al., 2009	-1.110	1.210	1.464	-3.482	1.262	-0.917	0.359
	-1.737	0.960	0.921	-3.618	0.144	-1.810	0.070



< 240 cc/day

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
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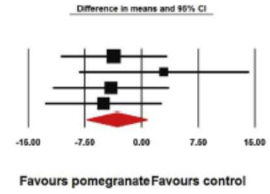
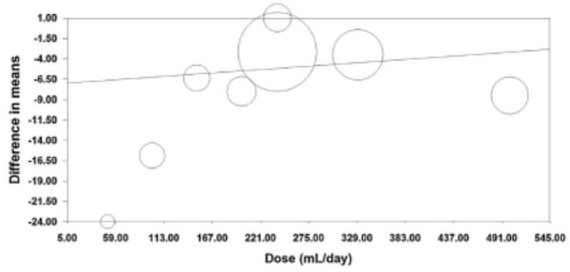
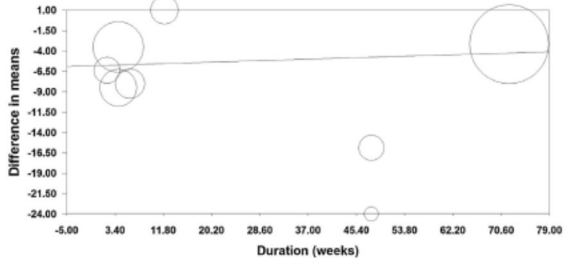
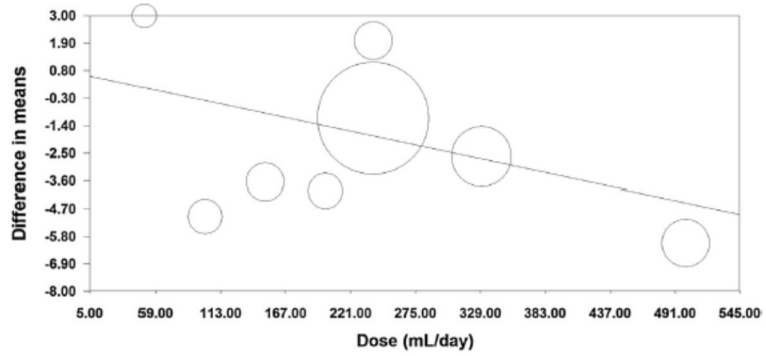
Aviram et al., 2004	3.000	5.733	32.862	-8.236	14.236	0.523	0.601
Sohrab et al., 2008	-4.000	3.910	15.291	-11.664	3.664	-1.023	0.306
Shema-Didi et al., 2014	-5.000	3.934	15.476	-12.710	2.710	-1.271	0.204
	-3.261	2.046	4.186	-7.271	0.749	-1.594	0.111








Difference in means
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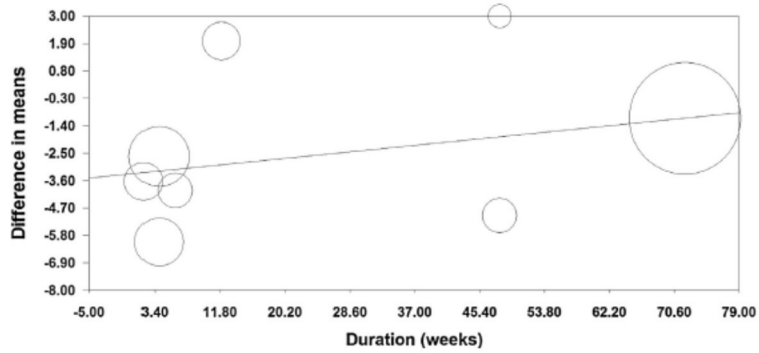
Dose (mL/day)


Difference in means
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-5.00
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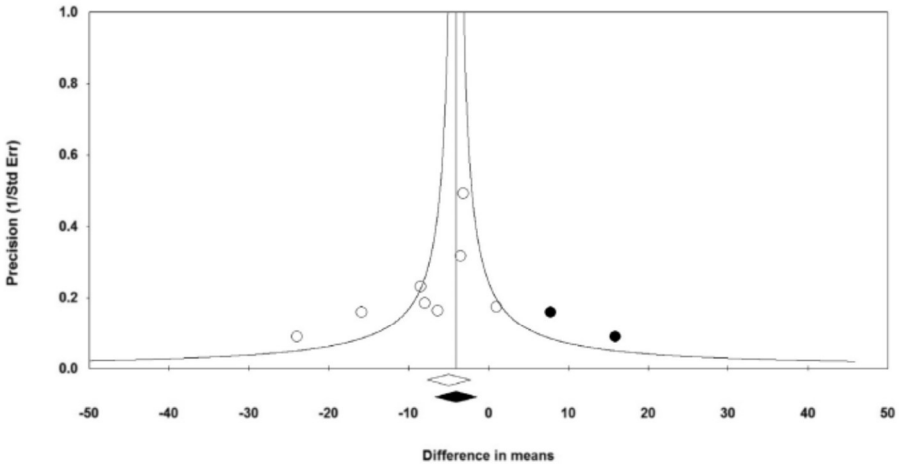
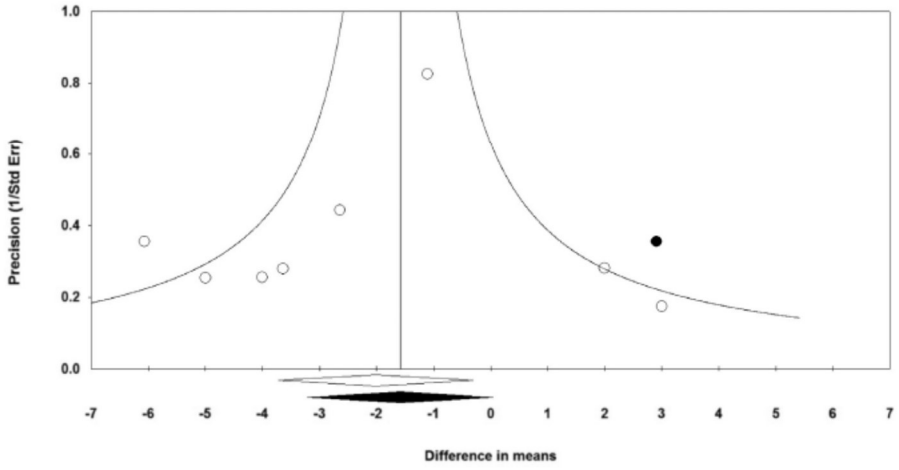
20.20
28.60
37.00
45.40
53.80
62.20
70.60
79.00
Duration (weeks)


Precision (1/Std Err)
1.0
0.8
0.6
0.4
0.2
0.0
-50
-40
-30
-20
-10
0
10
20
30
40
50
Difference in means


Precision (1/Std Err)
1.0
0.8
0.6
0.4
0.2
0.0
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
Difference in means