Tomato and lycopene supplementation and cardiovascular risk factors: A systematic review and meta-analysis

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Short title: Tomato, lycopene and cardiovascular risk factors: A Meta-analysis

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Abstract

Background and aims

Epidemiological evidence suggests an association between consumption of tomato products or lycopene and lower risk for cardiovascular diseases (CVD). Our aim was to evaluate the state of the evidence from intervention trials on the effect of consuming tomato products and lycopene on markers of cardiovascular (CV) function. We undertook a systematic review and meta-analysis on the effect of supplementing tomato and lycopene on CV risk factors.

Methods

Three databases including Medline, Web of science, and Scopus were searched from inception to August 2016. Inclusion criteria were: intervention randomised controlled trials reporting effects of tomato products and lycopene supplementation on CV risk factors among adult subjects >18 years of age. The outcomes of interest included blood lipids (total-, HDL-, LDL-cholesterol, triglycerides, Oxidised-LDL), endothelial function (flow-mediated dilation (FMD), pulse wave velocity (PWV)) and blood pressure (BP). Random-effects models were used to determine the pooled effect sizes.

Results

Out of 1189 publications identified, 17 fulfilled inclusion criteria and were meta-analysed. Overall, interventions supplementing tomato were associated with significant reductions in LDL-cholesterol (-0.22 mmol/L; p=0.006) and improvements in FMD (2.53%; p=0.01); while lycopene supplementation reduced Systolic-BP (-5.66 mmHg; p=0.002). No other outcome was significantly affected by these interventions.

Conclusions

The available evidence on the effects of tomato products and lycopene supplementation on CV risk factors supports the view that increasing the intake of these has positive effects on blood lipids, blood pressure and endothelial function. These results support the development of promising individualised nutritional strategies involving tomatoes to tackle CVD.

Keywords

Tomato, Lycopene, Intervention, cardiovascular risk factors, endothelial function, blood pressure, blood lipids, systematic review, meta-analysis

Introduction

Globally, behavioural risk factors including a range of dietary risks, e.g. low intakes of fruit and vegetables, have the greatest potential to promote disease and impair human health [1]. A wealth of epidemiological evidence indicates that particularly cardiovascular health is strongly influenced by a healthy diet; fruit and vegetables are considered an important element of a cardio-protective diet [2].

The benefit of consuming fruit and vegetables is often ascribed to specific components of food. Recent systematic reviews of the literature indicate that supplementation with dietary nitrates, or foods rich in these compounds such as beetroot, have the potential to lower blood pressure [3] and improve endothelial function [4], both regarded as early indicators of cardiovascular diseases (CVD). These benefits are valuable when developing effective nutritional strategies targeting specific key metabolic risk factors for the prevention and management of CVD.

Vegetables such as tomato are ubiquitous in most dietary patterns across the world and their contribution to health has been documented in longitudinal epidemiologic studies. High self-reported intakes of tomato and tomato products, and of dietary lycopene (a carotenoid compound) are associated with lower risk for CVD [5, 6]. Lycopene is one of the most potent antioxidants and the most predominant carotenoid in human plasma and it is assumed to be one of the active compounds on the health benefits of tomato [7]. While the epidemiological evidence indicates a consistent association between tomato products and/or lycopene and lower CVD risk [5, 6], the effect of nutritional interventions on tomato products and lycopene have been studied only recently and their efficacy on improving vascular function remains to be evaluated. The evidence from human intervention trials on the efficacy of tomato products or lycopene supplementation on oxidative stress and marker of subclinical inflammation (hs-CRP, IL-6) have been previously reviewed and meta-analysed [8]. However, others cardiovascular risk biomarkers, such as blood lipids (total-, HDL-, LDL-cholesterol,

triglycerides, Oxidised-LDL) and endothelial function (FMD, PWV) have not been reviewed previously and a critical appraisal of the literature should be useful in testing this hypothesis. Here, we report the findings of a systematic review and meta-analysis of the evidence from intervention trials investigating the efficacy of tomato products or lycopene supplementation on cardiovascular (CV) risk factors in adult human individuals.

Methods

This systematic review was conducted according to Cochrane [9] and the Centre for Reviews and Dissemination guidelines [10] and is reported according to PRISMA guidelines [11] (Figure 1 and Table S1). The protocol has been registered with PROSPERO, the International Prospective Register of Systematic Reviews (Registration number CRD42016042092).

In August 2016, three electronic databases were searched systematically from inception: Medline, Web of science, and Scopus. Reference lists of identified publications were hand searched to identify other studies potentially eligible for inclusion.

The search strategy included the following terms 1) tomato; 2) lycopene; 3) trial/clinical trials; 4) vascular risk factors; 5) biomarkers; 6) vascular function; 7) endothelial function; 8) blood lipids. The systematic review was restricted to articles published in English.

Two researchers (HMC, JL) assessed articles independently for eligibility. The decision to include studies was hierarchical and made initially on the basis of the studies titles and abstracts. When a study could not be excluded with certainty based on the screening of titles and abstract, the full-text of the article was evaluated to decide its inclusion or exclusion. When full agreement had been reached, the article was either discarded or moved to the next phase (full text screening). The full text of the selected articles was independently assessed by the same researchers.

Inclusion/exclusion criteria

The selection of suitable references during the search strategy and the data extraction was performed according to specific criteria which are delineated below:

Inclusion criteria included: 1) Study Design: intervention studies; 2) Subjects: adult subjects >18 years of age; 3) Interventions: nutritional/dietary interventions (tomato and tomato-based products or lycopene supplements versus a control or placebo group); 4) Outcomes: CV health-related outcome measures (described below). Exclusion criteria included 1) Study Design: non-interventional studies; 2) Subjects: subjects <18 years of age; 3) Interventions: interventions not involving tomato or lycopene, or interventions combined interventions in which the effects of tomato and lycopene cannot be singled out; 4) Outcomes: non-vascular outcome measures.

Data extraction

A standardized, pre-piloted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information included: study design (country, methods of recruitment, follow-up length, methods of analysis, completion rates; participant characteristics (population and setting, inclusion/exclusion criteria, baseline characteristics); description of measurement methods; outcome measures (dietary/nutritional intake, body weigh/composition, CV biomarkers); intervention details (i.e. tomato or lycopene), and information to assess the risk of bias. Study quality was assessed using the Cochrane risk of bias tool [18].

Outcome measures

The primary outcomes of the analyses were changes in CV risk factors after tomato or lycopene supplementation. Measures included blood lipids (Total-, LDL-, and HDL-cholesterol, Triglycerides, Oxidized-LDL), assessment of endothelial function by flow-mediated dilation (FMD), pulse wave velocity (PWV) and resting blood pressure, systolic (SBP) and diastolic (DBP).

Statistical analysis

Review Manager (RevMan Version 5.1 for Windows Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to pool and meta-analyse results from the individual studies. Pooled results are reported as weighted mean differences with 95% CI and with two-sided P-values. A random effects model accounting for inter-study variation was used, thereby minimizing potential bias due to methodological differences between studies. Multiple dietary intervention arms from three studies were included in the meta-analysis. As suggested by Higgins et al. [9], excessive weightings from "double counts" originating from the "shared" group (that is, the control group) were controlled by splitting the sample size of the shared group into approximately equal smaller groups for the comparisons; the means and standard deviations were left unchanged. When available, we used results from multivariate models with the most complete adjustment for potential confounders reported in original studies.

Statistical heterogeneity was evaluated using the I^2 statistic [9, 10]; the 95% CI for I^2 were calculated using Higgins et al.'s method [12, 13]. Where I^2 was >50%, the degree of heterogeneity was considered high. Publication bias was appraised by visual inspection of a funnel plot of effect size against the standard error (SE), with asymmetry assessed formally with Egger's regression test [14]. Quality of studies was assessed using the Jadad system [15].

Results

The searches yielded 1189 publications after de-duplication and results of the screening process are described in **Figure 1**. Seventeen publications that met our inclusion criteria were included in the present systematic review and meta-analysis (**Table 1**) [16-32].

Study characteristics

Twelve studies used a RCT design while five were controlled trials using a non-randomised design. These 17 studies originated from the USA (n=3), UK (n=2), Greece (n=3), Israel (n=3), and single studies from Finland, Germany, Korea, Mexico, India, and Australia.

The pooled study population meta-analysed included 932 participants who were followed-up for 2 months on average (range from 1 day to 6 months). The mean ages of the samples in these studies ranged from 27 to 68 years. Two studies recruited women only. Mean BMI in these studies was 26.1 kg/m^2 (**Table 1**). Nine of the included studies assessed tomato products alone as the intervention agent [16-19, 27-29, 31, 32], seven studies used lycopene alone [20-26] and one study used both tomato products and lycopene [30]. The dose of tomato-products ranged from 70 to 400g/day, and lycopene dose ranged from 4 to 30mg/day.

Two-thirds (n=12) of the reports included in the systematic review came from studies involving healthy participants (**Table 1**). The remaining studies reported the recruitment of participants with underlying cardiometabolic disorders (n=6), such as metabolic syndrome (1 study), CVD (1 study), moderately overweight (1 studies), hypertensive (2 studies) and prehypertensive (1 study).

Meta-analysis of studies supplementing tomato

Six studies, including 401 participants, evaluated the impact of tomato supplementation on LDL-cholesterol. Overall, tomato supplementation significantly reduced LDL-cholesterol by 0.22 mmol/L (95% CI -0.37 to -0.06; p=0.006). Heterogeneity levels assessed by the I^2 test were low at 0% (**Figure 2**).

Six studies, including 233 participants evaluated the impact of tomato supplementation on FMD. Three studies measured FMD acutely (≤24hours) and three studies evaluated FMD in the short term (≥ 1 week). Short-term tomato supplementation significantly increased FMD

by 2.53 percent (95% CI 0.56 to 4.50; p=0.01). Heterogeneity levels assessed by the I^2 test were low at 0%; however acute studies did not show any improvements (**Figure 3**).

There was only weak evidence that tomato interventions had an effect on other CV factors including SBP, DBP, Total- or HDL-cholesterol, triglycerides, Oxidised-LDL, or PWV (Supplementary material Figures S1-S7).

Meta-analysis of studies supplementing lycopene

Seven studies/arms, including 492 participants, evaluated the impact of lycopene supplementation on resting SBP. Overall lycopene supplementation significantly reduced SBP by 5.66 mmHg (95% CI -9.31 to -2.01; p=0.002). Heterogeneity levels assessed by the I^2 test were significant at 65% (**Figure 4**).

There was only weak evidence that lycopene interventions had an effect on other CV factors including DBP, Total- LDL- or HDL-cholesterol, triglycerides, Oxidised-LDL or PWV, (Supplementary material Figures S8-S14).

Quality of studies

We assessed the methodological quality and risk bias of the studies included in this review. The average retention rate for the RCTs included in this review was >90% for all studies and the reason for the dropouts were often not related to the interventions themselves. Therefore, the majority of the included studies satisfied the criteria of the quality assessment tool. Blinding of participants and researchers delivering the intervention was implemented in interventions testing lycopene supplements. In addition, the included studies provided an adequate description of methods and randomization procedures, thus no studies were excluded from analysis based on quality assessment.

Discussion

Principal findings

To our knowledge, this report is the first systematic assessment through meta-analysis of the effectiveness of tomato and lycopene supplementation on CV risk factors among adult subjects >18 years of age within RCTs. This systematic review and meta-analysis revealed that there is strong evidence indicating that tomato supplementation is associated with significant reductions in LDL-cholesterol and improvements in FMD, which in agreement with previous meta-analysis on lycopene being effective in reducing LDL-cholesterol [33]. However, tomato supplementation has no effect on other blood lipids or measures of endothelial function. In addition, lycopene supplementation was associated with significant reductions in SBP but not on any other cardiovascular marker. In a meta-analysis of Li and Xu (2013), indicated that lycopene supplementation can lowering SBP [34]. Together, these results indicate that consuming tomato products and or supplementing lycopene may have important health implications. This systematic review has also revealed that current studies have mostly focused on studying well-established cardiovascular biomarkers such as blood lipids and FMD as a measure of endothelial function, however the evidence on the effect of tomato products or lycopene supplementation on novel biomarkers of vascular risk is scarce at present and requires further investigation.

Strengths and limitations

The strengths of these findings include a rigorous methodology in the systematic review of the literature, the low levels of heterogeneity surrounding the results. It is of note that the intervention studies included in this review were consistently, and significantly, successful in modifying the outcomes above described. The overall quality of the studies was high. All studies were randomized, and double-blind in the case of lycopene supplementation. The

studies reported a high compliance with the interventions, which may be explained by the relatively short duration of the studies.

This study is not without limitations. Due to the limited number of studies available, our analysis focused on examining the overall effects of interventions on the pre-specified outcomes preventing us of exploring the effects of common moderator variables such as age, gender, or other aspects of the interventions. This systematic review revealed that the evidence on the effect of tomato products or lycopene supplementation on novel biomarkers of CV risk is still scarce and needs further investigation. Overall, studies were characterized by a small sample size, short duration, and over-representation of young, healthy men. Heterogeneity was observed across lycopene supplementation, which could be due to the inconsistency of participants' health status; healthy adults, hypertension, CVD patients and metabolic syndrome patients were collected. In addition, studies included in meta-analysis originated from different geographic regions, and the dietary patterns, genetic and sensitivity of lycopene might preform differently. We did not conduct subgroup analysis due to the limited studies. Therefore, we were not able to confirm the whether processing of tomatoes have strongly affect lycopene concentration and bioavailability. In addition, most of studies on the fresh tomato/ tomato juice did not provide the lycopene content. We limited the choice of databases to three and although there might be a risk to have overlooked some studies, the databases included were considered the most relevant to the topic of study.

Scientific analysis of findings

This meta-analysis showed that tomato products supplementation was associated with significant reductions in LDL-cholesterol and improvements in short-term FMD, while lycopene supplementations reduced SBP. The beneficial effects of these interventions support the epidemiological evidence indicating an association between lower CVD risk and tomato

[5, 6] and suggest that these epidemiological findings may be explained by a potential combination of improvements in blood lipids, blood pressure, and endothelial function an early marker of cardiovascular risk [35].

A number of potential mechanisms are probably responsible behind the findings of this systematic review. Lycopene, the major carotenoid in tomato, might be more important than other carotenoids in preventing atherosclerosis and cardiovascular diseases, however the findings from supplementing lycopene this systematic review did not support a role in reducing LDL-cholesterol. This may be related to the fact that tomatoes contain also other compounds (eg antioxidants such as vitamin C) possessing lipid-lowering properties associated with increased faecal excretion and reduced intestinal absorption of cholesterol, in addition to increasing cellular LDL receptor activity [28, 36].

In addition, the results of the present meta-analysis are comparable to those achieved by other nutritional interventions such as dietary nitrates modifying SBP and FMD. In recent previous reports by our group, two systematic reviews of the literature showed that inorganic nitrate or beetroot juice consumption were associated with significant reductions in SBP (-4.4mmHg 95% CI: -5.9, -2.8; $P< 0.001$) [3] , and improvements in FMD (SMD 0.52; 95 % CI 0.15, 0.68; $P = 0.002$) [4].

Implications for health and future research

Our results showed a significant decline in vascular risk factors after short-term (1 day to 6 months) tomato-products and lycopene (tomato-products doses from 70 to 400g/day, and lycopene dose ranged from 4 to 30mg/day) supplementation, which may potentially have important implications in primary and secondary prevention of atherosclerosis, cardiovascular diseases and cardiovascular mortality. The seventh report of the Joint National Committee on BP estimated that a systolic BP reduction of at least 5 mm Hg (similar to the

observed decline in SBP after Lycopene supplementation) could decrease the risk of mortality due to stroke by 13-14% [37, 38] and mortality from cardiovascular diseases by 9% [37]. In addition, reductions of 1 mmol in LDL-cholesterol have been associated with a 23% reduction in myocardial infarction or coronary death and 12% reduction in all-cause mortality [39]. In relation with our findings on FMD, several recent systematic reviews and meta-analysis indicate that increases in FMD of 1% increase, independently of confounding factors, are associated with reductions ranging from 10-13% in the risk of cardiovascular events [40-42].

Conclusions

The available evidence on the effects of tomato and lycopene supplementation on vascular risk factors supports the view that increasing the intake of these has positive effects on blood lipids, blood pressure and endothelial function. These results have potential public health implications and support the development of promising individualised nutritional strategies to tackle cardiovascular diseases.

Competing interests

The authors declare that they have no competing interests

Financial support (if applicable)

This study had no financial support

Author contributions (mandatory)

JL, GK, and HMC conceived and designed the study. HMC and JL performed searches, extracted data, and conducted meta-analyses. GK, JKL, and MS oversaw the project. JL and HMC wrote the first draft. All authors reviewed the study findings and commented and approve the final version before submission.

Acknowledgments

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Legends

Figure1. PRISMA flow diagram of selection of studies on lycopene or tomato consumption and vascular risk factors

Table 1. Characteristics of studies included in systematic review.

M, Male; F, Female; RCT, randomised controlled trial; wk, weeks; BMI, Body mass index; TC, Total cholesterol; TG, Triglyceride; HDL, High density lipoprotein; LDL, Low density lipoprotein; OxLDL, Oxidised low-density lipoproteins; FMD, Flow-mediated dilation; SBP, Systolic blood pressure, DBP, Diastolic blood pressure; PWV, Pulse wave velocity

Figure 2. Meta-analysis of effect of interventions supplementing tomato on LDL cholesterol

Figure 3. Meta-analysis of effect of interventions supplementing tomato on Flow mediated dilation (%)

Figure 4. Meta-analysis of effect of interventions supplementing lycopene on systolic blood pressure (mmHg).

Reference (Country of origin)	Health status	Sample/Sex	Age (SD)	BMI	Study design	Duration	Intervention (Active component)	Dose	Control group	Outcomes studied
Blum et al., 2006 (Israel)	Healthy	Tomato (M=16, F=34); Control (M=16, F=32)	45.5±14.1	N/A	Parallel, controlled	4 wk	Usual diet supplement with tomato	300g tomato products per day	Usual diet without tomato (no placebo)	TC, TG, HDL, LDL
Burton-Freeman et al., 2012 (USA)	Healthy	M=13; F=12	27±8	22	Crossover RCT	360 min	Usual diet with tomato-containing meal	Around 85g of tomato paste	Usual diet without tomato-containing meal	TG, OxLDL, FMD
Collins et al., 2004 (USA)	Healthy	M=5, F=5	M (49 (43-68)); F (51 (35-63))	M=26.3; F=29.1	Crossover, RCT	3 wk	Low lycopene diet supplemented tomato juice	18.4mg lycopene per day	Low lycopene diet	TC, TG, HDL
Cuevas-Ramos et al., 2013 (Mexico)	Healthy	Tomato (M=6, F=20); Control (M=5, F=19)	42±15.5	27.1	Parallel, RCT, single-blind	4 wk	Usual diet supplemented with raw tomato	300g of raw tomato per day	Usual diet with 300g of raw cucumber	TC, TG, HDL, LDL
Devaraj et al., 2008 (USA)	Healthy	6.5mg lycopene (M=4, F=17); 15mg lycopene (M=4, F=13); 30mg lycopene (M=7, F=14); Placebo (M=4, F=14)	6.5mg lycopene (51.1±5.9); 15mg lycopene (49.8±8.2); 30mg lycopene (51.2±9.7); Placebo (49.9±15.8)	6.5mg lycopene=29.6; 15mg lycopene=25.4; 30mg lycopene=26.4; Placebo=28.1	Parallel, RCT, doubled-blind	8 wk	Lycopene restricted diet with supplemented lycopene capsules	6.5, 15, or 30mg per day	Placebo capsules (Lycopene restricted diet)	TC, TG, HDL, LDL

Reference (Country of origin)	Health status	Sample/Sex	Age (SD)	BMI	Study design	Duration	Intervention (Active component)	Dose	Control group	Outcomes studied
Engelhard et al., 2006 (Israel)	Hypertension, without concomitant diseases	M=18, F=12	48	29.5	Non-randomised single-blind placebo-controlled trial	8 wk	Usual diet supplemented with lycopene capsule (Lyc-O-Mato)	250mg of tomato extract capsule containing 15mg lycopene per day	Usual diet with identical-looking placebo capsule	TC, TG, HDL, LDL, SBP, DBP
Gajendragadkar et al., 2014 (UK)	Healthy and CVD patients	Healthy (7mg M=23, F=1; control M=10, F=2); CVD patients (7mg M=15, F=9; control M=10, F=2)	Healthy (7mg=61±13, control=68±5); CVD patients (7mg =67±6, control=68±5)	Healthy (7mg=25.2; control=26.7); CVD patients (7mg 28.6; control=28.4)	Parallel, RCT, double-blind	8 wk	Usual diet with lycopene capsule	7mg lycopene daily per day	Usual diet with identical-looking placebo capsule	HDL, LDL, OxLDL, SBP, DBP, PWV
Kim et al., 2011 (Korea)	Healthy	6mg lycopene (n=41); 15mg lycopene (n=37); Control (n=38)	6mg lycopene (34.8±1.28); 15mg lycopene (34.7±1.23); Control (33.5±1.13)	6mg lycopene=25.3; 15mg lycopene=23.9; Control=24.9	Parallel, RCT, double-blind	8 wk	Usual diet supplemented with lycopene capsules (Lyc-O-Mato)	6mg or 15mg lycopene per day	Usual diet with placebo containing soybean oil capsules	SBP
Misra et al., 2006 (India)	Healthy postmenopausal women	Lycopene supplement (F=20); Hormone replacement therapy (HRT) (F=21)	46	Lycopene=25.8; HRT=25.3	Parallel, RCT	6 months	Lycopene capsule (LycoRed)	2 lycopene capsules each containing 2mg of lycopene per day	Hormone replacement therapy (estradiol valerate 2mg and norethisterone acetate 1mg)	TC, TG, HDL, LDL

Reference (Country of origin)	Health status	Sample/Sex	Age (SD)	BMI	Study design	Duration	Intervention (Active component)	Dose	Control group	Outcomes studied
Paran et al., 2009 (Israel)	Hypertension patient	M=26, F=24	61.4±8.9	N/A	Crossover RCT	6 wk	Usual diet supplemented with lycopene capsules (Lyc-O-Mato)	250mg of tomato extract capsule containing 15mg lycopene per day	Usual diet with identical-looking placebo capsule	SBP, DBP
Ried et al., 2009 (Australia)	Prehypertensive	Lycopene (n=15); Control (n=10)	Tomato extract (51.2±12.1); Control (57.9±13.4)	N/A	Parallel, RCT	8 wk	Usual diet supplemented with lycopene capsules (Lyc-O-Mato)	Tomato extract capsule containing 15mg lycopene per day	Usual diet supplemented with identical-looking placebo capsule containing mainly soy oil	SBP, DBP
Samaras et al., 2014 (Greece)	Ultra-marathon runners	Tomato Juice (n=15); Control (n=12)	Tomato Juice (44.9±8.53); Control (46.6±15.3)	Tomato Juice=24.1; Control=24.3	Parallel, controlled	8 wk	Tomato juice	Amount required to match subjects usual carbohydrate supplementation	Continued any usual supplementation consumption	TC, TG, HDL, LDL, FMD
Silaste et al., 2007 (Finland)	Healthy	M=5; F=16	30	23.5	Sequential 3 weeks low tomato, 3 weeks high tomato	6 wk	Usual diet supplemented with tomato juice	400ml tomato juice containing 27mg lycopene	Usual diet without tomato products	TC, LDL
Stangl et al., 2011 (Germany)	Healthy postmenopausal women	F=19	58.9±6.3	25	Crossover, RCT	7 d	Tomato free diet supplemented with buttered roll with tomato puree	70g tomato puree containing 46.2mg lycopene	Tomato free diet supplemented with buttered roll without tomato puree	FMD

Reference (Country of origin)	Health status	Sample/Sex	Age (SD)	BMI	Study design	Duration	Intervention (Active component)	Dose	Control group	Outcomes studied
Thies et al., 2012 (UK)	Moderately overweight	High tomato (M=35, F=46); Lycopene (M=28, F=40); Control (M=30, F=46)	High tomato (51±0.7(SEM)); Lycopene (51.1±0.9(SEM); Control (51±0.7(SEM))	High tomato=26.4; Lycopene=26.7; Control=26.8	Parallel, RCT, single-blind	12 wk	1, High tomato based diet or 2, low tomato diet supplemented with lycopene capsule	1, High tomato diet were above the minimum target of 7mg per day 2, Low tomato diet with lycopene capsules containing 10mg lycopene	Low tomato diet (low in tomato-based foods)	TC, TG, HDL, LDL, OxLDL, SBP, DBP, PWV
Tsitsimpikou et al., 2014 (Greece)	Patients with metabolic syndrome	Tomato (M=13, F=2); Control (M=11, F=1)	Tomato (53.5±9.8); Control (56.6±10.2)	N/A	Parallel, controlled	8 wk	Usual diet supplemented with tomato juice	Tomato juice with 2.51mg lycopene per 100 ml	Usual diet without tomato juice	TC, TG, HDL, LDL
Xaplanteris et al., 2012 (Greece)	Healthy	M=8, F=11	39±13	24.8	Crossover, RCT, single-blinded	2 wk	usual diet supplemented with tomato paste	70g of tomato paste containing 33.3mg lycopene per day	Usual diet without tomato paste	FMD

Figure 1

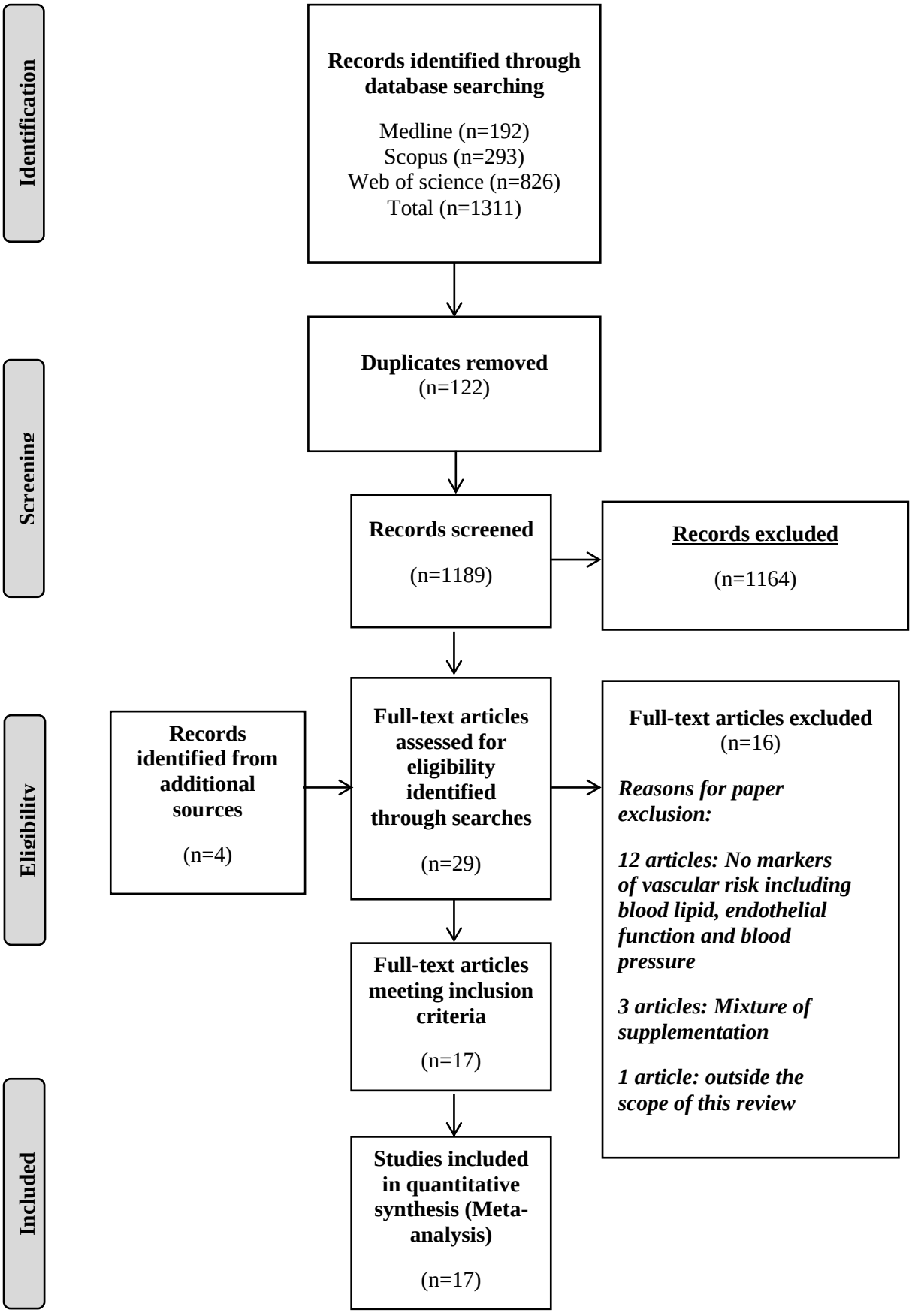

Identification
Screening
Eligibility
Included
Records identified through database searching
Medline (n=192)
Scopus (n=293)
Web of science (n=826)
Total (n=1311)
Duplicates removed
(n=122)
Records screened
(n=1189)
Records excluded
(n=1164)
Records identified from additional sources
(n=4)
Full-text articles assessed for eligibility identified through searches
(n=29)
Full-text articles excluded
(n=16)
Reasons for paper exclusion:
12 articles: No markers of vascular risk including blood lipid, endothelial function and blood pressure
3 articles: Mixture of supplementation
1 article: outside the scope of this review
Full-text articles meeting inclusion criteria
(n=17)
Studies included in quantitative synthesis (Meta-analysis)
(n=17)

Figure 2

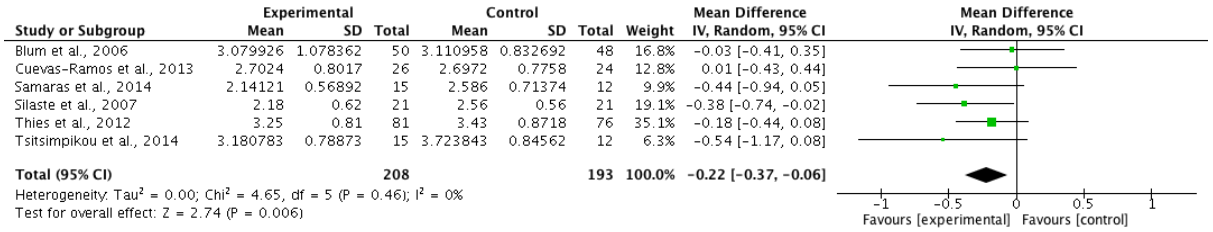

Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup
Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Blum et al., 2006 3.079926 1.078362 50 3.110958 0.832692 48 16.8% -0.03 [-0.41, 0.35]
Cuevas-Ramos et al., 2013 2.7024 0.8017 26 2.6972 0.7758 24 12.8% 0.01 [-0.43, 0.44]
Samaras et al., 2014 2.14121 0.56892 15 2.586 0.71374 12 9.9% -0.44 [-0.94, 0.05]
Silaste et al., 2007 2.18 0.62 21 2.56 0.56 21 19.1% -0.38 [-0.74, -0.02]
Thies et al., 2012 3.25 0.81 81 3.43 0.8718 76 35.1% -0.18 [-0.44, 0.08]
Tsitsimpikou et al., 2014 3.180783 0.78873 15 3.723843 0.84562 12 6.3% -0.54 [-1.17, 0.08]
Total (95% CI) 208 193 100.0% -0.22 [-0.37, -0.06]
Heterogeneity: Tau² = 0.00; Chi² = 4.65, df = 5 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)
-1
-0.5
0
0.5
1
Favours [experimental]
Favours [control]

Figure 3

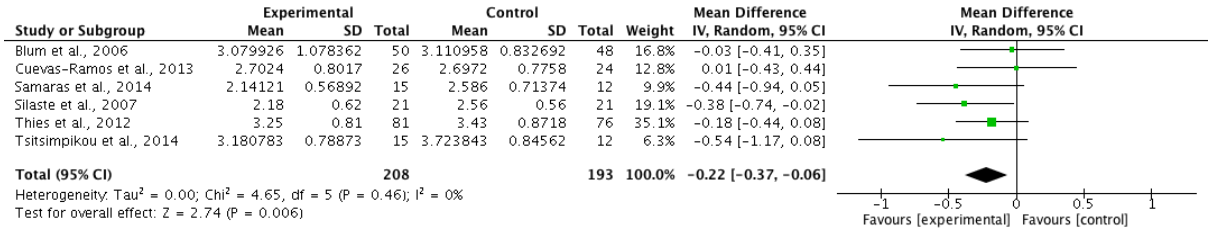
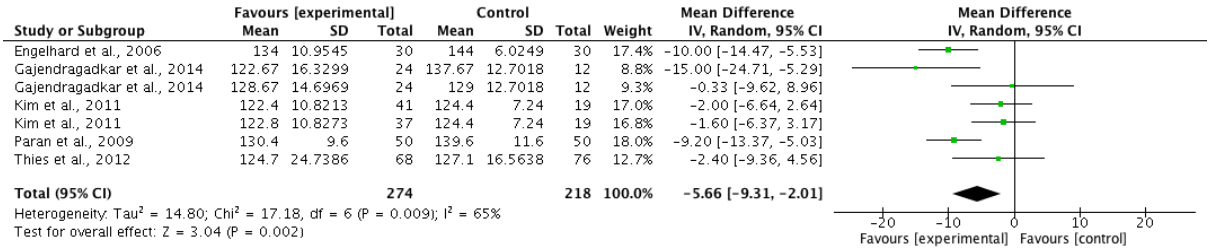

Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup
Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Blum et al., 2006 3.079926 1.078362 50 3.110958 0.832692 48 16.8% -0.03 [-0.41, 0.35]
Cuevas-Ramos et al., 2013 2.7024 0.8017 26 2.6972 0.7758 24 12.8% 0.01 [-0.43, 0.44]
Samaras et al., 2014 2.14121 0.56892 15 2.586 0.71374 12 9.9% -0.44 [-0.94, 0.05]
Silaste et al., 2007 2.18 0.62 21 2.56 0.56 21 19.1% -0.38 [-0.74, -0.02]
Thies et al., 2012 3.25 0.81 81 3.43 0.8718 76 35.1% -0.18 [-0.44, 0.08]
Tsitsimpikou et al., 2014 3.180783 0.78873 15 3.723843 0.84562 12 6.3% -0.54 [-1.17, 0.08]
Total (95% CI) 208 193 100.0% -0.22 [-0.37, -0.06]
Heterogeneity: Tau² = 0.00; Chi² = 4.65, df = 5 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)
-1
-0.5
0
0.5
1
Favours [experimental]
Favours [control]

Figure 4


Favours [experimental]
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Engelhard et al., 2006 134 10.9545 30 144 6.0249 30 17.4% -10.00 [-14.47, -5.53]
Gajendragadkar et al., 2014 122.67 16.3299 24 137.67 12.7018 12 8.8% -15.00 [-24.71, -5.29]
Gajendragadkar et al., 2014 128.67 14.6969 24 129 12.7018 12 9.3% -0.33 [-9.62, 8.96]
Kim et al., 2011 122.4 10.8213 41 124.4 7.24 19 17.0% -2.00 [-6.64, 2.64]
Kim et al., 2011 122.8 10.8273 37 124.4 7.24 19 16.8% -1.60 [-6.37, 3.17]
Paran et al., 2009 130.4 9.6 50 139.6 11.6 50 18.0% -9.20 [-13.37, -5.03]
Thies et al., 2012 124.7 24.7386 68 127.1 16.5638 76 12.7% -2.40 [-9.36, 4.56]
Total (95% CI) 274 218 100.0% -5.66 [-9.31, -2.01]
Heterogeneity: Tau² = 14.80; Chi² = 17.18, df = 6 (P = 0.009); I² = 65%
Test for overall effect: Z = 3.04 (P = 0.002)
-20
-10
0
10
20
Favours [experimental]
Favours [control]

Supplementary material

Figure S1. Meta-analysis of effect of interventions supplementing tomato on total cholesterol (mmol/L).

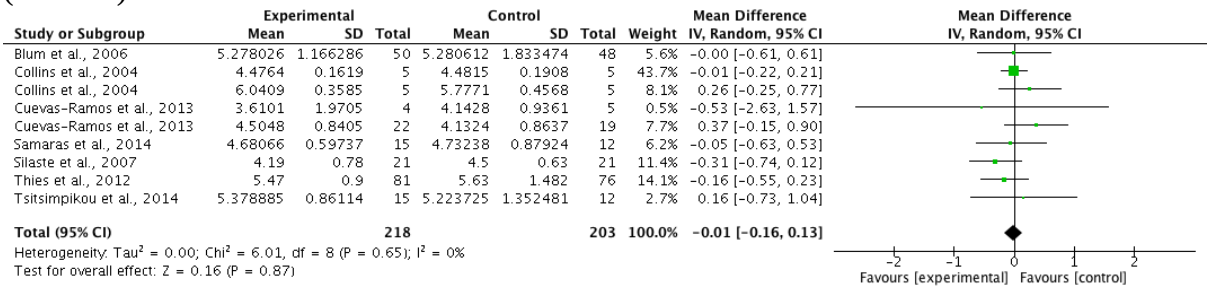


Figure S2. Meta-analysis of effect of interventions supplementing tomato on triglyceride (mmol/L).

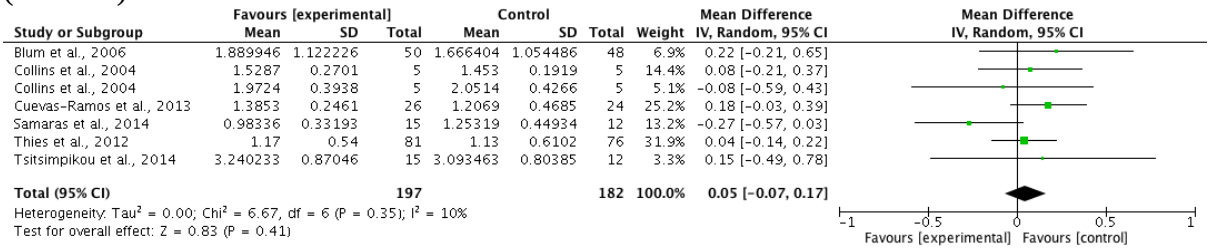


Figure S3. Meta-analysis of effect of interventions supplementing tomato on HDL cholesterol (mmol/L).

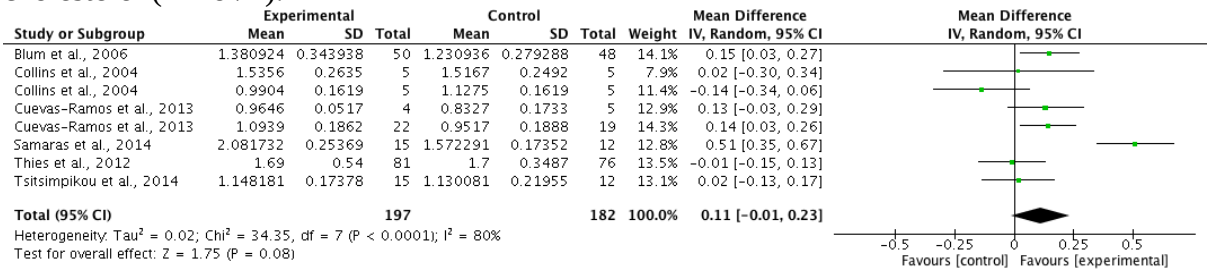


Figure S4. Meta-analysis of effect of interventions supplementing tomato on Oxidised-LDL (mmol/L).

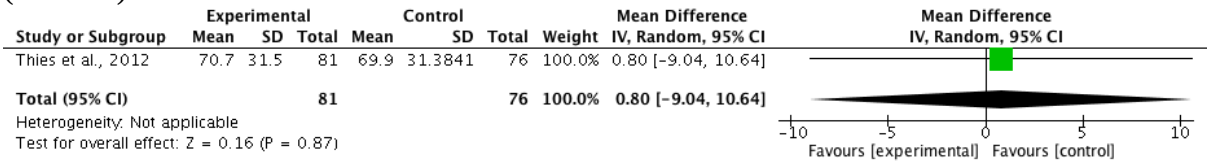


Figure S5. Meta-analysis of effect of interventions supplementing tomato on systolic blood pressure (mmHg).

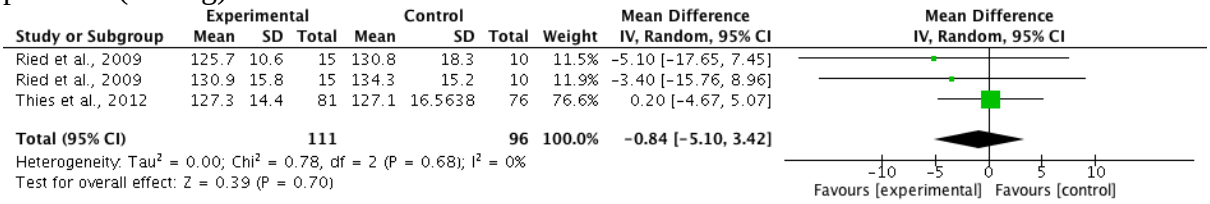


Figure S6. Meta-analysis of effect of interventions supplementing tomato on diastolic blood pressure (mmHg).

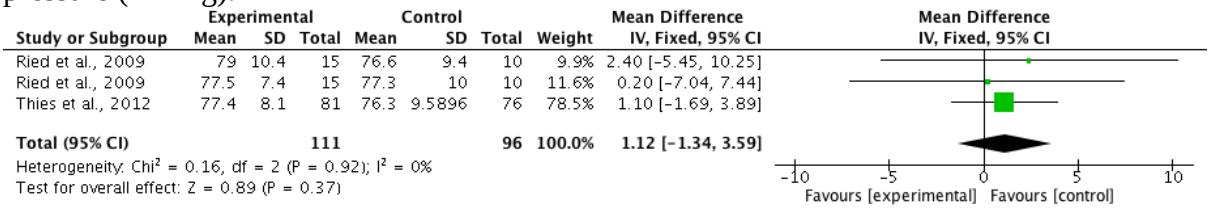


Figure S7. Meta-analysis of effect of interventions supplementing tomato on pulse wave velocity (m/s).

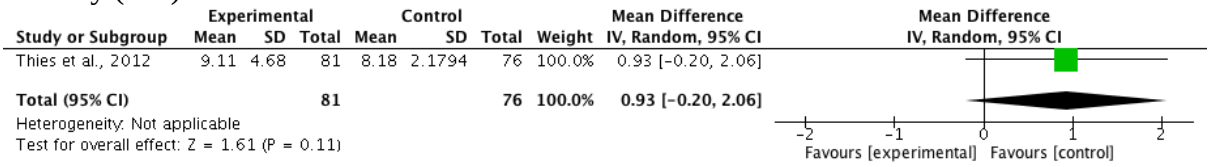


Figure S8. Meta-analysis of effect of interventions supplementing lycopene on total cholesterol (mmol/L).

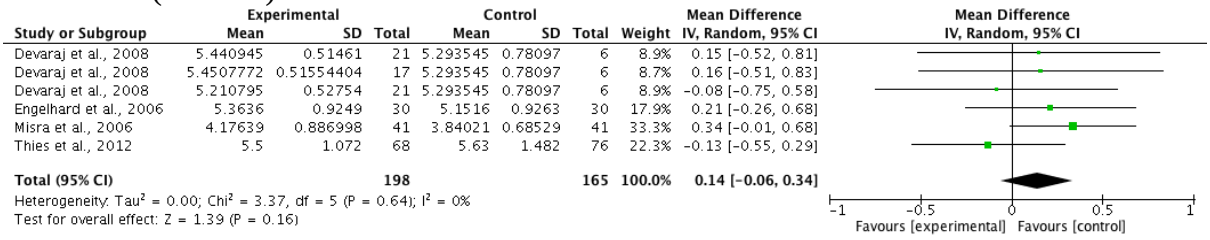


Figure S9. Meta-analysis of effect of interventions supplementing lycopene on triglyceride (mmol/L).

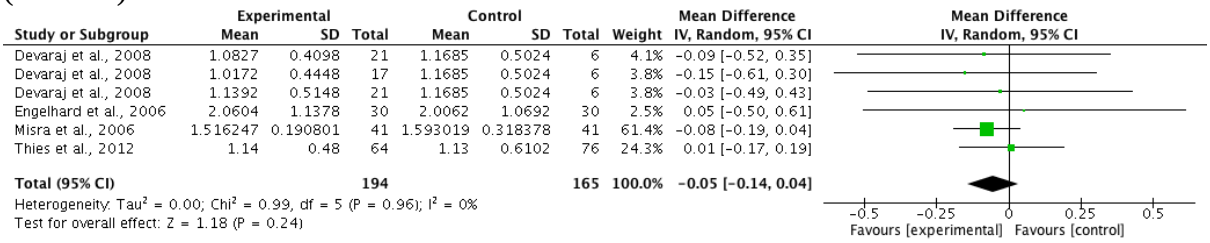


Figure S10. Meta-analysis of effect of interventions supplementing lycopene on HDL cholesterol (mmol/L).

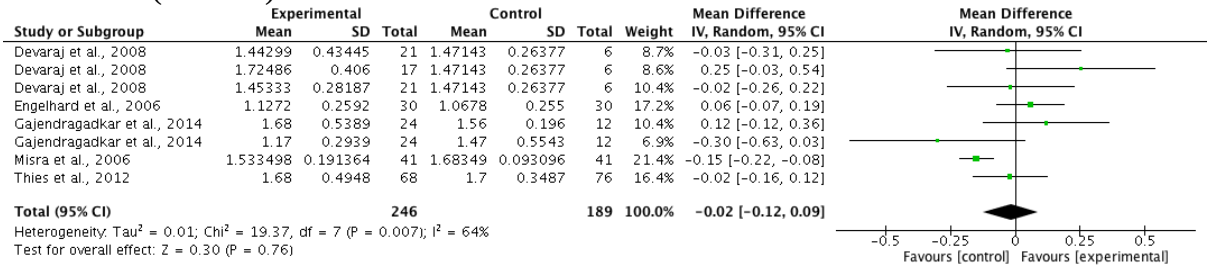


Figure S11. Meta-analysis of effect of interventions supplementing lycopene on LDL cholesterol (mmol/L).

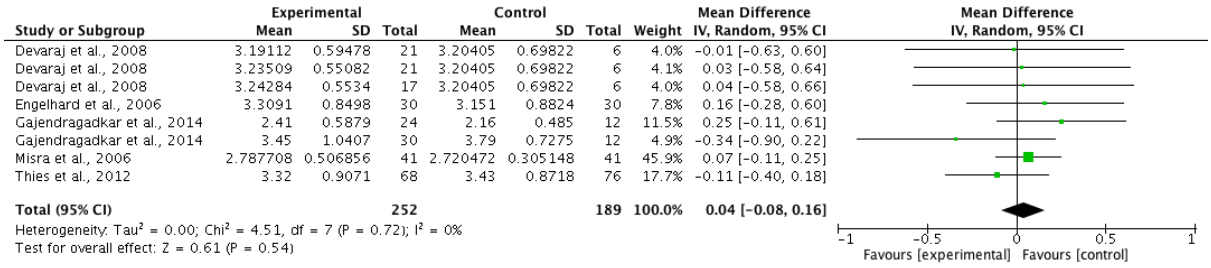


Figure S12. Meta-analysis of effect of interventions supplementing lycopene on Oxidised-LDL (mmol/L).

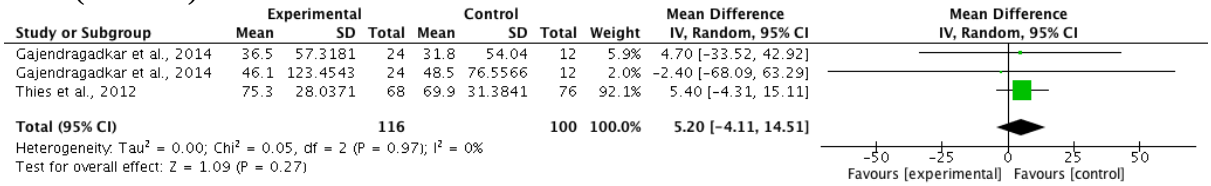


Figure S13. Meta-analysis of effect of interventions supplementing lycopene on diastolic blood pressure (mmHg).

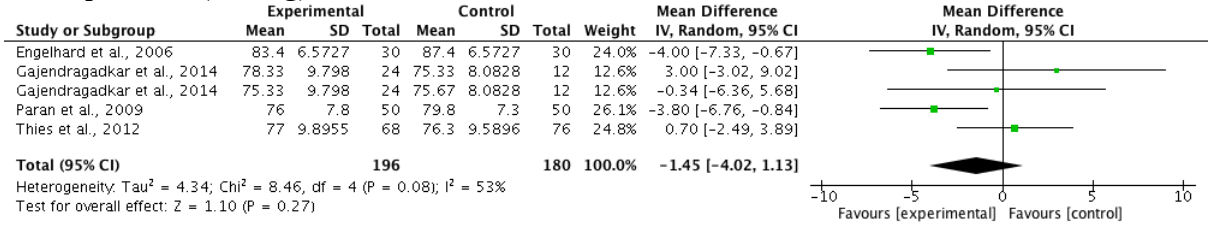


Figure S14. Meta-analysis of effect of interventions supplementing lycopene on pulse wave velocity (m/s).

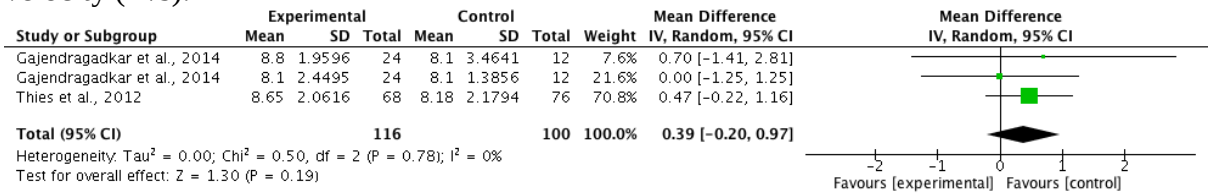


Table S1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7