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The effect of L-arginine supplementation on lipid profile: A systematic review and meta-analysis of randomized controlled trials

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Abstract

A number of clinical trials have examined the effect of L-arginine on lipid profile in recent years; however, the results remain equivocal. Therefore, the present study aims to summarize and quantitatively examine the available evidence on the effectiveness L-arginine supplementation on lipid parameters by employing a systematic review and meta-analytic approach. Online databases including PubMed, Scopus, ISI Web of Science, Cochrane library, and Google Scholar were searched up to April 2019 for randomized controlled trials that examined the effect of L-arginine supplementation on lipid profile in adults. Treatment effects were expressed as weighted mean difference (WMD) and the corresponding standard error (SE) in concentrations of serum lipids. To estimate the overall effect of L-arginine supplementation, we employed the random-effects model. In total, 12 studies were included in the systematic review. The meta-analysis revealed that L-arginine supplementation did not significantly change the concentrations of total cholesterol (WMD: -5.03 mg/dl; 95% CI: - 10.78 to 0.73, P= 0.08, I^2=39.0%), low-density lipoprotein (WMD: -0.47 mg/dl; 95% CI: -3.61

to 2.66, P=0.76, I^2=0.0%), or high-density lipoprotein (WMD: 0.57 mg/dl; 95% CI: -1.28 to 2.43, P=0.54, I^2=68.4%). A significant reduction was observed only in serum triglyceride (TG) levels (WMD: -7.04 mg/dl; 95% CI: -11.42 to -2.67, P<0.001, I^2=0.0%). This meta-analysis concludes that L-arginine supplementation can significantly reduce blood TG levels, however, there is insufficient evidence to support its hypocholesterolaemic effects. To draw straightforward conclusions regarding generalized recommendations for L-arginine supplementation for improving lipid profile, there is a need for more well-controlled trials targeting exclusively patients with dyslipidaemia.

Keyword: L-arginine, Supplementation, Lipid profile, Systematic review, Meta-analysis

Introduction

Cardiovascular diseases (CVDs) are the leading causes of death among non-communicable diseases, posing a significant health and economic burden worldwide [1; 2]. The American Heart Association reported that 17.7 million people (representing 31% of all global deaths) died from CVDs in 2015, and this number is projected to rise to 23.6 million deaths by 2030 [3]. Dyslipidemia has been identified as a major risk factor for CVDs [4; 5; 6]. Thus, regulating and maintaining an optimal lipid profile is critical for the prevention of CVDs. In this regard, statin therapy and diet modification are two of the most commonly prescribed approaches [7; 8]. However, statins, among other commonly used lipid lowering pharmacotherapies [9], have been established to pose some serious adverse effects, such as myopathies and hepatotoxicity [10; 11]. Thus, there is a demand to identify viable, anti-lipid agents that are able to pose cardio-protective effects without inducing any side-effects.

L-arginine is a semi-essential amino acid which our body derives either from dietary sources or from endogenous metabolism [12; 13]. L-arginine is involved in several biochemical processes, including polyamine synthesis, ammonia detoxification, immune modulation, and secretion of hormones such as glucagon and growth hormone and insulin [14; 15; 16]. What is more, this amino acid produces nitric oxide (NO), a key molecule involved in the regulation of cell metabolism, insulin signaling and secretion, neurotransmission and immune system function [17; 18]. It is suggested that L-arginine can be useful in improving lipid profile, due to its' potential to increase NO production. Therefore, L-arginine has been investigated as a potentially cardio-protective compound, and seven meta-analyses concluded that it can be an effective tool in blood pressure management [19]. Several trials investigated the potential of L-arginine supplementation for the treatment of abnormal lipid profile, however, the results are inconsistent. For instance, some trials report that L-arginine supplementation induced a reduction in circulating concentrations of lipid parameters [20; 21; 22; 23], while others report no significant effect [18; 24; 25; 26; 27; 28; 29; 30]. Discrepancies in the findings may conceivably be attributed to the differences in study designs, characteristics of study participants, duration and the supplementation dosage applied in the trials. Therefore, we conducted a meta-analysis of those randomized controlled trials (RCTs) to examine the efficacy of L-arginine supplementation as a lipid-lowering agent.

Methods

We conducted and reported the present systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 1) [31] for identification, screening, eligibility, and inclusion of articles. This study was not prospectively registered. Participants, interventions, comparisons, outcomes, and study design (PICOS) are shown in **Table 1**.

Search strategy

To carry out this meta-analysis, two independent investigators (A.H. and E.Gh) performed a systematic search of all articles published until April 2019 in the following online databases: PubMed, Scopus, Cochrane Library, ISI Web of Science, and Google Scholar. We used the following Medical Subject Headings (MeSH) and corresponding keywords: (“arginine” OR “L-arginine”) AND (“lipid” OR “hyperlipidaemia” OR “dyslipidemia” OR “cholesterol” OR “CHOL” OR “hypercholesterolemia” OR “lipoprotein” OR “hyperlipoproteinemia” OR “high density lipoprotein” OR “HDL” OR “low density lipoprotein” OR “LDL” OR “triglyceride” OR “TG”) AND ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment"). The two reviewers also performed screening of the reference lists of relevant review articles and original papers that were selected for full-text review to identify potential eligible studies. Additionally, an email alert service was employed to avoid missing any relevant articles. The language of the retrieved papers was restricted to English, while there were no restrictions regarding the year of publication.

Study selection

All studies retrieved from the electronic databases and reference lists were entered into endnote software (EndNote X6, Thomson Corporation, Stamford, USA) and duplicate studies were removed. In the next step, the titles and abstracts of the papers were examined by two independent reviewers (A.A and E.Gh) to exclude irrelevant articles. Afterwards, the full texts of the remaining publications were read and assessed according to the following four items: study design, participants, interventions and outcome measures. Finally, the studies were retained if they met the following inclusion criteria: (1) a randomized controlled design; (2) reporting the effect of L-arginine on at least one of the lipid profile parameters including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c); (3) intervention duration longer than 4 weeks. Studies were excluded if they: (1) involved L-arginine supplementation in combination with some drugs or other types of supplements (minerals, vitamins or herbal supplements, unless a separate arm controlled the effect of the mixed substance); (2) reported duplicate data (in this case, the data with complete follow-up and outcome measures was included), (3) included adolescents as the population; (4) were not peer-reviewed articles (protocol or conference proceeding). Any disagreements regarding the process of study selection were resolved in consultation with the principal investigator (A.H).

Data extraction

The major demographic and clinical data from each of the selected studies were screened and extracted independently by two investigators (A.H and E.Gh) using a pre-designed Excel sheet. Any controversy was solved via discussion with a third, independent researcher to reach a consensus. The extracted information was as follows: the first author's last name, publication year, study design, country, sample size, participants mean age, gender, baseline body mass index (BMI), follow-up duration, intervention duration (in weeks), type of intervention, dose of L-arginine (g/day), type of control, health status of the participants, and main results. Corresponding authors were contacted if there were any missing data.

Quality assessment

The Cochrane Collaboration tool [32] was used for quality assessment, and it includes seven items, namely: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. Each domain was classified into three categories: low risk of bias, high risk of bias and unclear risk of bias. Finally, the overall quality of the studies was categorized into weak, fair, or good, if <3, 3, or ≥ 4 domains were rated as low risk, respectively. Quality assessment was performed independently by two reviewers (A.A and E.Gh), while any disagreements were resolved by consulting the third reviewer (A.H).

Statistical analysis

For carrying out the meta-analysis, we employed the STATA software (version 11; StataCorp). If outcome measures were reported in mmol/l, they were converted to mg/dL. The reviewers then extracted the mean difference between the baseline and endpoint data and the corresponding standard deviations (SD) in both intervention and control groups. If such data were not available, the mean difference was obtained by subtracting the mean value of the baseline-point from that of the endpoint. If SD of the mean difference was not reported, it was calculated using the following formula: SD = square root [(SD pre-treatment)^2 + (SD post-treatment)^2 – (2 × R × SD pretreatment × SD post-treatment)]. To ensure the meta-analysis was not sensitive to the selected correlation coefficient (R = 0.5), all analyses were repeated using correlation coefficients of 0.2 and 0.8. Where a standard error (SE) was only reported, SD was estimated using the following formula: SD = SE × √n (n being the number of subjects in each group). Using random-effects model developed by DerSimonian and Laird[33], the summary estimate was pooled as weighted mean difference (WMD) and 95% confidence interval (CI). The inconsistency index (I^2) was used to quantify statistical heterogeneity in the meta-analyses, and values greater than 50% were considered indicative of high heterogeneity. To identify the source of heterogeneity, subgroup analysis was conducted focusing on: mean age, baseline BMI, dose of L-arginine supplementation, study duration, and participant's health status. Sensitivity analysis was also performed to explore the extent to which inferences might depend on a particular study using the leave-one-out method (i.e. deleting one trail at a time and re-calculating the effect size). To assess publication bias, Begg [34] and Egger's [35] regression tests were performed. In all statistical analyses, level of significance was set at $P < 0.05$.

Results

Flow of study selection

A total of 2216 publications were identified after the search of the electronic databases, out of which 755 were removed as being duplicate (**Figure 1**). By reviewing the title and abstracts of the remaining articles, 1438 publications not meeting the inclusion criteria were excluded. Subsequently, 23 full-text articles were carefully reviewed and 11 clinical trials were excluded because of the following reasons: five studies had a duration of supplementation period less than 4 weeks, one study enrolled adolescents, two studies involved interventions that were a combination of other components together with L-arginine and the design did not enable evaluating L-arginine effect only, one study enrolled less than 10 participants, and two articles reported the results from a same population. Finally, 12 trials
(18; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30)

including 15 treatment arms were considered eligible for the systematic review. However, one of the included articles [28] did not report the data required for the meta-analysis. We contacted the corresponding author of the study twice, but did not receive any response, and therefore it was subsequently, excluded, leaving 11 studies for inclusion in the meta-analysis. [18; 20; 21; 22; 23; 24; 25; 26; 27; 29; 30]

Study and participant characteristics

Characteristics of the included trials are outlined in **Table 2**. In total, 631 participants were enrolled in the selected articles, out of which 359 individuals were allocated to L-arginine supplementation group and 272 subjects to the control group. These studies were published between 1996 and 2019 and were carried out in the Iran [20; 21; 22; 23; 29], Italy [27], Poland [18; 24; 26], Israel [28], United Kingdom [30], and Germany [25]. All studies except two [28; 30] adopted a parallel study design. The mean age of the participants ranged from 20.86 to 64.5 years old and the mean baseline BMI varied from 23.67 to 38.35 kg/m^2. Only one [21] of included studies involved exclusively male population, two involved women, and the other trials involved [28; 29] populations of mixed genders. The follow-up period ranged from 4 to 77 weeks. Daily supplementation dosage of L-arginine varied between 1 and 21 g/day in these studies. The health status of the included participants was mixed, and included: type 2 diabetes patients [22], postmenopausal women [28], patients with CVD [26], subjects with hypercholesterolemia [30], obese individuals [18; 20; 24; 29], subjects with hypertriglyceridemia [25], individuals with metabolic syndrome [23], healthy subjects [21], and those with impaired glucose tolerance and metabolic syndrome [27]. No major adverse effects attributable to intervention or control were reported in RCTs.

In a study by Pourghassem Gargari et al. [29], there were three intervention groups (arginine + hypocaloric diet enriched in legumes (HDEL), arginine + HDEL + selenium, HDEL +

selenium) and one control group (HDEL). We considered the result of the arginine + HDEL, and HDEL groups as one arm and the result of the arginine + HDEL + selenium and HDEL+ selenium groups as another arm. Furthermore, Rahimi et al.[22] and Dashtabi et al.[20], included 2 different arginine doses in their trials (3 or 6 g/day); therefore, we considered these imputations as 4 different arms.

Quality assessment

Among 12 studies included in the present review, nine trials [18; 20; 21; 23; 24; 25; 26; 27; 29] were categorized as good quality, and 3 trials [22; 28; 30] were fair quality. The details of the risk of bias in individual studies according to the domains used by the Cochrane Collaborations tool are provided in **Table 3**.

Findings from the systematic review

The present systematic review revealed that 3 trials [20; 21; 22] reported that L-arginine supplementation managed to reduce TC levels, while 8 studies [18; 23; 25; 26; 27; 28; 29; 30] failed to find any significant effect on this parameter. In terms of changes in TG levels, 3 trials observed a significant reduction after L-arginine supplementation in [20; 21; 23], while 8 studies [18; 22; 25; 26; 27; 28; 29; 30] did not find such an effect. Evidence points out that arginine may pose favorable effects on LDL-c concentration as well - three trials [20; 21; 22] found that supplementation induced a decrease in plasma LDL-c, while other trials report no significant changes on this outcome [23; 24; 25; 26; 27; 28; 29; 30]. Finally, L-arginine may induce favorable changes in HDL-c levels as confirmed in 2 trials[20; 21], however, the remaining studies[22; 23; 24; 25; 26; 27; 28; 29; 30] did not reach the same conclusion.

Findings from the meta-analysis

In total, we pooled the data from 13 arms corresponding to 10 studies [18; 20; 21; 22; 23; 25; 26; 27; 29; 30] which included 561 participants, to estimate the effect of L-arginine supplementation on plasma TC levels. After employing a meta-analysis random-effects model, we found that L-arginine supplementation did not significantly affect serum TC levels (WMD: -5.03 mg/dl; 95% CI: -10.78 to 0.73, P= 0.08) **(Figure2)**. The between-study heterogeneity was non-significant (P=0.07, I^2=39.0%). Subgroup analysis based on participants' mean age, baseline BMI, study duration, participants health status, and L-arginine dose confirmed that the effect is not statistically significant in none of the subgroups **(Table 4)**. Findings from the sensitivity analysis revealed that the exclusion of any single study from the analysis did not alter the overall effect.

Thirteen arms from 10 studies [18; 20; 21; 22; 23; 25; 26; 27; 29; 30] including 561 participants reported the effect of L-arginine on serum TG concentration. The pooled effect demonstrated a significant decrease in TG levels following L-arginine supplementation (WMD: -7.04 mg/dl; 95% CI: -11.42 to -2.67, P<0.001) with a non-significant heterogeneity among included studies (P=0.59, I^2=0.0%) **(Figure 3)**. Subgroup analysis based on participants' mean age, baseline BMI, study duration, participants health status, and L-arginine dose revealed that the effect was significant in studies which included participants with a mean age≥50 years (WMD: - 9.08mg/dl; 95% CI: -16.70 to -1.45, P=0.02), a baseline BMI≥30 kg/m^2(WMD: -9.86mg/dl; 95% CI: -16.22 to -3.50, P<0.001), L-arginine dose<6 g/day (WMD: -7.89mg/dl; 95% CI: - 15.04 to -0.73, P=0.03), type two diabetes/metabolic syndrome (WMD: -11.77mg/dl; 95% CI:

-19.39 to -4.14, P<0.001), and intervention duration ≥10 weeks (WMD: -9.21mg/dl; 95% CI: -15.20 to -3.21, P<0.001) **(Table 4)**. The sensitivity analysis demonstrated that by removing the study conducted by Bahrami et al.[23], the effect of L-arginine supplementation on TG levels becomes non-significant (WMD: -4.65 mg/dl; 95% CI: -9.51 to 0.19, P=0.06).

The impact of L-arginine supplementation on LDL-c levels was assessed in 10 trials [20; 21; 22; 23; 24; 25; 26; 27; 29; 30] with 13 treatment arms including 533 participants. The meta-analysis revealed that L-arginine supplementation did not significantly affect LDL-c levels (WMD: -

0.47 mg/dl; 95% CI: -3.61 to 2.66, P=0.76) while the heterogeneity among the included studies was not significant (P=0.53, I^2=0.0%) **(Figure 4)**. The subgroup analysis based on participants' mean age, baseline BMI, study duration, participants health status, and L-arginine dose also showed that the effect is not statistically significant in none of the subgroups **(Table 4)**. Furthermore, removing each individual study by sensitivity analysis did not change the pooled effect size.

Ten studies [20; 21; 22; 23; 24; 25; 26; 27; 29; 30] including 533 participants from 13 intervention arms measured changes in serum HDL-c concentrations following L-arginine supplementation. Pooled results from the random-effects model revealed that L-arginine supplementation had no significant effect on serum HDL-c levels (WMD: 0.57 mg/dl; 95% CI: -1.28 to 2.43, P=0.54) **(Figure 5)**. There was a significant heterogeneity among the studies (P<0.001, I^2=68.4%), and the subgroup analysis showed that baseline BMI (<30 kg/m^2: P=0.96, I^2=0.0%), duration of follow up (<10 weeks: P=0.23, I^2=25.6%), participants health status (dyslipidemia: P=0.69, I^2=0.0%), or type two diabetes/metabolic syndrome: P=0.93, I^2=0.0%), and L-arginine dosage (<6 g/day: P=0.96, I^2=0.0%) were significant contributors to the between-study heterogeneity. Besides, the subgroup analysis showed that L-arginine supplementation increases HDL levels in trials with a follow-up duration <10 weeks (WMD: 2.04 mg/dl; 95% CI: 0.52 to 3.56, P=0.01) (**Table 4**). Findings from the sensitivity analysis revealed that the exclusion of any single study from the analysis did not alter the overall effect.

Publication bias

Although the visual inspection of funnel plots showed slight asymmetries, no significant publication bias was detected in the meta-analyses in the case of TC (Begg's test, P=0.54; Egger's test, P=0.45), TG (Begg's test, P=0.54; Egger's test, P=0.56), LDL-c (Begg's test, P=0.39; Egger's test, P=0.80), or HDL-c (Begg's test, P=0.39; Egger's test, P=0.86).

Discussion

To the best of our knowledge, this study is the first systematic review and meta-analysis that measured the effect of L-arginine supplementation on lipid profile by summarizing the data from published RCTs. Our results indicate that L-arginine supplementation was not able to induce changes in TC, LDL-c, and HDL-c concentrations however it did induce a significant decrease in TG levels. Subgroup analyses further confirmed that L-arginine supplementation imposed a significant TG-lowering effect in studies that implemented long-term treatment (≥10 weeks), as well as in studies where participants had a baseline BMI≥30 kg/m^2, mean age ≥50 years, supplementation dosage <6 g/day, and where participants were type 2 diabetes or metabolic syndrome patients. Although the pooled effect size of L-arginine supplementation on HDL-c levels was not significant, subgroup analysis revealed that this effect was significant only in studies that lasted longer than 10 weeks.

In this meta-analysis, we concluded that L-arginine was able to induce favorable changes only on TG levels, while this was not observed in the case of other lipid parameters. The possible explanation for the observed lack of significant effect for all parameters except TG might be the fact that the included population had only TG levels above the recommended upper value according to the definition of metabolic syndrome. Thus, this observation may imply that individuals with higher TG levels are better respondents to L-arginine therapy.

The biological plausibility of lipid-associated L-arginine implications comes from the existing relationship between this amino acid and glucose metabolism. Human clinical trials have concluded so far that L-arginine can be an effective tool in reducing blood glucose levels in diabetes type 2 patients (36), in increasing insulin sensitivity (37) and in improving insulin resistance (38). One of the proposed explanations for the observed results is that insulin resistance of the adipocytes can lead to an increased release of fatty acids into the circulation.

Increased free fatty acid flux reaches the liver where it stimulates the assembly and secretion of very-low-density lipoprotein, which results in hypertriglyceridemia [39; 40]. Another possible mechanism might be related to the lowering effect of L-arginine on blood glucose, the decrease in blood glucose levels leads to an increase in the concentration of cyclic adenosine monophosphate which in turn decreases TG levels [41; 42]. Therefore, given the beneficial role of L-arginine in the glucose homeostasis, it is proposed that supplementation with this amino acid can lower serum TG levels [42; 43].

Other putative mechanisms may be related to the arginine nitric oxide synthase pathway. All nitric oxide synthase isoforms utilize L-arginine as a substrate, which undergoes a two-step metabolic conversion, yielding at the end L-citrulline and NO [44]. Elevated NO production, consequently increases lipoprotein lipase activity[45] and finally, by performing hydrolysis of TGs it reduces its concentration in the plasma [25; 46]. Animal study data also confirm L-arginine to be an effective lipid lowering agent by decreasing the white fat expansion, and improving serum TG levels in rats[41; 47].

A neutral effect of L-arginine supplementation on TC, LDL-c and HDL-c was observed in the present meta-analysis. Subgroup analysis of the effect of L-arginine supplementation on cholesterol or lipoprotein levels did not moderate the outcome. These findings are generally in line with the majority of individual studies selected for this review. Only three studies [20; 21; 22] showed a significant change in TC, LDL-c and HDL-c levels and others failed to find such a relationship. Furthermore, not all animal studies reported consistent results; as, reducing [48; 49] or even increasing effect of L-arginine supplementation on cholesterol level has been reported[50]. Madeira et al. reported that dietary L-arginine supplementation increase concentrations of total lipids, very low-density lipoproteins (VLDL) and TG[51]. However, Hu et al.[52] reported that L-arginine supplementation decrease TG, and cholesterol levels in the plasma. In addition, He et al.[53] showed that L-arginine supplementation reduces VLDL, lipids and TG concentrations in piglets. However, Some animal studies reported that L-arginine might reduce cholesterol or lipoprotein levels by these mechanisms: 1) decrease the expression of hepatic 3-hydroxyl-3-methylglutaryl-CoA reductase mRNA, which shows interaction of L-arginine with cholesterol metabolism [54] 2) increased the lipolysis as well as the oxidation of fatty acids; 3) increase plasma adiponectin levels which improved FFAs β-oxidation. On the other hand, others reported that possible TC increasing effect of L-arginine could be due to increased fat accretion in the carcass[55]. L-arginine can also increase the level of HDL-c through its effect on inflammation [47; 56; 57].

L-arginine has generally been well tolerated when administered in small doses (≤ 30 g/day) [58]. There were some reported benign side effects, however, which include: abdominal pain, bloating, nausea and vomiting, airway inflammation, diarrhea, hypotension, worsening of asthma, and allergic reactions [58; 59; 60]. Furthermore, given that a major part of L-arginine is metabolized to ornithine and urea[58; 61], patients with gout or renal function impairment should pay special caution when consuming it. Finally, due to its vasodilating properties, L-arginine has also been shown to interfere with certain medications (including Viagra and blood pressure medications) thus imposing negative reactions.[58].

This meta-analysis has certain limitations that should be noted. Firstly, the included studies involved individuals with different health status, resulting in a heterogeneous sample. Secondly, the sample sizes of individual trials were small, thus our results might more easily suffer from sample imbalances and an influence of baseline confounding factors. Third, the influence of gender remains unknown, since there was just one article that involved men. Women have different sex hormones compared with men that may affect lipid profile, thus implying that L-arginine may impose gender-dependent effects. Lastly, most RCTs were not primarily designed to assess the effects of L-arginine on lipid concentrations. In order to draw straightforward conclusions regarding recommending L-arginine supplementation as a lipid lowering agent, we need more RCTs designed to specifically address this issue in a target population of patients with abnormal lipid profile.

This study also has its strengths. It is only systematic review and meta-analysis to investigate the effect of arginine supplementation on lipid profile. Our systematic search makes it unlikely that large reports were missed, and error and bias were minimized by independent, duplicate decisions on whole process of review by adhering to the PRISMA guidelines. Also, subgroup analysis and assessment of mean age, baseline BMI, dose of L-arginine, study duration, and health status were done on the overall effect sizes.

Conclusion

The current systematic review and meta-analysis demonstrated that L-arginine supplementation leads to a significant reduction in TG levels. However, no significant effect was observed in the case of other lipid parameters including TC, LDL-c, and HDL-c. In order to confirm the results of our study, further clinical trials that exclusively examine the effects of L-arginine on participants with dyslipidemia are required.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

None.

Author Contribution

A.H and E.Gh wrote the concept, design, and carried out drafting of this study. A.A and E.Gh performed searches of the electronic databases, screened the articles and extracted the data. A.H performed the acquisition, analysis, and interpretation of data. A.H and E.Gh critically

revised the manuscript. A.P. performed a final revision and proofread of the article. All authors approved the final version of the manuscript. A.H and C.C are the guarantors of this study.

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Reference:

1. Yusuf S, Reddy S, Ôunpuu S *et al.* (2001) Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation* **104**, 2855-2864.
2. Leal J, Luengo-Fernández R, Gray A *et al.* (2006) Economic burden of cardiovascular diseases in the enlarged European Union. *European heart journal* **27**, 1610-1619.
3. Mozaffarian D, Benjamin EJ, Go AS *et al.* (2016) Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* **133**, e38-360.
4. Rader DJ (2007) Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *The American journal of medicine* **120**, S12-S18.
5. Lehto S, Rönnemaa T, Haffher SM *et al.* (1997) Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* **46**, 1354-1359.
6. McPherson R, Frohlich J, Fodor G *et al.* (2006) Canadian Cardiovascular Society position statement–recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Canadian Journal of Cardiology* **22**, 913-927.
7. Ito MK (2012) Dyslipidemia: management using optimal lipid-lowering therapy. *Annals of Pharmacotherapy* **46**, 1368-1381.
8. Chang Y, Robidoux J (2017) Dyslipidemia management update. *Current opinion in pharmacology* **33**, 47-55.
9. Björnsson ES (2017) Hepatotoxicity of statins and other lipid-lowering agents. *Liver International* **37**, 173-178.
10. Padala S, Thompson PD (2012) Statins as a possible cause of inflammatory and necrotizing myopathies. *Atherosclerosis* **222**, 15-21.
11. Chalasani N (2005) Statins and hepatotoxicity: focus on patients with fatty liver. *Hepatology* **41**, 690-695.
12. McNeal CJ, Meininger CJ, Reddy D *et al.* (2016) Safety and effectiveness of arginine in adults. *The Journal of nutrition* **146**, 2587S-2593S.
13. Ástvaldsdóttir Á, Naimi-Akbar A, Davidson T *et al.* (2016) Arginine and caries prevention: a systematic review. *Caries research* **50**, 383-393.
14. McRae MP (2016) Therapeutic benefits of l-arginine: an umbrella review of meta-analyses. *Journal of chiropractic medicine* **15**, 184-189.
15. Stechmiller JK, Childress B, Cowan L (2005) Arginine supplementation and wound healing. *Nutrition in Clinical Practice* **20**, 52-61.
16. Popovic PJ, Zeh III HJ, Ochoa JB (2007) Arginine and immunity. *The Journal of nutrition* **137**, 1681S-1686S.
17. Rodrigues-Krause J, Krause M, Rocha I *et al.* (2019) Association of l-Arginine Supplementation with Markers of Endothelial Function in Patients with Cardiovascular or Metabolic Disorders: A Systematic Review and Meta-Analysis. *Nutrients* **11**, 15.
18. Suliburska J, Bogdanski P, Szulinska M *et al.* (2014) Changes in mineral status are associated with improvements in insulin sensitivity in obese patients following L-arginine supplementation. *European journal of nutrition* **53**, 387-393.
19. McRae MP (2016) Therapeutic Benefits of l-Arginine: An Umbrella Review of Meta-analyses. *J Chiropr Med* **15**, 184-189.
20. Dashtabi A, Mazloom Z, Fararouei M *et al.* (2016) Oral L-arginine administration improves anthropometric and biochemical indices associated with cardiovascular diseases in obese patients: a randomized, single blind placebo controlled clinical trial. *Research in cardiovascular medicine* **5**.
21. Pahlavani N, Jafari M, Sadeghi O *et al.* (2014) L-arginine supplementation and risk factors of cardiovascular diseases in healthy men: a double-blind randomized clinical trial. *F1000Research* **3**.

22. Rahimi M, Naghizadeh MM (2014) The Effect of L-Arginin Supplementation on lipid profiles in patients with diabetes type 2. *Journal of Fasa University of Medical Sciences* **4**, 99-110.
23. Bahrami D, Mozaffari-Khosravi H, Zavar-Reza J The effect of oral L-arginine supplementation on lipid profile, glycemic status, and insulin resistance in patients with metabolic syndrome: A randomized, double-blind, placebo-controlled trial. *Mediterranean Journal of Nutrition and Metabolism*, 1-12.
24. Bogdanski P, Suliburska J, Grabanska K *et al.* (2012) Effect of 3-month L-arginine supplementation on insulin resistance and tumor necrosis factor activity in patients with visceral obesity. *Eur Rev Med Pharmacol Sci* **16**, 816-823.
25. Schulze F, Glos S, Petruschka D *et al.* (2009) L-Arginine enhances the triglyceride-lowering effect of simvastatin in patients with elevated plasma triglycerides. *Nutrition research* **29**, 291-297.
26. Lucotti P, Monti L, Setola E *et al.* (2009) Oral L-arginine supplementation improves endothelial function and ameliorates insulin sensitivity and inflammation in cardiopathic nondiabetic patients after an aortocoronary bypass. *Metabolism* **58**, 1270-1276.
27. Monti LD, Galluccio E, Villa V *et al.* (2018) Decreased diabetes risk over 9 year after 18-month oral L-arginine treatment in middle-aged subjects with impaired glucose tolerance and metabolic syndrome (extension evaluation of L-arginine study). *European journal of nutrition* **57**, 2805-2817.
28. Blum A, Cannon III RO, Costello R *et al.* (2000) Endocrine and lipid effects of oral L-arginine treatment in healthy postmenopausal women. *Journal of Laboratory and Clinical Medicine* **135**, 231-237.
29. Pourghassem Gargari B, Alizadeh M, Safaeiyan A *et al.* (2015) Effect of L-arginine and selenium on metabolic features, insulin resistance and hepatic function tests in obese women. *Current Nutrition & Food Science* **11**, 93-98.
30. Clarkson P, Adams MR, Powe AJ *et al.* (1996) Oral L-arginine improves endothelium-dependent dilation in hypercholesterolemic young adults. *The Journal of clinical investigation* **97**, 1989-1994.
31. Moher D, Liberati A, Tetzlaff J *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine* **151**, 264-269.
32. Higgins J, Green S (2014) Cochrane handbook for systematic reviews of interventions Version 5.1. 0 [updated March 2011]. 2011. *The Cochrane Collaboration* .
33. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Controlled clinical trials* **7**, 177-188.
34. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics*, 1088-1101.
35. Egger M, Smith GD, Schneider M *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *Bmj* **315**, 629-634.
36. Wascher TC, Graier WF, Dittrich P *et al.* (1997) Effects of low-dose L-arginine on insulin-mediated vasodilatation and insulin sensitivity. *European journal of clinical investigation* **27**, 690-695.
37. Natarajan Sulochana K, Lakshmi S, Punitham R *et al.* (2002) Effect of oral supplementation of free amino acids in type 2 diabetic patients-- a pilot clinical trial. *Medical science monitor : international medical journal of experimental and clinical research* **8**, Cr131-137.
38. Bogdanski P, Suliburska J, Grabanska K *et al.* (2012) Effect of 3-month L-arginine supplementation on insulin resistance and tumor necrosis factor activity in patients with visceral obesity. *Eur Rev Med Pharmacol Sci* **16**, 816-823.
39. Grundy SM (1999) Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *The American journal of cardiology* **83**, 25-29.
40. Ginsberg HN (2000) Insulin resistance and cardiovascular disease. *The Journal of clinical investigation* **106**, 453-458.
41. Wu Z, Satterfield MC, Bazer FW *et al.* (2012) Regulation of brown adipose tissue development and white fat reduction by L-arginine. *Current Opinion in Clinical Nutrition & Metabolic Care* **15**, 529-538.
42. Paolisso G, Tagliamonte MR, Marfella R *et al.* (1997) L-arginine but not D-arginine stimulates insulin-mediated glucose uptake. *Metabolism* **46**, 1068-1073.
43. Li X, Bazer FW, Gao H *et al.* (2009) Amino acids and gaseous signaling. *Amino acids* **37**, 65-78.

44. Forstermann U, Sessa WC (2012) Nitric oxide synthases: regulation and function. *Eur Heart J* **33**, 829-837, 837a-837d.
45. Ricart-Jane D, Casanovas A, Jane N *et al.* (2008) Nitric oxide and the release of lipoprotein lipase from white adipose tissue. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* **22**, 525-530.
46. Mendez J, Balderas F (2001) Regulation of hyperglycemia and dyslipidemia by exogenous L-arginine in diabetic rats. *Biochimie* **83**, 453-458.
47. de Castro Barbosa T, Jiang LQ, Zierath JR *et al.* (2013) L-Arginine enhances glucose and lipid metabolism in rat L6 myotubes via the NO/c-GMP pathway. *Metabolism* **62**, 79-89.
48. El-Kirsh AAA, Abd El-Wahab HMF, Abd-Ellah Sayed HF (2011) The effect of L-arginine or L-citrulline supplementation on biochemical parameters and the vascular aortic wall in high-fat and high-cholesterol-fed rats. *Cell biochemistry and function* **29**, 414-428.
49. Emadi M, Jahanshiri F, Kaveh K *et al.* (2011) Nutrition and immunity: the effects of the combination of arginine and tryptophan on growth performance, serum parameters and immune response in broiler chickens challenged with infectious bursal disease vaccine. *Avian pathology* **40**, 63-72.
50. Kumar P, Kumar A, Tiwari S (2005) L-Arginine supplementation increases serum cholesterol level. *Indian journal of pharmacology* **37**, 183.
51. dos Santos Madeira MSM, Rolo ESA, Pires VMR *et al.* (2017) Arginine supplementation modulates pig plasma lipids, but not hepatic fatty acids, depending on dietary protein level with or without leucine. *BMC veterinary research* **13**, 145.
52. Hu S, Li X, Rezaei R *et al.* (2015) Safety of long-term dietary supplementation with L-arginine in pigs. *Amino Acids* **47**, 925-936.
53. He Q, Kong X, Wu G *et al.* (2009) Metabolomic analysis of the response of growing pigs to dietary L-arginine supplementation. *Amino acids* **37**, 199.
54. Fouad A, El-Senousey H, Yang X *et al.* (2013) Dietary L-arginine supplementation reduces abdominal fat content by modulating lipid metabolism in broiler chickens. *Animal* **7**, 1239-1245.
55. Madeira M, Alfaia C, Costa P *et al.* (2014) The combination of arginine and leucine supplementation of reduced crude protein diets for boars increases eating quality of pork. *Journal of animal science* **92**, 2030-2040.
56. Tan B, Yin Y, Liu Z *et al.* (2011) Dietary L-arginine supplementation differentially regulates expression of lipid-metabolic genes in porcine adipose tissue and skeletal muscle. *The Journal of nutritional biochemistry* **22**, 441-445.
57. Harisa G (2011) L-Arginine ameliorates arylesterase/paraoxonase activity of paraoxonase 1 in hypercholesterolemic rats. *Asian Journal of Biochemistry* **6**, 263-272.
58. Böger RH, Bode-Böger SM (2001) The clinical pharmacology of L-arginine. *Annual review of pharmacology and toxicology* **41**, 79-99.
59. Böger RH (2014) The pharmacodynamics of L-arginine. *Alternative Therapies in Health & Medicine*
20.
60. Utagawa T (2004) Arginine metabolism: enzymology, nutrition, and clinical significance. *J Nutr* **134**, 2854S-2857S.
61. Morris Jr SM (2007) Arginine metabolism: boundaries of our knowledge. *The Journal of nutrition* **137**, 1602S-1609S.

Legends of figures:

Figure 1. PRISMA flow diagram of study selection process

Figure 2. Forest plot of the effect of L-arginine supplementation on TC

Figure 3. Forest plot of the effect ofL-arginine supplementation on TG

Figure 4. Forest plot of the effect of L-arginine supplementation on LDL-c

Figure 5. Forest plot of the effect of L-arginine supplementation on HDL-c

Table 1: PICOS criteria used to perform the systematic review and Meta-analysis

Parameter	**Criteria**
Population	Adults
Intervention	Arginine
Comparator	Matched control group
Outcome	Circulating TC, TG, LDL-c, and HDL-c
Setting or study design	Randomized controlled trials

TC, total cholesterol; TG, triglyceride; LDL-c, low density lipoprotein cholesterol; HDL-c, low-density lipoprotein cholesterol

First author (publication year)	Country	Sample size	RCT design (blinding)	Gender	Mean age (year)	Mean BMI (kg/m^2)	Duration (week)	Target population	Intervention (name and daily dose)	Control	Results
Clarkson (1996)	UK	27	Crossover (Yes)	Both	29	26	4	Subjects with hypercholesterolemia	21 g/day arginine	Placebo	TC ↔ TG ↔ LDL-c ↔ HDL-c↔
Blum (2000)	Israel	10	Crossover (Yes)	Women	55	26.6	4	Postmenopausal women	9 g/day arginine	Placebo	TC ↔ TG ↔ LDL-c ↔ HDL-c↔
Lucotti (2009)	Poland	30	Parallel (Yes)	Both	64.5	34	26	Patients with CVD	6.4 g/day arginine	Placebo	TC ↔ TG ↔ LDL-c↔ HDL-c↔
Schulze (2009)	Germany	33	Parallel (Yes)	Both	54.3	28.40	6	Subjects with hypertriglyceridemia	3 g/day arginine	Placebo	TC ↔ TG ↔ LDL-c ↔ HDL-c↔
Bogdanski (2012)	Poland	60	Parallel (Yes)	Both	42.4	38.35	13	Obese	9 g/day arginine	Placebo	LDL-c ↔ HDL-c↔
Rahimi (2014) a	Iran	33	Parallel (Yes)	Both	50.89	29.07	13	T2DM	3 g/day arginine	Placebo	TC ↔ TG ↔ LDL-c ↔ HDL-c↔
Rahimi (2014) b	Iran	35	Parallel (Yes)	Both	51.98	28.55	13	T2DM	6 g/day arginine	Placebo	TC ↓ TG ↔ LDL-c ↓ HDL-c↔
Suliburska (2014)	Poland	88	Parallel (Yes)	Both	42.3	36.45	26	Obese	9 g/day arginine	Placebo	TC↔ TG ↔
Pahlavani (2014)	Iran	52	Parallel (Yes)	Male	20.86	23.67	7	Healthy	2 g/day arginine	Placebo	TC ↓ TG ↓ LDL-c↓

											HDL-c↑
PourghassemGargari (2015) a	Iran	34	Parallel (Yes)	Women	35.2	31.80	6	Obese	HDEL + 5 g/day arginine	HDEL	TC ↔ TG ↔ LDL-c ↔ HDL-c↔
PourghassemGargari (2015) b	Iran	34	Parallel (Yes)	Women	35.3	32.45	6	Obese	HDEL + 5 g/day arginine + 200 µg/day selenium	HDEL + 200 µg/day selenium	TC ↔ TG ↔ LDL-c ↔ HDL-c↔
Dashtabi (2016) a	Iran	41	Parallel (Yes)	Both	42.36	35.44	8	Obese	3 g/day arginine	Placebo	TC ↓ TG ↔ LDL-c ↓ HDL-c↔
Dashtabi (2016) b	Iran	42	Parallel (Yes)	Both	43.23	34.09	8	Obese	6 g/day arginine	Placebo	TC ↓ TG ↓ LDL-c ↓ HDL-c↑
Monti (2018)	Italy	56	Parallel (Yes)	Both	56.4	35	77	Subjects with impaired glucose tolerance and metabolic syndrome	6.4 g/day arginine	Placebo	TC ↔ TG ↔ LDL-c ↔ HDL-c↔
Bahrami (2019)	Iran	56	Parallel (Yes)	Both	50.7	30	13	Metabolic syndrome	5 g/day arginine	Placebo	TC ↔ TG ↓ LDL-c ↔ HDL-c↔

Table 2. Characteristics of included studies

RCT, randomized controlled trial; BMI, body mass index; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; HDL-c, low-density lipoprotein cholesterol.

Table 3. Quality assessment of included studies based on Cochrane guidelines

Study	Random Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	**Overall quality**
Clarkson (1996)	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Fair
Blum (2009)	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Fair
Lucotti (2009)	Low	Low	Low	Low	Low	Low	Low	Good
Schulze (2009)	Low	Low	Low	Unclear	Low	Low	Unclear	Good
Bogdanski (2012)	Low	Low	Low	Unclear	Low	Low	Low	Good
Rahimi (2014)	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Fair
Suliburska (2014)	Low	Low	Low	Unclear	Low	Low	Low	Good
Pahlavani (2014)	Low	Low	Low	Low	Low	Low	Low	Good
PourghassemGargari (2015)	Low	Low	Low	Low	Low	Low	Low	Good
Dashtabi (2016)	Low	Low	Low	Unclear	Low	Low	Unclear	Good
Monti (2018)	Low	Low	Low	Unclear	Low	Low	Low	Good
Bahrami (2019)	Low	Low	Low	Unclear	Low	Low	Low	Good

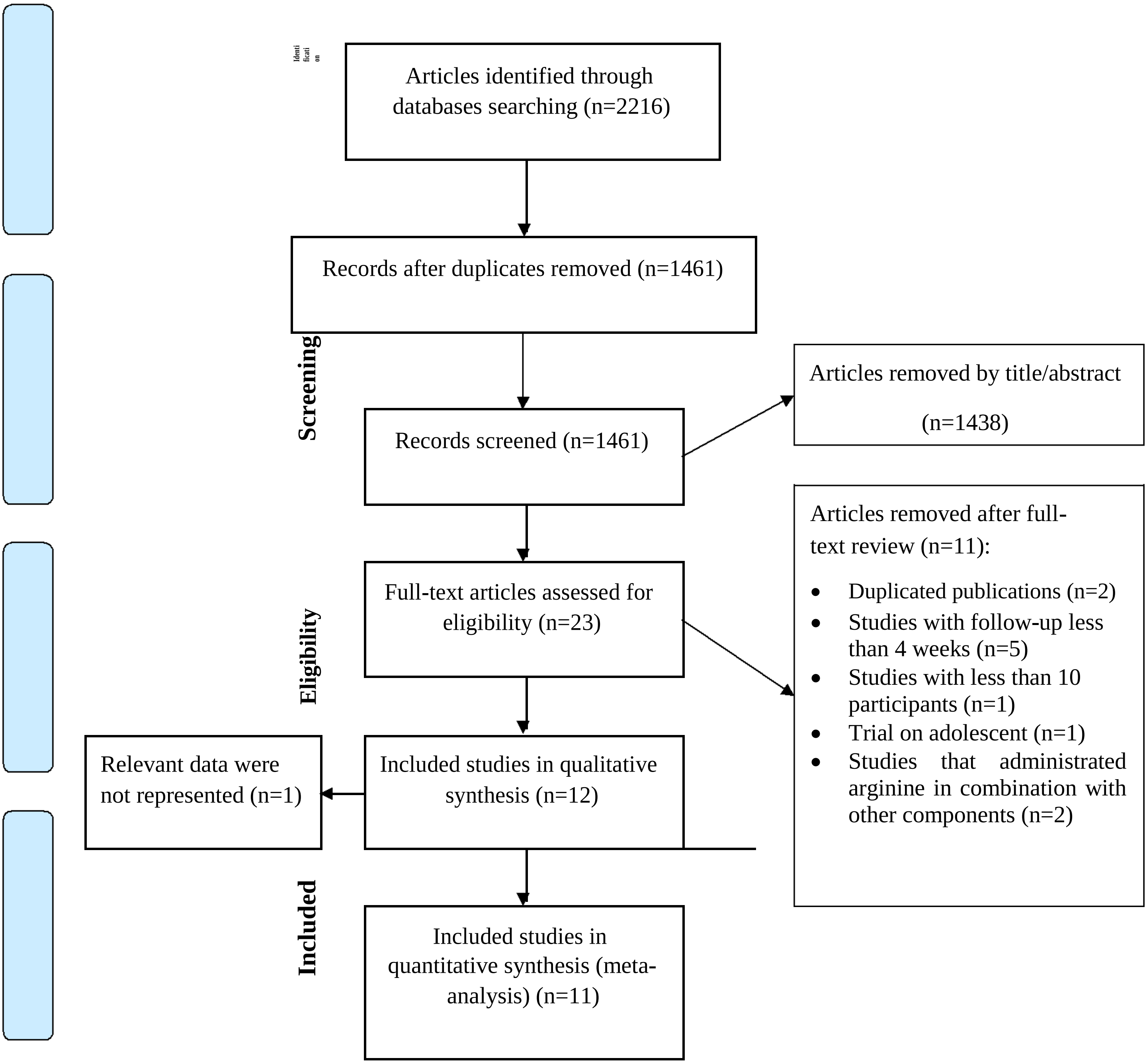
Table 4. Result of subgroup analysis of included studies in meta-analysis.

Sub-grouped by	**No. of trials**	**Effect size[1]**	**95% CI**	**I^2 (%)**	**P for heterogeneity**	**P for Effect size**
TC						
Mean age						
≥50 years	6	-7.47	-19.97, 5.04	72.5	<0.001	0.24
<50 years	7	-2.66	-8.46, 3.14	0.0	0.97	0.41
Baseline BMI						
≥30 kg/m^2	8	-0.23	-5.01, 4.54	0.0	0.97	0.92
<30 kg/m^2	5	-11.95	-26.64, 2.75	68.5	0.01	0.16
Intervention duration						
≥10 weeks	6	-7.38	-18.78, 4.02	72.4	<0.001	0.20
<10 weeks	7	-2.72	-8.81, 3.36	0.0	0.96	0.43
Dose						
≥6 g/day	6	-7.74	-19.74, 4.25	71.9	<0.001	0.26
<6 g/day	7	-2.69	-8.61, 3.23	0.0	0.94	0.37
Health status						
Dyslipidemia	2	-1.80	-25.28, 21.69	0.0	0.48	0.88
T2D/MetS	4	-12.58	-28.19, 3.02	65.2	0.03	0.11
Other	7	-0.79	-5.09, 3.51	0.0	0.94	0.71
TG						
Mean age						
≥50 years	6	-9.08	-16.70, -1.45	36.7	0.16	0.02
<50 years	7	-3.56	-10.91, 3.79	0.0	0.98	0.31
Baseline BMI						
≥30 kg/m^2	8	-9.86	-16.22, -3.50	0.0	0.50	<0.001
<30 kg/m^2	5	-4.51	-10.54, 1.53	0.0	0.63	0.13
Intervention duration						
≥10 weeks	6	-9.21	-15.20, -3.21	12.0	0.33	<0.001
<10 weeks	7	-3.09	-10.53, 4.35	0.0	0.81	0.38
Dose						
≥6 g/day	6	-5.50	-12.58, 1.58	0.0	0.76	0.11
<6 g/day	7	-7.89	-15.04, -0.73	18.9	0.28	0.03
Health status						
Dyslipidemia	2	26.73	-34.47, 87.93	13.5	0.28	0.39
T2D/MetS	4	-11.77	-19.39, -4.14	17.9	0.30	<0.001
Other	7	-3.46	-9.50, 2.23	0.0	0.99	0.22
LDL-c						
Mean age						
≥50 years	6	-0.44	-7.23, 6.34	42.1	0.12	0.89
<50 years	7	-1.69	-6.31, 2.93	0.0	0.94	0.44
Baseline BMI						
≥30 kg/m^2	8	2.39	-1.93, 6.71	0.0	0.75	0.21
<30 kg/m^2	5	-3.66	-8.22, 0.90	0.0	0.53	0.10
Intervention duration						
≥10 weeks	6	-0.17	-6.58, 6.24	42.5	0.12	0.95
<10 weeks	7	-2.00	-6.75, 2.76	0.0	0.96	0.38
Dose						
≥6 g/day	6	-0.48	-7.82, 6.87	47.1	0.09	0.85
<6 g/day	7	-1.65	-6.21, 2.91	0.0	0.98	0.47
Health status						
Dyslipidemia	2	6.1	-17.79, 29.79	0.0	0.99	0.62
T2D/MetS	4	-4.47	-11.68, 2.73	13.8	0.32	0.22

Other	7	0.82	-2.81, 4.44	0.0	0.58	0.66
HDL-c						
Mean age						
≥50 years	6	-0.15	-2.77, 2.47	51.0	0.07	0.90
<50 years	7	1.29	-0.62, 3.21	58.0	0.05	0.21
Baseline BMI						
≥30 kg/m^2	8	0.36	-2.03, 2.75	81.2	<0.001	0.76
<30 kg/m^2	5	1.24	-1.51, 3.99	0.0	0.96	0.36
Intervention duration						
≥10 weeks	6	-0.85	-3.28, 1.58	48.9	0.08	0.49
<10 weeks	7	2.04	0.52, 3.56	25.6	0.23	0.01
Dose						
≥6 g/day	6	-0.25	-4.36, 3.87	86.0	<0.001	0.90
<6 g/day	7	1.18	-0.16, 2.52	0.0	0.96	0.08
Health status						
Dyslipidemia	2	1.88	-5.26, 9.02	0.0	0.69	0.60
T2D/MetS	4	1.25	-1.09, 3.59	0.0	0.93	0.29
Other	7	0.21	-2.42, 2.85	83.8	<0.001	0.87

[1]Calculated by Random-effects model

BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-c, low density lipoprotein cholesterol; HDL-c, low-density lipoprotein cholesterol.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Screening
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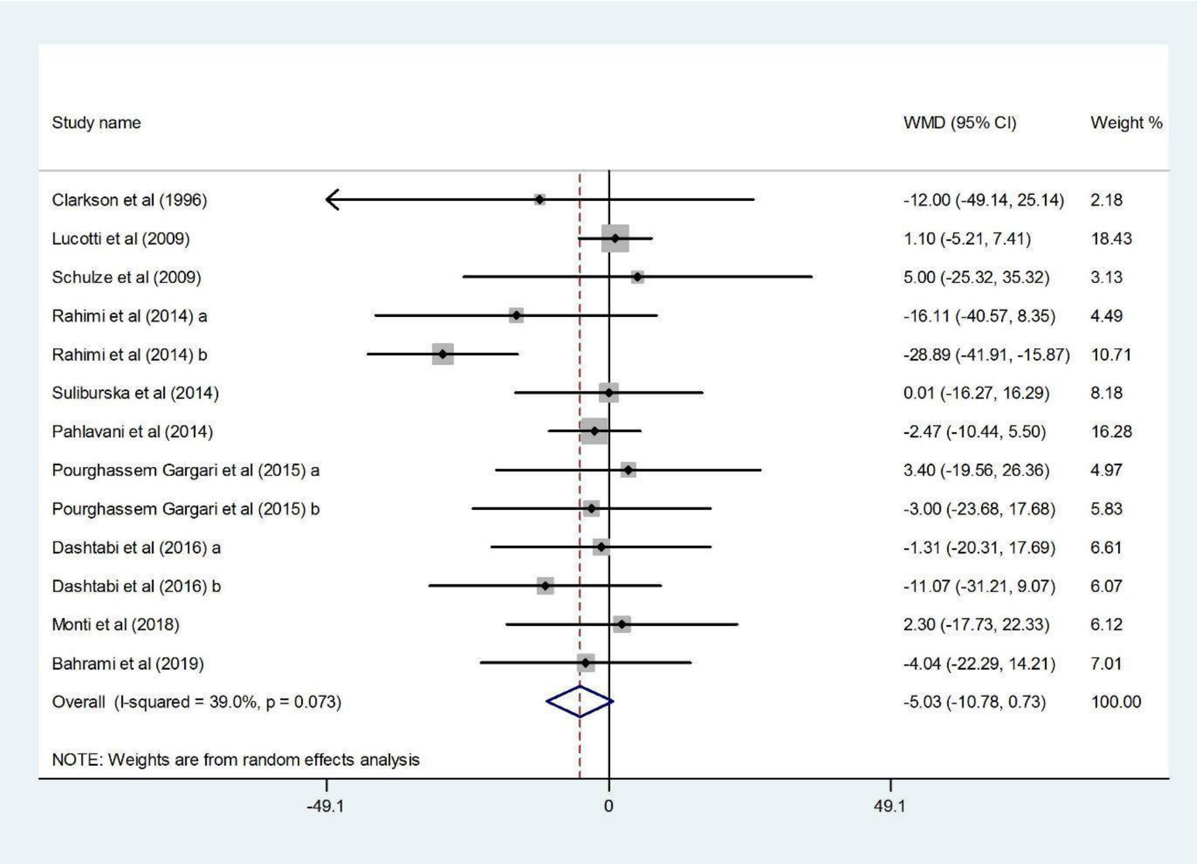
Articles removed after full-text review (n=11):
Duplicated publications (n=2)
Studies with follow-up less than 4 weeks (n=5)
Studies with less than 10 participants (n=1)
Trial on adolescent (n=1)
Studies that administrated arginine in combination with other components (n=2)
Included
Included studies in qualitative synthesis (n=12)
Relevant data were not represented (n=1)
Included studies in quantitative synthesis (meta-analysis) (n=11)

Figure 1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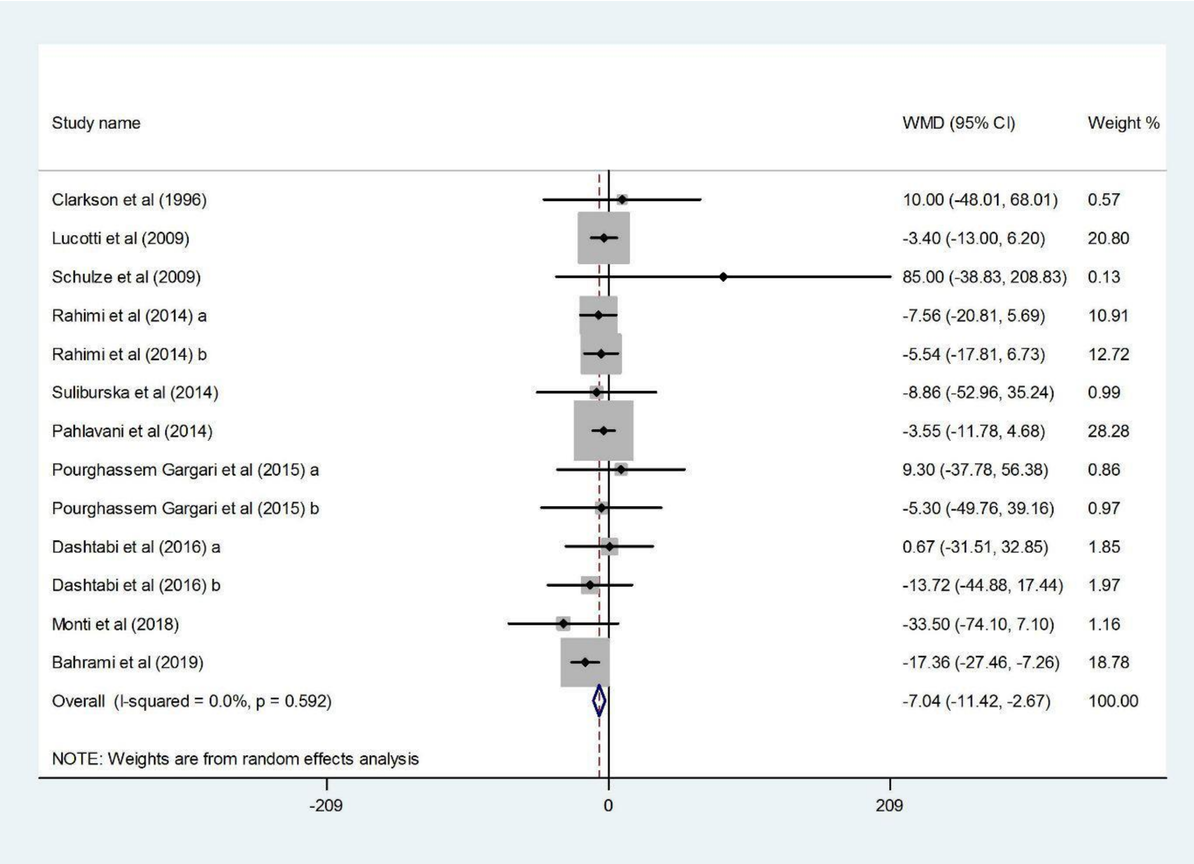
2.18
Lucotti et al (2009)
1.10 (-5.21, 7.41)
18.43
Schulze et al (2009)
5.00 (-25.32, 35.32)
3.13
Rahimi et al (2014) a
-16.11 (-40.57, 8.35)
4.49
Rahimi et al (2014) b
-28.89 (-41.91, -15.87)
10.71
Suliburska et al (2014)
0.01 (-16.27, 16.29)
8.18
Pahlavani et al (2014)
-2.47 (-10.44, 5.50)
16.28
Pourghassem Gargari et al (2015) a
3.40 (-19.56, 26.36)
4.97
Pourghassem Gargari et al (2015) b
-3.00 (-23.68, 17.68)
5.83
Dashtabi et al (2016) a
-1.31 (-20.31, 17.69)
6.61
Dashtabi et al (2016) b
-11.07 (-31.21, 9.07)
6.07
Monti et al (2018)
2.30 (-17.73, 22.33)
6.12
Bahrami et al (2019)
-4.04 (-22.29, 14.21)
7.01
Overall (I-squared = 39.0%, p = 0.073)
-5.03 (-10.78, 0.73)
100.00
NOTE: Weights are from random effects analysis
-49.1
0
49.1

Figure 2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Lucotti et al (2009)
-3.40 (-13.00, 6.20)
20.80
Schulze et al (2009)
85.00 (-38.83, 208.83)
0.13
Rahimi et al (2014) a
-7.56 (-20.81, 5.69)
10.91
Rahimi et al (2014) b
-5.54 (-17.81, 6.73)
12.72
Suliburska et al (2014)
-8.86 (-52.96, 35.24)
0.99
Pahlavani et al (2014)
-3.55 (-11.78, 4.68)
28.28
Pourghassem Gargari et al (2015) a
9.30 (-37.78, 56.38)
0.86
Pourghassem Gargari et al (2015) b
-5.30 (-49.76, 39.16)
0.97
Dashtabi et al (2016) a
0.67 (-31.51, 32.85)
1.85
Dashtabi et al (2016) b
-13.72 (-44.88, 17.44)
1.97
Monti et al (2018)
-33.50 (-74.10, 7.10)
1.16
Bahrami et al (2019)
-17.36 (-27.46, -7.26)
18.78
Overall (I-squared = 0.0%, p = 0.592)
-7.04 (-11.42, -2.67)
100.00
NOTE: Weights are from random effects analysis
-209
0
209

Figure 3

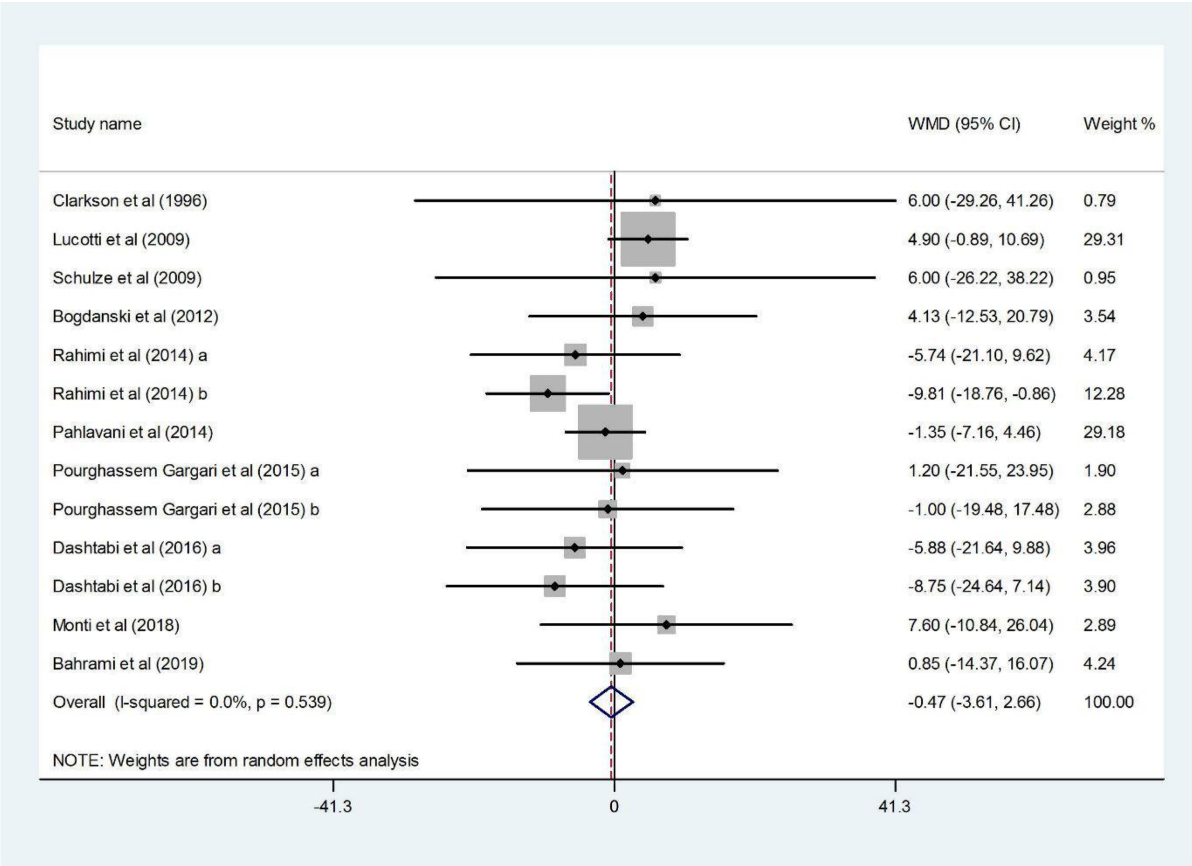
Study name
WMD (95% CI)
Weight %
Clarkson et al (1996)
6.00 (-29.26, 41.26)
0.79
Lucotti et al (2009)
4.90 (-0.89, 10.69)
29.31
Schulze et al (2009)
6.00 (-26.22, 38.22)
0.95
Bogdanski et al (2012)
4.13 (-12.53, 20.79)
3.54
Rahimi et al (2014) a
-5.74 (-21.10, 9.62)
4.17
Rahimi et al (2014) b
-9.81 (-18.76, -0.86)
12.28
Pahlavani et al (2014)
-1.35 (-7.16, 4.46)
29.18
Pourghassem Gargari et al (2015) a
1.20 (-21.55, 23.95)
1.90
Pourghassem Gargari et al (2015) b
-1.00 (-19.48, 17.48)
2.88
Dashtabi et al (2016) a
-5.88 (-21.64, 9.88)
3.96
Dashtabi et al (2016) b
-8.75 (-24.64, 7.14)
3.90
Monti et al (2018)
7.60 (-10.84, 26.04)
2.89
Bahrami et al (2019)
0.85 (-14.37, 16.07)
4.24
Overall (I-squared = 0.0%, p = 0.539)
-0.47 (-3.61, 2.66)
100.00
NOTE: Weights are from random effects analysis
-41.3
0
41.3

Figure 4

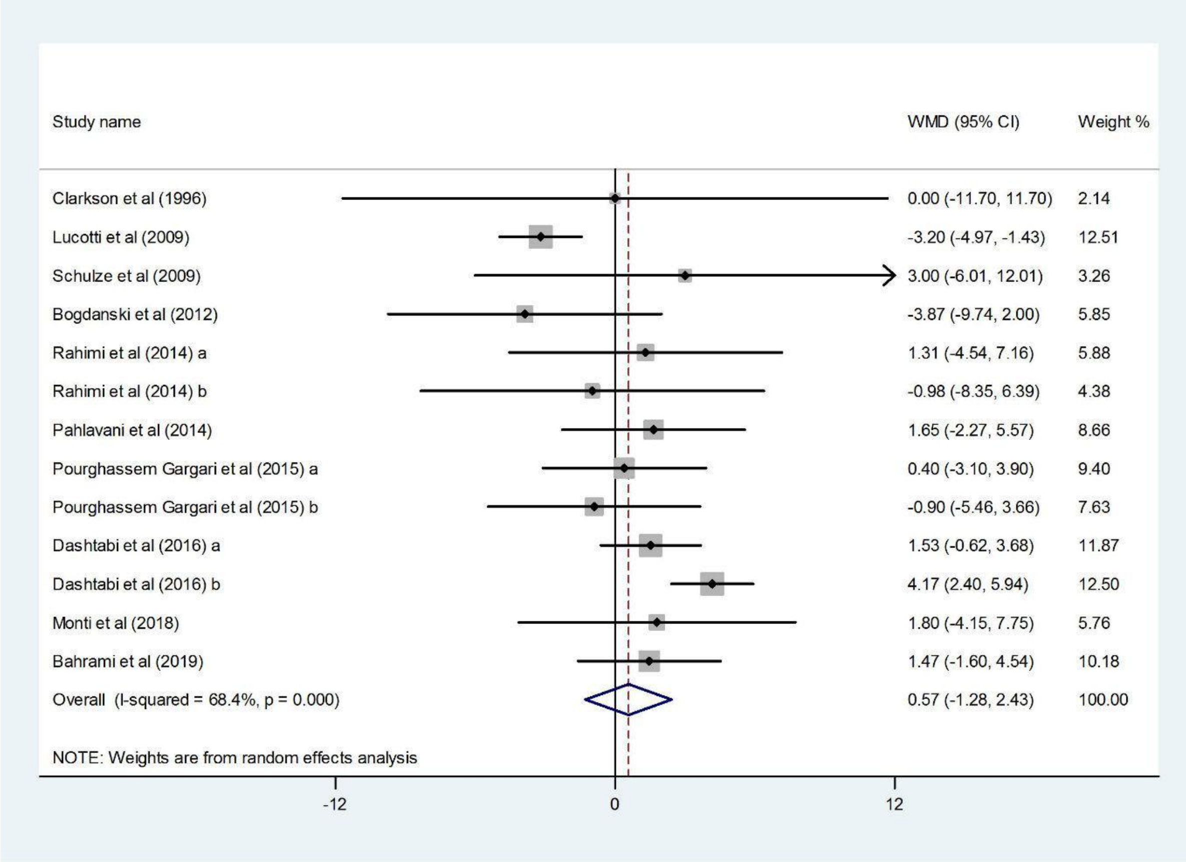
Study name
WMD (95% CI)
Weight %
Clarkson et al (1996)
0.00 (-11.70, 11.70)
2.14
Lucotti et al (2009)
-3.20 (-4.97, -1.43)
12.51
Schulze et al (2009)
3.00 (-6.01, 12.01)
3.26
Bogdanski et al (2012)
-3.87 (-9.74, 2.00)
5.85
Rahimi et al (2014) a
1.31 (-4.54, 7.16)
5.88
Rahimi et al (2014) b
-0.98 (-8.35, 6.39)
4.38
Pahlavani et al (2014)
1.65 (-2.27, 5.57)
8.66
Pourghassem Gargari et al (2015) a
0.40 (-3.10, 3.90)
9.40
Pourghassem Gargari et al (2015) b
-0.90 (-5.46, 3.66)
7.63
Dashtabi et al (2016) a
1.53 (-0.62, 3.68)
11.87
Dashtabi et al (2016) b
4.17 (2.40, 5.94)
12.50
Monti et al (2018)
1.80 (-4.15, 7.75)
5.76
Bahrami et al (2019)
1.47 (-1.60, 4.54)
10.18
Overall (I-squared = 68.4%, p = 0.000)
0.57 (-1.28, 2.43)
100.00
NOTE: Weights are from random effects analysis
-12
0
12

Figure 5