Review

The effect of L-arginine supplementation on obesity-related indices: A systematic review and meta-analysis of randomized clinical trials

Editor's Choice

Seyed Mohammad Mousavi[1], Alireza Milajerdi[1,3], Somaye Fatahi[4], Jamal Rahmani[2], Meysam Zarezadeh[1], Ehsan Ghaedi[1], and Hamed Kord Varkaneh[2]

[1] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[2] Student Research Committee, Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Obesity and Eating Habits Research Center, Endocrinology and Metabolism Molecular – Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[4] Student Research Committee, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

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Abstract: The clinical studies regarding the effect of L-arginine in human anthropometry have not been fully consistent, therefore, we carried out a systematic review and meta-analysis of randomized clinical trials in order to precisely evaluate and quantify the efficacy of L-arginine on weight, waist circumference, and BMI. We searched online databases including PubMed, SCOPUS, and Google Scholar for relevant articles up to September 2017. Eligible articles were reviewed by two independent investigators. Mean differences of the outcomes were used for calculation of weighted mean difference (WMD) derived from the random-effects model. Statistical heterogeneity between studies was examined using Cochran's Q-test and I^2 index. Funnel plot and Egger's tests were performed to assess the publication bias. In our initial search, we found 1598 publications, of which 8 RCTs (9 treatment arms) were included. The results of the meta-analysis displayed a significant reduction in WC following L-arginine supplementation (WMD: −2.97 cm; 95% CI: −4.75 to −1.18, P = 0.001). However, L-arginine intervention had not elicited a significant effect on BMI (WMD: −0.51 kg/m^2; 95% CI: −1.11 to .08, P = 0.09) and body weight (WMD: −0.57 kg; 95% CI: −1.77 to 0.61, P = 0.34). Subgroup analyses displayed that longer-term interventions (≥8 weeks) had a positive effect on body weight and using < 8 g/day L-arginine with longer duration (≥8 weeks) could significantly decrease BMI. In conclusion, this meta-analysis result suggested L-arginine supplementation could reduce waist circumference without any significant effect on body weight and body mass index.

Keywords: L-arginine, Weight, Waist circumference, BMI, Meta-analysis

Introduction

Obesity is a global epidemic which impacts a wide range of ages and ethnicities [1]. According to the World Health Organization (WHO), approximately 600 million adults all over the world were classified as obese in 2016 [2]. Obesity is a major contributing risk factor for various chronic diseases such as cardiovascular disease (CVD), Type 2 Diabetes Mellitus (T2DM), joint and muscular diseases, and psychological disorders [2–4].

The serum concentrations of Nitric Oxide (NO) in overweight subjects is higher than individuals with normal weight. This may be partially due to the increased inducible NO Synthase (iNOS) expression in obesity [5]. NO decreases oxidative stress and improves insulin sensitivity which contributes to weight balance [6]. The oxidative stress in relation to NO is due to unpaired electron and free uncharged radical of NO [7]. On the other hand, the white adipose tissue is a potential source of NO production through Endothelial and inducible NO synthase (eNOS

and iNOS). NO through insulin-stimulated uptake of glucose could be involve in adipose tissue metabolism [8]. However, iNOS tends to increase the NO concentration to detrimental levels in overweight subjects [9–11].

In recent years, due to the failure of conventional approaches (diet and exercise) in weight reduction, use of alternative medicines such as weight loss supplements have been proposed [12, 13]. L-arginine is a semi-essential amino acid which participates in NO production thorough NO synthase (NOS), free radical scavenging and nitrogen balance improvement [5, 9, 10]. Prior studies have demonstrated L-arginine supplementation can improve endothelial function, insulin secretion and sensitivity, and inflammation; all of which have been linked to obesity-related complications like T2DM and CVDs [14–17]. NO synthase pathway has been proposed as a possible mechanism which improve peripheral and hepatic insulin sensitivity following arginine administration [18]. Therefore, the elevated concentration of NO induced by L-arginine supplementation may also improve weight control among overweight patients. Several studies evaluated the potential effect of L-arginine supplementation in obese patients. Previous publications indicated that arginine can reduce waist circumference (WC) [19, 20], BMI and body weight [20–22]. In contrast, some other studies could not find a significant effect of arginine supplementation on anthropometric measurements, including BMI, body fat mass and lean body mass [6, 23, 24].

Given these evidences, clinical trials concerning the effect of L-arginine on human anthropometric indices have not been fully consistent. Therefore, we aimed to perform a comprehensive systematic review and meta-analysis of available randomized controlled trials (RCTs) to assess the efficacy of L-arginine on body weight, BMI, and waist circumference in adults.

Methods

The current meta-analysis was performed and reported based on the PRISMA guideline [25].

Search strategy

We searched online databases including PubMed, SCOPUS, and Google Scholar for relevant articles up to September 2017. Keywords that we used in our search strategy were selected from MeSH and non-MeSH terms including: ("Arginine OR "L-arginine" OR "L-Arg" OR "Arg") AND ("Obesity" OR "Weight Loss" OR "weight reduce" OR "weight decrease" OR "weight change" OR "Body Weight" OR "Obesity, Abdominal" OR "Body Mass Index" OR "Waist Circumference" OR "obes*" OR "central obesity " OR "overweight" [tiab] OR "adipose tissue" OR "fat mass" OR "adiposity"). We did not limit our search to time and language of publication. Moreover, we reviewed the reference lists of all review articles to avoid missing any publication. Unpublished studies were not included in this meta-analysis.

Inclusion criteria

Any clinical trial that examined the effect of L-arginine supplementation on body weight and/or BMI and/or WC in adults were included in this systematic review and meta-analysis. Amongst articles with the same data set, only the most complete one was included [19].

Exclusion criteria

Studies were excluded if they were: (1) not randomized clinical trials in design (2) carried out in children, pregnant women and animals (3) trials with less than 2-weeks intervention duration (4) not written in English (5) examined the effect of L-arginine in combination with other interventions (6) lacked a suitable control group (7) not reported adequate information on baseline or after the intervention for outcomes of interest.

Data extraction

Two investigators reviewed the eligible articles independently (S.M.M and H.K.V), and the relevant data including first author's name, year of publication, type of study population, sample size, participants' gender, L-arginine dosage, Duration of intervention, mean (SD) of participants' weight before and after intervention, mean (SD) of BMI before and after intervention, mean (SD) of WC before and after intervention were extracted. All reported Standard Errors (SEs), interquartile ranges, and 95% confidence intervals were converted to SDs. If a study was performed on two separate groups with different dosage of supplementation, we considered this study as two disparate studies. In order to obtain missing data in studies without a complete dataset, we contacted the corresponding author.

Statistical analysis

Changes in body weight, BMI, and WC during the intervention, for the intervention and placebo groups, were used to calculate the weighted mean difference (WMD) by the random-effects model. In the studies which not reported SD of the changes, it was calculated by the following formula: $SD^2 = ((SD_{besline})^2 + (SD_{final})^2 - (2R \times SD_{besline} \times SD_{final}))$. A correlation coefficient of 0.8 was considered as R-value in the aforementioned formula [26]. Statistical heterogeneity between studies was examined using the Cochran's Q-test and I^2 static. To find possible sources of heterogeneity, we carried out subgroup analyses based on the L-arginine

dosage (<8 mg/d and ≥ 8 mg/d) and supplementation duration (8 weeks and ≥ 8 weeks). We also performed sensitivity analysis to explore the extent to which inferences might depend on an individual study or group of studies [27]. Visual inspection of funnel plots as well as Egger's test were used to assess publication bias. All statistical analyses were conducted using the Stata software (version 14, StataCorp LP, College Station, Texas). P values less than 0.05 was considered as statistically significant.

Results

General characteristics of included studies

Our initial search resulted in 1598 probably related articles. After removing 303 duplicate articles, 1295 records remained and were reviewed based on title and abstract. Out of these articles, 51 relevant records were nominated for a careful full-text assessment. At this stage, 43 studies were excluded due to: were done on children or patients with chronic illnesses (n = 4), animal studies (n = 9), were not available as English full-text (n = 4), trials with the same population (n = 6), examined the effect of other interventions, along with L-arginine supplementation (n = 6), did not have a suitable control group (n = 7), and studies which reported incomplete data (n = 7). Finally, 8 randomized controlled trials met our criteria and were included in this systematic review and meta-analysis. The flow-diagram of study selection is shown in Figure 1.

General characteristics of 8 eligible articles are outlined in Figure 1. Data were composed of eight studies including 9 treatment arms; 222 subjects in the treatment arm and 239 subjects in control group. These studies were published between 2001 to 2017; and were done in the European countries [6, 18, 28, 29] as well as in Iran [19, 22, 23, 30]. The largest trial enrolled 88 subjects and the smallest had a sample size of 33 subjects. Two trials were carried out exclusively on men [16] and women [19], while others were done on both sexes. All qualified studies recruited obese individuals except two studies which were conducted on subjects with type 2 diabetes [18] and healthy athletes [23]. The participants' age ranged from 18 to 75 years. A single study was performed on two separate populations with two different doses of L-arginine, thus we considered it as two studies [30]. L-arginine was used in various ranges of between 2 g/day to 9 g/day among these studies. Supplementation periods ranged from 3 up to 25 weeks.

Among studies that examined the impact of L-arginine supplementation on body weight, 3 studies reported a significant reduction [28, 30], while changes in body weight were not significant in the other trials [18, 19, 22, 23]. With regards to BMI, a significant reduction was achieved in 2 studies [30], however, the remaining studies failed to find a significant effect [6, 22, 23, 28, 29]. In addition, half of the included studies obtained a significant reduction in WC after L-arginine administration than the control group [28, 30] and in the other half of the studies, such significant results were not observed (Table I).

Effect of L-arginine supplementation on body weight

Pooled results from 6 studies with 7 treatment arms indicated that body weight was not significantly reduced with L-arginine supplementation as compared to placebo (WMD: −0.57 kg; 95% CI: −1.77 to 0.61, P = 0.34); with significant between-study heterogeneity (I^2 = 66.2 %, P = 0.007) (Figure 2). Subgroup analysis based on treatment dosage (I^2 = 0.0%, P = 0.84), duration (I^2 = 2.1%, P = 0.38), and baseline BMI (I^2 = 0.0%, P = 0.78) disappeared the heterogeneity (Table II). Interestingly, a significant reduction in body weight was reached in studies in which L-arginine was consumed over or equal a period of 8 weeks (WMD: −3.28 kg, 95% CI: −5.55, −1.01, P = 0.005).

Effect of L-arginine supplementation on body mass index

Combining findings from 7 treatment arms demonstrated that L-arginine supplementation, as compared to placebo, was not associated with a significant reduction in BMI (WMD: −0.51 kg/m^2; 95% CI: −1.11 to .08, P = 0.09) (Figure 3), when the between-study heterogeneity was high (I^2 = 82.1%, P = <0.001). Subgroup analysis by the intervention dosage (I^2 = 0.0%, P = 0.86), follow-up duration (I^2 = 59.8%, P = 0.11), and baseline BMI (I^2 = 0.0%, P = 0.97 & I^2 = 0.0%, P = 0.61) disappeared the heterogeneity (Figure 2). Although the majority of our subgroup analyses did not change the findings, a significant reduction in BMI was detected among studies which used < 8 g/day L-arginine (WMD: −0.22 kg/m^2, 95% CI: −0.42, −0.02, P = 0.03) and those with a duration of ≥ 8 weeks (WMD: −0.71 kg/m^2, 95% CI: −1.12, −0.30, P = 0.001).

Effect of L-arginine supplementation on waist circumference

Pooling effect sizes from 5 studies with 6 treatment arms, L-arginine supplementation comparing to placebo

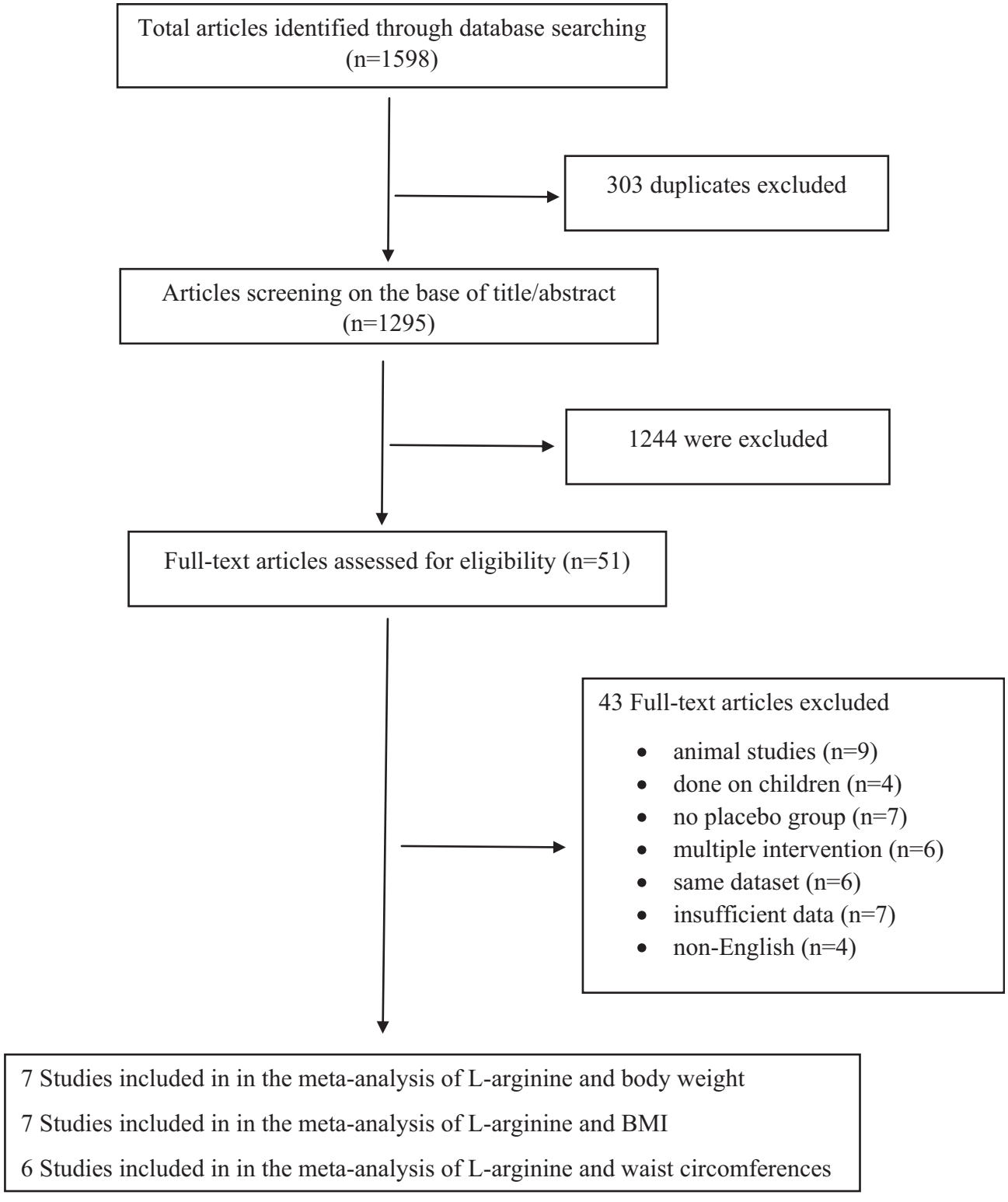

Figure 1. Summary of the process of study selection

significantly reduced waist circumference (WMD: −2.97 cm; 95% CI: −4.75 to −1.18, P = 0.001) (Figure 4), with a significant between-study heterogeneity (I^2 = 82.2%, P = < 0.001). Between-study heterogeneity was disappeared after subgroup analysis by baseline BMI (I^2 = 0.0%, P = 0.56).

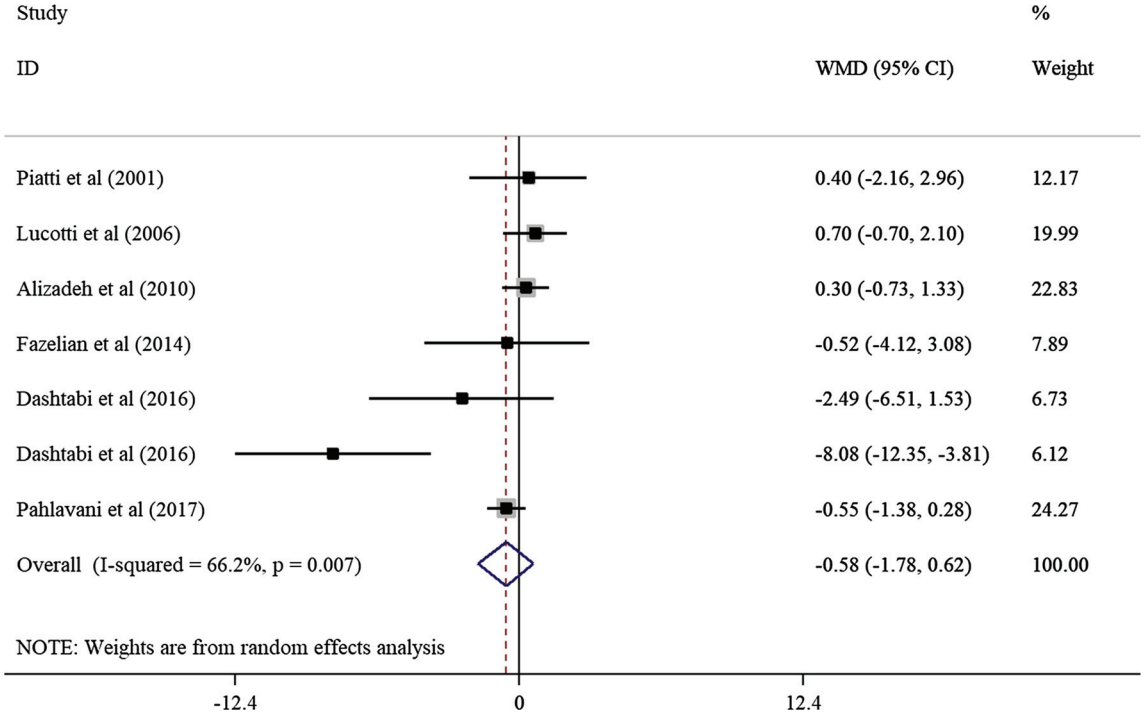

Figure 2. Forest plot of randomized controlled trials investigating the effects of L-arginine on body weight.

Sensitivity analysis

To explore the influence of each single study on the overall effect size, we excluded studies from the analysis, step by step. We found no significant effect of any individual study on the overall effect sizes of body weight, BMI and waist circumference.

Publication bias

Visual inspection of the funnel plots of standard error versus effect size (WMD) for our three outcomes did not show any evidence of asymmetry (Figure 5). These findings were confirmed by the use of Egger's regression tests for body weight (P = 0.27), BMI (P = 0.37), and WC (P = 0.54).

Discussion

In the present meta-analysis, we found a significant reduction in WC after L-arginine supplementation. However, L-arginine supplementation had no significant effect on body weight and BMI. Subgroup analyses indicated that body composition indices might significantly reduce in trials lasting $\geq$ 8 weeks and used < 8 g/d L-arginine.

L-arginine supplementation tends to significantly lower waist circumference by 2.97 cm, compared to placebo. Several studies are available to support the anti-adiposity effects of L-arginine. In line with the present study, a pilot study by Ryan et al showed that receiving 3 g of L-arginine three times a day for 12 weeks, led to significant reduction in waist circumference [20]. Also, several animal Studies demonstrated that L-arginine supplementation reduces fat mass and increases lean body mass [31–33]. In contrast, Alizadeh et al in a clinical trial examined the effect of hypocaloric diet with or without L- arginine, the anthropometric measures were not significantly different before and after the intervention [19].

This meta-analysis did not show a significant reduction in weight and BMI after L-arginine supplementation. In accordance with our findings, a randomized clinical trial by Pahlavani et al did not show a significant effect of L-arginine supplementation on body weight and BMI in male athletes [23]. Moreover, two other trials have reached the same findings [14, 18]. Otherwise, there are only two studies showed a significant reduction in body weight and BMI after L-Arginine supplementation [28, 30]. It should be noted that body weight and body mass index are not valid tools for measuring fat mass tissue because they could not differentiate fat and muscle and bone masses, while, waist circumference is considered as a better indicator of body fat [34, 35].

The controversial findings from different studies in this area can be partially explained by the different dosages of L-arginine supplementation and duration of studies. L-arginine dosage and study duration were as the potential

Table I. Characteristics of included studies

Author, year (Reference Number)	Country	Study Design (duration)	Gender	Mean age (year)	Patient Features	Sample size	Dose (g)	Intervention		Outcome(s) (yes/no)
								Intervention	Placebo	
Piatti, 2001 [14]	Italy	Randomized, double-blind, controlled (4 weeks)	Both	57.8	type 2 diabetes	37	9	orally 3 g L-arginine three times per day	Placebo	Body weight (no)
Lucotti, 2006 [24]	Italy	Randomized, double-blind, controlled (3 weeks)	Both	56.4	obese	33	8.3	L-arginine (8.3 g/d)	Placebo	Body weight (yes) waist circumference (yes) BMI (no)
Alizadeh, 2010 [15]	Iran	Randomized, double-blind, controlled (6 weeks)	Female	33.8	central obese	34	5	L-arginine (5 g/d) + HDEL	HDEL	Body weight (no) waist circumference (no)
Bogdanski, 2012 [25]	Poland	Randomized, clinical trial (13 weeks)	Both	43.8	visceral obesity	60	9	L-arginine (9 g/d)	Placebo	Waist circumference (no) BMI (no)
Bogdanski, 2013 [6]	Poland	Randomized, double-blind, controlled (25 weeks)	Both	43.1	obese	88	9	L-arginine (9 g/d)	Placebo	Waist circumference (no) BMI (no)
Fazelian, 2014 [18]	Iran	Randomized, double-blind, controlled (8 weeks)	Both	40.34	obese	46	3	L-arginine (3 g/d)	Maltdextrin	Body weight (no) BMI (no)
Dashtabi, 2016 [26]	Iran	Randomized, single-blind, controlled (8 weeks)	Both	42.33	Obese	55	3	L-arginine (3 g/d)	Placebo	Body weight (yes) waist circumference (yes) BMI (yes)
Dashtabi, 2016 [26]	Iran	Randomized, single-blind, controlled (8 weeks)	Both	44.07	Obese	56	6	L-arginine (6 g/d)	Placebo	Body weight (yes) waist circumference(yes) BMI (yes)
Pahlavani, 2017 [19]	Iran	Randomized, single-blind, controlled (6 weeks)	Male	21.32	athletes	52	2	L-arginine (2 g/d)	Maltodextrin	Body weight (no) BMI (no)

BMI, body mass index; HDEL, Hypocaloric Diet Enriched in Legumes

Table II. Results of subgroup analysis of included randomized controlled trials in meta-analysis of L-arginine supplementation and obesity indices

Group	No. of comparisons	Net change (95% CI)	P significance	P-heterogeneity	I^2 (%)
Body weight					
L-arginine dose (g)					
< 8 g	5	−0.44 (−1.06, 0.17)	0.15	0.004	73.9
≥ 8 g	2	0.63 (−0.59, 1.85)	0.31	0.84	0.0
Trial duration					
< 8weeks	4	−0.03 (−0.60, 0.53)	0.91	0.38	2.1
≥ 8 weeks	3	−3.28 (−5.55, −1.01)	0.005	0.02	72.4
Baseline BMI					
Overweight (<30)	3	−0.46 (−1.23, 0.30)	0.23	0.78	0.0
Obesity grade 1 (30 < BMI < 35)	3	0.13 (−0.68, 0.94)	0.75	0.001	86.6
Obesity grade 2 (≥35)	1	−2.49 (−6.50, 1.52	0.22	–	–
BMI					
L-arginine dose (g)					
< 8 g	5	−0.22 (−0.42, −0.02)	0.030	<0.001	88.0
≥ 8 g	2	0.01 (−1.11,1.14)	0.979	0.863	0.0
Trial duration					
< 8 weeks	2	−0.06 (−0.29,0.16)	0.576	0.115	59.8
≥ 8 weeks	5	−0.71 (−1.12, −0.30)	0.001	<0.001	83.1
Baseline BMI					
Overweight (<30)	2	−0.19 (−0.43, 0.05)	0.12	0.97	0.0
Obesity grade 1 (30 < BMI < 35)	2	−0.24 (−0.61, 0.12)	0.19	<0.001	96.9
Obesity grade 2 (≥35)	3	−0.33 (−1.21, 0.53)	0.44	0.61	0.0
WC					
L-arginine dose (g)					
< 8 g	3	−3.33 (−4.15, −2.50)	<0.001	0.035	70.2
≥ 8 g	3	−3.74 (−4.71, −2.77)	<0.001	<0.001	90.4
Trial duration					
< 8 weeks	2	−3.86 (−4.56, −3.16)	<0.001	0.006	86.5
≥ 8 weeks	4	−2.02 (−3.43, −0.61)	0.005	0.002	80.5
Baseline BMI					
Obesity grade 1 (30 < BMI < 35)	3	−4.03 (−4.71, −3.35)	<0.001	0.003	82.4
Obesity grade 2 (≥35)	3	−0.50 (−2.12, 1.11)	0.54	0.56	0.0

sources of heterogeneity in our study. Moreover, ≥ 8weeks supplementation with L-arginine and with a dose of < 8 g/day significantly reduced BMI and body weight and BMI in our subgroup analysis, respectively. However, the highest dosage in which one can be relatively assured that no side effects will occur over a lifetime, has been recommended at 20 g of L-arginine per day in supplemental form [36].

L-arginine is a semi-essential amino acid consisted of 7% of total amino acids in the usual human diet [37]. L-arginine improves endothelial function, insulin sensitivity, and immune cell function. Furthermore, it is used in protein synthesis [14, 15, 38]. L-arginine induces the expression of key genes in adipose tissue which may subsequently increase fatty acid and glucose oxidations [33]. These effects might be due to increasing NO production and subsequent up-regulation of AMP-activated protein kinase, NO synthase-1, and peroxisome proliferators expression, and activation of the receptor γ coactivator-1α and heme oxygenase-3 [32, 33, 39]. Increases in AMP-activated protein kinase and peroxisome proliferator-activated receptor gamma coactivator-1alpha concentrations will induce lipid utilization, insulin signaling and glucose transport [40, 41]. Therefore, L-arginine may increase NO concentration which has been associated with lower risk of abdominal adiposity [42]. In addition, L-arginine might enhance lipogenesis in adipose tissue [43] by increasing the expression of peroxisome proliferator-activated receptor (PPAR) gamma, which stimulates differentiation and proliferation of preadipocytes [44]. However, according to our subgroup analysis, WC was significantly reduced only in grade 1 obese subjects, but not in individuals with grade 2 obesity.

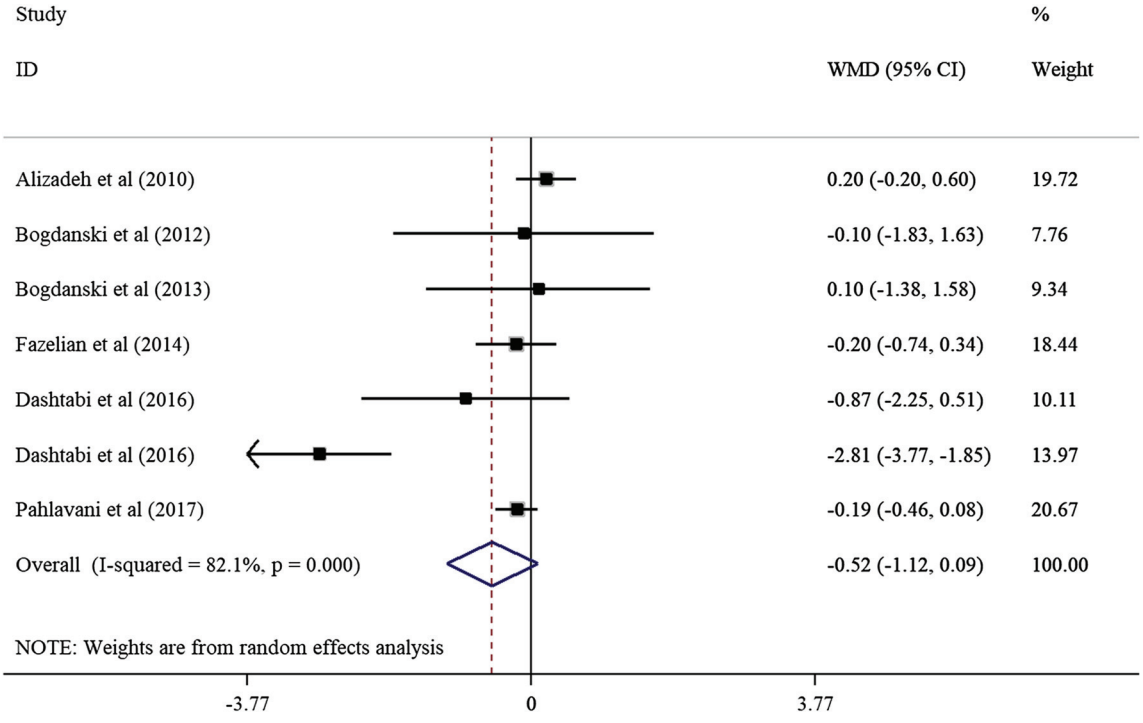

Figure 3. Forest plot of randomized controlled trials investigating the effects of L-arginine on Body mass index (BMI).

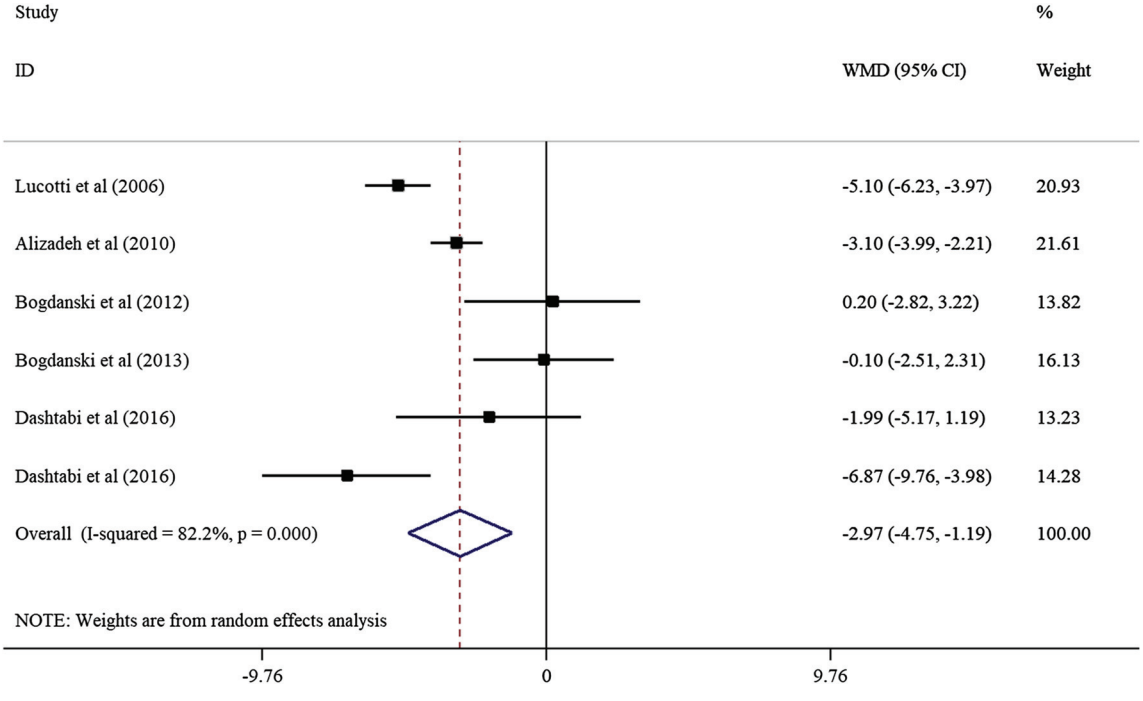

Figure 4. Forest plot of randomized controlled trials investigating the effects of L-arginine on waist circumference (WC).

To the best of our knowledge, this is the first systematic review and meta-analysis which evaluated the effects of L-arginine supplementation on obesity indices including body weight, BMI, and waist circumference. Egger regression tests for the effect of L-arginine supplementation provided no evidence of substantial publication bias in this meta-analysis. However, there were some limitations in the current study including (i) high levels of heterogeneity

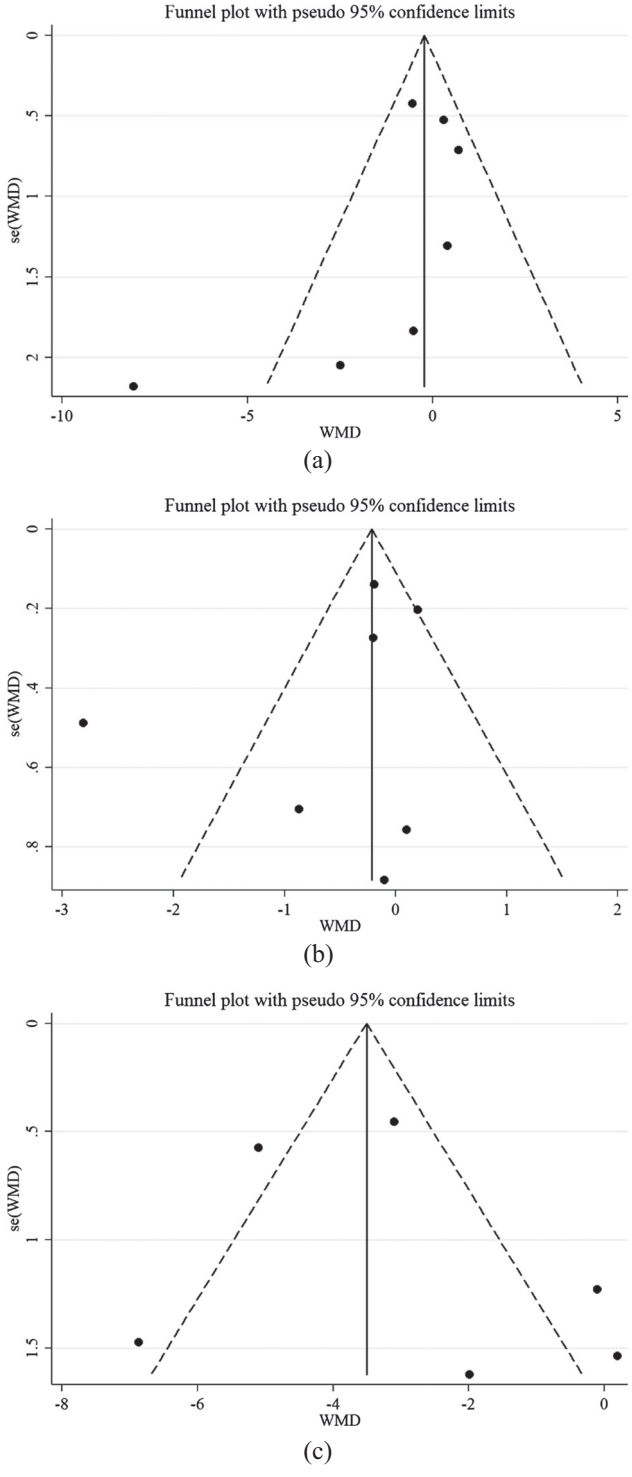

Figure 5. Funnel plot detailing publication bias in the studies reporting the effect of L-arginine on a) body weight b) body mass index and c) waist circumference

was observed in combined analysis, (ii) the type of study population, dosage of L-arginine supplementation and duration of trials were different, (iii) there were some studies that did not provide admissible data or lacked a placebo group.

The present meta-analysis pooled results from RCTs in regard to the effect of the L-arginine administration on body weight, BMI, and waist circumference; Our findings indicate that L-arginine supplementation might reduce waist circumference. However, there was no significant effect on body weight and BMI.

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Author contributions
S.M.M and H.K.V designed the study. S.M.M and J.R searched the publications, screening and extracted data. H.K.V evaluated the included studies and performed statistical analyses. S.M.M and E. G were writing the manuscript. The manuscript has been read and approved by all authors.

Hamed Kord Varkaneh
Student Research Committee
Department of Clinical Nutrition and Dietetics
Faculty of Nutrition Sciences and Food Technology
Shahid Beheshti University of Medical Sciences
Tehran, Iran
Tel: (+98) 9185427366

hamedkord39@yahoo.co

