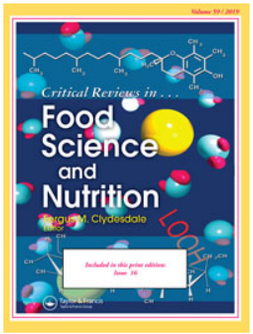

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Reza Tabrizi, Parvane Saneei, Kamran B Lankarani, Maryam Akbari, Fariba Kolahdooz, Ahmad Esmaillzadeh, Somayyeh Nadi-Ravandi, Majid Mazoochi & Zatollah Asemi (2019) The effects of caffeine intake on weight loss: a systematic review and dos-response meta-analysis of randomized controlled trials, Critical Reviews in Food Science and Nutrition, 59:16, 2688-2696, DOI: 10.1080/10408398.2018.1507996

To link to this article: https://doi.org/10.1080/10408398.2018.1507996

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2019, VOL. 59, NO. 16, 2688–2696
https://doi.org/10.1080/10408398.2018.1507996

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REVIEW

The effects of caffeine intake on weight loss: a systematic review and dos-response meta-analysis of randomized controlled trials

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ABSTRACT

This systematic review and meta-analysis of randomized controlled trials (RCTs) was performed to summarize the effect of caffeine intake on weight loss. We searched the following databases until November 2017: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The relevant data were extracted and assessed for quality of the studies according to the Cochrane risk of bias tool. We estimated an intake-status regression coefficient (Beta) for each primary study and estimated the overall pooled Beta and SE using random effects meta-analysis on a double-log scale. Heterogeneity between studies was assessed by the Cochran Q statistic and I-squared tests (I^2). Thirteen RCTs with 606 participants were included in the meta-analyses. The overall pooled Beta for the effect of caffeine intake was 0.29 (95%CI: 0.19, 0.40; Q = 124.5, $I^2 = 91.2\%$) for weigh, 0.23 (95%CI: 0.09, 0.36; Q = 71.0, $I^2 = 93.0\%$) for BMI, and 0.36 (95% CI: 0.24, 0.48; Q = 167.36, $I^2 = 94.0\%$) for fat mass. For every doubling in caffeine intake, the mean reduction in weight, BMI, and fat mass increased 2 Beta-fold (20.29 = 1.22, 20.23 = 1.17, and 20.36 = 1.28), which corresponding to 22, 17, and 28 percent, respectively. Overall, the current meta-analysis demonstrated that caffeine intake might promote weight, BMI and body fat reduction.

KEYWORDS
Caffeine; weight loss; meta-analysis

Introduction

An estimated 64% of American populations are overweight or obese [body mass index (BMI) $\geq 25\,kg/m^2$] (Flegal et al. 2002). Obesity is a major risk factor for a number of metabolic diseases, including coronary heart diseases (CHD), hypertension, type 2 diabetes mellitus (T2DM), pulmonary dysfunction, and non-metabolic such as osteoarthritis, and certain types of cancer (Kromhout 1983; Lynch et al. 2009). Common treatments for managing obesity include lifestyle changes such as weight loss, appropriate diet, and increased physical activity, as well as the appropriate use of pharmacological agents to reduce the specific risk factors (Villareal et al. 2011).

Modest weight loss, 5–10% of the initial body weight, would result in beneficial health effects (Wing et al. 1992).Caffeine has been widely used as an practical approach in obesity management (Astrup 2000). Caffeine increases both noradrenaline and dopamine release, and therefore stimulates the neuronal activity in several brain regions (Zheng and Hasegawa 2016), which in turn can decrease weigh and body fat. Caffeine may increase fat oxidation through inhibiting phosphodiesterase and the suppression of negative effects of adenosine on increased noradrenaline release (Dulloo, Seydoux, and Girardier 1992). Despite reported anti-obesity effects and weight maintenance of caffeine in some clinical trials (Boozer et al. 2002; Coffey et al. 2004; Molnar et al. 2000; Westerterp-Plantenga, Lejeune, and Kovacs 2005), few studies did not show any beneficiary effect of caffeine for body weight and weight maintenance after weight loss (Hursel and Westerterp-Plantenga 2009; Lee et al. 2005).Therefore, the effect of caffeine consumption to improve weight loss diet and reduce percentage of body fat remains controversial.

We are aware of no systematic review and meta-analysis of RCTs about the effect of caffeine intake on weight loss. This meta-analysis was performed to summarize the available evidence of RCTs to investigate the effect of caffeine intake on weight loss.

Methods

Search strategy and study selection

This meta-analysis was undertaken according to PRISMA (Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses) guideline. Two authors were independently conducted the search, data selection, data extraction, and evaluation of risk of bias. In the case of a disagreement, it is resolved by consensus and/or discussion with a third author. The following online databases were searched for relevant RCTs studies published through November 2017: Cochrane Library, EMBASE, MEDLINE, and Web of Science databases. In addition, ongoing trials were searched from databases including the International Standard Randomized Controlled Trial Number Register and Meta-register for RCTs. In addition, we did not publish the review protocol. We conducted searches on gray literature using databases including institute for scientific and technical information (INIST) and the healthcare management information consortium (HMIC), also to find other unpublished studies, we contacted with experts and centers of related field. Trials retrieved that examined the effect of caffeine intake on weight, BMI and/or body fat by using the following MeSH and text words [("caffeine"[Mesh] OR "coffee"[Mesh] OR caffeine [tiab] OR coffee [tiab]) OR caffeinated beverages [tiab] AND ("body weight"[Mesh] OR "body mass index"[Mesh] OR "body fat"[Mesh] OR body weight [tiab] OR body mass index [tiab] OR body fat [tiab]) AND (randomized clinical trial [pt] OR controlled clinical trials [pt] OR randomized [tiab] OR placebo [tiab] OR randomly [tiab] OR trial [tiab])].

The reference lists of all known related studies, including original research papers and review articles, were reviewed as an additional manual search. Trials applied that were published in the English language without time restrictions for

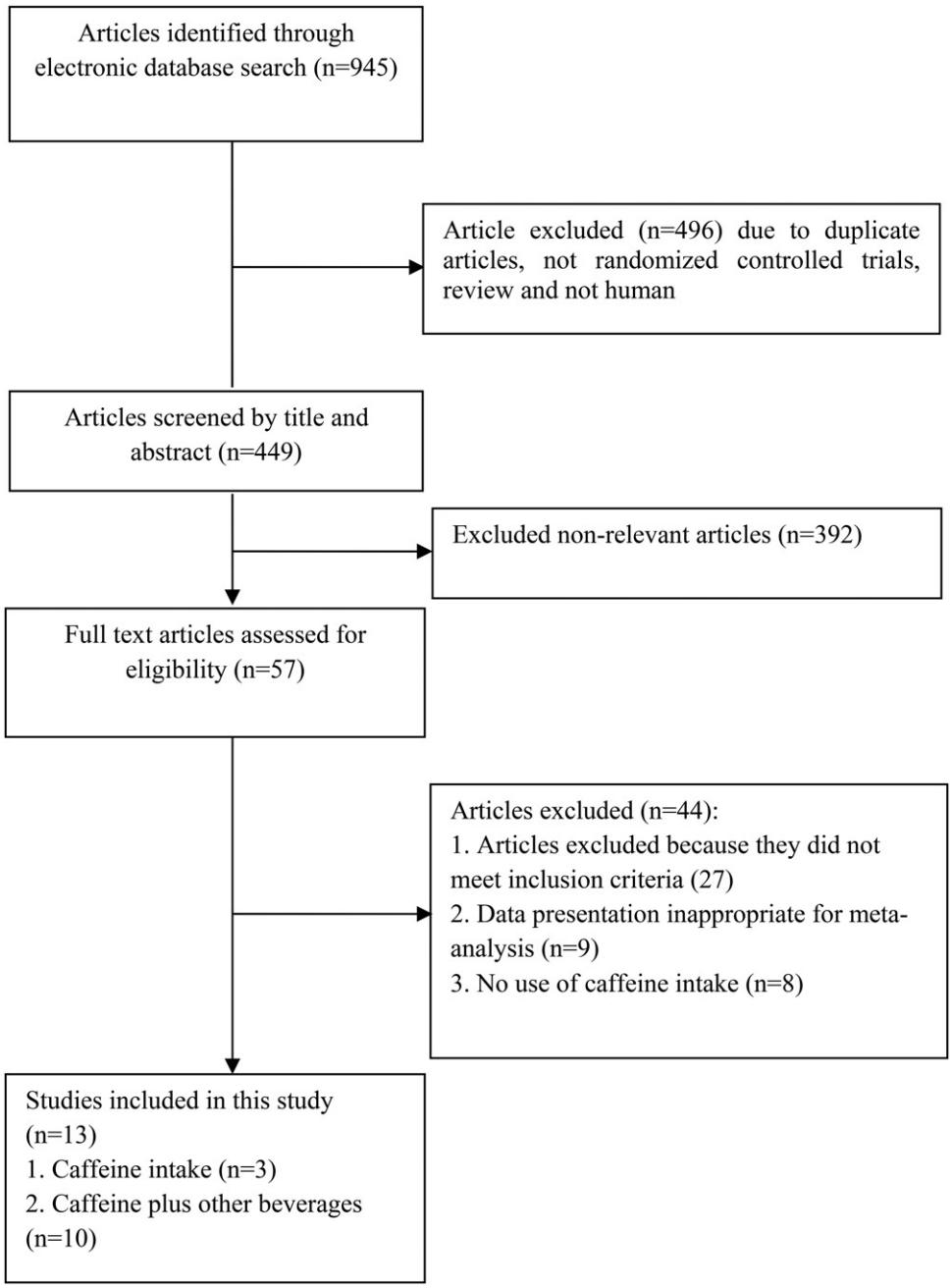

Figure 1. Literature search and review flowchart for selection of studies.

Table 1. The effect of caffeine on weight, BMI and body fat reduction: overview of selected studies for dose-response meta-analysis.

Authors (y)	Country	Publication year	Age (y)	Gender	Sample size (control/ intervention)	RCT type	Energy restriction	Intervention (name and daily dose)	Dosage of caffeine (mg/day)	Control	Duration (wk)	Presented data	Participants
Colker et al. (1999)	USA	1999	Range: >21 y	F/M	7/9	Parallel	No	975 C aurantium, 528 mg C, 900 mg St. Johns	240	Maltodextrin placebo	6	Weight, body fat	Overweight
Molnar et al. (2000)	Hungary	2000	Mean: 16 ± 1	F/M[1]	13/16	Parallel	Yes	<80 kg:300 mg C/30 mg E[2] Or >80 kg: 600 mg C/60 mg E	450	Placebo	20	Weight, BMI, body fat	Obese
Boozer et al. (2002)	USA	2002	Range: 18-80	F/M	38/39	Parallel	Yes	192 mg C/90 mg E	192	Placebo	24	Weight, body fat	Obese
Boozer et al. (2002)	USA	2002	Range: 25-55	F/M	24/24	Parallel	No	240 mg C/72 mg E	100	Placebo	8	Weight, body fat	Overweight/ Obese
Coffey et al. (2004)	USA	2004	Range: 18-65	F/M	50/52	Parallel	No	360 mg C/60 mg E/ 90 mg salicin	360	Placebo	12	Weight, BMI, body fat	Obese
Greenway et al. (2004)	USA	2004	Range: 18-65	F/M	20/20	Parallel	Yes	210 mg C/72mg E	210	Placebo	12	Weight	Healthy
Hackman et al. (2006)	USA	2006	Range: 25-74	F	23/19	Parallel	No	100 mg C/40 mg E	100	Placebo	36	Weight, body fat	Overweight/ Obese
Thom (2007)	Norway	2007	Mean: 24.2 ± 3.2	F/M	15/15	crossover	No	10 g of Coffee Slender	528	10 g of decaf-feinated coffee	12	Weight, body fat	Overweight/ Obese
Hursel and Westerterp-Plantenga, (2009)	Netherla-nds	2009	Mean: 44 ± 2	F/M	20/20	Parallel	No	150 mg C/270 mg green tea	150	Placebo	13	Weight, BMI, body fat	Overweight/ Obese
Bakuradze et al. (2011)	Germany	2011	Range: 20-44	M	33/33	Consecuti-ve	No	750 ml freshly brewed coffee	720	Water	8	Weight, BMI, body fat	Healthy
Liu et al. (2013)	USA	2013	Range: 18-60	F/M	26/17	Parallel	Yes	600 mg C/60 mg E	600	60 mg Leptin	24	Weight, body fat	Obese
Bracale et al. (2014)	Italy	2014	Mean: 36.3 ± 10.3	F	7/6	Parallel	Yes	60 mg C/600 mg E	60	Placebo	4	Weight, BMI	Obese
Davoodi et al. (2014)	Iran	2014	Mean: 39.22 ± 5.81	F	30/30	Parallel	Yes	5 mg C/kg BW	425	Nothing	6	Weight, BMI, body fat	Overweight/ Obese

[1]F, Female; M, Male.
[2]C, caffeine; E, ephedrine; OBLI, online basic lifestyle information; OBWM, online behavioral weight management; BEV, fortified diet cola beverage, soluble fiber dextrin and caffeine.

publication. Two authors (RT, MA) independently selected studies in a two-steps process. In the first stage, authors screened the titles and/or abstract for eligible trials. In the second stage, the full-texts of related studies were retrieved to assess the eligibility of selected studies using inclusion and exclusion criteria. Studies did not contain proper data to be included in the met-analysis, though presented the other inclusion criteria were considered for a qualitative analyses to help identify confounding parameters. Trials that met the following criteria were selected for meta-analysis: (1) human RCTs; (2) intervention group consumed caffeine or caffeinated coffee, whereas the control group received placebo; and (3) the trials reported mean changes or mean difference of weight and/or BMI and/or body fat loss with standard deviation (SD) for the intervention and control groups or reported enough data acquirable to assess Beta (B) and its Standard Error (SE) for the assumed linear regression on the $\log_e$-$\log_e$ scale.

Data extraction and quality assessment

Two independent authors (ZA and MA) extracted data from each trial. The Cochrane Collaboration risk of bias tool was used to assess the quality of all relevant RCTs based on the following domains: random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of bias. The following data were extracted: first authors' name, publication year, age, gender, country, sample size, study design, energy restriction, the dose of caffeine intake in intervention and control groups, the duration of intervention, the mean change and standard deviation on weight, BMI, and body fat in intervention and control groups at the end of the intervention. We converted the reported dosage of caffeine intake into milligram per day (mg/d).

Data analysis

We estimated a caffeine intake-status regression coefficient (Beta) for each primary study on the baseline value when the assumption of a linear correlation on the $\log_e$-$\log_e$ scale exists; caffeine intake compared with mean change weight, BMI, and body fat. Algebraically derivation of an estimate from primary study of the Beta and its SE, we compared findings from studies with heterogeneously reported associations and the associated effects. The overall pooled Beta and its SE were estimated by using random effects meta-analysis following DerSimonian and Laird method (DerSimonian and Laird 1986). In the meta-regression model, the equation intercepts were calculated by using the meanX (the mean of the caffeine intake on the ln scale) and the meanY (the change of mean for weight, BMI, and fat mass status on the ln scale) for every trial and weighted these by multiplying with the weighting agent of the trial. Finally, we took the mean of the weighted meanX and mean of the weighted meanY as the coordination point at that the regression lines were hung up. This point, together with Betas, presented the intercept. All statistical transformation to provide Beta and its SE were conducted using the Microsoft Excel version 7.0 (Microsoft, Inc). For each trial, we weighted these by multiplying with the weighting agent of the trial. Heterogeneity between studies was assessed by Cochran Q test and I-squared statistic (I^2). I^2 higher than 50 percent with P-value <0.05 represented significant heterogeneity. Potential source of heterogeneity between studies such as duration of study ($\geq$12 weeks vs. $<$12 weeks), geographic area (US vs. non-US), gender (female vs. male), and energy restriction (no vs. yes) were examined by using subgroup analysis based on stratified random effects meta-analysis. We used the median of intervention duration, which was 12 weeks to do subgroup analyses in order to have equal distribution of data for comparison analyses. For linear dose response analyses, we used the transformations method to derive coherent single-study calculates from available summary statistics (Souverein et al. 2012). The present study applied a base–e logarithmic transformation on the caffeine intake and mean change of weight, BMI, and body fat before estimation of trial-specific Betas, therefore the overall Beta provides the difference in the loge-transformed and predicted mean change of weight, BMI, and body fat for each 1 unit difference in the loge transformed value in caffeine intake. Egger's test was used to detect the existence of potential publication bias for the primary outcome measure. To measure the pooled estimates, nonparametric test (Duval and

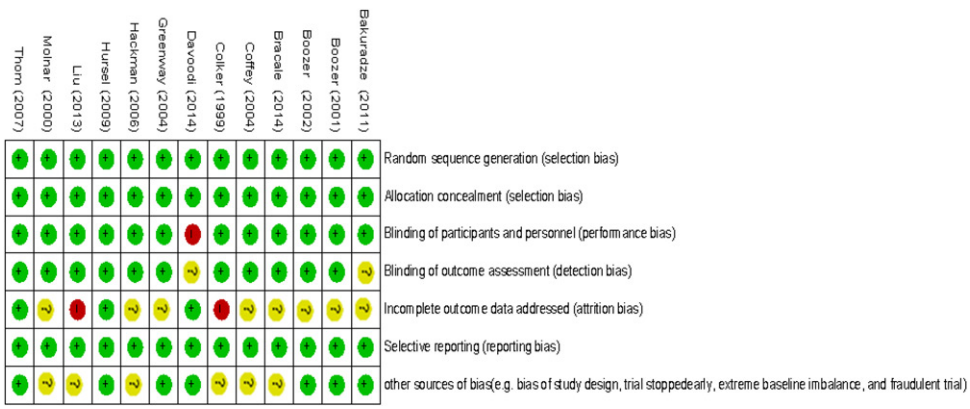

Figure 2. The methodological quality of included studies based on review authors' judgments about each risk of bias item presented as percentages across all included studies.

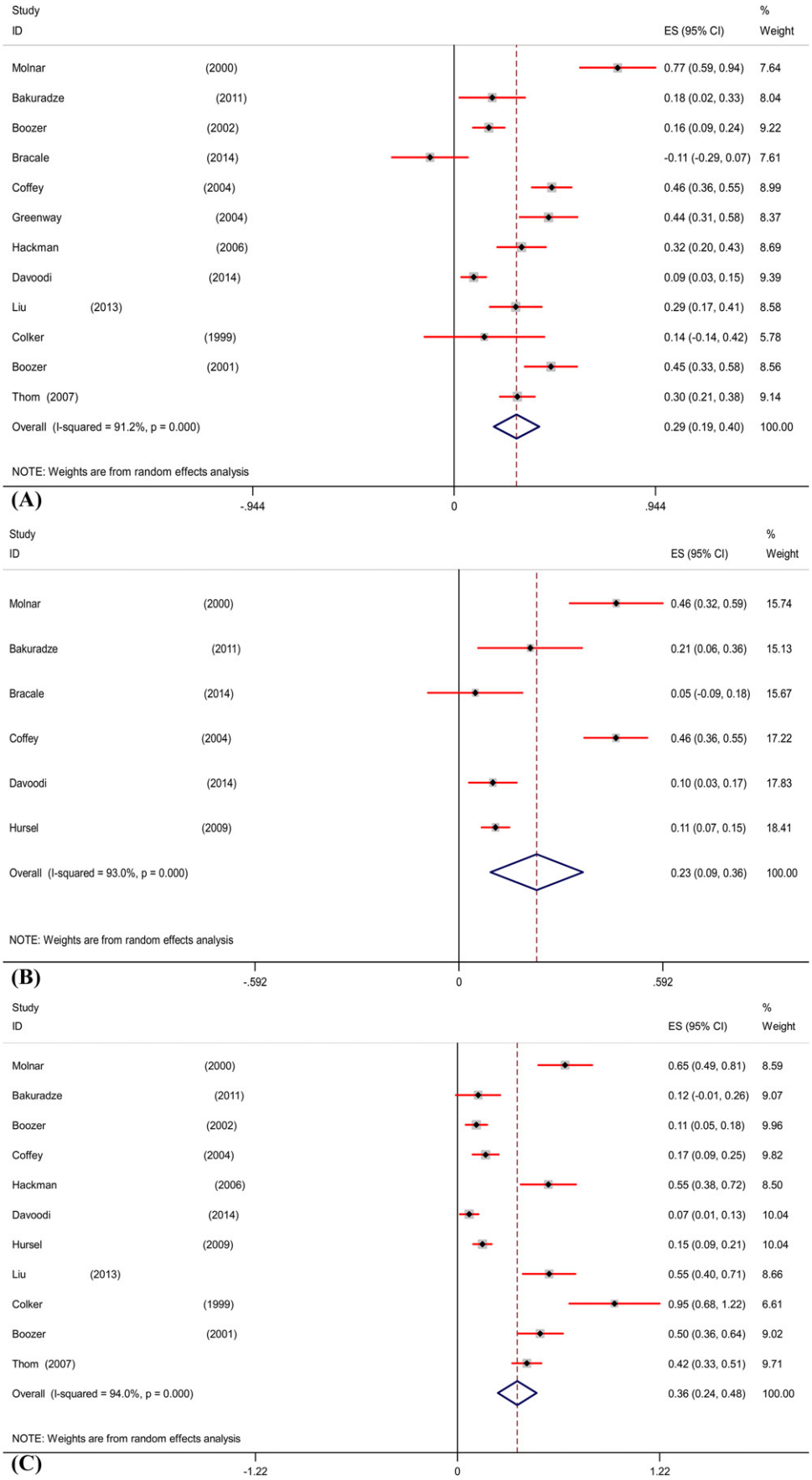

Figure 3. **A–C.** Random effects meta analysis of 13 randomized controlled trials that examined the association or effect of caffeine intake on change mean (A) weight, (B) for BMI, (C) for body fat in intervention and control groups by using regression coefficients (Bets) for the liner association between loge-transformed caffeine intake and loge transformed change mean in weight, BMI, and fat mass status (CI = 95%).

Tweedie) was used. We used STATA version 12.0 (Stata Corp., College Station, TX) and RevMan V.5.3 software (Cochrane Collaboration, Copenhagen, Denmark) for data analyses. *P*-Values <0.05 were considered as statistically significant.

Results

Our initial search found 945 potential citations, after screening 13 trials with total of 606 participants were potentially relevant and was included in the meta-analysis. Figure 1 shows the details of the study selection and Table 1 shows the characteristics of the included studies that were published between 1999 to 2014. Sample size varied between 13 to 102 participants. A consecutive design was performed in one study, cross-over design in one study, and parallel group design in the remaining 11 trials. To incorporating cross-over trials, we were included only data from the first period. Twelve trials have reported mean changes on weight (Bakuradze et al. 2011; Boozer et al. 2002; Bracale et al. 2014; Coffey et al. 2004; Colker et al. 1999; Davoodi et al. 2014; Greenway et al. 2004; Hackman et al. 2006; Hursel and Westerterp-Plantenga, 2009; Liu et al. 2013; Molnar et al. 2000; Thom, 2007), six on BMI (Bakuradze et al. 2011; Bracale et al. 2014; Coffey et al. 2004; Davoodi et al. 2014; Hursel and Westerterp-Plantenga, 2009; Molnar et al. 2000), and one on body fat loss (Greenway et al. 2004). The duration of intervention among trials varied between 4 and 36 weeks. The dosage of caffeine or caffeinated coffee in intervention group was from 60 to 4000 mg/day (median: 360 mg/day). Seven trials were conducted in USA (Boozer et al. 2002; Coffey et al. 2004; Colker et al. 1999; Greenway et al. 2004; Hackman et al. 2006; Liu et al. 2013), and one in each of the following countries, Iran (Davoodi et al. 2014), Italy (Bracale et al. 2014), Germany (Bakuradze et al. 2011), Netherlands (Hursel and Westerterp-Plantenga, 2009), Hungary (Molnar et al. 2000), and Norway (Thom, 2007). Figure 2 shows risk of bias of included trials.

The pooled analyses yielded a Beta coefficient of 0.29 (95%CI: 0.19, 0.40; Q = 124.5, $I^2 = 91.2\%$) for weight, 0.23 (95%CI: 0.09, 0.36; Q = 71.0, $I^2 = 93.0\%$) for BMI, and 0.36 (95%CI: 0.24, 0.48; Q = 167.36, $I^2 = 94.0\%$) for body fat (Figures 3 and 4). The dose-response analyses showed that a person who consumed 2 mg of caffeine per day compared to 1 mg of caffeine intake per day have 22% more reduction in weight, 17% more reduction in BMI, and 28% more reduction in body fat.

The subgroup analysis for potential confounder variables for heterogeneity including the dosage of caffeine intake, the duration of the intervention, geographic area, gender, and energy restriction are summarized in Table 2. The results of subgroup analyses showed that the Betas were different in some specific strata of suspected variables.

Egger's regression tests indicated no significant publication bias for the effect of caffeine intake on mean reduction in weight (B = 3.23, $P = 0.22$), and BMI (B = 3.79, $P = 0.29$). There was evidence of possible publication bias in the effect of caffeine intake and fat mass (B = 7.81, $P = 0.001$). The results showed that the summary regression coefficient (Beta) on body fat significantly decreased between before (Beta 0.36; 95%CI, 0.24, 0.24) and after (Beta 0.22; 95%CI, 0.10, 0.34) censored trials were included into the analysis.

Discussion

This systematic review and meta-analysis is the first report of the effect of caffeine intake on weight, BMI and body fat and showed that caffeine intake might promote weight, BMI and body fat reduction.

Obesity is associated with multiple metabolic and non-metabolic disorders such as CHD, T2DM, and certain types of cancer (Kromhout, 1983; Lynch et al. 2009). The current meta-analysis of RCTs demonstrated that caffeine consumption resulted in a significant decrease in weight, BMI and body fat. In a meta-analysis by Phung et al.(Phung et al. 2010), it was documented that the administration of green tea catechins (GTCs) with caffeine was correlated with a significant decrease in BMI, body weight, and waist circumference. Among healthy people intake of green tea extract containing 270 mg of

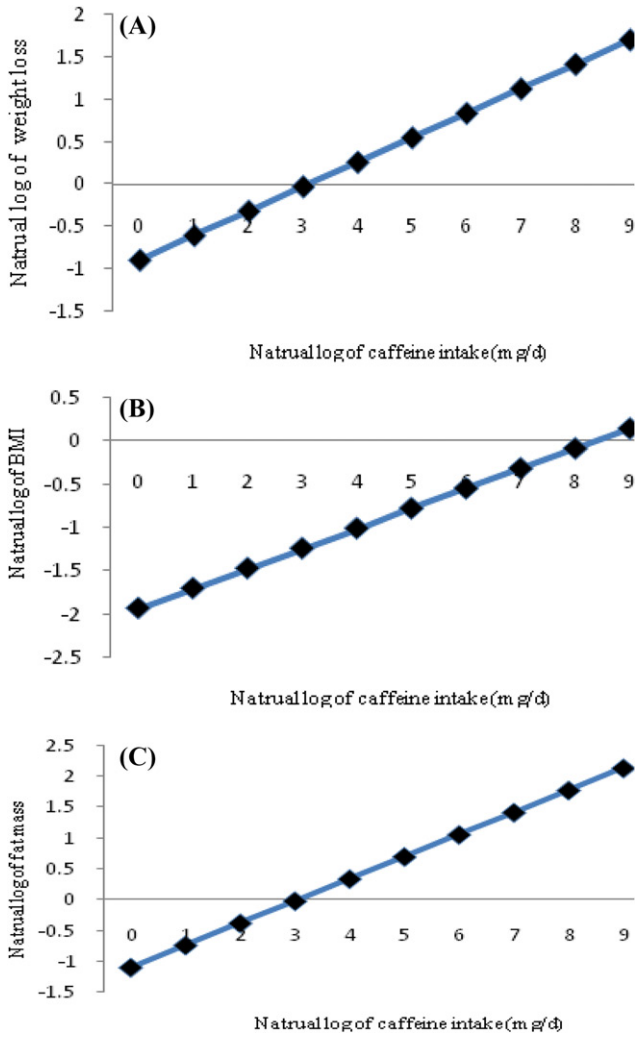

Figure 4. A–C. The change of mean weight, BMI, and fat mass status as a function of dietary of caffeine intake (mg/d) calculated using random effects meta-analyses of randomized controlled trails on)A) weight [loge(y) = 0.29 × loge(x) − 0.90],)B) BMI [loge(y) = 0.23 × loge(x) − 1.93],)C) body fat loge(y) = 0.36 × loge(x) − 1.10].

Table 2. The effects of caffeine intake on weight, BMI and body fat reduction based on subgroup analysis.

Parameter		Number of trials	Subgroups	Pooled Beta (random effect)	95% CI	I-squared (%)	Overall I-squared (%)
Weight	Dosage of caffeine (mg/day)	3	< 200	0.18	0.04, 0.32	86.2	91.2
		5	200- 450	0.44	0.21, 0.67	95.9	
		3	450 <	0.24	0.15, 0.33	0.0	
	Duration of study (week)	8	≤ 12	0.25	0.12, 0.39	91.7	
		4	≥ 13	0.37	0.17, 0.58	92.3	
	Geographic area	7	US	0.33	0.23, 0.44	82.8	
		5	Non US	0.24	0.04, 0.45	94.2	
	Gender	3	Female	0.11	−0.09, 0.30	89.3	
		1	Male	0.18	0.02, 0.33	–	
		8	Both	0.38	0.26, 0.50	88.2	
	Energy restriction	6	No	0.33	0.24, 0.42	70.0	
		6	Yes	0.27	0.10, 0.44	93.7	
BMI	Dosage of caffeine (mg/day)	2	< 200	0.10	0.06, 0.14	0.0	93.0
		3	200- 450	0.33	0.07, 0.60	95.7	
		1	450 <	0.21	0.06, 0.36	–	
	Duration of study (week)	4	≤ 12	0.20	0.01, 0.40	93.0	
		2	≥ 13	0.28	−0.07, 0.62	95.8	
	Geographic area	1	US	0.46	0.36, 0.55	–	
		5	Non US	0.17	0.07, 0.28	85.1	
	Gender	2	Female	0.09	0.03, 0.15	0.0	
		1	Male	0.21	0.06, 0.36	–	
		3	Both	0.34	0.06, 0.61	96.8	
	Energy restriction	3	No	0.26	0.01, 0.50	95.7	
		3	Yes	0.20	−0.03, 0.42	91.7	
Fat mass	Dosage of caffeine (mg/day)	4	< 200	0.29	0.13, 0.46	94.0	94.0
		4	200- 450	0.34	0.11, 0.56	95.6	
		3	450 <	0.53	0.10, 0.96	94.3	
	Duration of study (week)	6	≤ 12	0.34	0.17, 0.52	94.6	
		5	≥ 13	0.39	0.20, 0.58	94.6	
	Geographic area	6	US	0.45	0.25, 0.65	94.1	
		5	Non US	0.27	0.11, 0.44	94.8	
	Gender	2	Female	0.30	−0.17, 0.77	96.4	
		1	Male	0.12	−0.01, 0.26	–	
		8	Both	0.41	0.27, 0.56	94.3	
	Energy restriction	7	No	0.38	0.23, 0.53	92.8	
		4	Yes	0.33	0.11, 0.55	95.7	

epigallocatechin gallate and 150 mg of caffeine, were associated with a significant increase in energy expenditure (by 4%) compared with people who consumed caffeine alone. It was also found that; there was a significant decrease in fat oxidation (by 41%) for people who consumed green tea compared with people who consumed caffeine (by 33%) (Dulloo et al. 1999). Few studies have reported the beneficial effects of caffeine on metabolic profiles. In a meta-analysis by Shi et al. (Shi et al. 2016), caffeine intake significantly reduced insulin sensitivity in healthy people. In another meta-analysis, the administration of GTCs with or without caffeine led to a significant drop in fasting glucose concentrations (Zheng et al. 2013). Earlier, it was reported that the family of insulin-like growth factors and their binding proteins involved in energy restriction (Hamilton-Fairley et al. 1993), might interfere with reduction in weight, BMI and body fat (Kiddy et al. 1989). Increased insulin sensitivity would result in elevated IGF-binding protein-1 during short-term energy restriction (Moran et al. 2003).

In the current meta-analysis, we selected weight, BMI, and body fat because they are known as the main diagnostic variables in overweight and obese people, as well as being the independent risk factors for CVD and diabetes (NHLBI Obesity Education Initiative Expert Panel 1998). Despite the statistical significance found between caffeine intake and reduction in weight, BMI, and body fat in the current study, the observed changes might not possibly be clinically relevant. For instance, for anti-obesity agents available in the market, subjects are considered to have failed their treatment if they have not achieved a weight loss of 2 kg after 4 weeks of the therapy (NHLBI Obesity Education Initiative Expert Panel 1998). It is noteworthy to mention that, in the current meta-analysis, caffeine consumption provided an average weight loss of <2 kg after 4 weeks of intervention compared with the control group.

Caffeine intake may contribute to a decrease in anthropometric measures through increased energy expenditure (Astrup et al. 1990; Dulloo et al. 1989), and increased thermogenesis (Astrup et al. 1990). Current evidence indicates the presence of caffeine antagonize adenosine receptors (Graham 2001; Thong and Graham 2002b) both in skeletal muscle (Graham 2001; Han et al. 1998) and in the central nervous system, with the latter results in an elevation in sympathetic activity (Thong and Graham 2002a), which might results in weight loss.

The strengths of the current study include: (1) we made a quantitative evaluation on how caffeine intake may influence weight and BMI, based on the best available evidence from RCTs; and (2) we combined all available dose in our dose-response meta-analysis across a large range of exposure, and the validity of the dose-response estimates have been increased.

There are several limitations in this meta-analysis, which should be taken into consideration when assess the results. Firstly, the number of studies, which were included in low-grade and high-grade subgroup analyses, was too small to gain solid conclusions; therefore more relevant studies are

needed to further explore this association. Secondly, substantial heterogeneity was observed across studies, which was expected considering differences in types of caffeine (e.g., only caffeine vs. caffeine plus other compositions), and participants' characteristics (e.g., gender, geographic region, genetic background, and gene-environment interactions). Thirdly, our search was limited to English language.

Overall, the current meta-analysis demonstrated that caffeine intake promoted weight, BMI and body fat reduction. Additional prospective studies investigating the effect of caffeine supplementation on weight, BMI, and body fat loss are necessary.

Disclosure statement

None.

Funding

The current study was founded by a grant from the Vice-chancellor for Research, Shiraz University of Medical Sciences, Shiraz, and Iran.

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