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Clinical evidence on the effects of saffron (Crocus sativus L.) on cardiovascular risk factors: A systematic review meta-analysis

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ABSTRACT

Cardiovascular disease is a one of most common causes of mortality around the world. This meta-analysis aims to summarize and conclude the clinical evidence regarding the use of saffron and its constituents, in particular crocin, on cardiovascular risk factors. A systematic review was conducted with PubMed, Scopus, Web of Science, Cochrane library and Google Scholar up to 24 May 2018. Randomized controlled trials (RCTs) that assessed the clinical effects of saffron and/or its constituents on blood lipid profile, glycemic parameters, blood pressure and anthropometric indices in human subjects were included. Eleven publication from ten studies comprising 622 participants included in quantitative analysis. Pooling of results showed significant effect of saffron on diastolic blood pressure (−1.24 mmHg; 95% CI: −1.51 to −0.96; I^2 = 0%), body weight (−1.29 kg; 95% CI: −2.14 to −0.44; I^2 = 70%) and waist circumstance (−1.68 cm; 95% CI: −3.31 to −0.04; I^2 = 51%). When subgroup analysis was performed based on quality of studies, a significant reduction in fasting plasma glucose levels was observed in subgroup with high quality studies (−10.14 mg/dl; 95% CI: −13.80 to −6.48; I^2 = 0%). Meta-analysis did not reveal any significant change in lipid profile, fasting insulin, systolic blood pressure and body mass index following saffron consumption. Present meta-analysis suggests that saffron might be beneficial in several outcomes related with cardiovascular disease. However, further RCTs with long term intervention with different dose of administration are needed.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death by non-communicable diseases [1]. Prevalence of CVD has dramatically increased across the world due to its close association with lifestyle transition such as physical inactivity, smoking and unhealthy dietary habits [1–4]. It is predicted that by the year 2030, almost 23.6 million people will die from CVD [5]. Furthermore, CVD lead to decrease the living standards of patients and creating a huge burden for individuals and governments [6]. Therefore, adoption of appropriate strategies to manage CVD and its related diseases is necessary for any healthcare system. In this context, lifestyle modification, in particular diet, and the use of synthetic agents are the most common therapeutic options [7,8]. Despite the significant benefits of these approaches, lifestyle changes are difficult to maintain in the long term and pharmacological interventions may be associated with undesirable side effects such as myopathy and hepatotoxicity [9,10]. Thus, it is important to find natural agents with cardiovascular protective effects beside mentioned solutions to overcome these limitations. In this regard, herbal medicine approach can be a promising adjunctive therapy due to its multi-pronged mechanisms of action [11–15]. Historically, many herbal agents have been tested and applied in the prevention and management of CVD and its risk factors [11–14,16–18]. Among these compounds, saffron has attracted significant attention recently, both in the scientific

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Table 1
PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5,6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8,9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.
For more information, visit: www.prisma-statement.org.

Table 2
PICO (participants, intervention/exposure, comparison, outcomes, and study design) criteria for inclusion and exclusion of studies.

Parameters	Descriptions
Participants	All population
Intervention	Any intervention in which saffron or crocin was administered
Comparison	Any comparator/control that incorporated a nonintervention group
Outcomes	Lipid profile, glycemic factor and anthropometrics measure
Setting	Randomized controlled trials

and consumer societies.

Saffron, the dried red-orange stigmas of *Crocus sativus L*, is an expensive spice that used as a food coloring and flavoring agent in different parts of the world since ancient times [19]. This spice is native to Iran [20]. It has been applied in folk medicine as antidepressant, analgesic, anticonvulsant, anti-inflammatory, antioxidant, anti-hyperlipidemic and anti-diabetic agent, and several medicinal effects of this plant and its constitutents hav ebeen confirmed in modern pharmacological studies [21–24,65–67]. Cardiovascular protective effects of saffron and its constituents, in particular crocin, have been investigated in several human trials [19,25,26]. However, the results are not fully conclusive in this context. For example, some researchers have reported

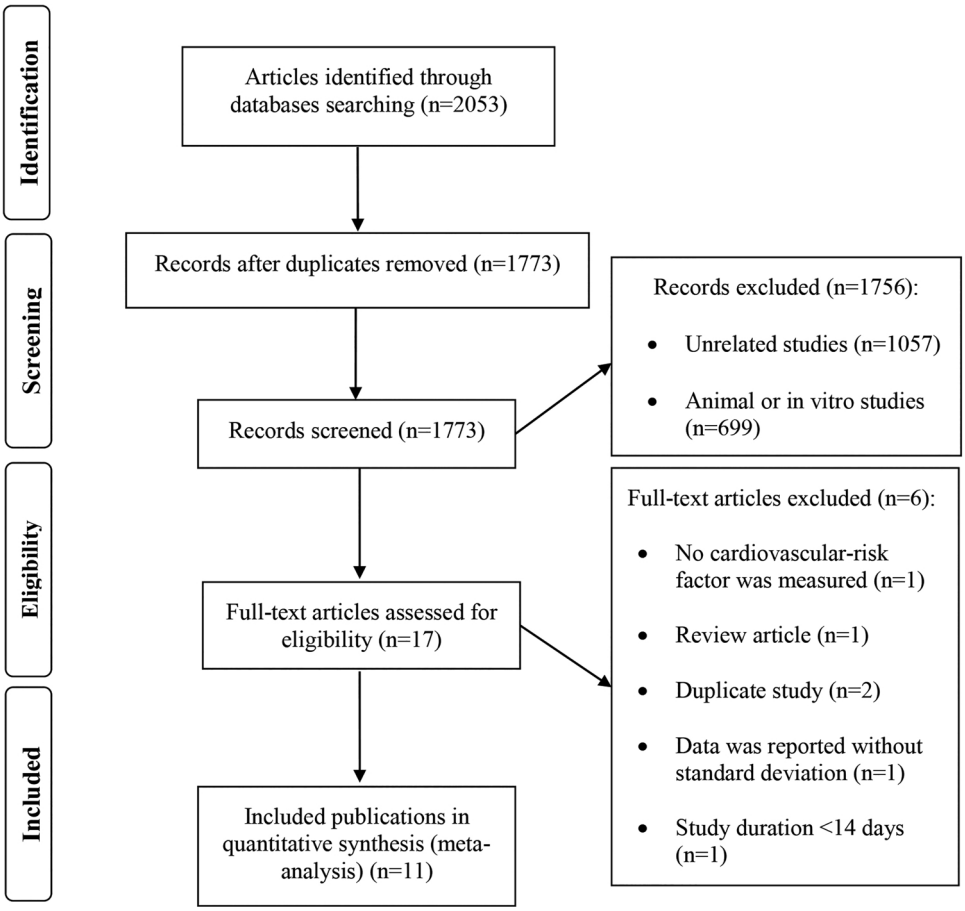

Fig. 1. Flow chart of the process of the study selection.

beneficial effects of saffron and crocin in this context [25,27], while others did not observe these effects [19,20].

Given that no comprehensive review has been performed in this field, so far; we conducted a systematic review and meta-analysis of all available randomized controlled trials (RCTs) to provide a precise estimate of the overall effects and safety of saffron and its derivatives on cardiovascular risk factors.

2. Materials and methods

Present systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [28] (Table 1).

2.1. Search strategy

A systematic electronic search was deployed, using the five following databases: (1) PubMed (http://www.ncbi.nlm.nih.gov/pubmed); (2) Scopus (http://www.scopus.com); (3) Web of Science (http://www.webofscience.com); (4) Cochrane library (http://www.cochranelibrary.com); and (5) Google Scholar (http://scholar.google.com), last searched on 24 May, 2018. The search strategy was designed as a combination of the following search terms: “saffron” or “Crocus sativus” or “crocin” or “safranal” or “crocetin” or “picrocrocin”, without any time or language restriction. To minimize chances of missing relevant studies, the reference lists of selected papers were checked manually. Furthermore, automated search update is set up in Google Scholar database to ensure that the latest publications in this field are entered.

2.2. Study selection

Thereafter elimination of duplicate records, two authors (A.H. and M.P.) independently reviewed the remained publications to determine their suitability for inclusion. Screening process was performed in two stages. At first, titles and abstracts of articles were scanned, studies that were clearly irrelevant were removed. Then, the remaining articles were evaluated for eligibility using full text version in the second stage. Finally, all human RCTs that assessed the impact of saffron and/or its constituents on the target outcomes including lipid profile, glycemic factors, blood pressure and anthropometric indices were included in meta-analysis. Publications with inappropriate data and RCTs with follow up duration less than 2 weeks were excluded. Where more than one publication of one study exists, publication with the most complete data was included in our analyses. Any differences during the study selection process were resolved by face-to-face discussion. The PICOS (Participants, Intervention, Comparators, Outcomes, Study Design) criteria are presented in Table 2.

2.3. Data extraction and assessment of quality

After screening and inclusion of studies were completed, a standardized data abstraction form was applied to extract the following data by A.H. and repeated by A.N.: (1) study identification data (first author, year and location of publication), (2) key study characteristics (design, type of interventions and control, follow up duration and daily dose of intervention), (3) participants' characteristics (total sample size, gender, age and health status) and (4) overall result about target outcomes. Any differences between assessors during the process of data extraction were resolved by consultation.

Table 3
Demographic characteristics of the included studies.

First author (publication year)	Country	Number and gender (M/F)	Mean age	Clinical Trial design /randomized/ Blinding	Notes about participants	Duration (Days)	Comparison group	Type and amount of intervention	Main outcomes			
									Blood lipids	Glycemic parameters	Blood pressure	Anthropometric measurements
Azimi et al. (2016)	Iran	81 (Both gender)	54.33	Parallel/ randomized/ single-blind	Type 2 diabetes mellitus	56	three glasses of tea without any herbals	Saffron stigmas 1 g/ day combination with 3 glasses of black tea	–	–	SBP DBP	BMI Waist
Azimi et al. (2015)	Iran	81 (Both gender)	54.33	Parallel/ randomized/ single-blind	Type 2 diabetes mellitus	56	three glasses of tea without any herbals	Saffron stigmas 1 g/ day combination with 3 glasses of black tea	TC TG LDL HDL	FPG Insulin HbA1c	–	–
Fadai et al. (2014)	Iran	61 (Male)	48.4	Parallel /randomized/ triple -blind	Schizophrenia	84	Placebo adjunctive to olanzapine	Crocin adjunctive to olanzapine)30 mg/day(	TG TC LDL HDL	FPG Insulin HbA1C	SBP	Waist
								Saffron adjunctive to olanzapine)30 mg/day(	TG TC LDL HDL	FPG Insulin HbA1C	SBP	Waist
Kermani et al. (2018)	Iran	48 (Both gender)	67.35	Parallel/ randomized/ double -blind	Metabolic syndrome	42	Placebo	Crocin (100 mg/ day)	TG TC LDL HDL	FPG SBP DBP	–	BMI Waist
Mansoori et al. (2011)	Iran	20 (Both gender)	38.85	Parallel/ randomized/ double -blind	Major depressive disorder	28	Placebo	Saffron (30 mg/day)	TG TC	FPG	–	–
Milajerdi et al. (2016)	Iran	36 (Both gender)	55	Parallel /randomized/ triple -blind	Type 2 diabetes mellitus	56	Placebo	Saffron (30 mg/day)	TG TC LDL HDL	FPG HbA1C	SBP DBP	–
Mohamadpour et al. (2013)	Iran	42 (Both gender)	31.1	Parallel /randomized /double -blind	Healthy	30	Placebo	Crocin (20 mg/day)	TG TC LDL HDL	FPG	–	–
Abedimanesh et al. (2017)	Iran	75 (Both gender)	55.24	Parallel /randomized /double -blind	Coronary artery disease	56	Placebo	Crocin (30 mg/day)	TG TC LDL HDL	FPG	–	BMI Waist Weight
								Saffron (30 mg/day)	TG TC LDL HDL	FPG	–	BMI Waist Weight
Nikbakht-Jam et al. (2015)	Iran	58 (Both gender)	41.24	Parallel /randomized /double -blind	Metabolic syndrome	56	Placebo	Crocin (30 mg/day)	TG TC LDL HDL	FPG	–	–
Gout et al. (2010)	France	60 (Female)	36.02	Parallel /randomized /double -blind	Mildly overweight	56	Placebo	Saffron (353 mg/ day)	–	–	–	Waist Weight
Sepahi et al. (2018)	Iran	60 (Both gender)	61.5	Parallel /randomized /double -blind	Diabetic macular edema	90	Placebo	Crocin (5 mg/day)	TG TC LDL HDL	FPG HbA1C	–	–
								Crocin (15 mg/day)	TG TC LDL HDL	FPG HbA1C	–	–

Abbreviations: TG triglyceride; TC total-cholesterol; LDL Low-density lipoprotein; HDL High-density lipoprotein; FPG Fasting plasma glucose; HbA1C hemoglobin A1C; BMI Body mass index; SBP Systolic blood pressure; DBP Diastolic blood pressure.

The quality of the RCTs included in this meta-analysis was evaluated separately by the two authors who performed the data extraction using Cochrane Collaboration tool [29]. This validated tool consists of the following risk of bias domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential bias. Each category was scored as high risk of bias (H), unclear risk of bias (U) or low risk of bias (L), based on the available information in the study. A judgment of "yes"' and "no" indicated L and H risk of bias, respectively. "Unclear" was applied when description in the text was not enough to assess risk of bias. Studies were considered as High risk of bias when

Table 4
The summary of review authors' judgments about each risk of bias item for included studies.

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Azimi et al. (2015)	L	L	H	L	L	L
Fadai et al. (2014)	L	L	U	L	L	U
Kermani et al. (2018)	U	U	L	L	L	U
Mansoori et al. (2011)	L	L	U	U	L	U
Milajerdi et al. (2016)	L	L	L	L	L	L
Mohamadpour et al. (2013)	U	U	U	L	L	U
Abedimanesh et al. (2017)	L	L	L	L	L	L
Nikbakht-Jam et al. (2015)	U	U	L	L	L	L
Gout et al. (2010)	L	L	U	L	L	U
Sepahi et al. (2018)	L	L	L	L	L	U

H: high risk of bias; L: low risk of bias; U: unclear or unrevealed risk of bias. Criteria defined for risk of bias assessment are according to the Cochrane guidelines. According to Cochrane criteria, study consider as a poor quality if it had high risk of bias in ≥2 items or unclear risk of bias in ≥3 criteria.

receive (H) in ≥2 or (U) in ≥3 criteria. Scoring disagreements were resolved through discussion between authors.

2.4. Statistical analysis

This meta-analysis was performed using Cochrane Program Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK) and STATA version 12.0 (Stata Corp., College Station) software. The mean differences (MD) and standard deviation (SD) of relevant variables were collected in similar units to estimate the pooled effects. In the case that net changes were not directly reported in intervention and control groups, MD was calculated by the minus of the post-intervention data from the baseline value. Also, the SD of changes was estimated by [SD = SEM × sqrt (n); n = number of subjects] where standard error of mean (SEM) was reported. SD of mean change were calculated according to the following formula: [SD = square root (SD pre-treatment) ^{2} + (SD post-treatment) ^{2} - (2R × SD pre-treatment × SD post-treatment); (R) = 0.5] [30]. Based on the heterogeneity between studies, a random effect or fixed model was applied in the meta-analysis [30,31]. The degree of heterogeneity was quantified using the I-squared (I^2) statistic, which is an estimate of percentage of the discrepancy across studies [32]. When, meaningful heterogeneity was observed (I^2 value greater than 50%), subgroup analysis was applied to find out potential sources of the heterogeneity. Sensitivity analysis is also conducted to detect the influence of a single study on the overall estimate via eliminating one study and repeating analysis [33–35]. P-Values < 0.05 were considered statistically significant.

2.5. Meta-regression

Random-effects meta-regression was performed to assess the potential impact of putative moderators i.e. saffron dose and duration of supplementation on calculated net changes [36].

2.6. Publication bias

Potential publication bias was explored using visual inspection of funnel plot asymmetry, Egger's regression asymmetry test and Begg's rank-correlation method [37,38].

3. Result

The flow diagram of the literature searches and the reason for excluding of each study was outlined in Fig. 1. Initially 2053 unique records were identified from systematic search in electronic databases. After excluding duplicate studies, 1773 article were screened by title/abstract in which 1756 studies did not meet the predefined inclusion criteria and were omitted. 17 articles were retrieve for assessment in detail of which 6 studies were removed because of no cardiovascular-related risk factor was reported (n = 1), review article (n = 1), no appropriate data for pooling analysis was provided (n = 1), study duration less than 2 weeks (n = 1) and duplicate data (n = 2). Of 11 publications that were eligible to include in qualitative analysis, 1 study [39] used 2 different dose of crocin, 2 studies [26,40] administrated saffron and crocin as 2 separate active group and 2 publication [41,42] was from same study. Thus, we considered each one as a separate arm. Finally, 11 publications (10 studies) comprising 14 arms met eligibility criteria and included for quantitative analysis.

3.1. Studies characteristics

Details of studies' characteristics is summarized in Table 3. Eleven RCTs comprising 622 with nearly 49 mean age provided data on effect of saffron/crocin on cardiovascular related risk factors. Except Gout et al. [43], all studies were conducted in Iran and published between 2010 and 2018. One study [41] was single-blinded, 2 study [26,44] used triple-blinded design and rest of them [27,39,40,43,45–47] were double-blinded. All studies employed parallel design and majority of them enrolled both genders as participants. The subject's condition varied between studies. Three studies [39,41,44] included diabetic patients, in 2 studies [27,47] subjects had metabolic syndrome, 1 study [26] included subjects with schizophrenia, 1 study [45] conducted on patients with major depressive disorder, 1 study [40] enrolled participants with coronary artery disease, 1 study [46] conducted on healthy volunteers and 1 study [43] included mildly overweight women. Saffron was administrated in 4 studies [41,43–45], crocin was administrated in 4 studies [27,39,46,47] and in 2 studies [26,40] both saffron and crocin were supplemented in separate active arms. Duration of intervention ranged between 28 and 90 days. Dose of saffron and crocin supplementation was 30 mg/day in most of studies.

Table 5
Summary of effect estimates of saffron for all indications.

Outcome category	Outcome	Number of participants	References	Mean difference (95%CI)	heterogeneity
Lipid	Triacylglycerol (mg/dl)	481	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2015 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Kermani et al. 2018 Mansoori et al. 2011 Milajerdi et al. 2016 Mohamadpour et al. 2013 Nikbakht-Jam et al. 2015 Sepahi et al. (a) 2018 Sepahi et al. (b) 2018	−4.36 [−12.67, 3.96]	I^2 = 0%
	Total-cholesterol (mg/dl)	481	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2015 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Kermani et al. 2018 Mansoori et al. 2011 Milajerdi et al. 2016 Mohamadpour et al. 2013 Nikbakht-Jam et al. 2015 Sepahi et al. (a) 2018 Sepahi et al. (b) 2018	−4.39 [−11.21, 1.35]	I^2 = 0%
	Low-density lipoprotein (mg/dl)	462	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2015 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Kermani et al. 2018 Milajerdi et al. 2016 Mohamadpour et al. 2013 Nikbakht-Jam et al. 2015 Sepahi et al. (a) 2018 Sepahi et al. (b) 2018	−2.23 [−6.81, 2.35]	I^2 = 0%
	High-density lipoprotein (mg/dl)	462	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2015 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Kermani et al. 2018 Milajerdi et al. 2016 Mohamadpour et al. 2013 Nikbakht-Jam et al. 2015 Sepahi et al. (a) 2018 Sepahi et al. (b) 2018	0.71 [−0.64, 2.06]	I^2 = 0%
Glycemic	Fasting plasma glucose (mg/dl)	481	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2015 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Kermani et al. 2018 Mansoori et al. 2011 Milajerdi et al. 2016 Mohamadpour et al. 2013 Nikbakht-Jam et al. 2015 Sepahi et al. (a) 2018 Sepahi et al. (b) 2018	−5.32 [−11.33, 0.69]*	I^2 = 65%
	Fasting Insulin (mIU/mL)	142	Azimi et al. 2015 Fadai et al. (C) 2014 Fadai et al. (S) 2014	0.09 [−0.38, 0.56]	I^2 = 0%
	HbA1C (%)	157	Fadai et al. (C) 2014 Fadai et al. (S) 2014 Milajerdi et al. 2016 Sepahi et al. (a) 2018 Sepahi et al. (b) 2018	−0.16 [-0.34, 0.01]	I^2 = 19%
Blood pressure	Systolic blood pressure (mm Hg)	190	Azimi et al. 2016 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Kermani et al. 2018	−1.49 [−3.78, 0.81]*	I^2 = 25%
	Diastolic blood pressure (mm Hg)	129	Azimi et al. 2016 Kermani et al. 2018	−1.24 [−1.51, −0.96]	I^2 = 0%
Anthropometric	Body weight (kg)	216	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017	−1.29 [−2.14, −0.44]*	I^2 = 70%

(*continued on next page*)

Table 5 (*continued*)

Outcome category	Outcome	Number of participants	References	Mean difference (95%CI)	heterogeneity
	Body mass index (kg/m^2)	204	Azimi et al. 2016 Gout et al. 2010 Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2016 Kermani et al. 2018	−0.35 [−0.81, 0.11]*	I^2 = 79%
	Waist circumference (cm)	325	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2016 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Gout et al. 2010 Kermani et al. 2018	−1.68 [−3.31, −0.04]*	I^2 = 51%

Abbriviations: (C): Crocin; (S): Saffron. (a) and (b) in Sepahi et al. study represent different dose (a: 5 mg/day crocin; b: 15 mg/day crocin). *Obtain from random-effect model.

3.2. Risk of bias assessment

Although all included studies were randomized, only 7 RCTs [26,39–41,43–45] provided adequate information for methods which used for performing random sequence generation and allocation concealment. 5 studies [27,39,40,44,47] reported sufficient data in blinding methodology and reasons of withdrawal were well-addressed in 9 studies [26,27,39–41,43,44,46,47]. Also, reporting bias was low in all studies and none of the studies reported any industry-funded support. 4 studies [40,41,44,47] exhibited sufficient information regarding compliance, assessing saffron ingredient activity and adjustment of confounders. Details on the author judgment's risk in each item of bias among included RCTs are presented in Table 4.

3.3. Quantitative analysis

3.3.1. Effect of saffron on blood lipids levels

Result from meta-analysis did not suggest any significant effect of saffron on triacylglycerol (TG) (-4.36 mg/dl; 95% CI: -12.67 to 3.96; I^2 = 0%), total cholesterol (TC) (-4.39 mg/dl; 95% CI: -11.21 to 1.35; I^2 = 0%), low-density lipoprotein cholesterol (LDL-C) (-2.23 mg/dl; 95% CI: -6.81 to 2.35; I^2 = 0%) and high-density lipoprotein cholesterol (HDL-C) (0.71 mg/dl; 95% CI: -0.64 to 2.06; I^2 = 0%) (Table 5). The lack of statistical significance remained unchanged when studies were subgroup based on type, dose and duration (data not shown).

3.3.2. Effect of saffron on glycemic factors

The meta-analysis for the mean difference in fasting plasma glucose (FPG) revealed a trend to significant reduction following saffron administration (-5.32 mg/dl; 95% CI: -11.33, 0.69; P = 0.08). However, between-studies heterogeneity was high (I^2 = 65%) (Fig. 2A, Table 5). Stratified analysis according to result of quality assessment of studies showed a significant reduction of FPG concentration in higher quality studies (-10.14 mg/dl; 95% CI: -13.80 to -6.48; I^2 = 0%) whilst no favorable effect was observed in the subgroup of studies with lower quality (4.39 mg/dl; 95% CI: -0.26 to 9.03; I^2 = 0%) (Table 6). The meta-analysis showed a trend to significant decrease in HbA1C (-0.16 (%); 95% CI: -0.34 to 0.01; P = 0.07) by saffron supplementation with negligible within-study heterogeneity (I^2 = 19%) Fig. 2B, Table 5). No significant effect was observed on fasting insulin (0.09 mIU/mL; 95% CI: -0.38 to 0.56; I^2 = 0%) following saffron supplementation (Table 5).

3.3.3. Effect of saffron on Blood pressure

The result of pooled analysis did not reveal a significant reduction in systolic blood pressure (SBP) (-1.49 mmHg; 95% CI: -3.78 to 0.81; I^2 = 25%). A significant reduction was demonstrated in diastolic blood pressure (DBP) following saffron administration (-1.24 mmHg; 95% CI: -1.51 to -0.96; I^2 = 0%) (Table 5).

3.3.4. Effect of saffron on anthropometric measures

The pooled estimates demonstrated that supplementation with saffron significantly reduced waist circumstance (-1.68 cm; 95% CI: -3.31 to -0.04; I^2 = 51%) (Fig. 2C, Table 5). When, studies were stratified according to saffron or crocin administration, the result remain significant in crocin subgroup with no between studies heterogeneity circumstance (-2.30 cm; 95% CI: -4.25 to -0.36; I^2 = 0%). Whilst, no significant effect was observed in subgroup with saffron administration (-0.55 cm; 95% CI: -1.61 to 0.50; I^2 = 63%) (Table 6). In addition, the meta-analysis showed that saffron significantly decrease body weight (-1.29 kg; 95% CI: -2.14 to -0.44; I^2 = 70%) (Fig. 2D, Table 5). However, subgroup analysis did not lead to find source of heterogeneity in body weight variable. Result from meta-analysis did not show any significant effect of saffron on body mass index (BMI) (-0.35 kg/m^2; 95% CI: -0.81 to 0.11; I^2 = 79%). Subgroup analysis based on type of administration was revealed a significant decrease in BMI in subgroup with crocin administration (-0.31 kg/m2; 95% CI: -0.55 to -0.07; I^2 = 0%). Whilst, no significant BMI-lowering effect was observed in subgroup with saffron supplementation (-0.63 kg/m^2; 95% CI: -0.86 to -0.40; I^2 = 90%) (Table 6).

3.4. Sensitivity analysis

Sensitivity analysis was conducted by removing each RCTs one by one to estimate effectiveness of individual study on pooled effect size [33–35]. Sensitivity analysis showed that, after excluding Azimi et al. [42], result from SBP (-3.96 mmHg; 95% CI: -7.74 to -0.18; I^2 = 0%) and BMI (-0.53 kg/m^2; 95% CI: -1.00 to -0.05; I^2 = 76%) changed to significant. After removing Mohamadpour et al. [46] and Mansoori et al [45], pooled effect size change to significant in FPG (-10.14 mg/dl; 95% CI: -13.80 to -6.48; I^2 = 0%). In addition, excluding Abedimanesh et al. [40] arm in which saffron was administered, the heterogeneity reduced in body weight but the result remained significant (-0.91 kg; 95% CI: -1.41 to -0.41; I^2 = 0%). Due to the pooled effect size in waist variable was marginally significant, excluding each of 4 arms from 2 studies [26,40] led to change result. The overall result was not significantly changed by excluding individual studies in remained variables.

3.5. Meta-regression

Meta-regression analysis was conducted to evaluate whether the in FPG concentrations response to saffron supplementation was associated with dose or/and duration of intervention. The results showed that the effect of saffron on FPG was independent of dose (coefficient = 0.004; P = 0.78). However, an inverse association between the changes in FPG concentrations and duration of supplementation was observed (coefficient = -0.29; P = 0.001).

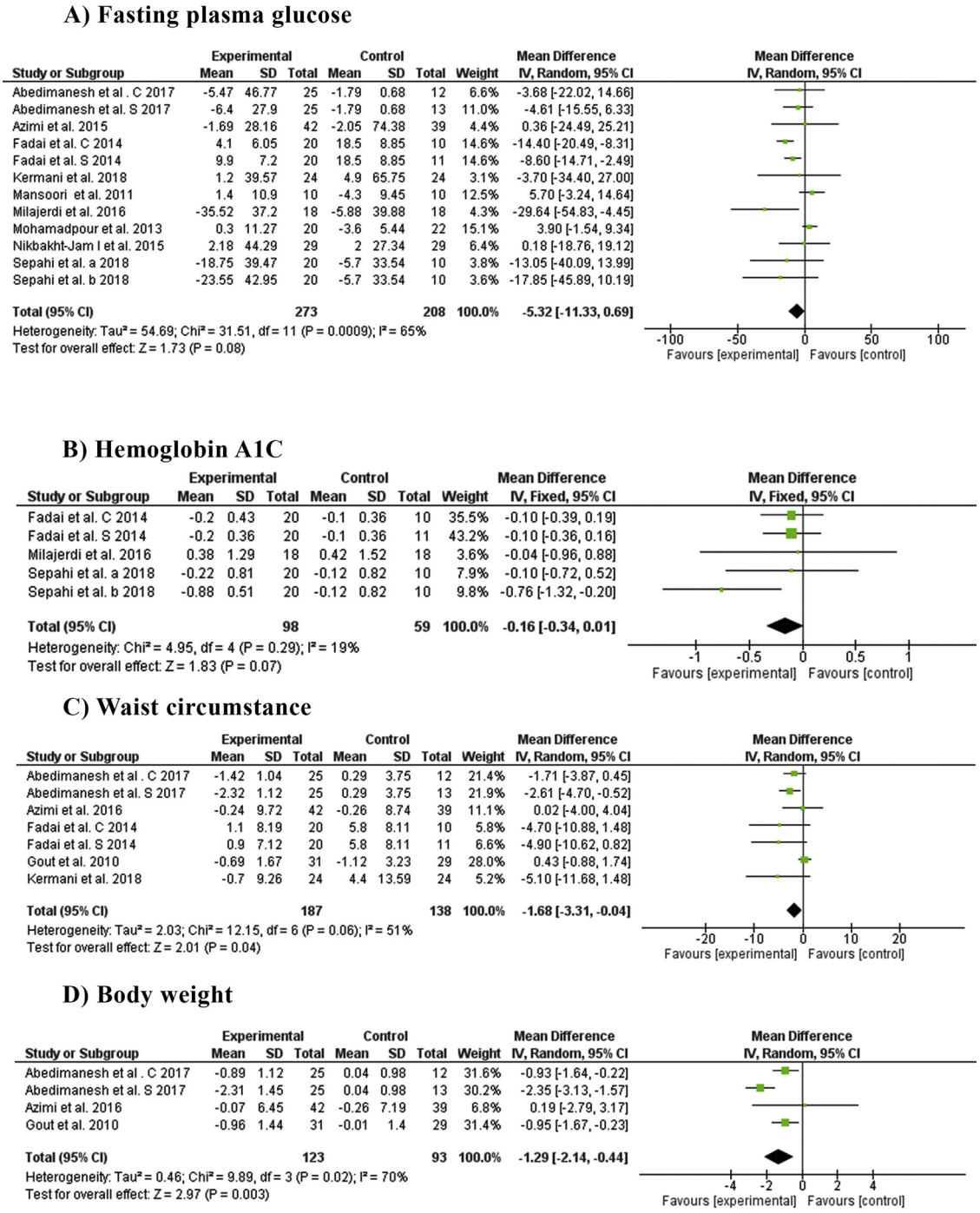

Fig. 2. Forest plot detailing mean difference and 95% confidence intervals (CI) for the effect of saffron on fasting plasma glucose, hemoglobin A1C, waist circumstance and body weight.

3.6. Publication bias

Fig. 3 presents the visual inspection of funnel plots of the effect of saffron on CVD risk factors. The visual inspection of funnel plot did not show asymmetry for TG, TC and LDL-C. These observations were confirmed by Begg's rank-correlation method (TG: P = 0.68; TC: P = 0.27; LDL-C: P = 0.48) and Egger's regression asymmetry test (TG: P = 0.68; TC: P = 0.66; LDL-C: P = 0.50). Visual inspection of funnel plot asymmetry suggested a potential publication bias for the effect of saffron on FPG. However, this observation was not confirmed by Begg's rank-correlation method (Begg's test P = 0.58) and Beggs rank-correlation test (Egger's test P = 0.64). Furthermore, visual inspection of funnel plot suggested a slight asymmetry for HDL-C. Similarly, the Egger's regression asymmetry test showed a potential evidence of publication bias in HDL-C (Egger's test P = 0.03). However, similar result was not observed in Begg's rank-correlation method (Begg's test P = 0.07). Due to inadequate number of studies in insulin, HbA1C, SBP, DBP, weight, waist and BMI outcomes, publication bias test was not applicable.

4. Discussion

This meta-analysis contains 11 RCTs that investigated the efficacy of saffron supplementation for cardiovascular risk factors. The results did

Table 6
Subgroup analysis.

Outcome (unit of measurement)	Subgroup analysis based on	References	Number of participants	Mean difference (95%CI)	heterogeneity
Fasting plasma glucose (mg/dl)	High risk of bias	Mansoori et al. 2011 Mohamadpour et al. 2013	110	4.39 [−0.26, 9.03]	I^2 = 0%
	Low risk of bias	Abedimanesh et al. (C) 2017 Abedimanesh et al. (S) 2017 Azimi et al. 2015 Fadai et al. (C) 2014 Fadai et al. (S) 2014 Kermani et al. 2018 Milajerdi et al. 2016 Nikbakht-Jam et al. 2015 Sepahi et al. (a) 2018 Sepahi et al. (b) 2018	371	−10.14 [−13.80, −6.48]	I^2 = 0%
Body mass index (kg/m^2)	Saffron	Abedimanesh et al. (S) 2017 Azimi et al. 2016	119	−0.63 [−0.86, −0.40]	I^2 = 90%
	Crocin	Abedimanesh et al. (C) 2017 Kermani et al. 2018	85	−0.31 [−0.55, −0.07]	I^2 = 0%
Waist circumference (cm)	Saffron	Abedimanesh et al. (S) 2017 Azimi et al. 2016 Fadai et al. (S) 2014 Gout et al. 2010	210	−0.55 [−1.61, 0.50]	I^2 = 63%
	Crocin	Abedimanesh et al. (C) 2017 Fadai et al. (C) 2014 Kermani et al. 2018	115	−2.30 [−4.25, −0.36]	I^2 = 0%

Abbriviations: (C): Crocin; (S): Saffron.

not suggest any benefit of saffron supplementation on blood lipid concentration, FPG, fasting insulin, HbA1C and BMI. However, meta-analysis showed a significant favorable effect on DBP, body weight and waist circumstance. Subgroup analysis showed a significant FPG-lowering effect of saffron in high quality studies. In addition, meta-regression indicated that longer supplementation can lead to greater reduce in FPG. When studies were categorized based on type of intervention, BMI and waist circumstance significantly reduced in crocin subset. Furthermore, the result from SBP and BMI change to significant after excluding one study.

The possible explanation for null result in some factors maybe refer to the different activity and efficiency of saffron on the mode of extraction. Another reason could be related with dosage of saffron which may not be sufficient to show a beneficial effect. Dose of saffron which used in animal studies, which demonstrated a considerable decrease in blood lipids, was substantially higher than our included RCTs. The amount of saffron administration in different animal model studies such as diazinon-induced rats [48], high fat diet rats [49] and streptozotocin-induced rats [50] were 25 mg/kg, 80 mg/kg, 100 mg/kg respectively.

Documents from *in-vitro* study suggested several possible mechanisms for saffron cardio protective properties. Saffron might reduce blood lipids via inhibiting pancreatic and gastric lipase activity which is key enzyme for fat absorption, and increasing in fecal excretion of fat [51]. It could stimulate Langerhans islets, induce glucose-stimulated insulin secretion and improve peripheral sensitivity to the remnant insulin [50,52]. Hypotensive effect of saffron seems to be endothelium dependent and contributing with a inhibitory effect on smooth muscles by blocking calcium channel [53]. Furthermore, saffron can act as an antianxiety, antidepressant and appetite-suppressant [32]. These activities might be reason for body weight loss as a consequence of saffron supplementation.

Current meta-analysis is conducted on several cardiovascular disease risk factors from human documents. However, many aspects of supportive effects of saffron have not comprehensively been assessed on human subjects. Saffron has been traditionally used to improve the cardiovascular functions, increase heart tonic and treatment of palpitation [23]. Besides that, several animal and *in-vivo* studies [54–56] suggested an anti-atherosclerotic effect of saffron bioactive ingredient specially crocin, and crocetin via inhibiting foam cell formation, nuclear factor kappa B (NF-κB) activation, vascular cell adhesion molecule-1 (VCAM-1) expression and aortic intima thickening [54]. Also, saffron can alleviate inflammation, which is associated with risk of cardiovascular disease, through enhancing antioxidant enzymes and scavenging of reactive oxygen species, and consequently preventing inflammatory response [57,58].

Saffron administration was sufficiently tolerable and no serious adverse event was reported from included studies that may be elicited by saffron toxicity. Saffron has been used as a foodstuff in many centuries, and except anecdotal evidences, no serious complication was reported for saffron toxicity [59]. In addition, the safety of saffron has been evaluated in several studies and showed that it is absolutely safe and non-toxic when used in low doses. Documents from human studies showed the doses up to 1.5 g/day can be considered as a safe dosage. However, doses more than 5 g/day are reportedly caused for harmful effect and at 20 g/day are led to death [60]. Haematuria, enitourinary, vomiting, vertigo and gastrointestinal bleeding are common adverse effects that been reported during saffron intake in doses of > 10 g/day [60,61]. In the other hand, saffron has a special ability to enhance drugs absorption and bioavailability. This ability can be a privilege for preventing unsatisfied side-effect of drugs by enhancing potent drug in lower dose prescription [23,62,63]. However, it should be noted that arbitrary use of saffron along with drug can increase possible drug toxicity. Furthermore, saffron had a potential oxytocic properties and its consumption during pregnancy should be with caution [64].

To the best of our knowledge, present meta-analysis is the first to assess the effect of saffron on cardiovascular risk factors and provides better insight of result from RCTs. However, it had several limitations that should be acknowledge when interpreting the results. First, the number of study in some of outcome was insufficient to perform subgroup analysis. Also, the result from low number of studies does not lead to reliable finding and should be interpret with caution. Second, the quality of studies is not acceptable in some sort of methodological approach which was used to RCT methodology (nearly all studies had an unclear or high risk of bias). In addition, many potential confounders such as smoking, diet and physical activity can influence the outcomes and no adjustment was reported for those parameters. In this case, future studies should improve methodological gaps and limit the undesirable effect of cofounder on result of outcomes. And finally, there

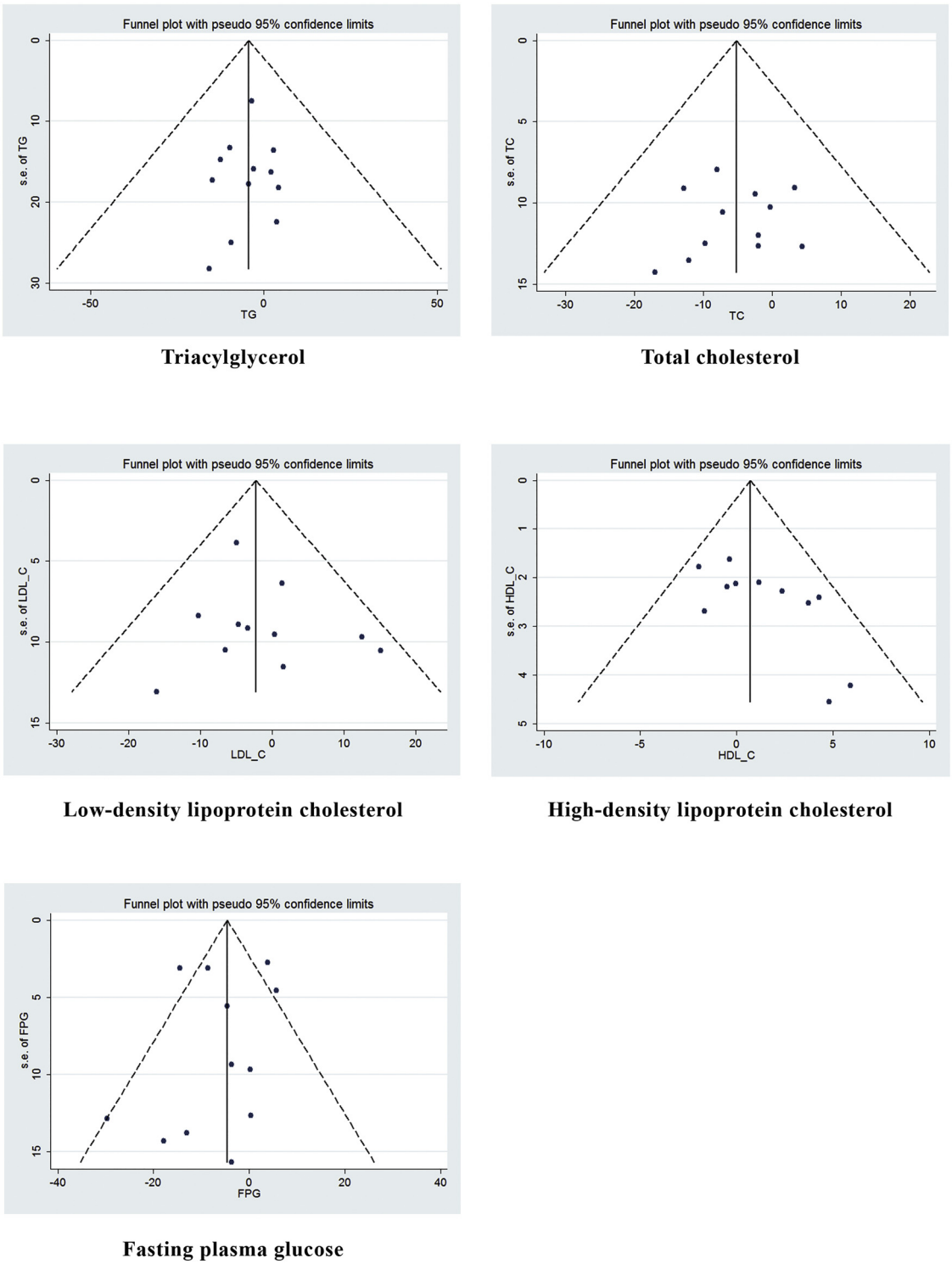

Fig. 3. Funnel plot detailing publication bias in the studies reporting effect of saffron on triacylglycerol, total-cholesterol, low-density lipoprotein, high-density lipoprotein, fasting plasma glucose.

are concerns about several potential heterogeneities in term of type, dose, duration and participants condition which may have affected the efficacy of the results.

5. Conclusion

This meta-analysis provides comprehensive information for health-care providers and general people to have a better understanding of health claims concerning saffron. The present evidence suggests that saffron might be beneficial for several cardiovascular risk factors and support some aspect underling cardiovascular protective properties of saffron. It could be considered as an adjuvant therapy along with other conventional medicine which have been used to treat cardiovascular disease and cardiovascular disease at risk patients. Furthermore, several methodological gaps which identified in included study by using standard mythological quality assessment tools (Cochrane risk of bias), provide a reference for future RCTs.

Authorship

M.P., A.H. and M.K. carried out the concept, design and drafting of this study. A.N., A.H. and M.P. searched databases, screened articles and extracted data. M.P. and A.H. performed the acquisition, analysis, and interpretation of data. A.S critically revised the manuscript. All authors approved the final version of the manuscript. M.P. and A.S. are the guarantors of this study.

Conflict of interest

There are no conflicts to declare.

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