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Meta-analysis

The effects of magnesium and vitamin E co-supplementation on some cardiovascular risk factors: A meta-analysis

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SUMMARY

Background: Growing attention has been paid to use the combination of magnesium and vitamin E, which might improve metabolic profiles in patients with metabolic diseases. Consequently, we conducted a meta-analysis of published randomized controlled trials (RCTs) to systematically analyze the effects of magnesium and vitamin E co-supplementation on some cardiovascular risk factors in patients with metabolic disorders.

Methods: We searched the National Library of PubMed, Scopus, Web of Science, the Cochrane library and Embase databases for studies published before February 2020 and included controlled trials in which used mentioned intervention. Finally, we extracted 4 trials satisfying our selection criteria. Two reviewers selected studies independently of each other and if they disagreed, was asked a third reviewer. The risk of bias of individual studies was assessed using the Cochrane Collaboration risk of bias tool. Data were pooled using the random-effects method and were expressed as weighted mean difference (WMD) and 95% confidence intervals (CI).

Results: A total of 4 studies meet the eligibility criteria. 119 individuals allocated to intervention and 118 participants allocated to control group. Our meta-analysis indicated that the co-supplementation with magnesium and vitamin E resulted in a significant decrease in FPG, Insulin, HOMA-IR, TG, TC, and LDL-C in comparison with placebo. The co-supplementation with magnesium and vitamin E had no significant effects on the body weight, BMI, and HDL. However, there were no significant heterogeneity for all of the variables except for FPG ($I^2 = 56.0\%$, $P = 0.103$) and TG ($I^2 = 80.7\%$, $P = 0.006$).

Conclusions: Our meta-analysis indicated that the co-supplementation with magnesium and vitamin E resulted in a significant decrease in FPG, Insulin, HOMA-IR, TG, LDL-C. Moreover, no significant effects on the body weight, BMI and HDL were observed. However, the glycemic-improving properties of magnesium and vitamin E co-supplementation were small and may not reach clinical importance.

1. Introduction

Metabolic diseases are significant public health subject [1]. The dominant oxidative and inflammatory conditions contribute to the development of several pathologies such as cardiovascular complications [2]. The pathological process of cardiovascular diseases (CVDs) includes atherosclerosis, which is a chronic inflammatory and progressive disease. The prevalence of CVD has been increasing worldwide [3]. According to a world health organization report, an estimated 17.9 million people died from CVDs, representing 31% of all global deaths and the number one cause of death globally [4]. Trying to improve the health of CVD patients is to decrease morbidity and mortality, improve quality of life and reduce increasing healthcare costs. Several factors contribute to CVD such as obesity, aging, and high levels of low-density lipoprotein (LDL), hyperhomocysteinemia, insulin resistance, high blood pressure,

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Abbreviations

RCT	randomized controlled trial
CI	confidence interval
PRISMA	Preferred Reporting Items Systematic Reviews and Meta-Analyses
SD	standard deviation
WMD	weighted mean difference
CVD	cardiovascular disease
LDL	low-density lipoprotein
VLDL	very low-density lipoprotein
HDL	high density lipoprotein
TC	total cholesterol
TG	triglyceride
FPG	fasting plasma glucose, insulin
HOMA-IR	homeostatic model assessment for insulin resistance
BMI	body mass index
SDH	social determinants of health
PCOS	polycystic ovary syndrome
PICOS	population, intervention, comparator and outcomes, and study design
GDM	gestational diabetes mellitus
RDA	recommended dietary allowances
α-TTP	α-tocopherol transfer protein
CAT	catalase
GPX	glutathione peroxidase
SOD	superoxide dismutase
ATP	adenosine triphosphate
NMDA	N-methyl-D-aspartate

social determinants of health (SDH), type of lifestyle, and poor nutrition [3,5–17].

Micronutrients (vitamins and minerals) are involved in pathways that can modify inflammation and oxidative detriment and thus maybe play a role in reducing CVD risk [17]. A linear inverse relationship exists between serum levels of antioxidants such as vitamin C and vitamin E and CVD [16]. Hence, vitamin E has been postulated to diminish the risk of CVD [18] and high intake of vitamin E from supplements/dietary sources is related to decrease risk of CVD [19].

Magnesium is a necessary micronutrient for enzymes that contribute to carbohydrate and lipid metabolism and has anti-inflammatory agents activity by modulating inflammatory pathways [20–22]. Recently, there is a rising interest to use the combination of magnesium and vitamin E, which might improve metabolic profiles in patients with metabolic diseases [9,22,23]. For example, a recent randomized, double-blind, placebo-controlled trial showed that magnesium and vitamin E co-supplementation in women with polycystic ovary syndrome (PCOS) had beneficial effects on insulin metabolism and some cardio-metabolic risk factors [9]. Moreover, a randomized controlled trial (RCT) indicated that magnesium and vitamin E co-supplementation had beneficial effects on some cardiovascular risk factors including fasting plasma glucose (FPG), insulin resistance, triglycerides (TG), very low-density lipoprotein (VLDL), LDL and high density lipoprotein (HDL) levels in patients with diabetic foot ulcer [20]. Following magnesium and vitamin E co-supplementation, there is no clear consensus regarding the overall utility of them for modulation of some CVD risks including glycemic and lipid profiles and body weight. To the best of our knowledge, there are no systematic review and meta-analysis study evaluating the effects of magnesium and vitamin E co-supplementation on some CVD risk factors. Consequently, we performed a meta-analysis to systematically analyze the effects of magnesium and vitamin E co-supplementation on some cardiovascular risk factors in patients with metabolic disorders to establish current evidence for the role of this intervention.

2. Methods

2.1. Literature search and selection

This systematic review and meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline. We searched the National Library of PubMed, Scopus, Web of Science, the Cochrane library and Embase databases for studies published before February 2020, with no restrictions in time or language. The search terms were as follows (((“magnesium”) AND “Vitamin E″ OR “Alpha-Tocopherol” OR “Vit E″ OR “Tocopherol” AND “Intervention” OR “controlled trial” OR “randomized” OR “random” OR “randomly” OR “placebo” OR “clinical trial” OR “Trial” OR “RCT"))). Data were extracted independently by two study investigators (HAM and MGH), and if they disagreed, we asked a third reviewer (OA) for her advice.

2.2. Eligibility criteria

Two researchers separately selected eligible articles by reading titles, abstracts and whenever required in the full-text of the articles. All human RCTs which reported the effects of magnesium and vitamin E co-supplementation on metabolic status on cardiovascular risk factors in patients with metabolic disorders were considered. By using the PICOS strategy, we determined the eligibility of studies including P-Population: patients with metabolic disorders; I-Intervention: magnesium and vitamin E co-supplementation; C-Comparison: control group with placebo; O-Outcome: changes in cardiovascular risk factors; S-Study design: human RCTs either parallel or cross-over designs. The following studies were excluded 1) studies without any control group 2) they were published as letters, reviews, conference abstracts, case reports.

2.3. Data extraction

We skimmed via the topics and abstracts to primarily assign the eligible studies. We then evaluated the full texts to determine the studies that were ultimately included in the meta-analysis. We screened 1668 study reports, of which 475 were excluded because of duplicate publications. After reading the title and abstract, 1183 articles were also excluded, and 10 articles were retained. Among them, 6 articles did not meet the inclusion criteria. Finally, we identified 4 trials satisfying our selection criteria [9,20,22,23]. PRISMA flow diagram is shown in Fig. 1.

2.4. Quality assessment of studies

Two investigators (HAM and MGH) independently evaluated the methods. The bias of the studies was evaluated as illustrated in the Cochrane Collaboration and included characteristics such as random sequence generation, allocation of hidden methods, blinding of patients, blinding of outcome evaluations, incomplete of outcome data, selective reporting of results, and other biases.

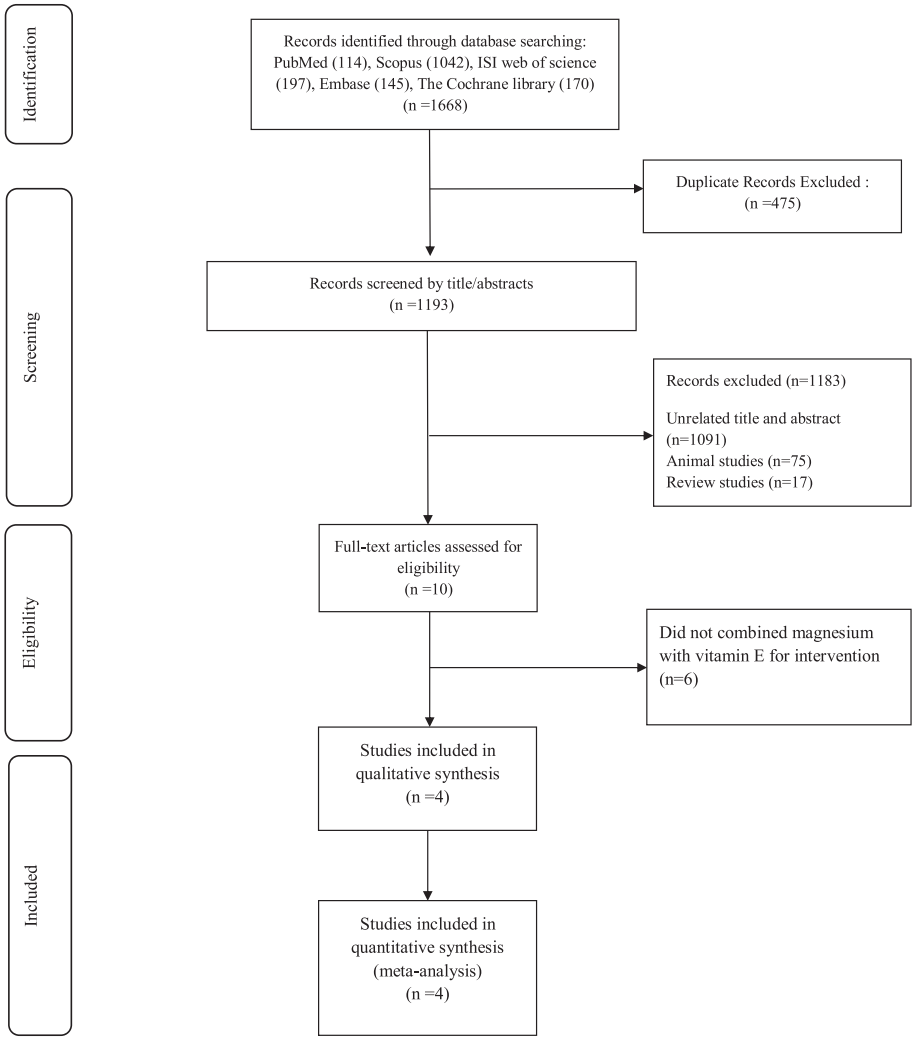

Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

Differences were resolved by discussion or by a third reviewer (OA). The support for judgment provides a brief free text description or summary of the relative trial characteristic on which judgments of risk of bias are based and aims to ensure lucidity in how judgments are reached [24]. Moreover, each domain was scored into three classes: low risk, high risk, and unclear risk of bias. According to the guidelines, the general quality of each study was determined as good (low risk for more than two cases), fair (low risk for two cases) or weak (low risk for less than two cases).

2.5. Meta-analysis of data

Data were pooled using the random-effects method and were expressed as weighted mean difference (WMD) and 95% confidence intervals (CI). The mean net changes (mean values ± standard deviation (SD)) in the FPG, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), total cholesterol (TC), TG, LDL, HDL, body mass index (BMI), for each study before and after the intervention in both groups were estimated. SDs of the mean were calculated using the following formula: SD = square root [(SD pre-treatment)^2 + (SD post-treatment)^2 - (2 × 0.8 × SD pre-treatment × SD post-treatment)] [25]. In addition, when several publications were existed from a same cohort, the study with the longest follow-up and the biggest sample size was elected. Moreover, when an article had multiple intervention periods, the longest period was extracted and when a study contained different doses of supplementation, all doses were considered as separate arms. Heterogeneity was estimated by the I^2 statistics. Studies with $I^2 >$ 50% were considered to have notable heterogeneity. The study-level data were pooled by using a random-effects model. Sensitivity analysis was conducted by removing each study one by one and recalculating the pooled evaluations. Egger's regression asymmetry test was performed for detecting potential publication bias. Statistical analysis was conducted using STATA, version 11.2 (Stata Corp, College Station, TX). The statistically significant value was defined as P values < 0.05.

3. Results

3.1. Study selection

In our primary search, we detected 1668 records. Through the elimination of duplicate 1193 articles remained, these articles being screened in terms of title and abstract. At this stage, 1183 unrelated articles were excluded, and the full text of the remaining 10 records was reviewed to confirm eligibility. 6 articles excluded from the

study. A total of 4 RCTs [9,20,22,23] were included. The process of the study selection is shown in the flow diagram (Fig. 1).

3.2. Characteristics of studies

The general characteristics of the included studies are summarized in Table 1. All articles were RCT published in 2018 and carried out in Iran [9,20,22,23]. The follow-up period ranged from 6 to 12 weeks. Magnesium supplementation dose was 250 mg and vitamin E supplementation dose was 400 IU in all 4 studies. 119 individuals allocated to intervention and 118 participants allocated to control group. Study participants included: patients with diabetic foot ulcer [20], PCOS [9,23] and gestational diabetes mellitus (GDM) [22].

3.3. Meta-analysis of data

Our meta-analysis indicated that the co-supplementation with magnesium and vitamin E resulted in a significant decrease in FPG (WMD: −3.99 mg/dL, 95% CI: −7.23, −0.75, p = 0.016) (Fig. 2A), Insulin (WMD: −2.15 micro IU/ml, 95% CI: −3.01, −1.30, p < 0.001) (Fig. 2B), HOMA-IR (WMD: −0.71, 95% CI: −1.00, −0.42, p=<0.001) (Fig. 2C), TG (WMD: −26.97 mg/dL, 95% CI: −46.03, −7.90, p = 0.006) (Fig. 2D), TC (WMD: −15.89 mg/dL, 95% CI: −24.39, −7.39, p < 0.001) (Fig. 2E), and LDL (WMD: −11.37 mg/dL, 95% CI: −19.32, −3.41, p = 0.005) (Fig. 2F) in comparison to a placebo. The co-supplementation with magnesium and vitamin E had no significant effects on body weight (WMD: −0.08 kg, 95% CI: −0.22, 0.06, p = 0.267) (Fig. 2G), BMI (WMD: 0.00 kg/M^2, 95% CI: −0.05, 0.06, p = 0. 960) (Fig. 2H), and HDL (WMD: 1.59 mg/dL, 95% CI: −0.17, 3.35, p = 0.076) (Fig. 2I). Moreover, there was no significant heterogeneity for all of the variables except for FPG (I^2 = 56.0%, P = 0.103) and TG (I^2 = 80.7%, P = 0.006) (Table 2).

3.4. Publication bias

Egger's regression test did not show publication bias for body weight (egger's regression test: p = 0.587), BMI (egger's regression test: p = 0.286), FPG (egger's regression test: p = 0.519), insulin (egger's regression test: p = 0.548), HOMA-IR (egger's regression test: p = 0.729), TG (egger's regression test: p = 0.573), TC (egger's regression test: p = 0.595), LDL (egger's regression test: p = 0.738), and HDL (egger's regression test: p = 0.073). In addition, Funnel plots indicated no evidence of asymmetry in the effects of magnesium and vitamin E co-supplementation on cardiovascular risk factors (Fig. 3A–I).

4. Discussion

To our knowledge, this meta-analysis is the first to evaluate the impact of magnesium and vitamin E co-supplementation on some cardiovascular risk factors in patients with metabolic disorders. Our analysis from 4 eligible RCTs shows a significant decrease in FPG, Insulin, HOMA-IR, TG, TC, and LDL but did not show significant effect on the body weight, BMI, and HDL in patients with metabolic disorders.

The mechanisms underlying the effects of magnesium and vitamin E co-supplementation on cardiovascular risk factors remain unclear. However, it seems the glycemic-improving effects of magnesium and vitamin E co-supplementation is related to the mechanism of insulin action. A meta-analysis by Veronese et al. showed that magnesium supplementation improved insulin-sensitivity and glycemic parameters in subjects with prediabetes and diabetes [26]. Moreover, it has been shown that vitamin E supplementation for 8 weeks in patients with type 2 diabetes mellitus significantly decreased serum insulin levels and insulin resistance [27]. In regards to the lipid profile-improving effects, there is no study investigating the mechanism of magnesium and vitamin E co-supplementation on lipid profile. However, it has been reported that magnesium may improves lipid profile by decreasing TG and VLDL through increased excretion of fecal fat [28] and increased lipoprotein lipase activity [29]. Furthermore, vitamin E may stimulate the peroxisome proliferator-activated receptor gamma signaling pathway [30,31], which may improves lipid profiles. Further study is needed to determine the possible mechanisms of magnesium and vitamin E co-supplementation on cardiovascular risk factors in patients with metabolic disorders.

Some studies carried out to assess the effects of magnesium and vitamin E co-supplementation on varies disorder conditions in patients. In agreement with our findings, Maktabi M et al. [22] reported that magnesium and vitamin E co-supplementation in women with GDM decreased TG, VLDL, TC, LDL and TC/HDL, but did not affect HDL levels. Moreover, consistent with our findings, Ekhlasi G et al. [32] reported that intake of symbiotic plus vitamin E supplements led to a significant decrease in concentrations of TG, TC, LDL and no effect on HDL after the intervention among patients with non-alcoholic fatty liver disease. Furthermore, Jamilian M et al. [9] showed that 12 weeks intervention with magnesium and vitamin E co-supplementation can reduce serum TG, VLDL concentrations and TC in patients with PCOS.

Recommended dietary allowances (RDA) for magnesium is 400–420 mg/day and 310–320 mg/day for men and women, respectively [33]. In addition, the RDA for vitamin E is 15 mg/day for both men and women [33]. In all included studies, subject consumed 250 mg magnesium and 400 IU vitamin E. Although vitamin E supplementation was higher than RDA in all included studies, magnesium supplementation was lower than RDA. Moreover, none of included studies reported dietary intake of magnesium and vitamin E before and following the interventions. In order to serum levels of magnesium, all studies reported circulating levels of magnesium before and after interventions. However, none of included studies reported serum levels of vitamin E. In order to circulating magnesium, a level of 1.46–2.68 mg/dL is considered normal for healthy people. The mean value of serum levels of magnesium in all included studies were in normal range. Therefore, the improving effects of magnesium and vitamin E co-

Table 1
Characteristic of included studies in meta-analysis.

Author	year	country	Study design	participants	sex	Mean age (intervention/control)	Mean BMI (intervention/control)	Trial duration (week)	Daily dose of Mg (mg)	Daily dose of Vitamin E (IU)	Sample size (intervention/control)
H. Afzali	2018	Iran	R/DB/PC	patients with diabetic foot ulcer	F/M	55.5/57.2	30.3/29.7	12	250	400	29/28
M. jamilian	2018	Iran	R/DB/PC	Polycystic Ovary Syndrome	F	29.2/28.3	25.526	12	250	400	30/30
M. Maktabi	2018	Iran	R/DB/PC	gestational diabetes	F	30.1/31.5	27.6/28	6	250	400	30/30
M. Shokrpour	2018	Iran	R/DB/PC	Polycystic Ovary Syndrome	F	27.2/26	27.1/27.9	12	250	400	30/30

Abbreviations: DB, double-blinded; PC, placebo-controlled; R, randomized; NR, not reported; F, Female; M, Male.

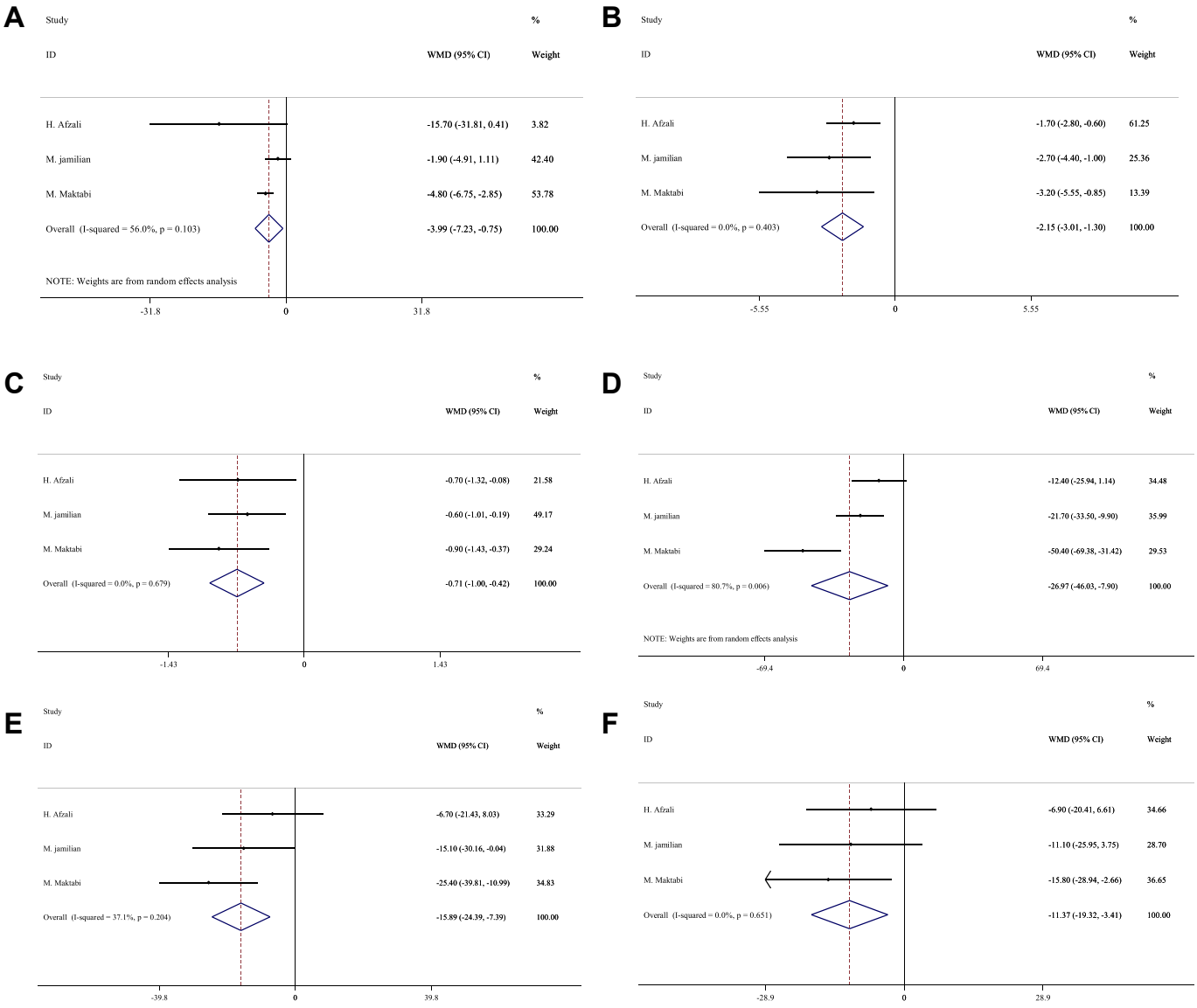

Fig. 2. A. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on fasting plasma glucose. **B.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on insulin leve. **C.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for insulin resistance. **D.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on triglycerides. **E.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on total cholesterols. **F.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on low-density lipoprotein. **G.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on body weight. **H.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on body mass index. **I.** Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of magnesium and vitamin E co-supplementation on high-density lipoprotein.

supplementation is not related to magnesium deficiency of participants. Additional RCTs conducted in individuals with different serum concentrations and dietary intakes of magnesium and vitamin E are needed to further evaluate and confirm these findings.

Vitamin E is a generic term for all four tocopherols (α-, β-, γ-, and δ-tocopherol) and four tocotrienols (α-, β-, γ-, and δ-tocotrienol) that illustrate the biological activity of a-tocopherol that carried by α-tocopherol transfer protein (α-TTP) in the bloodstream. Food sources of both vitamin E isomers including fruits, seafood, cheese, eggs vegetable oils and nuts which are rich in tocopherols; whilst oat, barley, palm oil, rice bran, wheat germ and rye that are rich in tocotrienols [34]. Antioxidants are divided into two categories: 1) enzymatic antioxidants such as catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD), and 2) non-enzymatic antioxidants which have a large subset, one of them is vitamin E [35]. Vitamin E is a one of the most important lipid-soluble antioxidant present in the cells body and is considered the significant line of protection against lipid peroxidation. Because of its central role in antioxidant defense, vitamin E have some protective properties against ischemic heart disease. Therefore, vitamin E exhibits useful effects on cardiovascular health by its

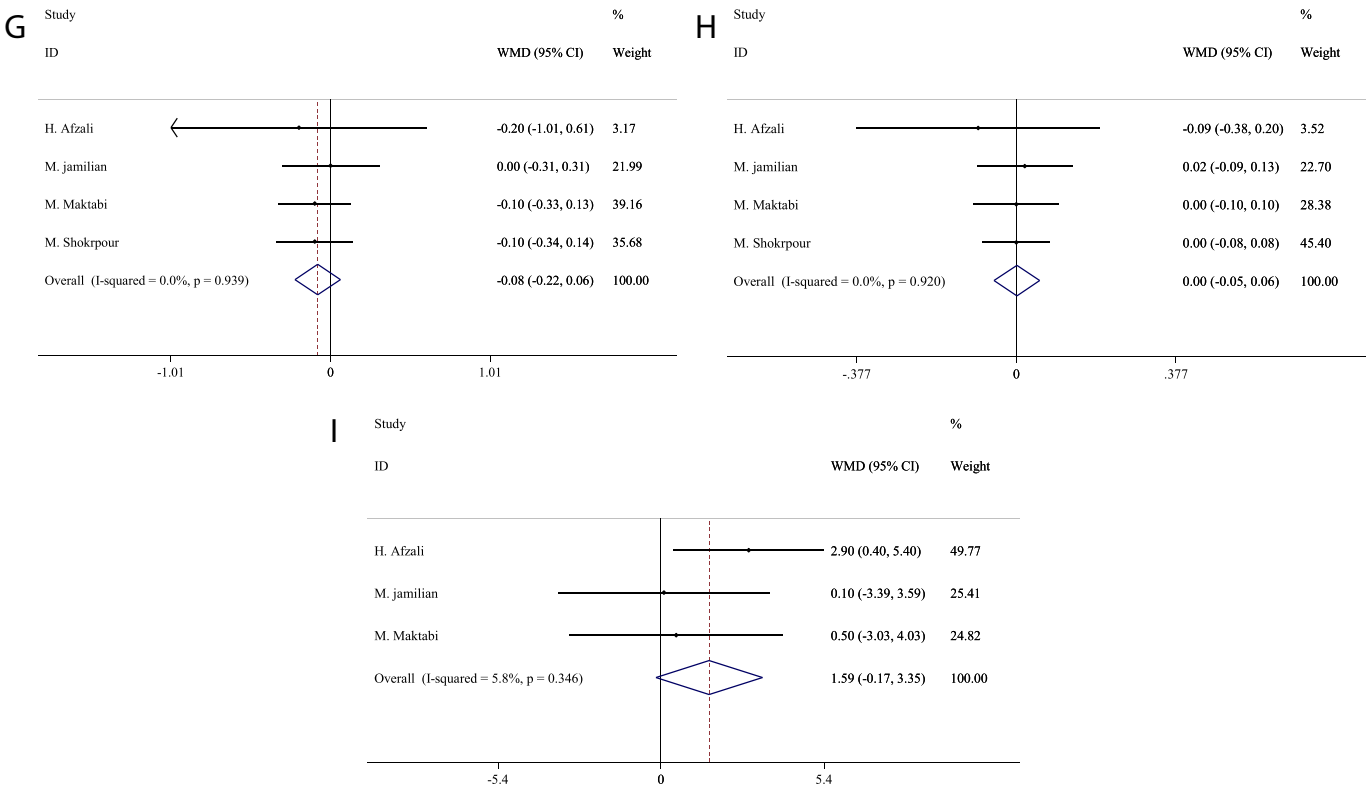

Fig. 2. (*continued*).

anti-cardiovascular, anti-atherogenic, anti-lipidemic, and anti-hypertensive effects [36].

Magnesium is an essential intracellular cation with concentrations vary between 5 and 20 mmol/L in the body; that is needed for desirable performance of metabolic function and set up ion channels [37]. Moreover, magnesium is a cofactor in numerous enzyme systems including Na^+/K^+-ATPase, creatine kinase, hexokinase, phosphofructokinase, adenylate cyclase, and tyrosine kinase activity of the insulin receptor which adjust various biochemical routes. In addition, magnesium have important roles in adenosine triphosphate (ATP) production (e.g., glycolysis, respiratory chain phosphorylation), calcium antagonist/N-methyl-D-aspartate (NMDA)-receptor antagonist, relocation of potassium and calcium across cell membranes, structural roles, exploitation of glutathione, vitamin D, and B-vitamins (e.g., thiamine) [38,39]. Magnesium also has a role in adjusting vascular tone and modulating blood pressure. As such, magnesium potentially has an important effect on the pathogenesis of CVD [37].

4.1. Limmitation

There are some limitations about this study that are worth to mention. First, only 4 studies met our inclusion criteria. Second, we only searched RCTs published in English. Hence, possibly omitting important studies which published only in non-English journals. Third, participants of included studies had different diseases with different pathophysiology. Fourth, most of the included studies only focused on a women cohort. Finally, the heterogeneity of the included studies was significant.

Table 2
The effects of magnesium and vitamin E co-supplementation on cardiovascular risk factors in patients with metabolic disorders.

Variables	Number of effect sizes	Weighted mean difference	(95%CI)	P within group	Heterogeneity	
					P heterogeneity	I^2
Body weight	4	−0.08	−0.22, 0.06	0.267	0.939	0.0%
BMI	4	0.00	−0.05, 0.06	0.960	0.920	0.0%
FPG	3	−3.99	−7.23, −0.75	**0.016**	0.103	56.0%
Insulin	3	−2.15	−3.01, −1.30	**<0.001**	0.403	0.0%
HOMA-IR	3	−0.71	−1.00, −0.42	**<0.001**	0.679	0.0%
TG	4	−26.97	−46.03, −7.90	**0.006**	0.006	80.7%
TC	4	−15.89	−24.39, −7.39	**<0.001**	0.204	37.1%
LDL-C	4	−11.37	−19.32, −3.41	**0.005**	0.651	0.0%
HDL-C	4	1.59	−0.17, 3.35	0.076	0.346	5.8%

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR: homeostatic model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. The statistically significant value was defined as P values < 0.05 (Bold).

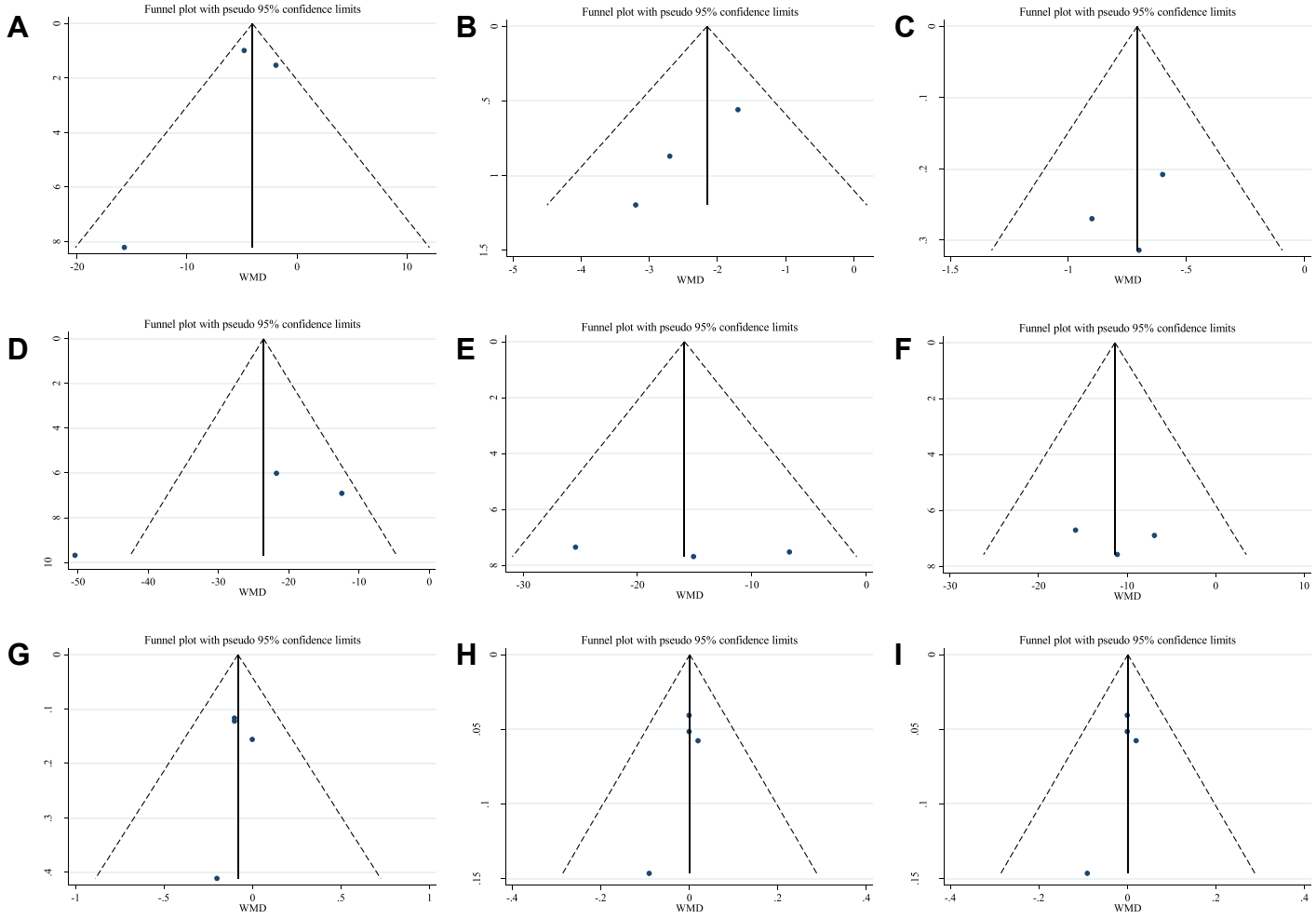

Fig. 3. A. Funnel plot for the effect of magnesium and vitamin E co-supplementation on fasting plasma glucose. **B.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on insulin level. **C.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for insulin resistance. **D.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for triglycerides. **E.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for total cholesterols. **F.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for low-density lipoprotein. **G.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for body weight. **H.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for body mass index. **I.** Funnel plot for the effect of magnesium and vitamin E co-supplementation on homeostatic model assessment for high-density lipoprotein.

5. Conclusion

In conclusion, our results highlight that magnesium and vitamin E co-supplementation might decrease some cardiovascular risks by improving glycemic and lipid profiles in patients with metabolic disorders. However, the glycemic-improving properties of magnesium and vitamin E co-supplementation were small and may not reach clinical importance. Further clinical trial studies are needed to confirm our findings.

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Author contributions

OA contributed in conception, data collection and manuscript drafting. HAM and MGD contributed in conception, data collection and manuscript drafting. DAL and ST substantially revised and critically reviewed the manuscript. All authors read and approved the final version of the paper.

Declaration of competing interest

None declared.

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