



The effect of magnesium supplementation on anthropometric indices: a systematic review and dose–response meta-analysis of clinical trials

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Abstract

The aim of this study was to determine the effects of Mg supplementation on anthropometric indices consisting of body weight, waist circumference (WC), BMI and body fat percentage. In this systematic review and dose–response meta-analysis, we searched PubMed, Cochrane Library, Scopus, Web of Science and Google Scholar from databases inception up to February 2020 for relevant randomised controlled trials. Quality of evidence was evaluated using the Cochrane Collaboration Tool. All the outcomes of this meta-analysis were pooled using the random effect model. Analysis of dose–response for Mg dosage was carried out using a fractional polynomial model. The systematic review and meta-analysis include twenty-eight randomised clinical trials, comprising 2013 participants. There were no significant changes in anthropometric indices after Mg supplementation in the overall analysis. However, subgroup analysis revealed that Mg supplementation decreases WC in subjects with BMI > 30 kg/m² (obese) (twelve trials, *n* 997 participants; weighted mean difference = –2.09 cm, 95 % CI –4.12, –0.07, *P* = 0.040; *I*² = 0 %). Dose–response analysis revealed a non-significant non-linear effect of supplementation dosage on anthropometric indices. The results suggest that Mg supplementation is associated with lower WC only in obese subjects. However, more high-quality studies are needed to clarify the nature of this association.

Key words: Magnesium: Anthropometric indices: Meta-analyses: Dose–response associations

Obesity is a medical situation with abnormal or excessive adipose tissue accumulation⁽¹⁾. Obesity is characterised by imbalance between energy intake and energy expenditure⁽²⁾. According to WHO report in 2016, the number of subjects with overweight and obesity in the world is approximately 1.9 billion and 650 million, respectively (almost 30 % of global population)⁽³⁾. Over 3 million people each year die from obesity (5 % of the worldwide deaths)⁽⁴⁾. Obesity is a major risk factor for range of chronic diseases including diabetes, CVD and cancer⁽⁵⁾. Also, it imposes plenty of economic burden into individuals, their families and nations. It is estimated that the burden costs 2.8 % of Global Gross Domestic Product (approximately 2 trillion USD)⁽⁶⁾. All the aforementioned reasons emphasis on priority of obesity in public health in both developed and developing countries⁽⁷⁾. The successful key for any weight loss is comprehensive lifestyle management including diet, physical activity and behaviour modification. Indeed, any safe and effective

weight loss programme should include following components: healthy eating plans that reduce energy without ruling out specific foods or food groups, regular physical activity and/or exercise instruction and behaviour changes that are based on your cultural needs, but these are extremely challenging over a long time period^(8–11). Many natural materials have been surveyed for obesity treatment that develop as anti-obesity products such as drugs, natural dietary and herbal products⁽¹²⁾. Recently, complementary and alternative treatments such as weight loss supplements are common⁽¹³⁾. Mg supplement is one of them, which possess potential anti-obesity effects⁽¹⁴⁾. Mg is most abundant the second and fourth in intracellular and body, respectively⁽¹⁵⁾. Mg is an essential cofactor for numerous biological processes and is required for energy production, oxidative phosphorylation, glycolysis, protein and nucleic acid synthesis, ion transport and cell signalling⁽¹⁶⁾. To produce energy from macronutrients, there are several metabolic pathways that are dependent on Mg.

Abbreviations: BF%, body fat percentage; BW, body weight; RCT, randomised clinical trial; WC, waist circumference; WMD, weighted mean difference.

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Furthermore, Mg and ATP make a complex (Mg-ATP) that provides energy for metabolic processes in mitochondria⁽¹⁷⁾. As a result of mentioned mechanisms, Mg deficiency has a role in aetiology of obesity. It is found that serum Mg has a correlation with obesity in several studies⁽¹⁸⁾. Thus, the serum Mg level was negatively correlated with BMI, systolic BP, diastolic BP, waist circumference (WC) and fasting insulin level⁽¹⁹⁾. It was hypothesised an anti-obesity effect of Mg due to capability of forming soaps with fatty acids in the intestine that can reduce the absorption of fat from the diet⁽²⁰⁾. Although, there are direct studies rarely about the effect of Mg supplement on obesity, but several studies have reported it as secondary outcome. Some clinical trials did not show any significant effect of Mg supplement on obesity parameters^(21–42). However, Mg supplementation improved anthropometric indices in five randomised clinical trials (RCT)^(43–47). Because of controversy of effects and also no existence of meta-analysis to date, the present study aimed to conduct a precise and vast systematic review and dose-response meta-analysis of all published reports on the effect of Mg supplementation on body weight (BW), BMI, WC and body fat percentage (BF%) in adults.

Methods

Protocol and registration

The reported items for systematic reviews and meta-analysis guidelines were followed in the conduct of the present study⁽⁴⁸⁾. The Population, Intervention, Comparison, Outcome, Study design (PICOS) criteria included Population: adult, Intervention: oral Mg supplementation, Comparison: placebo, Outcomes: anthropometric indices including BW, WC, BMI and FM% and Study design: RCT were used for this systematic review and meta-analysis. Our study protocol was not registered on any website; however, it is available from the authors upon request.

Literature search and inclusion criteria

An online search was conducted using the databases including PubMed, The Cochrane Library, Scopus, Web of Science and Google Scholar up to February 2020. We used text words and medical subject headings to identify the potential interest articles. The search terms included the following combinations of keywords: ('magnesium' OR 'magnesium'[tiab]) AND supplement*[Title/Abstract] OR 'magnesium'[Mesh] OR 'magnesium'[tiab] AND oral*[Title/Abstract] AND ('intervention studies' OR 'intervention' OR 'controlled trial' OR 'randomized' OR 'randomized' OR 'random' OR 'randomly' OR 'placebo' OR 'assignment' OR 'blind'). Our search is limited to studies that published randomised placebo-controlled trials (RCT). There is no restriction on language and time as per defined time frame. Because the anthropometric indices are secondary outcome, we used keywords of the intervention studies. Electronic database searches were completed along with reference list and citation hand searches.

Study selection and data extraction

First, electronic and manual search results were exported to End-Note software, version X7 (Thomson Reuters) and duplicate

publications were removed. Then, eligible articles were sorted by title, abstract and related full texts of publications. Finally, all human RCT (either parallel or cross-over designs) that examine the effects of Mg supplementation on anthropometric indices were included. If studies (1) Mg was administrated in combination with other components, minerals or botanicals (unless a separate arm controlled the effect of the mixed substance); (2) were publications with duplicate data; (3) without a placebo group; (4) without sufficient data and (5) unavailable full text were excluded. The following data were extracted: author's first name, year of publication, country of origin, study design, sex, mean age and BMI of participants, total sample size, study duration and dosage of Mg supplementation. When the data were reported at multiple measurements, only the outcomes at the end of the intervention were included in the analysis. All processes from systematic search to the data extraction were followed independently by two research experts (M. R. and A. Gh.) (kappa statistic for agreement for quality assessment; 0.91). Probable discrepancy was resolved under the supervision of the third expert's opinion (Gh. A.).

Assessment of methodological quality

The Cochrane Risk of Bias tool was used for quality assessment as follows: sequence generation, allocation and concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. According to the Cochrane guideline handbook, the words 'yes', 'no' and 'unclear' corresponded to low, high and unknown risk of bias, respectively. According to the mentioned domains, the overall quality of study was considered as good (low risk for all items), fair (low risk more than three items) and poor (low risk for equivalent and less than three items)⁽⁴⁹⁾. Also, quality assessment was also undertaken by two authors (M. R. and A. Gh.) separately.

Statistical analysis

All analyses were performed using STATA software version 12 (STATA Corp.). The pooled weighted mean difference (WMD) and its 95% CI was used to assess the effects of Mg supplementation on anthropometric indices. Mean change and its SD in anthropometric indices including weight (kg), WC (cm), BMI (kg/m^2) and body fat (%) within the intervention and placebo groups was used to calculate the effect size for meta-analysis. In studies in which mean change was not directly reported in intervention and control groups, it was calculated by the minus of the post-intervention data from the baseline value. Besides, if only SD for the baseline and final values were provided, the SD for the net changes was imputed according to the method of Borenstein *et al.*⁽⁵⁰⁾ using a correlation coefficient of 0.5. Due to the fact that included RCT were performed in different settings, random-effects models were used to conduct all meta-analyses. The heterogeneity between studies was examined by the *I*-squared (I^2) index. Heterogeneity was considered statistically significant if $P < 0.05$ or $I^2 > 50\%$ ⁽⁵¹⁾. We conducted subgroup analysis according to the median Mg supplement dose and the mean of duration of treatment, BMI, age and sex patients to assess the impact of this variable on outcomes. Rather, sensitivity analysis was performed to explore the extent to which



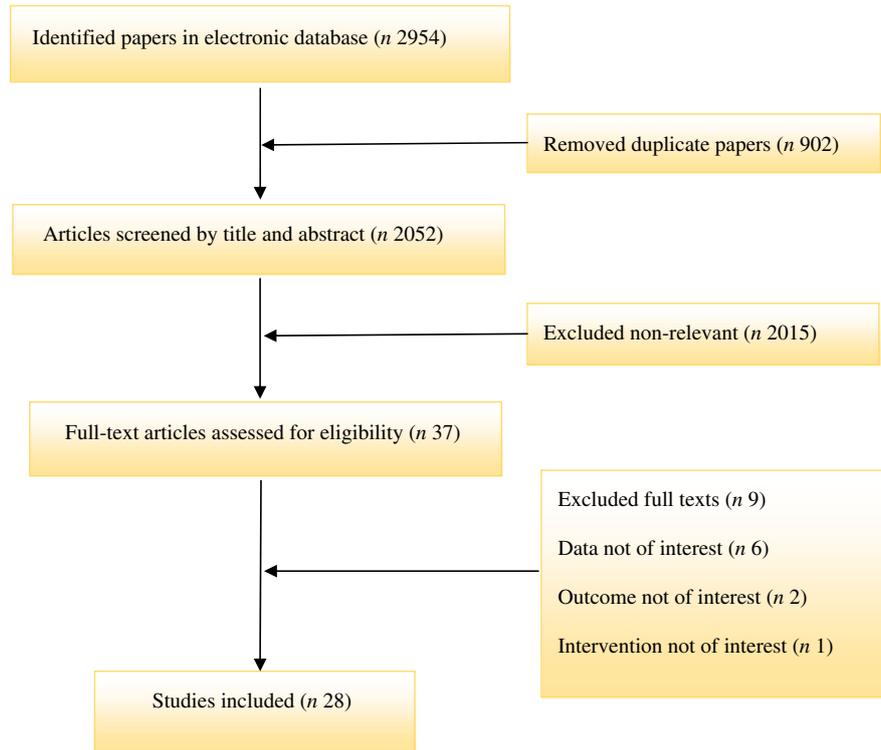


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram of the study selection process.

inferences might depend on a particular study or group of studies. Begg's rank correlation test and Egger's weighted regression test were used to investigate any possible bias. A *P* value of < 0.05 was considered as statistically significant.

Results

Literature search

Our search was based on 2954 articles through databases searching. Two thousand nine hundred seventeen records were excluded due to irrelevance to the inclusion criteria and duplication. Among thirty-seven remaining articles, nine records were excluded. Finally, twenty-eight articles (with thirty arms treatment)^(21–47,52) were calibrated in the present systematic review and meta-analysis. The process of study identification is presented in Fig. 1.

Study characteristics

Included studies have been published between 1994 and 2019. A total of 2013 subjects (1033 cases and 980 controls) were included in the analysis. All studies had parallel design. Out of twenty-eight included studies, four studies performed in Europe^(34,39,41,43), ten in America^(26,28,30–32,35,37,38,44,45) and fourteen studies in Asia^(21–24,27,29,33,36,40,42,46,47,52). The intervention period ranged between 4 and 48 weeks. The supplementation dose of Mg ranged from 168 to 625 mg/d. All of included studies were conducted on both sexes except six studies that were conducted in women^(35,36,41,45,47,52) and one study on men⁽³⁹⁾. Included studies were carried out in cases with

hypertension^(28,41), diabetes and prediabetes^(21,23–25,27,30,32,37,38,42–44), obesity^(22,33,34,52), the metabolic syndrome^(26,45,47), non-alcoholic fatty liver disease⁽⁴⁶⁾, insulin resistance^(34,37), depression⁽²⁹⁾ and healthy volunteers^(36,40). Detailed characteristics of included trial were presented in Table 1.

Quality assessment

Present quality assessment of included studies was based on the Cochrane Collaboration Risk of Bias tool. Among twenty-eight included RCT, the quality of twelve, fifteen and one study was poor, fair and good, respectively. All studies showed low risk of bias based on selective reporting. The details of the risk of bias in individual studies according to the domains used by the Cochrane Collaboration's tool are provided in Table 2.

Publication bias

Neither Begg's test nor Egger's test revealed any significant evidence for publication bias on anthropometric indices (*P* values for Begg's test for BW = 0.73, WC = 0.89, BMI = 0.10 and BF% = 0.34 and Egger's test for BW = 0.66, WC = 0.34, BMI = 0.88 and BF% = 0.66). The removing of studies, one by one, did not substantially change the effect of Mg supplementation on BW, BMI, WC and BF%.

Effect of magnesium supplementation on body weight

Totally, sixteen eligible studies^(21,23–25,27,30,33,36,38–41,45–47,52) with eighteen treatment arms, including a total of 1079 participants, examined the effect of Mg supplementation on BW. Combining their findings based on random-effects model, data

Table 1. Characteristics of eligible studies

Authors (year)	Country	Clinical trial design	Population	Mean age	Mean BMI	Sex	Sample size case/placebo	Dose (mg)	Period (weeks)	Outcomes
Witteaman <i>et al.</i> (1994)	Netherlands	Parallel	Women with HTN	57.2	–	Women	47/44	485 mg/d	24	Weight
Itoh <i>et al.</i> (1997)	Japan	Parallel	Healthy	65	23.6	Both	23/10	548 mg/d	4	Weight
Zorbas <i>et al.</i> (1999)	Greece	Parallel	Male athletes	24.5	24.8	Men	10/10	23 mg/kg weight body	48	Weight
Rodriguez Moran <i>et al.</i> (2003)	Mexico	Parallel	T2DM	56.9	28.1	Both	32/31	2.5 g MgCl ₂	16	Weight, BMI
Guerrero-Romero <i>et al.</i> (2009)	Mexico	Parallel	Diabetic hypertensive adults with hypomagnesaemia	59.5	29.5	Both	40/39	450 mg/d	16	BMI
Day <i>et al.</i> (2010)	Australia	Parallel	Postmenopausal women	58	24.6	Women	34/33	1500–1800 ml magnesium bicarbonate	12	Weight, BMI
Rodriguez-Hernandez <i>et al.</i> (2010)	Mexico	Parallel	Non-hypertensive obese women	48	36.8	Women	15/15	450 mg/d	16	BMI, WC
Mooren <i>et al.</i> (2011)	Germany	Parallel	Normomagnesaemia, overweight, insulin resistant, non-diabetic subjects	50	30.45	Both	25/22	365 mg/d	24	BMI
Moslehi <i>et al.</i> (2012)	Iran	Parallel	Middle-aged overweight women	58	28	Women	35/34	250 mg/d	8	Weight, BMI
Abbasi <i>et al.</i> (2012)	Iran	Parallel	Overweight or obese subjects	65	29.1	Both	21/22	500 mg/d	8	Weight, BMI
Solati <i>et al.</i> (2013)	Iran	Parallel	T2DM	48.4	26.54	Both	25/22	300 mg/d	12	BMI
Karandish <i>et al.</i> (2013)	Iran	Parallel	Participants with NAFLD	36	31.2	Both	34/34	350 mg/d	12	Weight, BMI
Rodriguez-Moran <i>et al.</i> (2014)	Mexico	Parallel	Metabolically obese, normal-weight individuals	35.7	22.5	Both	24/23	382 mg/d	16	BMI, WC
Navarrete-Cortes <i>et al.</i> (2014)	Mexico	Parallel	T2DM	52.8	30.5	Both	56/56	360 mg/d	12	BMI, WC
Lourdes Lima <i>et al.</i> (2014)	Brazil	Parallel	Women with MS without diabetes	45.6	35.3	Women	30/32	400 mg/d	12	Weight, BMI and WC
Simental-Mendia <i>et al.</i> (2014)	Mexico	Parallel	Prediabetes men and women (non-pregnant)	40.45	32.05	Both	58/56	382 mg/d	12	Weight, BMI and WC
Guerrero-Romero <i>et al.</i> (2015)	Mexico	Parallel	Prediabetes men and women (non-pregnant)	42.5	31.1	Both	59/57	382 mg/d	12	BMI and WC
Rajizadeh <i>et al.</i> (2016)	Iran	Parallel	Depressed people with hypomagnesaemia	32	27.1	Both	26/27	500 mg/d	8	BMI
Khammas <i>et al.</i> (2017)	Iraq	Parallel	MetS women	51.5	34.85	Women	30/17	168 mg/d	8	Weight, BMI and WC
Razzaghi <i>et al.</i> (2017)	Iran	Parallel	Subjects with grade 3 diabetic foot ulcer	59.6	27.2	Both	35/35	250 mg/d	12	Weight, BMI
Toprak <i>et al.</i> (2017)	Turkey	Parallel	Hypomagnesaemia, pre-diabetic and obese patients	56.3	33.9	Both	57/61	365 mg/d	12	BMI, WC
Rodriguez-Ramirez <i>et al.</i> (2017)	Mexico	Parallel	Pre-HTN men and women (non-pregnant) with hypomagnesaemia	51.7	28.3	Both	18/18	360 mg/d	16	BMI
Zghoul <i>et al.</i> (2018)	Kuwait	Parallel	Type 2 diabetes patients	52	33.7	Both	47/32	336 mg/d	12	Weight
Sadeghian <i>et al.</i> (2018)	Iran	Parallel	Hypomagnesaemia patients diagnosed with type 2 diabetes and early-stage nephropathy	42	31.05	Both	40/40	250 mg/d	12	Weight, BMI and WC
Rodriguez-Moran <i>et al.</i> (2018)	Mexico	Parallel	Individuals with the MetS and hypomagnesaemia	39.9	30.1	Both	100/98	382 mg/d	16	BMI, WC
Talari <i>et al.</i> (2019)	Iran	Parallel	Diabetic haemodialysis patients	60.3	26.6	Both	27/27	250 mg/d	24	Weight, BMI
Rashvand <i>et al.</i> (2019)	Iran	Parallel	T2DM	49	29.5	Both	18/19	500 mg/d	8	Weight, BMI and WC
Solati <i>et al.</i> (2019)	Iran	Parallel	Overweight and non-diabetic subjects	40.6	28.86	Both	35/35	300 mg/d	24	BMI

HTN, hypertension; T2DM, type 2 diabetes mellitus; WC, waist circumference; NAFLD, non-alcoholic fatty liver disease; MetS, metabolic syndrome.

Magnesium supplement and anthropometric indices

Table 2. Risk of bias assessment for included randomised controlled clinical trials

Authors (publication year)	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias	Overall risk of bias
Witteman <i>et al.</i> (1994)	U	L	L	L	L	U	L	Fair quality
Itoh <i>et al.</i> (1997)	U	L	L	L	L	U	L	Fair quality
Zorbas <i>et al.</i> (1999)	U	L	U	U	L	U	U	Poor quality
Rodriguez Moran <i>et al.</i> (2003)	U	L	L	L	H	U	U	Poor quality
Guerrero-Romero <i>et al.</i> (2009)	U	L	L	L	L	U	U	Fair quality
Day <i>et al.</i> (2010)	L	U	L	U	U	U	U	Poor quality
Rodriguez-Hernandez <i>et al.</i> (2010)	L	L	L	L	L	U	L	Fair quality
Mooren <i>et al.</i> (2011)	L	L	L	U	L	U	U	Fair quality
Moslehi <i>et al.</i> (2012)	L	L	L	H	U	U	U	Poor quality
Abbasi <i>et al.</i> (2012)	L	U	U	U	L	U	U	Poor quality
Solati <i>et al.</i> (2013)	U	L	L	U	L	U	U	Poor quality
Karandish <i>et al.</i> (2013)	U	L	L	U	L	U	L	Fair quality
Simental-Mendia <i>et al.</i> (2014)	L	L	L	U	L	U	U	Fair quality
Rodriguez-Moran <i>et al.</i> (2014)	L	L	L	U	L	U	U	Fair quality
Navarrete-Cortes <i>et al.</i> (2014)	L	L	L	U	L	U	L	Fair quality
Lourdes Lima <i>et al.</i> (2014)	U	U	L	H	L	U	U	Poor quality
Guerrero-Romero <i>et al.</i> (2015)	L	L	L	L	L	U	L	Good quality
Rajizadeh <i>et al.</i> (2016)	L	L	L	U	U	U	U	Poor quality
Khammas <i>et al.</i> (2017)	L	U	L	U	L	U	U	Poor quality
Razzaghi <i>et al.</i> (2017)	L	L	L	L	U	U	L	Fair quality
Rodriguez-Ramirez <i>et al.</i> (2017)	L	L	L	U	L	U	U	Fair quality
Toprak <i>et al.</i> (2017)	L	L	L	U	L	U	L	Fair quality
Sadeghian <i>et al.</i> (2018)	L	L	L	L	H	U	U	Poor quality
Talari <i>et al.</i> (2008)	L	L	L	U	U	U	U	Poor quality
Rodriguez-Moran <i>et al.</i> (2018)	L	L	L	U	L	U	L	Fair quality
Zghoul <i>et al.</i> (2018)	L	H	H	H	L	U	U	Poor quality
Rashvand <i>et al.</i> (2019)	L	L	L	U	L	U	U	Fair quality
Solati <i>et al.</i> (2019)	U	L	L	U	L	U	L	Fair quality

H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

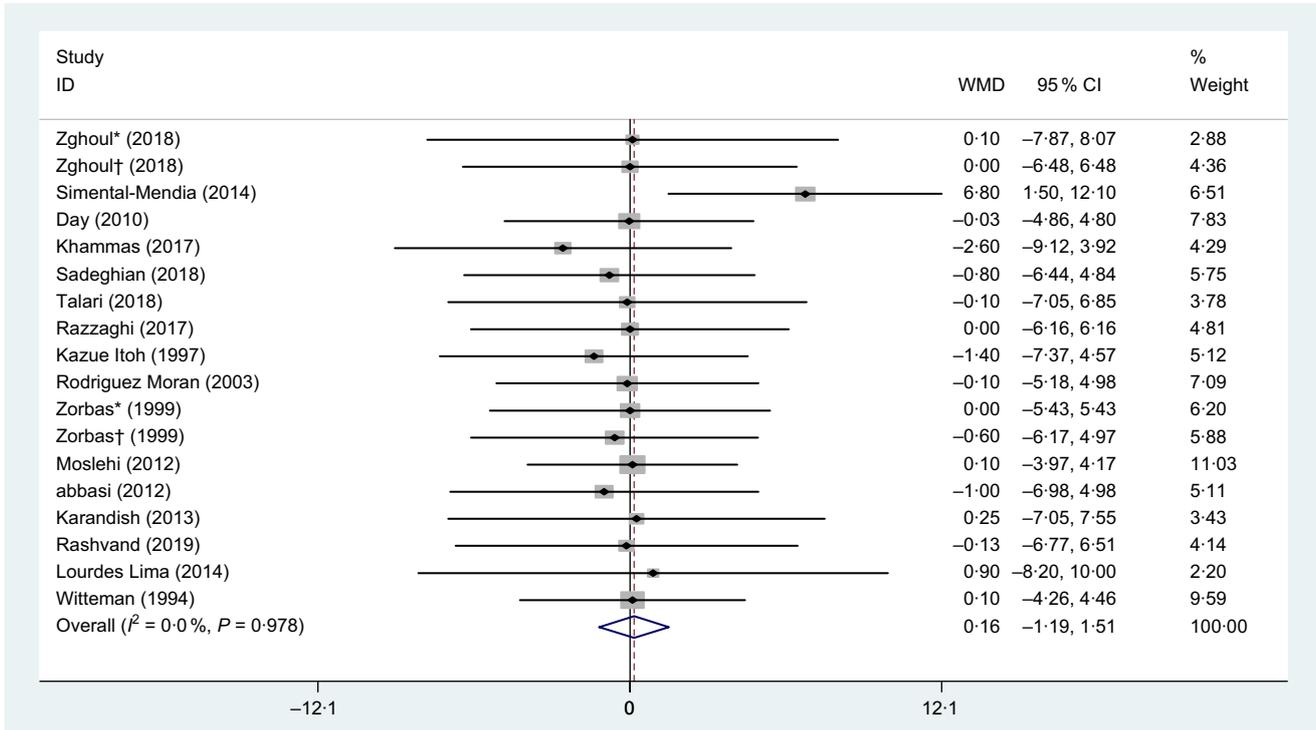


Fig. 2. Forest plot of the effect of magnesium supplementation on body weight. WMD, weighted mean difference. * Placebo group was obese; † placebo group was non-obese.

analysis did not show any significant effect of Mg supplementation on BW (WMD 0.16 kg, 95% CI -1.19, 1.51, $P = 0.810$) compared with the control group, also there were no significant heterogeneity for weight ($I^2 = 0.0\%$, $P = 0.97$), Fig. 2.

Subgroup analysis based on the median dose of intervention (>360 and ≤360 mg/d), duration of supplementation (>12 and ≤12 weeks), mean BMI of subjects (BMI > 28 and ≤28 kg/m²), mean age of participants (age of >50 and ≤50 years) and sex (men, women and both) effect remained non-significant in all of subgroup analysis as outlined in Table 3.

Effect of magnesium supplementation on waist circumference

Overall, twelve clinical trials^(23,24,26,28,30-32,35,43-45,47) including a total of 997 subjects reported the effect of Mg consumption on WC. Pooled effect size did not show any significant effect of Mg supplementation on WC (WMD -1.161 cm, 95% CI -2.78, 0.46, $P = 0.16$). Also, between-study heterogeneity was NS ($I^2 = 0.0\%$, $P = 0.450$), Fig. 3.

Subgroup analysis based on the median dose of supplementation (dose > 380 and ≤380 mg/d), mean BMI (> 30 and < 30), mean age (≤45 and >45 years), mean duration of intervention (≤12 and <12 weeks) and sex (women and both) showed only a significant effect in mean BMI > 30 kg/m² subset (WMD -2.09 cm, 95% CI -4.12, -0.07, $P = 0.040$) (Fig. 4) and also a similar reduction in WC was observed in the mean age >45 subset, but this is NS (WMD -2.10 cm, 95% CI -4.38, 0.18, $P = 0.070$) as outlined in Table 3.

Effect of magnesium supplementation on BMI

The pooled estimation from the random-effects model that performed on twenty-five studies^(21-38,42-47,52) (twenty-six treatment arms) including 1931 participants showed that Mg had no significant effect on BMI (WMD -0.10 kg/m², 95% CI -0.39, 0.19, $P = 0.500$). Also, between-study heterogeneity was NS ($I^2 = 0.0\%$, $P = 0.980$), Fig. 5.

Subgroup analysis based on the median dose of supplementation (>360 and ≤360 mg/d), mean duration of intervention (>12 and ≤12 weeks), mean BMI (BMI > 30 and ≤30 kg/m²), mean age (>50 and ≤50 years) and sex (women and both) showed non-significant effect of Mg supplementation on BMI as outlined in Table 3.

Effect of magnesium supplementation on body fat percentage

The pooled estimation from five studies^(24,35,39,46,52) (six treatment arms) including 244 participants showed that Mg had no significant effect on body fat (WMD 0.40%, 95% CI -0.61, 0.69, $P = 0.90$). Also, between-study heterogeneity was NS ($I^2 = 0.0\%$, $P = 0.900$), Fig. 6. Subgroup analysis based on the median dose of supplementation (>400 and ≤400 mg/d), mean duration of intervention (>14 and ≤14 weeks), mean BMI (BMI > 29 and ≤ 29 kg/m²), mean age (>38 and ≤38 years) and sex (men, women and both) showed a non-significant effect in short duration (≤14 weeks) subset (WMD -0.54%, 95% CI -2.08, 0.99, $P = 0.480$) as outlined in Table 3.

Table 3. Result of subgroup analysis on anthropometrics indices of included studies in the meta-analysis* (Weighted mean differences (WMD) and 95 % confidence intervals)

Subgrouped by	No. of trials	WMD	95 % CI	<i>P</i>	<i>P</i> for heterogeneity	<i>I</i> ² (%)	<i>P</i> for between subgroup heterogeneity
Body weight	18	0.160	-1.192, 1.512	0.816	0.978	0	
Dosage (mg) (≤ and > median)							
≤360	9	-0.293	-2.241, 1.655	0.768	1	0	0.526
>360	9	0.581	-1.296, 2.458	0.544	0.607	0	0.526
Intervention duration (weeks) (≤ and > mean)							
≤12	13	0.292	-1.354, 1.937	0.728	0.840	0	0.784
>12	5	-0.112	-2.482, 2.257	0.926	1	0	0.784
BMI (kg/m ²) (≤ and > mean)							
≤28	7	-0.229	-2.252, 1.794	0.825	1	0	0.865
>28	10	0.552	-1.446, 2.550	0.588	0.650	0	0.865
Age (years) (≤ and > mean)							
≤50	8	0.876	-1.136, 2.888	0.394	0.567	0	0.347
>50	10	-0.429	-2.254, 1.396	0.645	1	0	0.347
Sex							
Men	2	-0.29	-4.18, 3.60	0.883	0.880	0	0.866
Women	5	-0.21	-2.50, 2.08	0.857	0.961	0	0.866
Both	11	0.51	-1.35, 2.36	0.592	0.777	0	0.866
WC	12	-1.161	-2.787, 0.464	0.161	0.457	0	
Dosage (mg) (≤ and > median)							
≤380	9	-1.290	-3.089, 0.508	0.160	0.220	25	0.742
>380	3	-0.586	-4.384, 3.213	0.762	0.975	0	0.742
Intervention duration (weeks) (≤ and > mean)							
<12	8	-1.633	-3.432, 0.166	0.075	0.338	11.8	0.230
≥12	4	0.942	-2.855, 4.739	0.627	0.692	0	0.230
BMI (kg/m ²) (≤ and > mean)							
≤30	5	0.542	-2.188, 3.272	0.697	0.823	0	0.128
>30	7	-2.097	-4.120, -0.073	0.042	0.320	14.4	0.128
Age (years) (≤ and > mean)							
≤45	6	-0.193	-2.508, 2.122	0.870	0.965	0	0.250
>45	6	-2.103	-4.387, 0.180	0.071	0.128	41.5	0.250
Sex							
Women	2	-2.91	-7.15, 1.32	0.177	0.424	1.6	0.379
Both	10	0.51	-1.35, 2.36	0.353	0.337	0	0.379
BMI							
Dosage (mg) (≤ and > median)							
≤360	14	-0.021	-0.389, 0.348	0.912	1	0	0.484
>360	13	-0.240	-0.731, 0.251	0.338	0.616	0	0.484
Intervention duration (weeks) (≤ and > mean)							
<12 weeks (mean)	18	-0.230	-0.690, 0.229	0.326	0.892	0	0.469
≥12 weeks	9	-0.009	-0.393, 0.376	0.964	0.990	0	0.469
BMI (kg/m ²) (≤ and > mean)							
≤30	14	-0.063	-0.417, 0.292	0.729	0.923	0	0.711
>30	13	-0.183	-0.713, 0.347	0.498	0.930	0	0.711
Age (years) (≤ and > mean)							
≤50	14	-0.033	-0.386, 0.320	0.855	0.792	0	0.500
>50	13	-0.254	-0.788, 0.281	0.353	0.993	0	0.500
Sex							
Women	4	-0.07	-1, 0.87	0.892	0.954	0	0.939
Both	23	-0.1	-0.41, 0.21	0.512	962	0	0.939
Body fat (%)							
Dosage (mg) (≤ and > median)							
≤400	6	0.040	-0.619, 0.699	0.905	0.907	0	
>400	4	0.038	-0.637, 0.714	0.911	0.691	0	0.984
Intervention duration (weeks) (≤ and > mean)							
<14 weeks	3	-0.546	-2.082, 0.991	0.486	0.706	0	0.408
≥14 weeks	3	0.172	-0.557, 0.901	0.644	0.918	0	0.408
BMI (kg/m ²) (≤ and > mean)							
≤29	3	0.013	-0.681, 0.707	0.971	0.506	0	0.808
>29	3	0.285	-1.798, 2.367	0.789	0.938	0	0.808
Age (years) (≤ and > mean)							
≤38	3	0.183	-0.538, 0.904	0.620	0.904	0	0.341
>38	3	-0.678	-2.295, 0.939	0.411	0.802	0	0.341
Sex							
Men	2	0.0	-0.74, 0.74	1	1	0	1
Women	1	0.0	-2.07, 2.07	1	1	0	1
Both	3	0.0	-2.01, 2.01	1	1	0	1

WC, waist circumference.

* Effect size was calculated by random-effects model.

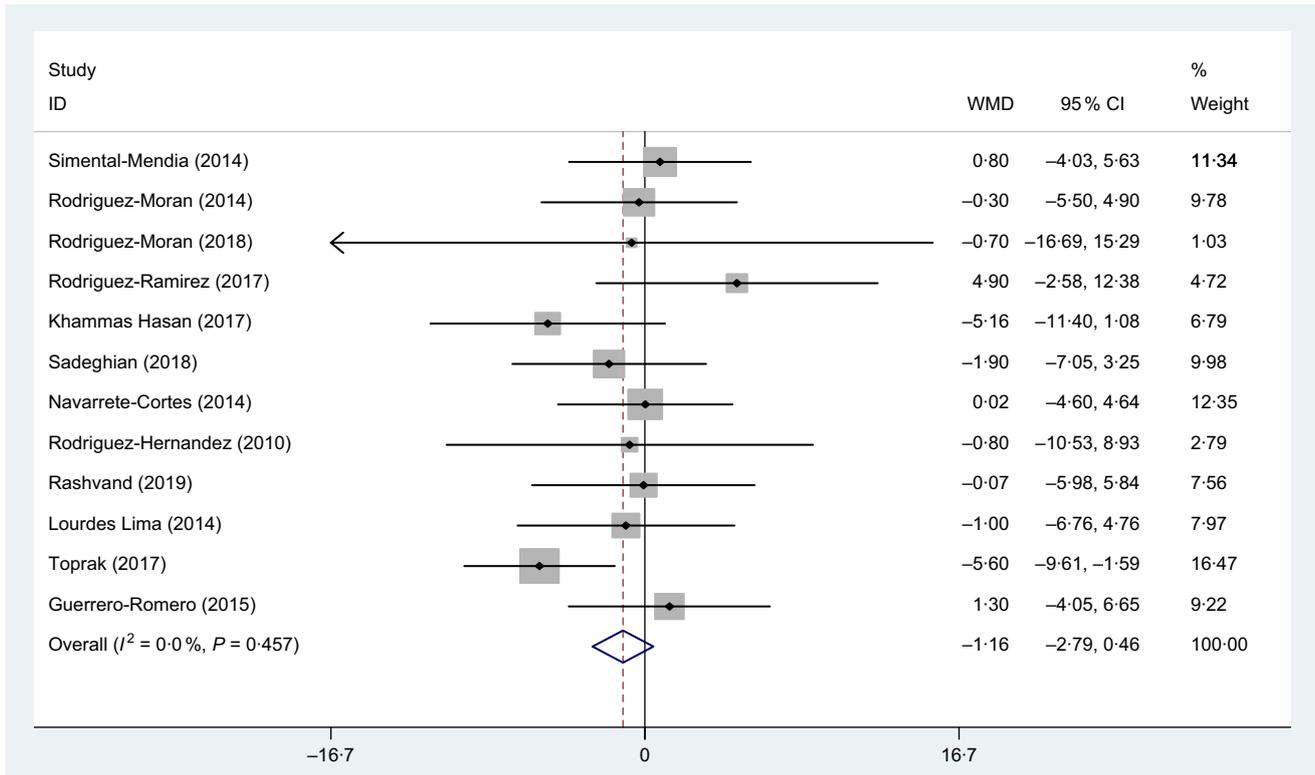


Fig. 3. Forest plot of the effect of magnesium supplementation on waist circumference. WMD, weighted mean difference.

Dose-response meta-analysis

Dose-response analysis not revealed a significant effect of Mg supplementation dosage on anthropometric indices including BW, BMI and WC (r 0.028, P -non-linearity = 0.543, r 0.288, P -non-linearity = 0.129, r 82.04, P -non-linearity = 0.246, respectively) and based on duration of intervention on BW, BMI and WC (r -0.20, P -non-linearity = 0.218, r 0.015, P -non-linearity = 0.776, r -1017.7, P -non-linearity = 0.552, respectively) (Fig. 7).

Discussion

The results of our meta-analysis of twenty-eight RCT studying the impact of Mg supplementation on anthropometric measurements in adults showed a reduction in WC measurement in obese (BMI > 30 kg/m²). However, there was no significant association between Mg supplement and others anthropometric parameters. Our meta-analysis verified the effectiveness of anti-obesity effect of Mg supplementation just in subjects with obesity of the population. The outcome that Mg supplement may have a decreasing effect on WC in certain subgroups (subjects with obesity) is supported by Mg capability of forming soaps with fatty acids in the intestine (and so reducing the digestible energy content of the diet)⁽⁵³⁾. On the other hand, Mg is a cofactor of enzyme cholesterol acyltransferase and lipoprotein lipase, which take part in lipoproteins metabolism⁽⁵⁴⁾. Numerous experimental studies have confirmed that Mg deficiency cause an increase in the TAG serum levels and abdominal obesity due

to decrease in chylomicron clearance and activity of lipoprotein lipase⁽⁵⁵⁾. With regard to all possible mechanisms of Mg anti-obesity effect, there is no an exact mechanism for it yet. Also, several human studies show that hypomagnesaemia is significantly associated with high risk of obesity especially abdominal obesity⁽⁵⁶⁻⁵⁹⁾. To the best of our knowledge, our study is the first meta-analysis on this topic, and the findings show that Mg supplementation may significantly reduce WC only in subjects with obesity but has no effect in other subjects and measurements related to obesity. Since the baseline BMI mean was more than 30 in most studies, one of the reasons for justification our results may be associated with BMI status. Another reason for explaining this finding may be related to healthy condition of participants. It is worth mentioning that there is no significant change after adjusting for duration of intervention, dose and age in all anthropometric indices. There are several limitations that should be mentioned when interpreting the findings in the present meta-analysis. First, there are a few studies on the topic 'the effect of magnesium supplementation on anthropometric indices in healthy subjects' and also the number of included studies in this meta-analysis was not adequate to reach a firm conclusion. Second, the most of the included studies were organised in the two countries, Mexico and Iran, which though strengthen internal validity of the findings but decrease their overall generalisability. Third, the magnitude of changes in anthropometric indices may not be equal and reliable during the intervention. Finally, the data analysis in most of studies was not adjusted for confounding variables such as lifestyle behaviours including diet, physical activity and tobacco use.

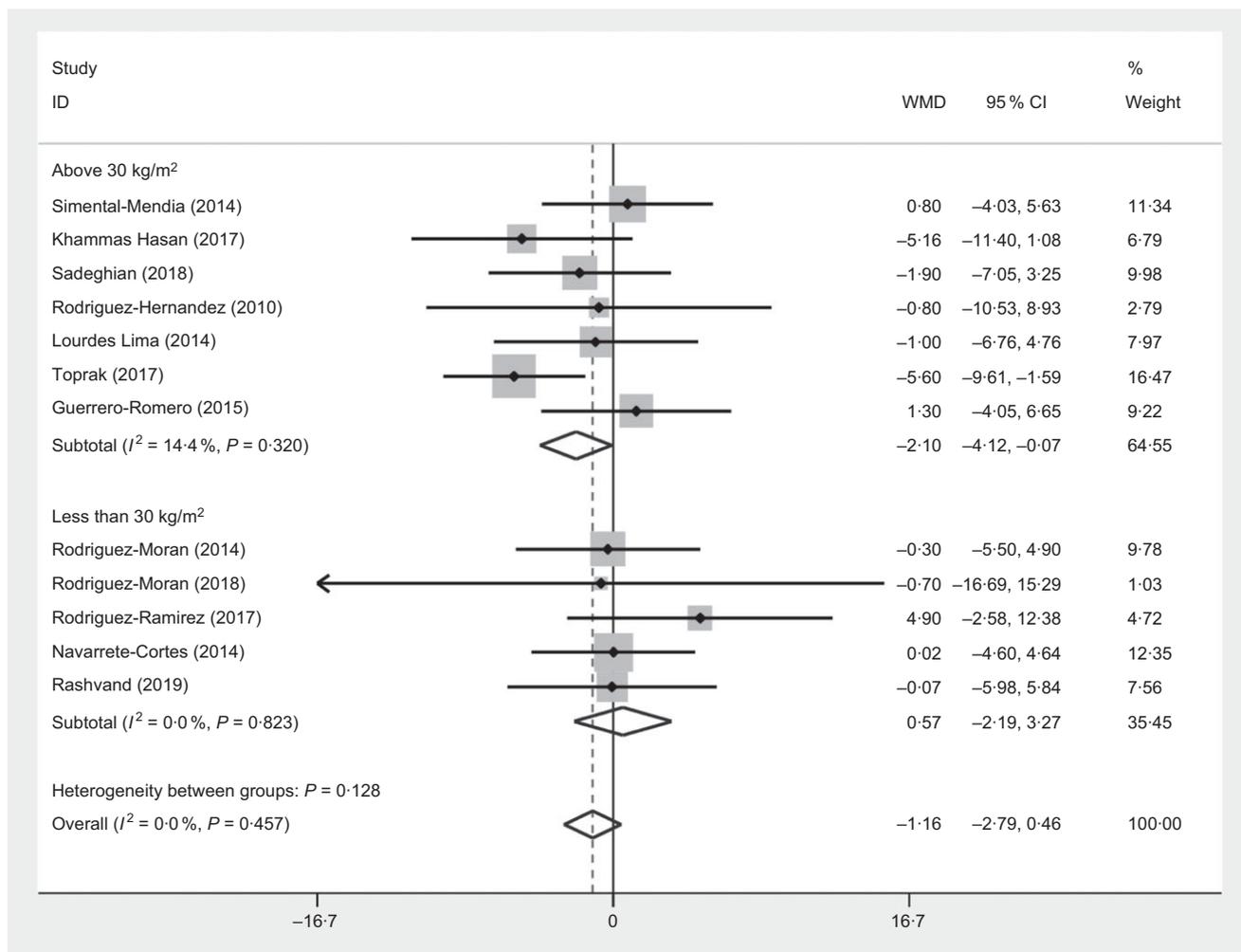


Fig. 4. Forest plot of the effect of magnesium supplementation sub grouped by BMI > 30 and ≤ 30 kg/m² on waist circumference. WMD, weighted mean difference.

Therefore, it is obvious that conducting well-designed randomised controlled trials with different racial populations are essential in future. Despite the above limitations, this is the first study to investigate systematically and meta-analytically the effect of Mg supplementation on anthropometric indices. So, our study can make a good perspective to the researcher in the future. Several studies have demonstrated that hypomagnesaemia was associated with the pathogenesis of obesity^(57,60,61). On the other hand, the anti-obesity effects of Mg supplements are not supported by firm evidence⁽⁶²⁾. It is valuable to note that, based on Recommended Dietary Allowances, Mg deficiency is a common global complication. The Institute of Medicine (USA) Food and Nutrition Board set estimated average requirement of Mg at level of 255–265 mg/d for females and 330–350 mg/d for males⁽⁶³⁾. Mg is a fundamental divalent metal ion and a critical cofactor for numerous enzymes involved in the metabolism of fats, proteins and carbohydrates and also helps insulin to act better^(63,64). As well as, it is essential for the activity of lecithin cholesterol acyltransferase and lipoprotein lipase enzyme, which has an important role in increasing level of serum HDL and decreasing TAG levels, respectively. Moreover, Mg is a regulatory factor in cholesterol biosynthesis⁽⁶⁵⁾. Mg-ATP complex is

also a main factor in glucose and insulin metabolism, mainly through its impact on kinase tyrosine activity, by transferring phosphate from ATP to protein. In addition, Mg may directly affect GLUT-4 and help to uptake glucose into cells⁽⁶⁶⁾. Eventually, Mg deficiency may promote pathogenesis of obesity by altering the aforementioned functions. In this regard, studies have found that low intake of Mg and hypomagnesaemia is strongly associated with obesity and insulin resistance^(67–70). Present meta-analysis showed that Mg supplementation caused reduction in WC in subjects with obesity. A high prevalence of Mg deficiency has been previously indicated in this population^(58,61). Hirschler *et al.*⁽⁷¹⁾ have showed that hypomagnesaemia was associated with central obesity, defined as WC more 90 cm. Also, numerous studies indicated that patients with central obesity and hypomagnesaemia are more susceptible to show abnormal parameters of fasting blood glucose and lipid profile^(57,72). The low serum level of Mg in patients with diabetes was principally caused by reduced insulin sensitivity, which leads to enhancement of Mg excretion in urine⁽⁷³⁾. Impacts of insulin resistance could illustrate a strong association between central obesity and low concentration of Mg^(74,75). We observed that Mg supplementation had no significant impact on BW, BMI

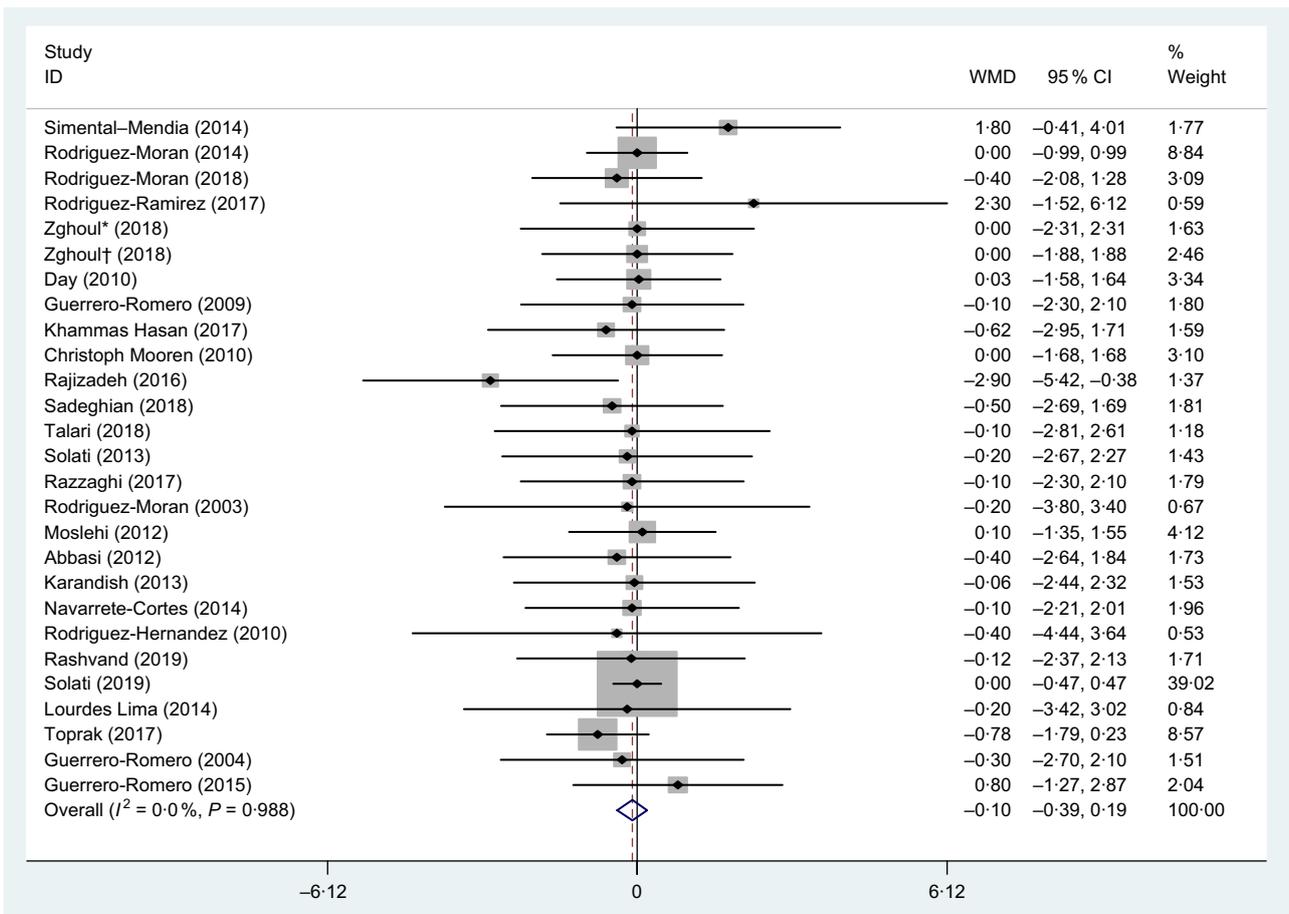


Fig. 5. Forest plot of the effect of magnesium supplementation on BMI. WMD, weighted mean difference. * Placebo group was obese; † placebo group was non-obese.

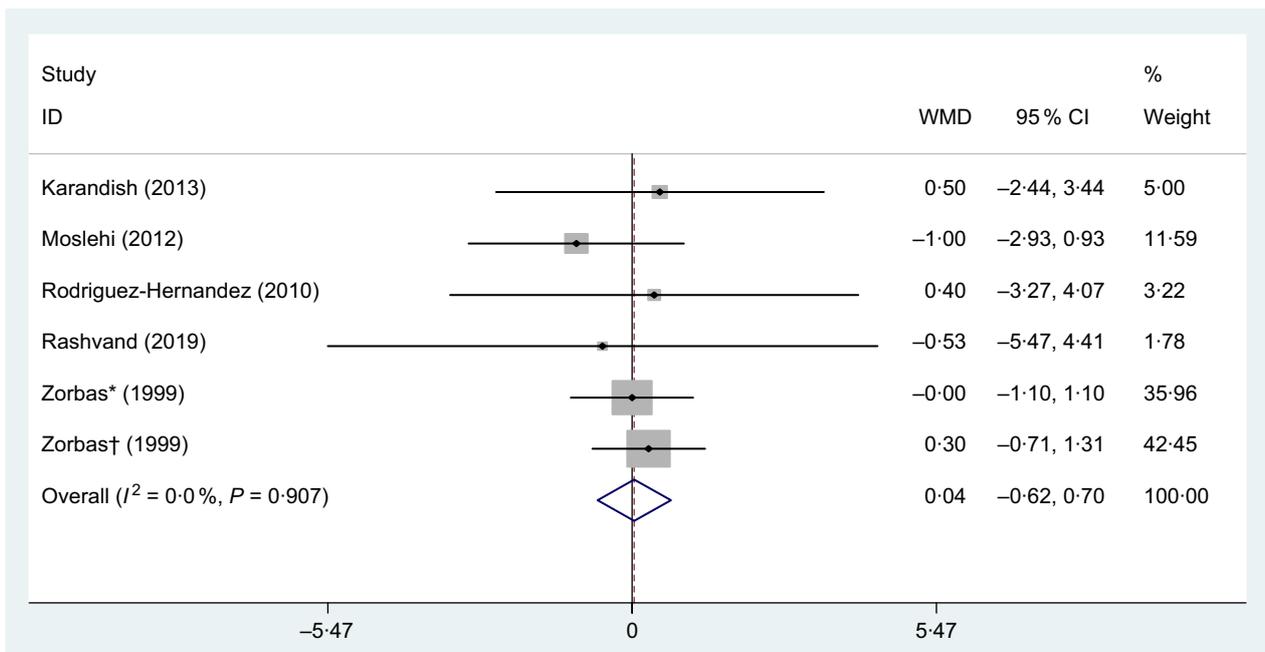


Fig. 6. Forest plot of the effect of magnesium supplementation on body fat percentage. WMD, weighted mean difference. * Placebo group was obese; † placebo group was non-obese.

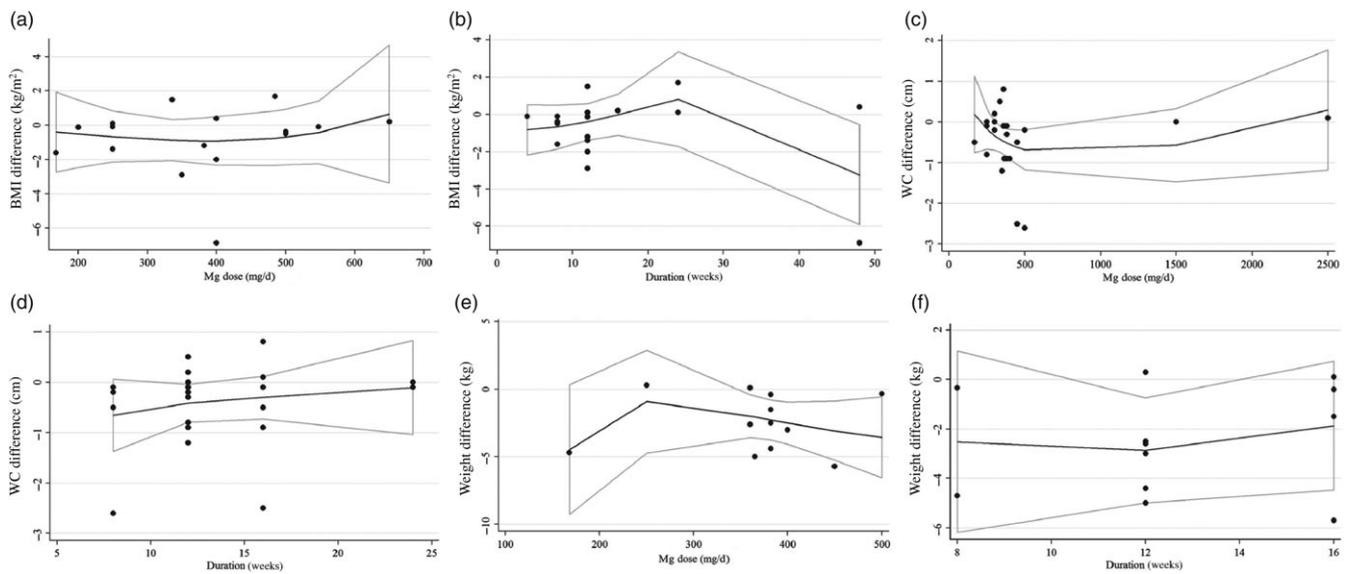


Fig. 7. Non-linear dose–response associations between magnesium supplementation and absolute mean differences. Dose–response relationships between magnesium supplementation and absolute mean differences in BMI (kg/m^2 – twenty-five trials) (a and b), waist circumference (WC) (cm – twelve trials) (c and d) and weight (kg – sixteen trials) (e and f) based on dose of magnesium (mg/d) are depicted.

and BF% in all subgroups. However, the Coronary Artery Risk Development study in 5115 American young adults, aged 18–30 years, after 30-year follow-up found that Mg intake was negatively associated with incidence of obesity. According to this follow-up, intakes of foods rich in Mg, including whole grains, nuts and seeds, legumes, and dark-green vegetables, can decrease obesity risk⁽⁷⁶⁾. In the present study, we found that Mg supplementation intake has a negative association with WC, which supports this hypothesis. It is important to note that most of included studies in this meta-analysis have reported anthropometric indices as secondary outcomes. Hence, difference in anthropometric measurement between intervention and placebo groups may be due to estimations bias. Our dose–response analysis showed that neither dosage nor duration of Mg supplementation led to significant changes in BMI, BW and WC. Further, this hypothesis ‘the high dose of supplementation Mg and/or long duration of intervention can have an effect to decrease anthropometric measurements’ seems to be not effective. The weakness of significant association between Mg supplementation and anthropometric indices may be related to several factors. First, the effect of Mg supplementation on anthropometric indices may depend on Mg status at the beginning of the study and variation of serum level of Mg at baseline. Second, diets with high content of Mg such as whole grains, nuts, fruits and vegetables may have more strong anti-obesity effects rather than the single nutrient intake as supplement. In addition to Mg, many other components of foods including fibres, vitamin E, several B-vitamins and lignans may contribute to the beneficial effects on obesity⁽⁷⁷⁾. Finally, the small number of trials led to decline our ability to diminish subgroup and publication bias analysis for BW, WC, BMI and BF%. Our study has several advantages. First of all, our study is the first meta-analysis of RCT to review systematically the effects of Mg supplementation on anthropometric indices in adults. Second, our results were firm and strong because all included studies were RCT. Finally, analysis was based on

subgrouping conducted to assess the effects of various subgroups and confounder variables.

In conclusion, the present meta-analysis on clinical trials revealed that supplementation with Mg significantly decreased WC in subjects with obesity ($\text{BMI} > 30 \text{ kg}/\text{m}^2$), and also it had no effect on BMI, BW and BF% in all subgroups. Although Mg supplementation generally had no statistically significant effects on anthropometric indices, but it may be effective on subjects with obesity. High-quality, long-time, large population studies and further investigation and assessment of the efficacy and effective dose of Mg supplementation on anthropometric indices in future research are required.

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The authors declare that they have no conflict of interest.

The present study was approved by the Ethical Committee of Isfahan University of Medical Sciences.

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