

Effect of magnesium supplements on serum C-reactive protein: a systematic review and meta-analysis

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Abstract

Introduction: The aim of the study was to undertake a systematic review and meta-analysis of prospective studies to determine the effect of magnesium (Mg) supplementation on C-reactive protein (CRP). Design: Systematic review and meta-analysis of randomised controlled trials (RCTs).

Material and methods: Data sources: PubMed-Medline, Web of Science, Cochrane Database, and Google Scholar databases were searched (up until December 2016). Eligibility criteria: Randomized controlled trials evaluating the impact of Mg supplementation on CRP. We used random effects models meta-analysis for quantitative data synthesis. For sensitivity analysis was used the leave-one-out method. Heterogeneity was quantitatively assessed using the I^2 index. Main outcome: Level of CRP after Mg supplementation.

Results: From a total of 96 entries identified via searches, eight studies were included in the final selection. The meta-analysis indicated a significant reduction in serum CRP concentrations following Mg supplementation (weighted mean difference (WMD) -1.33 mg/l; 95% CI: -2.63 to -0.02 , heterogeneity $p < 0.123$; $I^2 = 29.1\%$). The WMD for interleukin 6 was -0.16 pg/dl (95% CI: -3.52 to 3.26 , heterogeneity $p = 0.802$; $I^2 = 2.3\%$), and 0.61 mg/dl (95% CI: -2.72 to 1.48 , $p = 0.182$, heterogeneity $p = 0.742$; $I^2 = 6.1\%$) for fasting blood glucose. These findings were robust in sensitivity analyses. Random-effects meta-regression revealed that changes in serum CRP levels were independent of the dosage of Mg supplementation (slope: -0.004 ; 95% CI: -0.03 , 0.02 ; $p = 0.720$) or duration of follow-up (slope: -0.06 ; 95% CI: -0.37 , 0.24 ; $p = 0.681$).

Conclusions: This meta-analysis suggests that Mg supplementation significantly reduces serum CRP level. RCTs with a larger sample size and a longer follow-up period should be considered for future investigations to give an unequivocal answer.

Key words: meta-analysis, magnesium, C-reactive protein.

Introduction

Magnesium (Mg), as one of the most abundant minerals in the body, is essential for good health. The main food sources of Mg are whole grains, legumes, nuts, and green leafy vegetables [1]. More recent evidence indicates that dietary intake of Mg has an impact on several metabolic and inflammatory disorders including hypertension [2], type 2 diabetes [3], metabolic syndrome [4], insulin resistance [5] and cardiovascular diseases [1, 6]. Magnesium deficiency, either from inadequate intake, excess excretion or altered homeostasis, is often suspected to be associated with the initiation of many symptoms and diseases [7]. A growing body of evidence supports the important role of magnesium deficiency in the synthesis and release of pro-inflammatory cytokines and acute phase functions, in the impairment of peripheral insulin action, and in the progress of glucose metabolism disturbances [8, 9]. It has been proposed that the anti-inflammatory response of Mg may contribute to the beneficial effects on reducing the levels of C-reactive protein (CRP) – a well-known indicator of acute or chronic inflammation [10]. In this regard, one study has reported an inverse relationship between dietary magnesium intake and CRP levels in non-diabetic non-hypertensive obese individuals [11]. However, another cross-sectional study did not find an association between dietary Mg intake and CRP levels [12]. While these findings suggest that magnesium plays a role in the inflammatory response, single studies to date have been limited by sample size, research design and subject traits (gender, ethnicity, age, etc.), and underpowered to achieve a comprehensive and reliable conclusion. On the other hand, dietary supplementation with Mg with different dosage and duration can have different effects on some indices of inflammatory and anti-inflammatory indexes. Meta-analysis has the benefit of overcoming this limitation by increasing the sample size. Hence, to better understand this issue, the present study aimed to resolve this uncertainty by systematically reviewing the literature and performing a meta-analysis of all randomized control trials investigating the effects of Mg supplementation on serum CRP levels.

Material and methods

We followed the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13, 14]. Due to the study design (meta-analysis) neither Institutional Review Board (IRB) approval nor patient informed consent was needed or obtained. The study protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (registration no: CRD42016039482).

Literature search strategy

The primary exposure of interest was magnesium supplementation, while the primary outcome of interest was changes in serum C-reactive protein levels subsequent to magnesium supplementation. We searched multiple databases including PubMed/Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Web of Science and MEDLINE, until December 2016, using a combination of search terms available in Table I. We used the wild-card term “*” to increase the sensitivity of the search strategy. No language restriction was applied. This was complemented by hand searches of the reference list of eligible articles, and email correspondences with authors for additional data where relevant. All paper abstracts were screened by two reviewers (MM and PR) in an initial process to remove ineligible articles. The remaining articles were obtained in full text and assessed again by the same two researchers who evaluated each article independently, carried out data extraction and quality assessment. Disagreements were resolved by discussion with a third party (HV).

Selection criteria

All prospective studies evaluating the effect of Mg supplementation on the outcomes of interest were included in this analysis. Eligible studies had to meet the following criteria: (1) prospective controlled trial with either parallel or crossover design and of patients treated with magnesium supplementation compared to a control group (either no

Table I. Full search terms and strategy used for systematically reviewing the articles

No.	Concept	Search terms
1	Magnesium	((“magnesium”[Text Word]) OR “Mg”[Text Word])
2	C-reactive protein	“high sensitivity C-reactive protein”[MeSH Terms] OR “high-sensitivity C-reactive protein”[MeSH Terms] OR “C-reactive protein”[MeSH Terms] OR “high-sensitive C-reactive protein”[MeSH Terms] OR “high sensitive C-reactive protein”[MeSH Terms] OR “CRP”[Title/Abstract] OR “hsCRP”[Title/Abstract]
3	Combination	1 AND 2

Mg supplementation or placebo), (2) presentation of sufficient information on primary outcome at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were: (i) non-clinical studies; (ii) observational studies with case-control, cross-sectional or cohort design; and (iii) studies that did not provide mean (or median) plasma concentrations of our interested outcomes at baseline and/or at the end of trial. Narrative reviews, comments, opinion pieces, methodological, editorials, letters or any other publications lacking primary data and/or explicit method descriptions were also excluded. Study selection started with the removal of duplicates, followed by screening of titles and abstracts by two reviewers. To avoid bias, they were blinded to the names, qualifications or the institutional affiliations of the study authors. The agreement between the reviewers was excellent (κ index: 0.88; $p < 0.001$). Disagreements were resolved at a meeting between reviewers prior to selected articles being retrieved (a flow chart is available in Figure 1).

Data extraction and management

The full text of studies meeting the inclusion criteria was retrieved and screened to determine eligibility by two reviewers (MM, PR). Following assessment of methodological quality, the two reviewers extracted data using a purpose-designed data extraction form and independently summarized what they considered to be the most important results from each study. These summaries were compared and any differences of opinion resolved by discussion and consultation with a third reviewer (HV). Additional necessary calculations on study data were conducted by the first reviewer and checked by the second reviewer. Descriptive data extracted included the first author's name, reference, year of publication, country, design, duration of the study, inclusion criteria, dose, age range, sample size, and male gender (%).

Quality assessment

A systematic assessment of bias in the included RCTs was performed using the Cochrane criteria [15]. We used the following items for the assessment of each study: blinding of participants, allocation concealment, adequacy of random sequence generation, handling of drop-outs (incomplete outcome data), personnel and outcome assessment, selective outcome reporting, as well as any other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of 'yes' indicated low risk of bias, while 'no' indicated a high risk of bias. Labeling an item as 'unclear' indicated an unclear

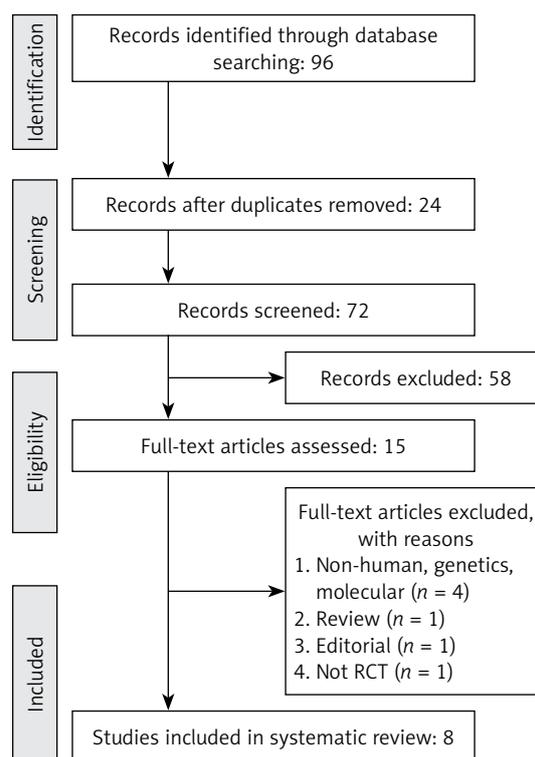


Figure 1. PRISMA flow chart for selection of studies

or unknown risk of bias. Risk-of-bias assessment was performed independently by 2 reviewers (MM and PR); disagreements were resolved by a third reviewer (HV).

Data synthesis

Following the Cochrane Handbook recommendations for calculating the effect size, we used the mean (SD) change from baseline in the concentrations of the variables of interest for both control and intervention groups [16]. In summary, we calculated the net changes in measurements (change scores) as follows: measure at the end of follow-up – measure at baseline. For RCTs, change scores were calculated as (measure at the end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at the end of follow-up in the control group – measure at baseline in the control group). In situations where only a standard error of the mean (SEM) was available, we estimated standard deviation (SD) using the following formula: $SD = SEM \times \text{square root } (n)$, where n is the number of subjects [17]. In situations where the outcome measures were reported in median and range (or 95% confidence interval (CI)), we estimated the mean (SD) values using the method described by Mazidi *et al.* [18]. When the outcome variable was available only in the graphic form, the software GetData Graph Digitizer 2.24 [19] was used to digitize and extract the data. Blood glucose level was collated in

mmol/l; a multiplication factor of 0.0555 was used to convert glucose levels from mg/dl to mmol/l as appropriate [20].

A random effects model (using the DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design and type of BAS being studied [21]. Heterogeneity was quantitatively assessed using the I^2 index. The I^2 values < 50% and \geq 50% corresponded with the use of fixed-effects and random-effects models, respectively. We expressed the effect sizes as the weighted mean difference (WMD) and 95% confidence interval (CI). To assess the influence of each study on the overall effect size, we conducted a sensitivity analysis using the leave-one-out method (removing one study each time and repeating the analysis) [22–24].

Meta-regression

Random-effects meta-regression was performed using the unrestricted maximum likelihood method to evaluate the association between calculated WMD and potential moderator including dose of magnesium supplementation.

Publication bias

Potential publication bias was explored using visual inspection of Begg’s funnel plot asymmetry, Begg’s rank correlation and Egger’s weighted regression tests. Duval & Tweedie ‘trim and fill’ and ‘fail-safe N’ methods were used to adjust the analysis for the effects of publication bias [25]. Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ) [26].

Results

Summary of searches and study selection process

A total of 96 unique citations were identified from searches, of which 72 records remained after removing duplicates. After screening via titles and abstracts, 15 articles remained for further evaluation, of which seven were excluded for the following reasons: non-human studies, genetic, or molecular studies ($n = 4$); reviews or editorial articles ($n = 2$) and not RCTs ($n = 1$) (Figure 1). Therefore, eight studies with 349 participants were finally included in the meta-analysis.

Risk of bias assessment

Several of the included studies were characterized by a lack of information about allocation concealment ($n = 1$) or blinding of outcome assessment ($n = 2$). However, one study had a moderate risk of bias [27] and other evaluated studies had a low risk of bias according to selective outcome reporting. Details of the quality of bias assessment are shown in Table II.

Characteristics of the included studies

The characteristics of included studies are summarized in Table III. These studies were published between 2004 and 2014 from four countries: the United States of America (5 studies), Mexico (4 studies), Iran and Turkey. The number of participants included in the studies ranged from 14 [28] to 100 [29]. Participants in one study were only female [30], while the proportion of females in five studies ranged from 29% [8] to 78% [29]. In two studies the percentage

Table II. Quality of bias assessment of the included studies according to the Cochrane guidelines

Studies	Random sequence generation	Allocation concealment	Selective reporting	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Other bias
Chacko, 2011 [28]	L	L	L	L	L	L	L
Simental-Mendía, 2012 [45]	L	L	L	L	U	L	L
Kazaks, 2010 [32]	L	L	L	H	L	L	L
Mortazavi, 2012 [46]	L	L	L	L	L	L	L
Nielsen, 2010 [29]	L	U	L	L	L	L	L
Resatoglu, 2004 [27]	L	H	H	L	U	L	L
Rodríguez-Hernandez, 2010 [30]	L	L	L	L	L	L	L
Simental-Mendia, 2014 [31]	L	H	L	L	L	L	L

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

Table III. General characteristics of the studies included

First author, reference	Country	Study design	Inclusion criteria	Treatment duration	Sample size	Age [years]	Female (n, %)	Mg dose	Baseline level of CRP [mg/dl]
Chacko, 2011 [28]	USA	Randomized, double-blind, controlled, crossover trial	Being aged 30–70 years and having a body mass index (BMI; in kg/m ²) ≥ 25, general good health, mobility, and no dietary restrictions or allergies	4 weeks	14	30–70	29%	500 mg/day	1.30
Simental-Mendia, 2012 [45]	Mexico	Clinical randomized double-blind placebo-controlled trial	Impaired fasting glucose (IFG) (fasting plasma glucose levels ≥ 5.5 mmol/l < 6.9 mmol/l), or IGT (plasma glucose levels 2-h post-load ≥ 7.7 mmol/l < 11 mmol/l)	3 months	22	20–65	63.6%	382 mg/day	4.1
Kazaks, 2010 [32]	USA	Randomized placebo-controlled, double-blind, parallel group intervention	–	6.5 months	52	21–55	66.6%	340 mg/day	3.5
Mortazavi, 2012 [46]	Iran	Double-blind, randomized, placebo-controlled trial	–	6 months	54	56.93 ± 12.19	48.3%	440 mg/day	1.85
Nielsen, 2010 [29]	USA	Double-blind, placebo-controlled, supplementation trial	–	7 weeks	100	51–85	78%	320 mg/day	2.92
Resatoglu, 2004 [27]	Turkey	Randomized control trial	–	8 hours	20	–	–	1500 mg	0.42
Rodriguez-Hernandez, 2010 [30]	Mexico	Non-randomized non-placebo controlled clinical trial	–	4 months	30	30–65	100%	450 mg/day	9.4
Simental-Mendia, 2014 [31]	Mexico	A clinical randomized double-blind placebo-controlled trial	New diagnosis of prediabetes (glucose 5.6 < 7.0 mmol/l and/or post-load glucose ≥ 7.7 < 11.1 mmol/l) and hypomagnesemia (serum magnesium levels < 0.74 mmol/l)	3 months	57	18–65	–	382 mg/day	0.72

of women was unknown [27, 31]. The mean age of participants ranged from 18 [31] to 85 years [29]. The range of duration of the supplementation intervention across studies was from 8 h [27] to 6.5 months [32]. The consumed range of Mg dose in these studies was from 320 [29] to 1500 [27] mg/day. The baseline level of the CRP varied between the studies from 0.42 mg/dl [6] as minimum to 9.4 mg/dl [7] as maximum, Table III.

Pooled estimate of the effect of Mg supplementation on CRP

The pooled estimate (weighted mean difference) of the effect of Mg supplementation on CRP levels was -1.33 mg/dl (95% CI: -2.63 to -0.02 , $p < 0.001$, heterogeneity $p < 0.123$; $I^2 = 29.1\%$) across all studies (Figure 2). We divided our studies according to the baseline level of the CRP; it was found that subjects with baseline CRP higher than or equal to 2 (CRP ≥ 2 mg/dl (4 studies)) have more significant reduction in the CRP level (-2.95 mg/dl; 95% CI: -3.35 to -2.25 , $p < 0.001$, heterogeneity $p = 0.952$; $I^2 = 1.1\%$) compared with the subjects with CRP < 2 mg/l (4 studies) (-0.23 ; 95% CI: -0.195 to -0.326 , $p < 0.001$, heterogeneity $p = 0.923$; $I^2 = 1.3\%$).

Pooled estimate of the effect of Mg supplementation on IL-6

The pooled estimate (weighted mean difference) of the effect of Mg supplementation on IL-6 levels was -0.16 pg/dl (95% CI: -3.52 to 3.26 , $p = 0.236$, heterogeneity $p = 0.802$; $I^2 = 2.3\%$) across all studies.

Pooled estimate of the effect of Mg supplementation on TNF- α

The pooled estimate (weighted mean difference) of the effect of Mg supplementation on TNF- α levels was 1.97 pg/dl (95% CI: 1.12 to 2.82 , $p = 0.043$, heterogeneity $p = 0.869$; $I^2 = 2.1\%$) across all studies.

Pooled estimate of the effect of Mg supplementation on fasting blood glucose (FBG)

The pooled estimate (weighted mean difference) of the effect of Mg supplementation on FBG levels was -0.61 mg/dl (95% CI: -2.72 to 1.48 , $p = 0.182$, heterogeneity $p = 0.742$; $I^2 = 6.1\%$) across all studies.

Pooled estimate of the effect of Mg supplementation on systolic blood pressure (SBP)

The pooled estimate (weighted mean difference) of the effect of Mg supplementation on SBP levels was -0.93 mm Hg (95% CI: -3.03 to 1.20 , $p = 0.293$, heterogeneity $p = 0.526$; $I^2 = 3.6\%$) across all studies.

Pooled estimate of the effect of Mg supplementation on diastolic blood pressure (DBP)

The pooled estimate (weighted mean difference) of the effect of Mg supplementation on DBP levels was -0.30 mm Hg (95% CI: -2.80 to 2.19 , $p = 0.639$, heterogeneity $p = 0.489$; $I^2 = 3.8\%$) across all studies.

Pooled estimate of the effect of Mg supplementation on body mass index (BMI)

The pooled estimate (weighted mean difference) of the effect of Mg supplementation on BMI levels was 0.27 kg/m² (95% CI: -0.59 to 1.15 , $p = 0.542$, heterogeneity $p = 0.906$; $I^2 = 2.0\%$) across all studies.

Sensitivity analysis

In leave-one-out sensitivity analyses, the pooled effect estimates remained similar across all studies for CRP (-1.33 mg/l; 95% CI: -2.63 to -0.02). This stability confirms that the significant difference between the studied groups is the overall effect of all included studies.

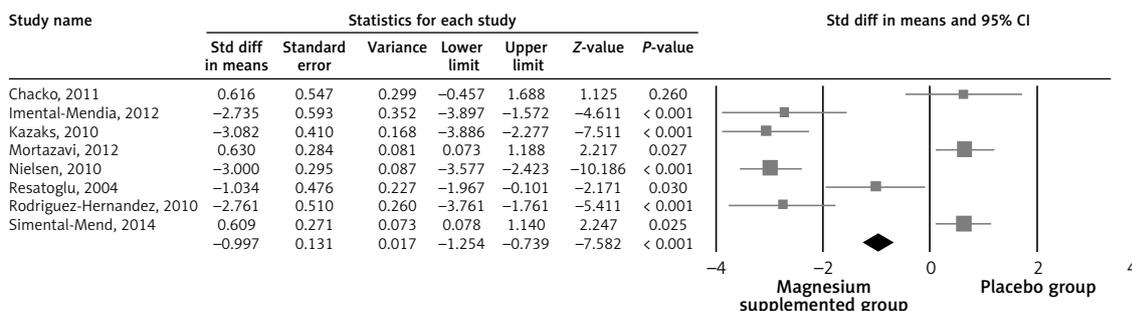


Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of magnesium supplementation on CRP levels

Meta regression

Random-effects meta-regression was performed to evaluate the impact of potential moderators on the estimated effect size. Changes in plasma CRP levels were independent of the dosage of Mg (slope: -0.004 ; 95% CI: $-0.03, 0.02$; $p = 0.720$, Figure 3) and duration (slope: -0.06 ; 95% CI: $-0.37, 0.24$; $p = 0.681$, Figure 4) of supplementation.

Publication bias

Visual inspection of funnel plot asymmetry suggested potential publication bias for the comparison of plasma CRP levels between Mg supplemented groups and placebo groups (Figure 5); however, the presence of publication bias was not suggested by Egger's linear regression (intercept = -5.69 , standard error = 6.10 ; 95% CI: $-20.64, 9.25$, $t = 0.93$, $df = 6.00$, two-tailed $p = 0.387$) and Begg's rank correlation test (Kendall's Tau with

continuity correction = -0.14 , $z = 0.49$, two tailed $p = 0.620$) was not indicative for publication bias. After adjustment of the effect size for potential publication bias using the 'trim and fill' correction, no potentially missing studies were imputed in the funnel plot (WMD -1.33 mg/l; 95% CI: -2.63 to -0.02 , Figure 6). The 'fail-safe N' test showed that 146 studies would be needed to bring the WMD down to a non-significant ($p > 0.05$) value.

Discussion

The present meta-analysis of 8 RCTs published in the last 10 years (2004–2014) showed that Mg supplementation significantly decreased the level of serum hs-CRP by -1.33 mg/l (-2.63 to -0.02). Evidence from this meta-analysis indicates that dietary Mg intake is inversely associated with serum CRP levels. Our results showed that Mg supplementation did not have a significant effect on IL-6 (-0.16 pg/dl). These results support the hypothesis that dietary Mg plays a beneficial role in the regu-

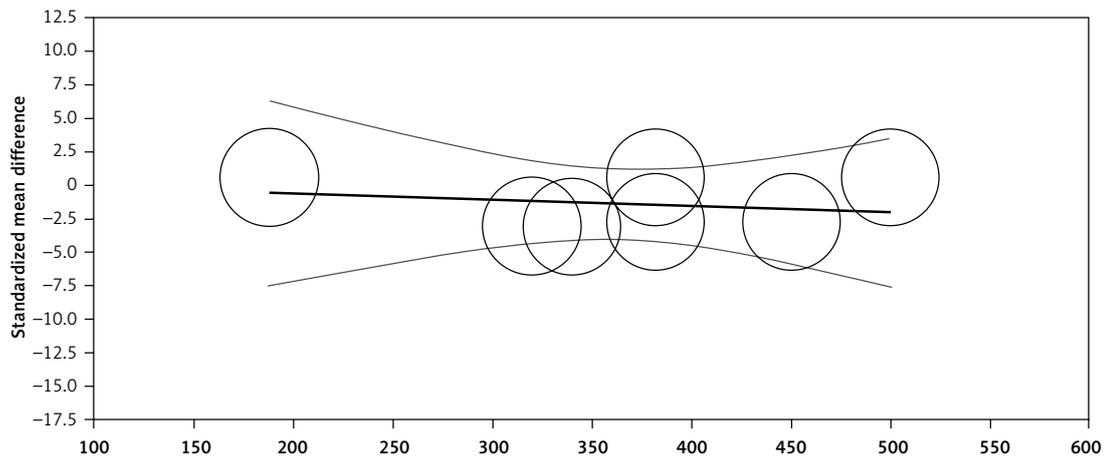


Figure 3. Meta-regression plots of the association between mean changes in CRP levels with doses of magnesium supplementation. Circles represent each study, middle line is the regression line, two lines around the middle line represent the 95% confidence interval

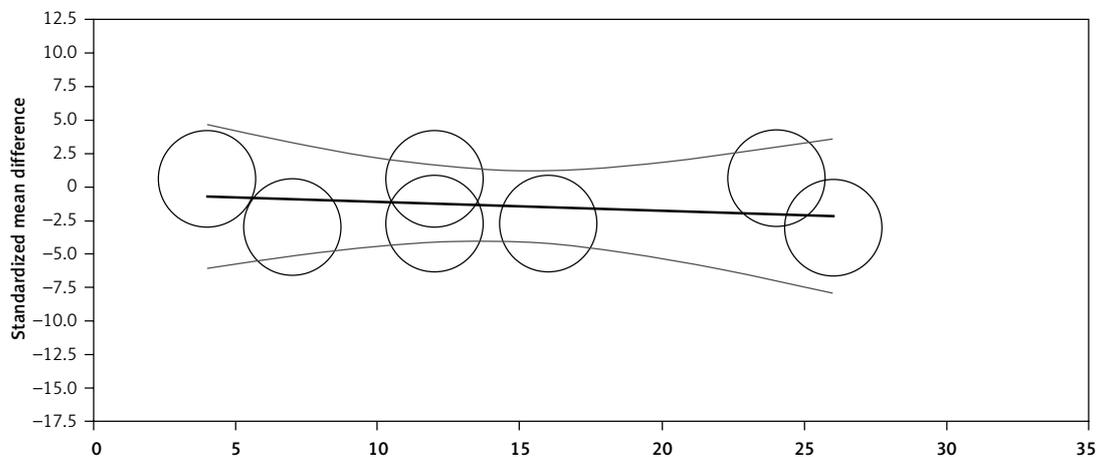


Figure 4. Meta-regression plots of the association between mean changes in CRP levels with duration of magnesium supplementation. Circles represent each study, middle line is the regression line, two lines around the middle line represent the 95% confidence interval

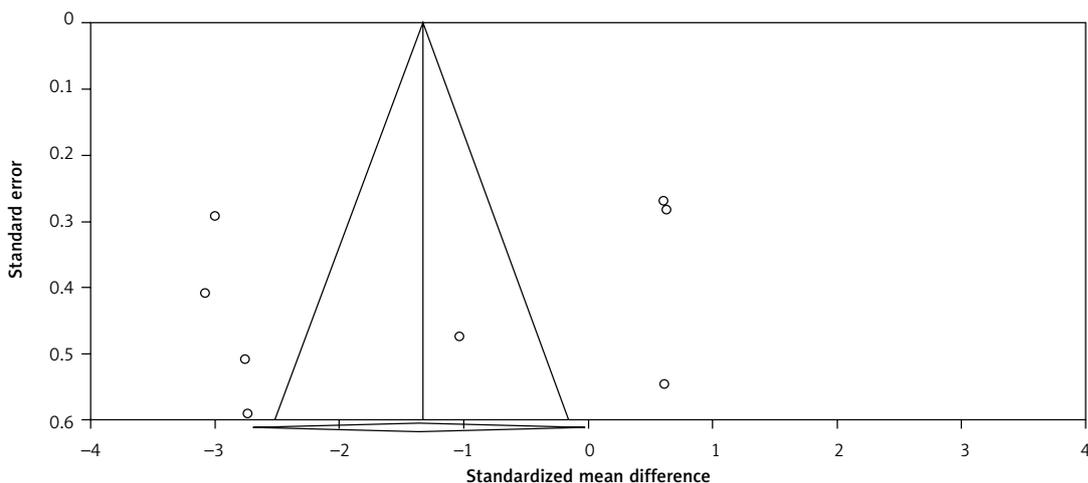


Figure 5. Funnel plots detailing publication bias in the studies selected for analysis. Open diamond represents observed effect size; open circles represent observed published studies

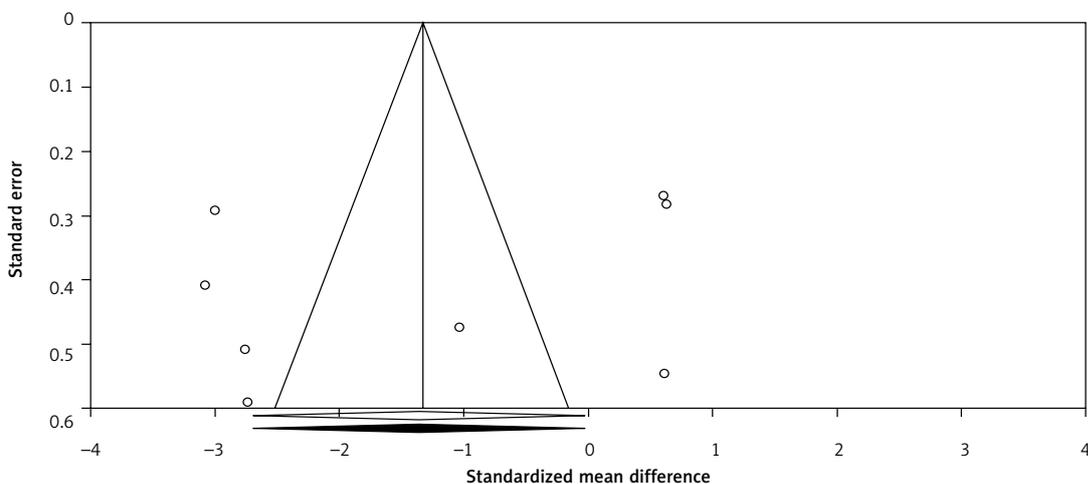


Figure 6. Trim and fill method was used to impute for potentially missing studies. No potentially missing study was imputed in funnel plot, open circles represent observed published studies; open diamond represents observed effect size; closed diamond represents imputed effect size

lation of inflammatory markers. In this regard, King [33] recently surveyed data of several cross-sectional and epidemiological studies highlighting that Mg possibly plays an important role in potentiating inflammatory processes. The inverse association found in our meta-analysis is supported by evidence from randomized controlled studies that have reported on patients with type 2 diabetes, admitted to an intensive care unit, and among patients with heart failure, oral Mg supplementation decreased CRP levels [34, 35]. However, previous data published regarding the efficacy of oral Mg supplementation for reducing CRP levels are scarce [35]. Regarding effects of Mg intake on IL-6 level, some studies have found inconsistent results, while others have shown an inverse association [36], but others did not demonstrate any correlation [37]. IL-6, which acts as both a pro-inflammatory and an anti-inflammatory cytokine, secreted by T cells and macrophages, is the major mediator of fever

and the acute phase response [38]. As raised IL-6 concentrations may be an early indicator of acute inflammation, increased serum IL-6 concentrations may be observed because of undetected underlying acute infection present simultaneously with Mg usage by chance [35]. Although the Mg-related primary events that produce the acute-phase response are not known with certainty, this complex process suggests that Mg deficiency might be among the initial elements that trigger the inflammatory response [39]. Evidence derived from an animal model have shown that acute Mg deficiency leads to an inflammatory response [40]. Moreover, human studies show that low serum Mg levels are strongly associated with raised CRP concentration [3, 41]. A potential mechanism for the association between Mg deficiency and inflammation is related to calcium. If dietary Mg intake is inadequate, it may deplete extracellular Mg ions and consequently cause stimulation of macrophages as well as an

influx of calcium ions into cells such as adipocytes, neuronal and peritoneal cells. N-methyl-D-aspartate receptors (NMDARs) are glutamate-gated cation channels with high calcium permeability. Augmented calcium levels in the cells enhanced Mg necessary to block the influx of calcium ions, which further led to increased stimulation of these receptors. Stimulation of these NMDAR results in the opening of channels nonselective to cations, consequently increasing calcium ions in neuronal cells [42]. This change causes the release of neurotransmitters (e.g., substance P) and inflammatory cytokines. IL-6 is released into the bloodstream and acts as a signaling molecule to enhance the release of CRP from the liver as a step in the acute phase response, which promotes prolongation of the inflammatory response in the body [1].

There are some potential limitations in our analysis that need to be addressed. Firstly, the majority of the included studies had relatively small sample sizes, potentially leading to unstable estimates of treatment effects, because smaller trials might be methodologically less robust and are prone to report larger effect sizes [43–46]. Moreover, due to the fact that the population at the baseline was very heterogeneous, we expect that it could also accept the output of the meta-analysis; however, to decrease the chance of bias based on the baseline level of the variables we performed a meta-regression and explored the impact of the dose and duration of the supplementation. Lastly, the number of available studies concerning the described topic was rather small, particularly in the case of TNF- α , which may lead to misinterpretation of the results.

In conclusion, this meta-analysis suggests that Mg supplementation significantly decreased serum CRP, especially with the baseline values ≥ 2 mg/dl. To provide more conclusive results and clarify the mechanistic pathways, RCTs with a larger sample size and a long-term follow-up period are warranted.

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Trial registration: Systematic review registration: CRD42016039482.

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Conflict of interest

The authors declare no conflict of interest.

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