Effects of Magnesium Supplementation on Blood Pressure: A Meta-Analysis of Randomized Double-Blind Placebo-Controlled Trials

Xi Zhang[1], Yufeng Li[2*], Liana C. Del Gobbo[3], Andrea Rosanoff[4], Jiawei Wang[5], Wen Zhang[6], Yiqing Song[1]

Affiliations:

1. Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA.
2. Department of Endocrinology, Beijing Pinggu Hospital, Beijing, China.
3. Department of Medicine, Division of Cardiovascular Medicine, Stanford University, Stanford, CA, USA.
4. Center for Magnesium Education and Research. Pahoa, HI, USA.
5. Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada.
6. Department of Epidemiology, School of Medicine, Fukushima Medical University, Fukushima, Japan.

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Correspondence to Yiqing Song, MD, ScD, Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, 1050 Wishard Blvd., RG 5117, Indianapolis, IN 46202-2782.
Tel: 317-274-3833; Fax: 317-274-3443; E-mail: yiqsong@iu.edu

* These authors contributed equally to this work.

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ABSTRACT

The antihypertensive effect of magnesium (Mg) supplementation remains controversial. We aimed to quantify the effect of oral Mg supplementation on blood pressure (BP) by synthesizing available evidence from randomized double-blind placebo-controlled trials. We searched trials of Mg supplementation on normotensive and hypertensive adults published up to February 1, 2016 from MEDLINE and EMBASE databases; 34 trials involving 2,028 participants were eligible for this meta-analysis. Weighted mean differences of changes in BP and serum Mg were calculated by random-effects meta-analysis. Mg supplementation at a median dose of 368 mg/day for a median duration of 3 months significantly reduced systolic BP by 2.00 mmHg (95% CI: 0.43, 3.58) and diastolic BP by 1.78 mmHg (95% CI: 0.73, 2.82); these reductions were accompanied by 0.05 mmol/L (95% CI: 0.03, 0.07) elevation of serum Mg compared to placebo. Using a restricted cubic spline curve, we found that Mg supplementation with a dose of 300 mg/day or duration of 1 month is sufficient to elevate serum Mg and reduce BP; and serum Mg was negatively associated with diastolic BP but not systolic BP (all $P < 0.05$). In the stratified analyses, a greater reduction in BP tended to be found in trials with high quality or low dropout rate (all P-values for interaction < 0.05). However, residual heterogeneity may still exist after considering these possible factors. Our findings indicate a causal effect of Mg supplementation on lowering BPs in adults. Further well-designed trials are warranted to validate the BP-lowering efficacy of optimal Mg treatment.

Keywords: magnesium, blood pressure, hypertension, randomized controlled trial, meta-analysis

Introduction

Magnesium (Mg), an essential element in the human body, may have beneficial health effects for the primary prevention of hypertension. Given the increasing prevalence and incidence of hypertension, the identification of effective and safe preventive measures that offer even modest blood pressure (BP)-lowering effects could have a significant public health impact. Several lines of evidence from laboratory research have suggested some underlying mechanisms. Mg may play a critical role in blood pressure (BP) regulation, through directly stimulating prostacyclin and nitric oxide formation [1], modulating endothelium-dependent and endothelium-independent vasodilation [2, 3], reducing vascular tone and reactivity [4], and preventing vascular injury via its antioxidant and anti-inflammatory functions [5, 6]. Numerous experimental studies have implicated a pathophysiological link between lower Mg content in the blood (hypomagnesemia) or tissue [7-9] and hypertension in various animal models.

There is long-standing interest in the promising yet unproven role of Mg in the regulation of BP for the prevention of hypertension, while evidence from human studies has been both inconsistent and controversial. Observational epidemiologic evidence also suggested a negative association between dietary Mg intake and BP [10]; however, Mg effects on both systolic and diastolic BPs were not consistent among individual trials of Mg supplementation [11]. Previous systematic reviews and meta-analyses based on randomized trials have also been less conclusive for both systolic and diastolic BP [11-13]. For instance, a recent meta-analysis reviewed 23 trials with a total of 1,173 participants and reported a significant decrease in systolic BP of 2-3 mmHg and diastolic BP of 3-4 mmHg elicited by a median dose of 410 mg/day Mg supplementation for an average of 11 weeks[14]. Nevertheless, there was considerable heterogeneity across trials in terms of trial quality, sample sizes, and participant characteristics. In particular, whether trial

quality, treatment compliance, or participants' baseline Mg status would modify the effects of Mg on lowering BPs remained unexplored in all previous studies, possibly due to the limited number of suitable trials, especially well-designed and conducted RCTs.

To reliably test the BP-lowering effects of oral Mg supplementation, we therefore conducted a comprehensive meta-analysis to synthesize only direct evidence from randomized double-blind placebo-controlled trials. To evaluate the robustness of the overall results, we also examined whether and to what extent changes in BP were related to elevation in serum Mg levels elicited by Mg supplementation.

Methods

Search strategy

We electronically searched and identified all relevant articles evaluating the anti-hypertension effect of Mg based on randomized controlled trials of Mg supplementation from the MEDLINE and EMBASE databased published up to February 1, 2016. We separately searched "magnesium" or "Mg" for magnesium, "hypertension" or "blood pressure" for blood pressure, "supplementation", "supplement", "intervention", "randomized controlled trial", "randomized clinical trial", "randomized trial", "controlled trial", or "clinical trial" for RCTs in article texts or Medical Subject Headings (MeSH) terms, and then combined these three search results using the Boolean logic operator "AND". All searches were limited to English language and human adults. Additionally, all bibliographies of related articles and current review articles were manually screened for additional potentially relevant articles.

Selection criteria

We included RCTs that assessed the response of BPs to Mg supplementation. To minimize

potential bias and confounding, we focused solely on randomized controlled trials of oral Mg supplementation. Exclusion criteria were as follows: 1). studies including pregnant or lactating women; 2). studies including patients with malignancy, severe infectious disease, active liver or renal disease, or other severe illnesses; 3). supplements combined with other minerals that affect BP and duration of Mg supplementation less than or equal to 1 week; and 4). nonrandom, open-label, or self-controlled trials. Trials with combined supplements were eligible only when the combined antihypertensive drugs or mineral were applied identically in control and treatment groups.

Study selection

Title and abstract screening was performed for each article to remove obviously irrelevant and duplicated reports. Articles deemed potentially eligible by title and abstract screening were re-examined by full-text review according to the above standard inclusion and exclusion criteria. The eligibility of articles was finally determined by two independent authors (X Zhang and Y Li). Any discrepancies were resolved through discussion.

Data extraction

Two researchers (X Zhang and A. Rosanoff) independently extracted available data and relevant information into a standard form, which included: general information on the publication (first author's last name and first initial, year of publication, and study location), participants (sex proportion, mean age or age range, number of participants, comorbidities, and combination therapy), study design (follow-up years, Mg formulation and dosage), as well as serum Mg and BP measures at baseline and after treatment. If repeated measures of Mg levels and BP at several time points were reported in a single trial, the last measures were selected for

overall analysis; they were both included in the subgroup analysis only if they were stratified into different separate subgroups. The accuracy of extracted data was double-checked by another researcher (Y Li).

Quality of trials

We applied the Agency for Healthcare Research and Quality criteria (AHRQ) for quality assessment of RCTs to evaluate the risk of bias in all identified trials [15, 16]. These criteria assessed adequate sequence generation for randomization, allocation concealment, blinding of outcomes assessors, similarity of groups at baseline, selective reporting, incomplete outcome data, and description of losses and exclusions by three different degrees for risk of bias (high, low, or unclear). We also assessed overall trial quality according to the five-point Jadad score of randomization, double-blinding, and withdrawals and dropouts. Points were awarded from 0 to 5. We sorted all trials into high-quality (> 3) and low-quality (≤ 3) groups, which were used for subgroup analysis stratified by trail quality.

Statistical methods

To evaluate the overall effects of Mg supplementation on BP, we compared the mean changes of systolic and diastolic BP between treatment and placebo groups after treatment by calculating weighted mean differences (WMDs) and 95% confidential intervals (CIs) using a random-effects meta-analysis model [17]. We also estimated WMDs for serum Mg concentrations to assess the effectiveness of Mg supplementation on Mg status. We assessed the between-study heterogeneity by calculating both τ statistic and I^2 statistics. The percentages of I^2 around 25% ($I^2 = 25$), 50% ($I^2 = 50$), and 75% ($I^2 = 75$) indicate low, medium, and high heterogeneity, respectively. Tau, τ, is the estimate of between-study standard deviation which indicates the

extent to which such heterogeneity affects the final meta-analysis results.

To explore major sources of heterogeneity and assess the robustness of the overall meta-analysis results, we conducted subgroup analyses stratified by predefined subgroups, including age (< 65 or ≥ 65 y), sex (trials with women ≥ 50% or men > 50%), study location (America, Asia, Europe, or Latin America), Mg formulation (organic: Mg lactate, Mg citrate, Mg pidolate, Mg asparate; or inorganic: MgO, $MgCl_2$, $Mg(OH)_2$), elemental Mg dosage in mg (< 300, 300-399, ≥ 400 mg/day) and duration (< 30, 30 - 89, ≥ 90 days) of trials, baseline Mg (quartiles categories of baseline serum Mg), prior BP status (hypertensive or normotensive), medication use history (taking antihypertensive or diabetic drugs or off medication), methods of BP measures (sphygmomanometer or automatic monitor), and crossover design (yes or no), were conducted. Furthermore, to assess whether trial quality contributed to between-study heterogeneity, we performed subgroup analyses stratified by quality assessment of RCTs, including overall trial quality (high vs. low), sample size (< 50 vs. ≥ 50), dropout rate (< 10% vs. ≥ 10%), and success of randomization. Success of randomization was assessed by examining the comparability of basal serum Mg and BPs between the randomly assigned Mg group and the placebo group in individual trials or according to the description of randomization in the individual article. Publication bias was evaluated first by visual inspection of the funnel plots and then by Begg's adjusted rank correlation test [18].

A restricted cubic spline regression analysis was performed to assess possible dose- and time-responses of BPs and serum Mg to Mg supplementation. For systolic or diastolic BPs or serum Mg, we calculated restricted cubic spline with three fixed knots at 10%, 50%, and 90% percentiles through the overall distributions based on all included studies for each eligible trial, separately, and then combined them to depict possible dose- and time-dependent relations of BPs

and serum Mg levels to Mg supplementation [19, 20].

Stata (Version 14; StataCorp, College Station, TX) software was used for all statistical analyses. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Our electronic and manual search identified a total of 615 potentially relevant publications. After excluding duplicative and irrelevant publications by screening titles and abstracts and reviewing the full-texts, 34 RCTs from 34 published articles met our inclusion criteria (**Figure S1**).

Characteristics of included trials and participants

We identified 34 eligible randomized double-blind placebo-controlled trials that included a total of 2,028 normotensive or hypertensive participants (range: 13 to 461), aged between 18 and 84 years, with 1,010 participants receiving Mg supplementation and 1,018 placebo (**Table 1**). Among them, 27 studies also measured serum Mg.

Eleven trials used a crossover study design, and others were parallel designed; 55% (908) of the study population were women, and 45% (751) were men. The studies were conducted in America (4 trials), Asia (3 trials), Europe (17 trials), Latin America (9 trials). Most of the participants were either clearly hypertensive or normotensive (16 and 18 trials, respectively), and only one trial included participants with borderline hypertension [21]. Most of the trials required that hypertensive patients go off medications ≥ 1 month (22 of 34 trials); and patients in four trials were still taking medications during the trials [22-25]. Additionally, two trials included participants with low serum Mg (< 0.74 mmol/L) [25, 26]. BPs were generally measured by sphygmomanometer (14 trials) or automatic monitor (9 trials) and only two trials applied

ambulatory monitor recording of 24-h BPs [27, 28].

The trial durations varied from 3 weeks to 6 months, though the vast majority (30 of 33 trials) were longer than 1 month. Mg supplements differed between studies in formulation and dosage. A total of seven types of organic (15 trials) and inorganic Mg (18 trials) supplements were used: MgO, $Mg(OH)_2$, $MgCl_2$, Mg aspartate, Mg lactate, Mg citrate, and Mg pidolate. The daily dosage of Mg supplements in elemental Mg ranged from 240 to 960 mg, most of which (28 trials, 82%) were equal or higher than the levels of U.S. Recommended Dietary Allowance for adults (310 - 320 mg/day for women, and 400 - 420 mg/day for men [29]). The characteristics of all identified trials are presented in **Table S1**.

Effects on lowering BPs and elevating serum Mg

Compared with the placebo groups of 34 trials, Mg supplementation at a median dose of 368 mg/day (range: 238 - 960 mg/day) for a median duration of 3 months (range: 3 weeks - 6 months) led to overall reductions in systolic BP (WMD = 2.00 mmHg; 95% CI: 0.43, 3.58; P = 0.01 and τ = 3.1, I^2 = 61.8) (**Figure 1**) and diastolic BP (1.78 mmHg; 95% CI: 0.73, 2.82; P = 0.001 and τ = 2.2, I^2 = 63.8) (**Figure 2**), while concomitantly elevating serum Mg levels by 0.05 mmol/L (95% CI: 0.03, 0.07; $P < 0.001$ and τ = 0.03, I^2 = 86.2) among 27 trials (**Figure S2**). Begger's tests did not reveal substantial publication bias for the overall effects of Mg on systolic BP, diastolic BP, or serum Mg ($P_{\text{Begger's}} > 0.05$).

Sources of between-study heterogeneity by subgroup analyses

As shown in **Table 1**, non-significant differences in Mg effects on BPs were found by subgroup analyses stratified by age, sex, study location, hypertensive status, baseline Mg status, antihypertensive or diabetic medication use history, method, times and position for BP measures,

study design, Mg formulation, dosage, and trial duration (all *P*-values for interaction > 0.05). Systolic and diastolic BPs were significantly decreased by 5.69 mmHg (95% CI: 1.00, 10.37; τ = 4.5, I^2 = 54.3) and 2.55 mmHg (95% CI: 0.19, 4.92; τ = 1.9, I^2 = 37.0), respectively, among participants taking anti-hypertensive or antidiabetic drugs (*n* = 7 trials), while reduction in BPs was non-significant among participants off antihypertensive or antidiabetic medications (systolic BP: -0.13 mmHg; 95% CI: -4.25, 4.00; τ = 5.6, I^2 = 73.1; and diastolic BP: 1.52 mmHg; 95% CI: -1.09, 4.12; τ = 3.7, I^2 = 80.5; *n* = 11 trials). However, *P*-value for interaction was > 0.05. The overall effects of Mg on serum Mg varied depending on the study location, Mg formulation, and baseline Mg status (all *P*-values for interaction ≤ 0.01).

Additionally, in the sensitivity analysis, inclusion or exclusion of any individual trial did not substantially change the overall results for BPs and serum Mg.

Dose- and time-responses of BPs to Mg supplementation

Our dose- and time-response analyses of data from 27 trials showed that oral Mg supplementations at a dose of 200 mg/day or with a duration of one month was sufficient to significantly raise serum Mg (all *P*-values < 0.001). Higher doses (≥ 300 mg/day) or longer durations (≥ 2 months) were required to achieve maximal levels of serum Mg by supplementation (**Figure 3 A and Figure 4 A**). Consistently, there was a significant reduction in systolic BP accompanying rises in serum Mg levels in a similar non-linear time- and dose-dependent manner (both *P*-linearity = 0.07; *n* = 34 trials) (**Figure 3 B and Figure 4 B**) while dose- and time-dependent reduction in diastolic BP seemed to be linear (all *P*- linearity = 0.02) (**Figure 3 C and Figure 4 C**). Furthermore, a positive relation between serum Mg elevation and the degree of diastolic BP lowering was found, neither the linear nor curvilinear dose- and time-dependent relationship was significant for systolic BP. On average, each 0.1 mmol/L increment in serum Mg was associated with a reduction of 2.26 mmHg (95% CI: 0.27, 4.26; *n* = 20 trials) in diastolic

BP (**Figure 5**).

Quality assessment of included trials

Trial quality may have an impact on the overall results of diastolic and diastolic BP (**Table 1**). However, the process of randomization was insufficiently described in identified studies, i.e., only 30% seemed to have adequate sequence generation and 15% had low risk of bias in allocation concealment (**Figure S3**). Of 24 high quality trials, both systolic and diastolic BP were significantly decreased by Mg treatment (systolic BP: -3.37 mmHg; 95% CI: -5.34, -1.40 and diastolic BP: -2.50 mmHg; 95% CI: -3.65, -1.36). In contrast, changes in systolic and diastolic BP were nonsignificant in the data from the ten low quality trials (systolic BP: 0.83 mmHg; 95% CI: -0.89, 2.56 and diastolic BP: 0.35 mmHg; 95% CI: -1.45, 2.15). The interactions were statistically significant between trials with high quality and trials with low quality for both systolic and diastolic BP (*P*-values for interaction < 0.05). Also, greater reductions in BPs tended to be observed among trials with low dropout rate (≥ 10% vs. < 10%; *P* for interaction < 0.05 for both systolic and diastolic BP).

Discussion

In this meta-analysis of 34 randomized double-blind placebo-controlled trials involving a total of 2,028 participants, we found that oral Mg supplementation led to a significant reduction in both systolic and diastolic BPs (2.00 and 1.78 mmHg, respectively), while systolic BP and diastolic BP responses differed slightly in dose- and duration-dependent manners, respectively. The BP-lowering effects of Mg supplementation were accompanied by elevated serum Mg levels. Greater reduction in both systolic and diastolic BP also tended to be present in trials with high quality, or low dropout rate. Taken together, our findings support a causal antihypertensive

effect of Mg supplementation in adults.

The mechanism of the anti-hypertension effects of Mg has been confirmed by laboratory studies. Mg plays a role in the pathogenesis of hypertension mainly through alerting vascular smooth muscle cell function and the peripheral vascular resistance. As a cofactor of enzymes in signal transduction pathways involved in vascular contraction, Mg is able to inhibit the vasoconstriction induced by cytosolic accumulation of calcium concentrations [30]. And high levels of extracellular Mg were correlated with the improvements in hemodynamic status, such as blood flow, vascular resistance and capacitance function of vessels, which contributes to the pathoetiology of hypertension [31-34]. Additionally, Mg has shown its antioxidant benefits in prevention of hypertension through attenuating the damage of vasculature from oxidative stress and preventing vascular injury [5, 6].

Although accumulating evidence from such studies has indicated that low dietary or circulating Mg may be related to the development of hypertension due to its calcium antagonist and endothelial effects [35], epidemiologic evidence for a relationship between Mg intake and hypertension has been controversial. Several observational studies have suggested an inverse association between Mg intake and BP [10, 36-39], although, evidence from observational studies is indirect because of potential selection bias, residual confounding, measurement errors of Mg intake, and statistical uncertainty due to highly correlated dietary or lifestyle factors. Many small and short-term randomized trials have been conducted to directly test the effect of Mg supplementation in normotensive and hypertensive participants, but those results were inconsistent and inconclusive. Nonsignificant associations between dietary Mg and systolic or diastolic BP were found based on a meta-analysis of 16 randomized controlled trials [40]. In contrast, Jee et al. showed a small overall dose-dependent BP reduction with Mg

supplementation from a meta-analysis involving 20 small randomized trials (13 to 461 participants per trial) of short duration (3 to 24 weeks per trial) [12]. A recent meta-analysis of 22 trials, including 1,220 normotensive or hypertensive patients, reported a mean reduction of 2-3 mmHg in systolic BP and of 3-4 mmHg in diastolic BP [14]. The results were consistent with our findings of 2.00/1.78 mmHg reduction in systolic/diastolic BP from 34 randomized, double-blind, placebo-controlled trials. Our data indicated that provision of Mg may slightly lower BP and might be effective in preventing hypertension in the general population.

Furthermore, our pooled results from 16 trials among hypertensive patients showed a 2.11 mmHg (95% CI: 4.17, 0.05) decrease in diastolic BP, but a non-significant decrease in systolic BP (-2.16 mmHg, 95% CI: -5.71, 1.40). A significant reduction in diastolic BP but not in systolic BP was consistently identified by a Cochrane review of 12 RCTs among hypertensive patients [13]. In our study, data from seven trials among 136 "treated" patients (those taking anti-hypertensive or diabetic drugs), suggest that both systolic (5.69 mmHg) and diastolic (2.55 mmHg) BP were significantly reduced. This discrepancy between "treated" and "untreated" patients might be partially caused by possibly lower baseline Mg status among treated patients, since loop and thiazide diuretics, mainly used among hypertensive and diabetic patients, may deplete potassium and Mg [41]. On average, serum Mg was 0.74 mmol/L for "treated" patients, slightly lower than the current lower limits of the clinical normal range for serum Mg, 0.75-0.96 mmol/L [42]. Moreover, our subgroup analysis indicated that the anti-hypertensive effect of Mg was significant only among the subgroup with Mg deficiency. Current evidence has also suggested that the anti-hypertensive effect of Mg might be valid only among patients with Mg deficiency or insufficiency [43]. However, this conclusion needs to be confirmed by further specific research.

Our dose-response analysis of 34 trials provided sufficient power to depict the dose-response

analysis for both BPs and serum Mg. Due to relative low power and limited information [13], a previous meta-regression analysis of 14 double-blind randomized trials showed that a 240 mg/day increase in Mg intake was associated with a nonsignificant decrease in systolic BP and diastolic BP among hypertensive patients [12]. In addition, a relative large numbers of identified RCTs let it possible to explore the possible dose- and time-responses of BPs to Mg supplementation. And we found curvilinear dose- and time-dependent relationships for Mg supplementation and BPs and serum Mg levels. Furthermore, we quantified the associations between changes in serum Mg and BPs based on data from 27 of the 34 trials reported changes in serum Mg levels in our meta-analysis; we found that a 0.1 mmol/L increment in serum Mg was associated with a 2.26 mmHg reduction in diastolic BP. However, the association of changes in serum Mg with systolic BP was non-significant. Meanwhile, the significant relations between elevated serum Mg and BP-lowering effects indirectly supported the causal hypothesis of antihypertensive effect of Mg.

Of note, there was considerable heterogeneity across the Mg studies in terms of trial quality, sample sizes, and participant characteristics, any of which could influence the accuracy of the pooled estimates. Although previous meta-analyses noted that heterogeneities might be induced by sex [13], study location, and types of study design [14], we found no evidence of modification from these factors on the effects of Mg supplementation on BPs. Non-significant heterogeneities were also found for age, Mg supplements, and methods of BP measurements. The results from high-quality trials (Jadad > 3) or trials with low dropout rates (< 10%) were more likely to show a significant reduction in both systolic and diastolic BP after Mg supplementation than trials with low quality scores and high dropout rates. These findings provide strong support for the robustness of our results, indicating the BP-lowering effects of Mg.

A major strength of this meta-analysis is the inclusion of only randomized double-blind placebo-controlled trials. With 34 trials, we achieved sufficient power to capture overall effects and assess the dose- and time-dependent relationships between BPs and Mg supplementation. Major sources of heterogeneity were explored by including 15 factors, including age, sex, study location, Mg formulation, dosage, trial duration, baseline Mg and BP status, antihypertensive or diabetic medication use history, methods, time, and position of BP measurements, and crossover design.

However, several limitations merit consideration. First, most trials included were small with relatively high dropout rates. Second, we used serum Mg to reflect Mg status, though it may not be an optimally sensitive biomarker of Mg status in the human body [44], because only 0.3% of total body Mg is present in serum and serum Mg levels are normally maintained within a very narrow range. Therefore, the measurement of serum total Mg may not accurately reflect Mg bioavailability. Third, the benefits of Mg supplementation may be most dramatic in individuals with insufficient Mg status and might have enhanced effects by antihypertensive or antidiabetic drugs. However, we have insufficient data to test this hypothesis. Also, detailed information on diet and lifestyles of subjects is unavailable. Fourth, significant heterogeneity was present among RCTs; despite this, results were generally consistent across trials. Furthermore, our subgroup and sensitivity analysis results suggested that overall treatment effects did not differ appreciably by most specified factors. Fifth, nearly all identified trials measured BP by sphygmomanometer or automatic monitor; there are spare studies using 24-h ambulatory BP monitoring. Sixth, lack of detailed information cannot allow us to disentangle acute versus chronic effects by taking Mg supplements. Seventh, the observational nature of our subgroup analysis and spline regression analysis require cautious interpretation of their results. Also, our subgroup analyses stratified by

study-level covariates, such as gender proportions and mean or median of ages, may be prone to aggregation bias or ecological bias because study-level covariates with limited variability may not precisely represent those at the individual or patient levels. We cannot completely rule out the possibility of a nonrandom impact of heterogeneity on the summary estimates, which cannot be easily handled by traditional statistical approaches. And residual heterogeneity may still exist after considering these possible factors. Finally, as in any meta-analysis, publication bias is possible.

Perspectives

The meta-analysis, based on evidence from 34 randomized double-blind placebo-controlled trials, showed a significant antihypertensive effect of Mg supplementation on both systolic and diastolic BP among normotensive or hypertensive adults. The significant BP reduction by Mg supplementation was accompanied by elevated levels of serum Mg, and also tended to be evident in trials with high quality or low dropout rate, indicating a causal BP-lowering effect of Mg supplementation. Our findings suggested that oral Mg supplements can be recommended for the prevention of hypertension or as adjuvant antihypertensive therapy, although future rigorously designed RCTs with BP assessment as primary outcomes are warranted to yield confirmatory evidence.

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Disclosures

The authors declare no conflict of interest.

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Novelty and significance

1. **What is new?**

- This study is much larger with 34 randomized double-blind placebo-controlled trials than previous meta-analyses. Therefore, we were able to achieve sufficient power to detect an overall modest effect and reliably assess the dose- and time-dependent relationships between Mg supplementation and BP changes.
- Major sources of heterogeneity were explored thoroughly by subgroup analyses stratified by 15 potential factors, which may potentially modulate the BP-lowering effects by Mg supplementation.
- Overall trial quality was qualitatively evaluated by AHRQ criteria and quantitatively assessed by the Jadad score. Also, we further performed subgroup analyses stratified by trial quality, trial sample size, randomization status, and dropout rate to evaluate the robustness of our results.
- Considering both intervention compliance and effectiveness, we evaluated changes in serum Mg levels produced by Mg supplementation and found a close association with concomitant BP reductions, indicating a causal effect.

2. **What is relevant?**

- The findings support that Mg supplementation provides a moderate lowing-BP effect among normotensive or hypertensive adults.
- The study indicates that future large and rigorously designed randomized controlled

trials among participants at risks for Mg insufficiency and hypertension will be required to reliably confirm the antihypertensive effects of Mg supplementation before it can be recommended for the prevention and treatment of hypertension.

3. Summary

- This meta-analysis, based on reliable data from 34 rigorously randomized double-blind placebo-controlled trials, provided robust evidence to support a causal effect of Mg supplementation on lowering BPs in adults.

Figures Legends

Figure 1. Forest plot of WMDs (95% CI) for systolic BP (mmHg) responses to Mg supplementation compared with placebo groups among 34 RCTs.

Figure 2. Forest plot of WMDs (95% CI) for diastolic BP (mmHg) responses to Mg supplementation compared with placebo groups among 34 RCTs.

Figure 3. Serum Mg (**A**), systolic (**B**) and diastolic BP (**C**) changes in response to Mg with different doses (elemental Mg, mg/day). The non-linear relation was fitted using a restricted cubic spline regression curve among 34 RCTs.

Figure 4. Serum Mg (**A**), systolic (**B**) and diastolic BP (**C**) changes in response to Mg with different duration (day). The non-linear relation was fitted using a restricted cubic spline regression curve among 34 RCTs.

Figure 5. Systolic (**A**) and diastolic BP (**B**) changes versus serum Mg changes (mmol/L) after Mg supplementation among 20 RCTs.

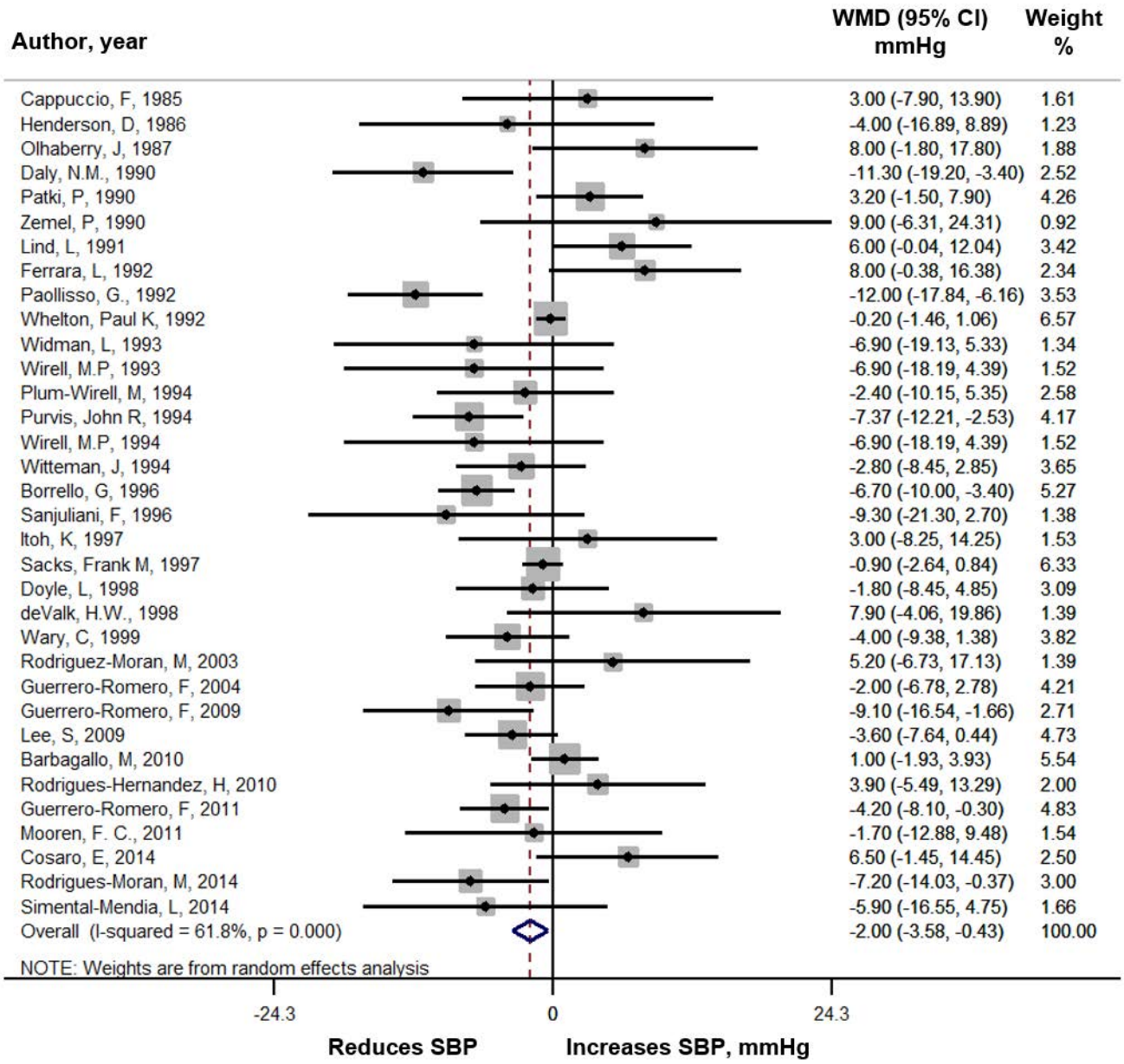

Author, year
WMD (95% CI) mmHg
Weight %
Cappuccio, F, 1985 3.00 (-7.90, 13.90) 1.61
Henderson, D, 1986 -4.00 (-16.89, 8.89) 1.23
Olhaberry, J, 1987 8.00 (-1.80, 17.80) 1.88
Daly, N.M., 1990 -11.30 (-19.20, -3.40) 2.52
Patki, P, 1990 3.20 (-1.50, 7.90) 4.26
Zemel, P, 1990 9.00 (-6.31, 24.31) 0.92
Lind, L, 1991 6.00 (-0.04, 12.04) 3.42
Ferrara, L, 1992 8.00 (-0.38, 16.38) 2.34
Paollisso, G., 1992 -12.00 (-17.84, -6.16) 3.53
Whelton, Paul K, 1992 -0.20 (-1.46, 1.06) 6.57
Widman, L, 1993 -6.90 (-19.13, 5.33) 1.34
Wirell, M.P, 1993 -6.90 (-18.19, 4.39) 1.52
Plum-Wirell, M, 1994 -2.40 (-10.15, 5.35) 2.58
Purvis, John R, 1994 -7.37 (-12.21, -2.53) 4.17
Wirell, M.P, 1994 -6.90 (-18.19, 4.39) 1.52
Witteman, J, 1994 -2.80 (-8.45, 2.85) 3.65
Borrello, G, 1996 -6.70 (-10.00, -3.40) 5.27
Sanjuliani, F, 1996 -9.30 (-21.30, 2.70) 1.38
Itoh, K, 1997 3.00 (-8.25, 14.25) 1.53
Sacks, Frank M, 1997 -0.90 (-2.64, 0.84) 6.33
Doyle, L, 1998 -1.80 (-8.45, 4.85) 3.09
deValk, H.W., 1998 7.90 (-4.06, 19.86) 1.39
Wary, C, 1999 -4.00 (-9.38, 1.38) 3.82
Rodriguez-Moran, M, 2003 5.20 (-6.73, 17.13) 1.39
Guerrero-Romero, F, 2004 -2.00 (-6.78, 2.78) 4.21
Guerrero-Romero, F, 2009 -9.10 (-16.54, -1.66) 2.71
Lee, S, 2009 -3.60 (-7.64, 0.44) 4.73
Barbagallo, M, 2010 1.00 (-1.93, 3.93) 5.54
Rodrigues-Hernandez, H, 2010 3.90 (-5.49, 13.29) 2.00
Guerrero-Romero, F, 2011 -4.20 (-8.10, -0.30) 4.83
Mooren, F. C., 2011 -1.70 (-12.88, 9.48) 1.54
Cosaro, E, 2014 6.50 (-1.45, 14.45) 2.50
Rodrigues-Moran, M, 2014 -7.20 (-14.03, -0.37) 3.00
Simental-Mendia, L, 2014 -5.90 (-16.55, 4.75) 1.66
Overall (I-squared = 61.8%, p = 0.000) -2.00 (-3.58, -0.43) 100.00
NOTE: Weights are from random effects analysis
-24.3
0
24.3
Reduces SBP
Increases SBP, mmHg

Figure 1

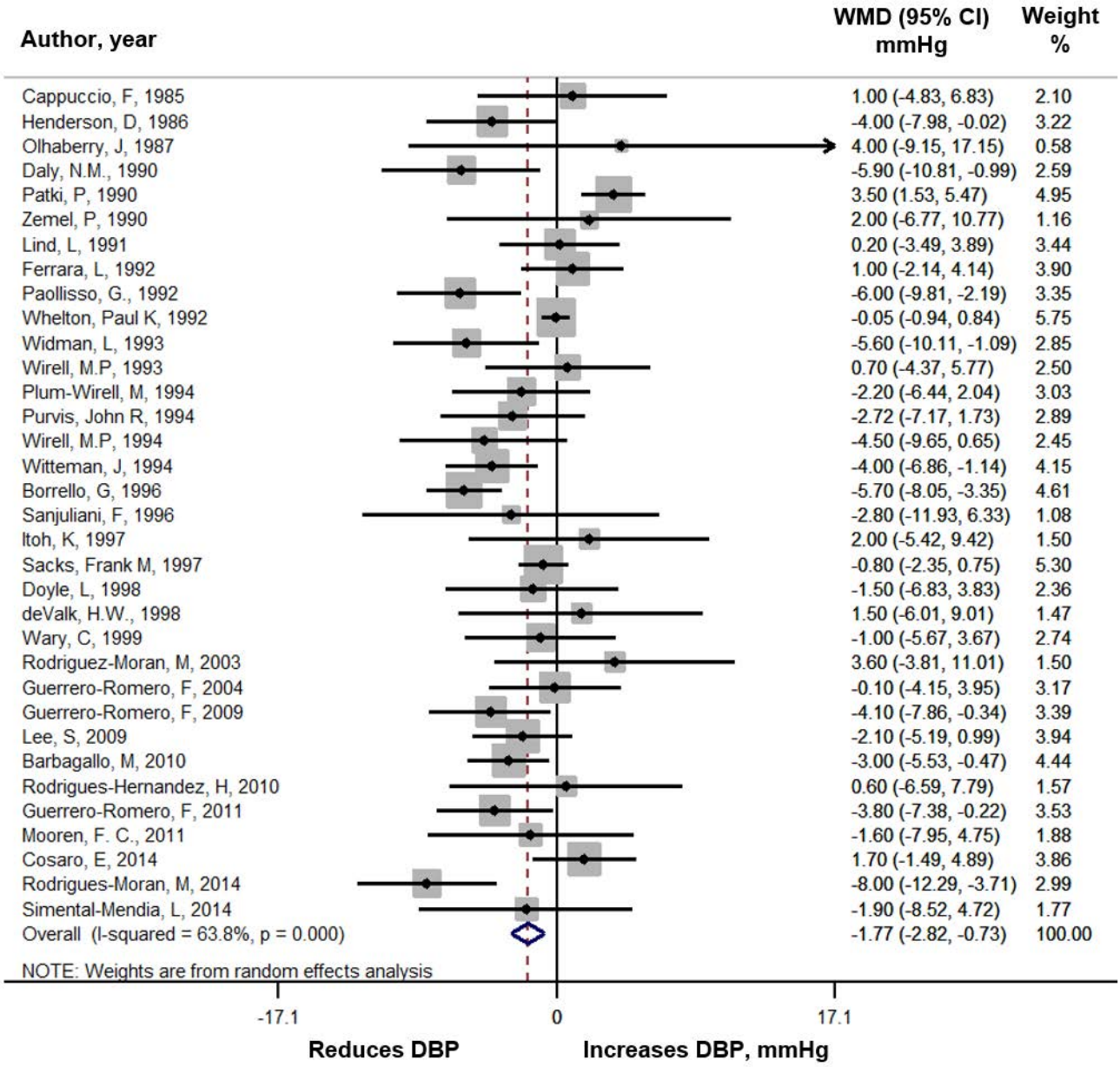
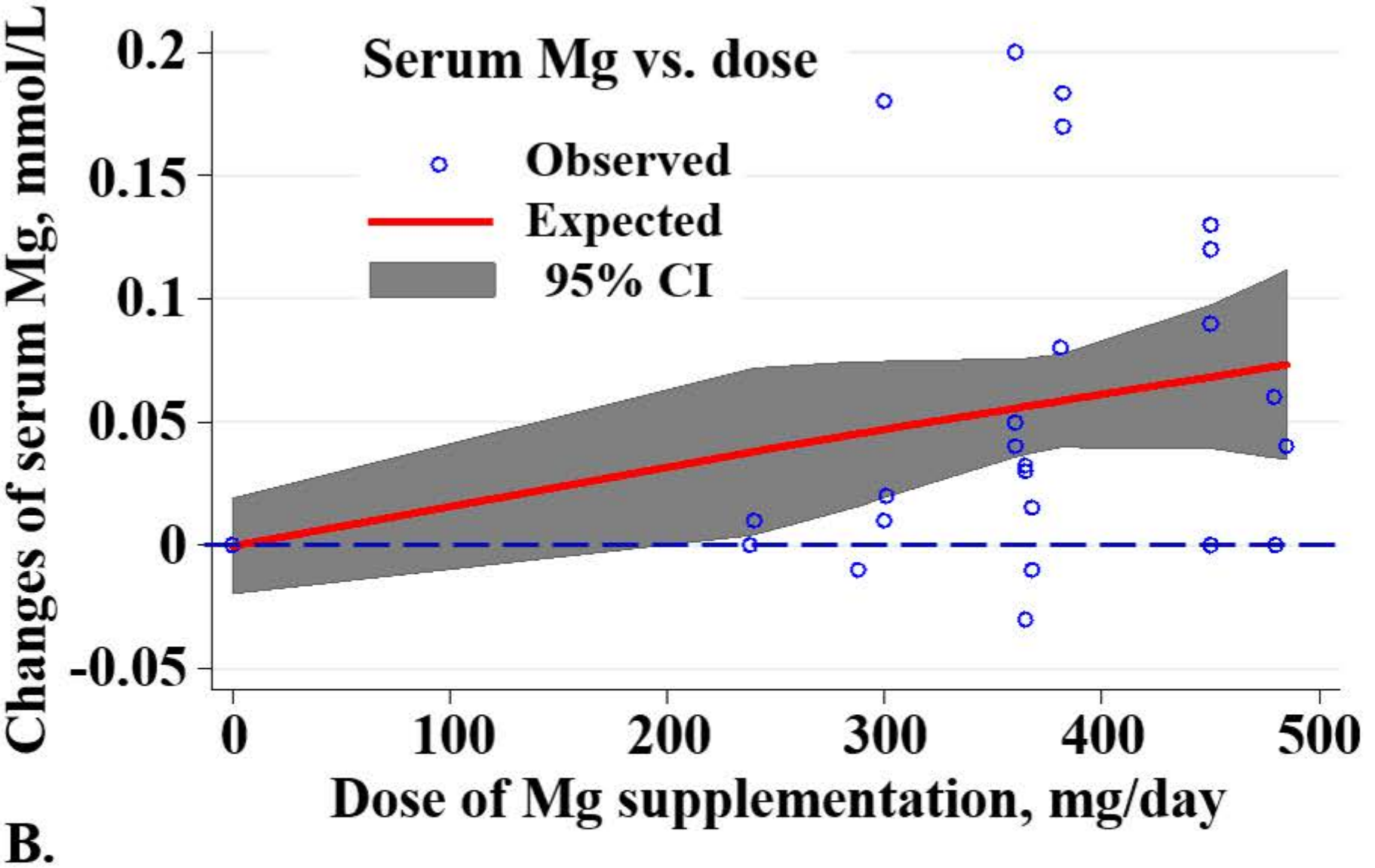
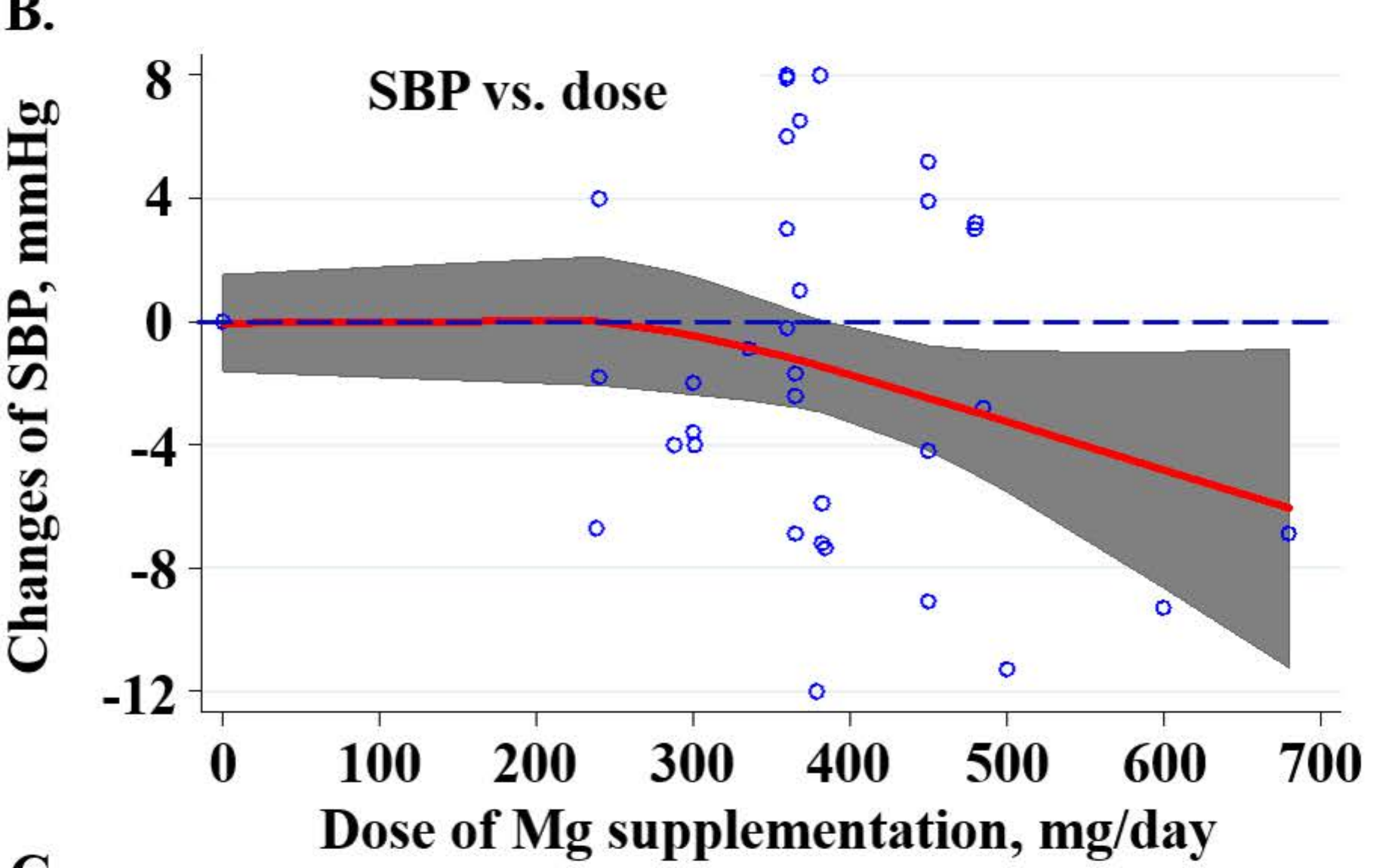

Author, year
WMD (95% CI) mmHg
Weight %
Cappuccio, F, 1985 1.00 (-4.83, 6.83) 2.10
Henderson, D, 1986 -4.00 (-7.98, -0.02) 3.22
Olhaberry, J, 1987 4.00 (-9.15, 17.15) 0.58
Daly, N.M., 1990 -5.90 (-10.81, -0.99) 2.59
Patki, P, 1990 3.50 (1.53, 5.47) 4.95
Zemel, P, 1990 2.00 (-6.77, 10.77) 1.16
Lind, L, 1991 0.20 (-3.49, 3.89) 3.44
Ferrara, L, 1992 1.00 (-2.14, 4.14) 3.90
Paollisso, G., 1992 -6.00 (-9.81, -2.19) 3.35
Whelton, Paul K, 1992 -0.05 (-0.94, 0.84) 5.75
Widman, L, 1993 -5.60 (-10.11, -1.09) 2.85
Wirell, M.P, 1993 0.70 (-4.37, 5.77) 2.50
Plum-Wirell, M, 1994 -2.20 (-6.44, 2.04) 3.03
Purvis, John R, 1994 -2.72 (-7.17, 1.73) 2.89
Wirell, M.P, 1994 -4.50 (-9.65, 0.65) 2.45
Witteman, J, 1994 -4.00 (-6.86, -1.14) 4.15
Borrello, G, 1996 -5.70 (-8.05, -3.35) 4.61
Sanjuliani, F, 1996 -2.80 (-11.93, 6.33) 1.08
Itoh, K, 1997 2.00 (-5.42, 9.42) 1.50
Sacks, Frank M, 1997 -0.80 (-2.35, 0.75) 5.30
Doyle, L, 1998 -1.50 (-6.83, 3.83) 2.36
deValk, H.W., 1998 1.50 (-6.01, 9.01) 1.47
Wary, C, 1999 -1.00 (-5.67, 3.67) 2.74
Rodriguez-Moran, M, 2003 3.60 (-3.81, 11.01) 1.50
Guerrero-Romero, F, 2004 -0.10 (-4.15, 3.95) 3.17
Guerrero-Romero, F, 2009 -4.10 (-7.86, -0.34) 3.39
Lee, S, 2009 -2.10 (-5.19, 0.99) 3.94
Barbagallo, M, 2010 -3.00 (-5.53, -0.47) 4.44
Rodrigues-Hernandez, H, 2010 0.60 (-6.59, 7.79) 1.57
Guerrero-Romero, F, 2011 -3.80 (-7.38, -0.22) 3.53
Mooren, F. C., 2011 -1.60 (-7.95, 4.75) 1.88
Cosaro, E, 2014 1.70 (-1.49, 4.89) 3.86
Rodrigues-Moran, M, 2014 -8.00 (-12.29, -3.71) 2.99
Simental-Mendia, L, 2014 -1.90 (-8.52, 4.72) 1.77
Overall (I-squared = 63.8%, p = 0.000) -1.77 (-2.82, -0.73) 100.00
NOTE: Weights are from random effects analysis
-17.1
0
17.1
Reduces DBP
Increases DBP, mmHg

Figure 2

A.


Serum Mg vs. dose
Observed
Expected
95% CI
Changes of serum Mg, mmol/L
0.2
0.15
0.1
0.05
0
-0.05
0
100
200
300
400
500
Dose of Mg supplementation, mg/day

B.


SBP vs. dose
Changes of SBP, mmHg
8
4
0
-4
-8
-12
0
100
200
300
400
500
600
700
Dose of Mg supplementation, mg/day

C.

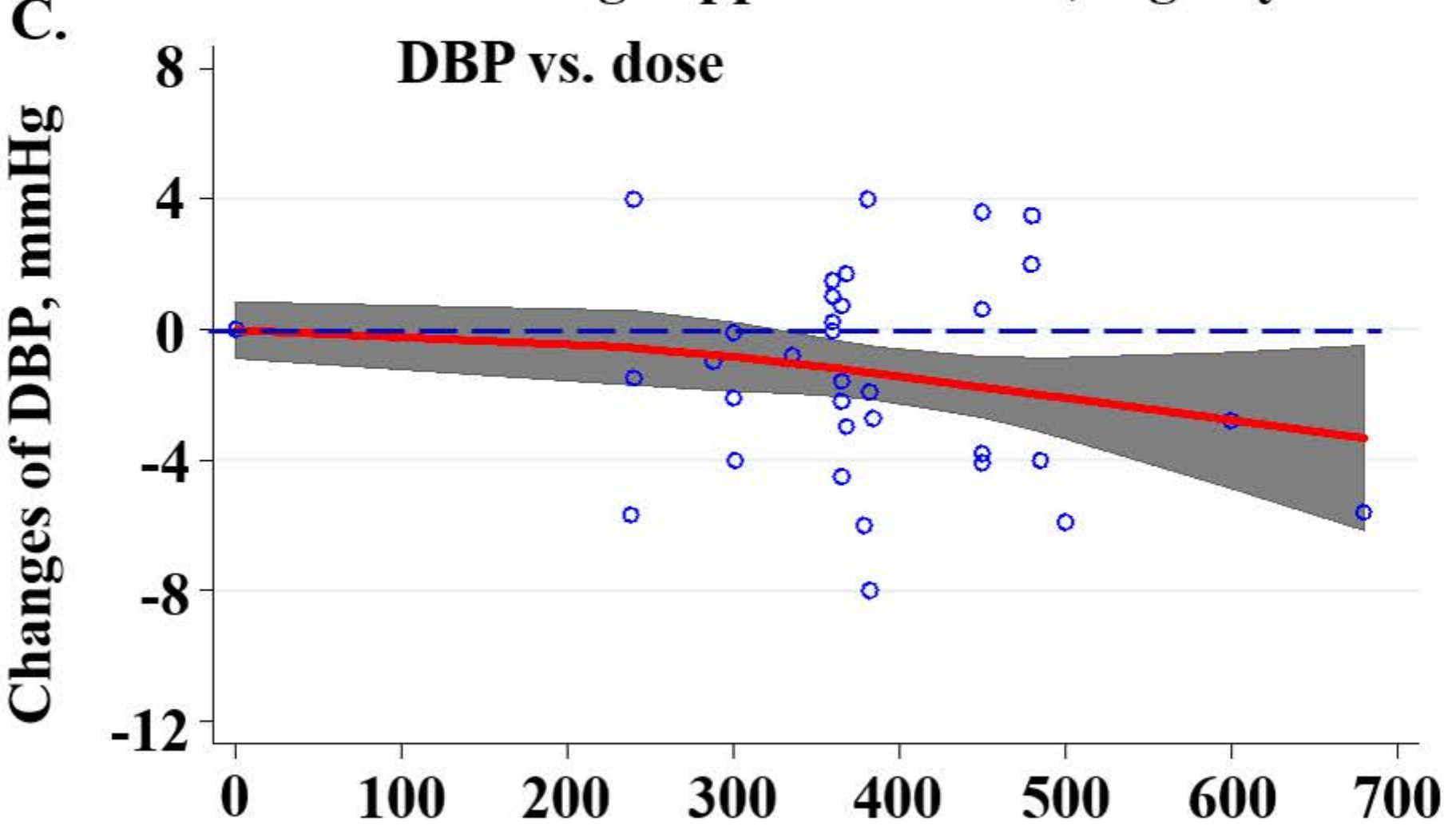
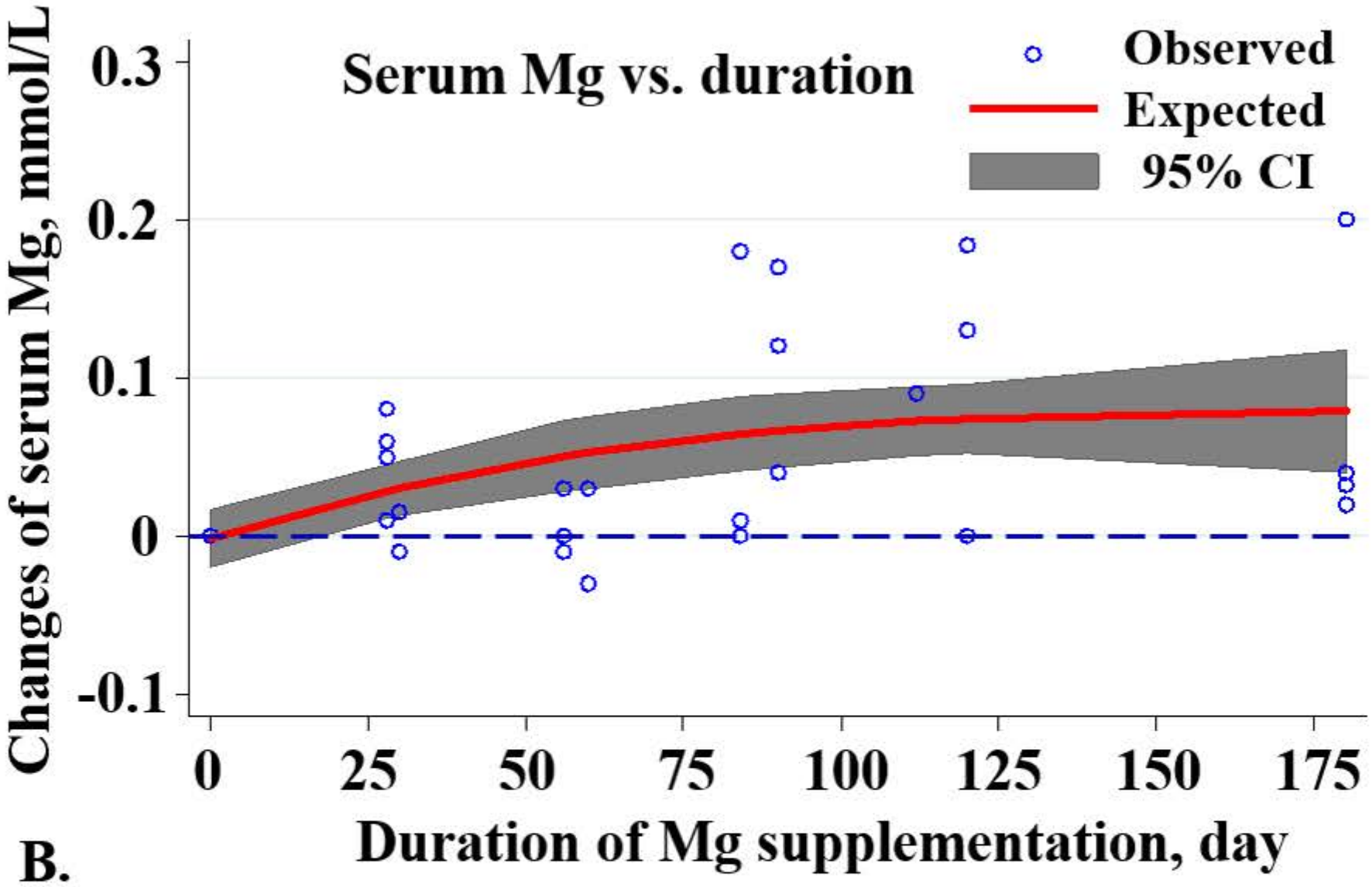
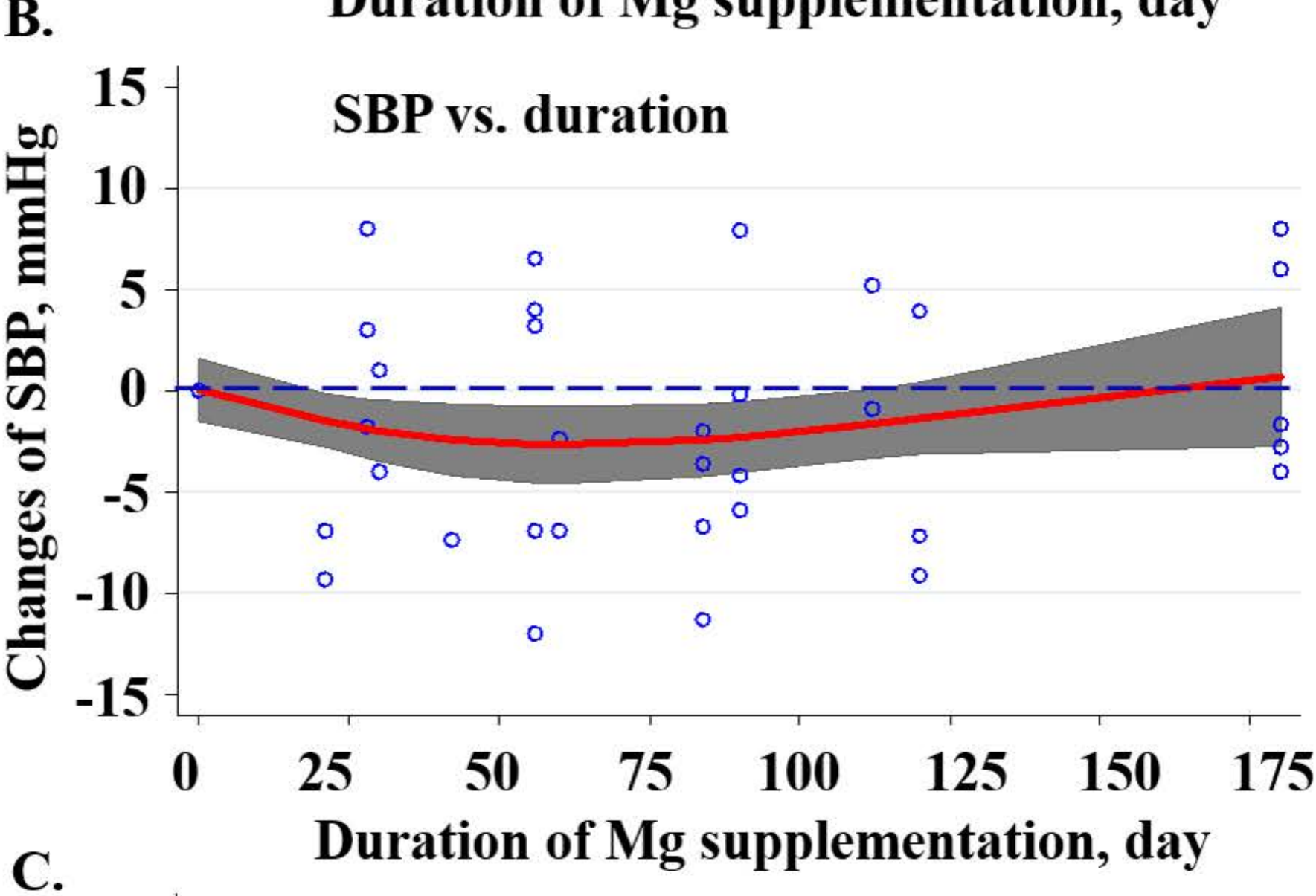

DBP vs. dose
Changes of DBP, mmHg
8
4
0
-4
-8
-12
0
100
200
300
400
500
600
700
Dose of Mg supplementation, mg/day

Figure 3

A.


Serum Mg vs. duration
Observed
Expected
95% CI
Changes of serum Mg, mmol/L
0.3
0.2
0.1
0
-0.1
0
25
50
75
100
125
150
175
Duration of Mg supplementation, day

B.


SBP vs. duration
Changes of SBP, mmHg
15
10
5
0
-5
-10
-15
0
25
50
75
100
125
150
175
Duration of Mg supplementation, day

C.

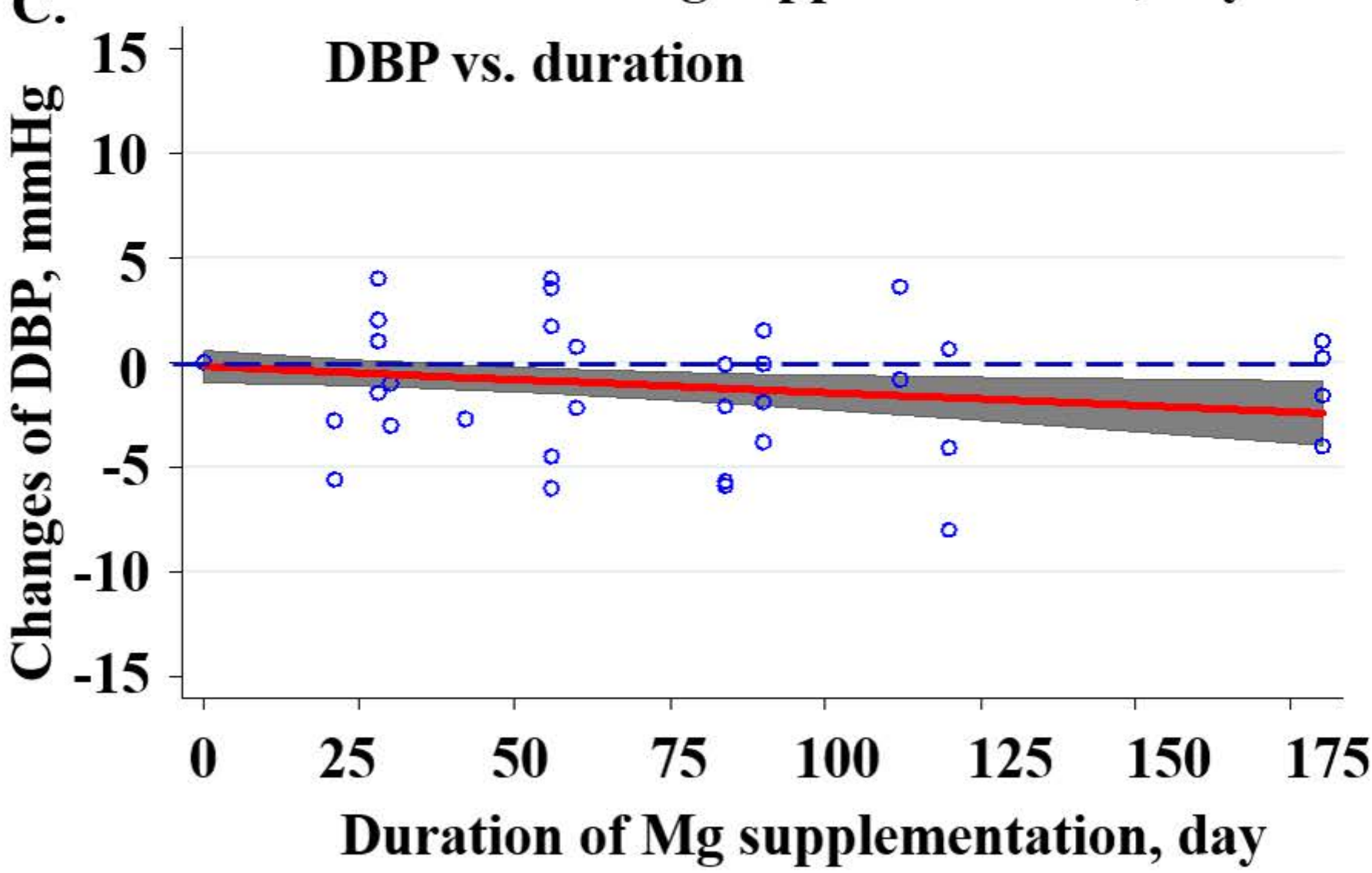

DBP vs. duration
Changes of DBP, mmHg
15
10
5
0
-5
-10
-15
0
25
50
75
100
125
150
175
Duration of Mg supplementation, day

Figure 4

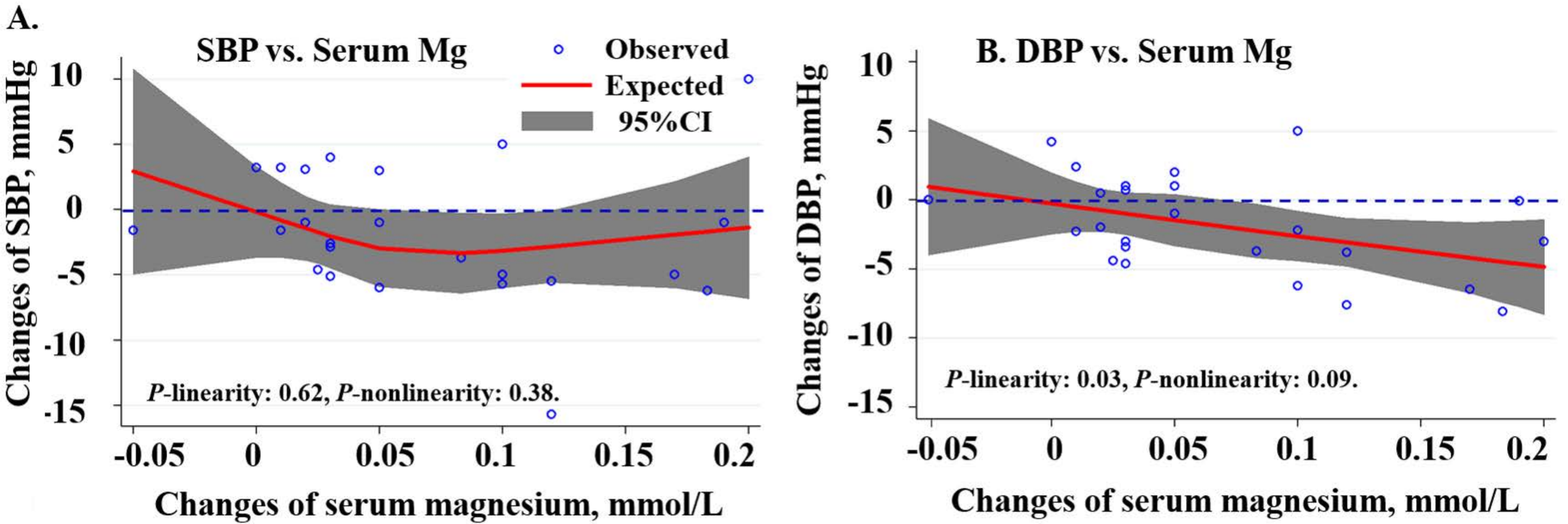

A.
SBP vs. Serum Mg
Observed
Expected
95%CI
Changes of SBP, mmHg
10
5
0
-5
-10
-15
P-linearity: 0.62, P-nonlinearity: 0.38.
-0.05
0
0.05
0.1
0.15
0.2
Changes of serum magnesium, mmol/L
B. DBP vs. Serum Mg
Changes of DBP, mmHg
10
5
0
-5
-10
-15
P-linearity: 0.03, P-nonlinearity: 0.09.
-0.05
0
0.05
0.1
0.15
0.2
Changes of serum magnesium, mmol/L

Figure 5

Table 1. Stratified meta-analysis of Mg supplementation on serum Mg, SBP, and DBP from RCT data

Subgroups	Serum Mg, mmol/L				SBP, mmHg				DBP, mmHg		
	No. of studies *	WMD (95% CI)	τ^2, %	*P* **	No. of studies *	WMD (95% CI)	τ^2, %	*P* **	WMD (95% CI)	τ^2, %	*P* **
Total	27 (822/800)	0.05 (0.03, 0.07)	0.001		34 (1010/1018)	-2.00 (-3.58, -0.43)	9.4		-1.78 (-2.82, -0.73)	4.8	
Demographic											
Age, yrs				0.92				0.52			0.15
< 65	15 (490/495)	0.05 (0.02, 0.08)	0.0003		18 (612/674)	-1.55 (-3.42, 0.33)	6.9		-1.17 (-2.61, 0.27)	5.6	
≥ 65	12 (332/305)	0.05 (0.03, 0.07)	0.0008		16 (398/343)	-2.61 (-5.62, 0.40)	19.8		-2.97 (-4.05, -1.88)	0.0	
Sex				0.15				0.86			0.88
Women (≥ 50%)	16 (404/374)	0.07 (0.04, 0.09)	0.003		21 (521/518)	-2.10 (-4.35, 0.14)	9.4		-1.95 (-3.49, 0.41)	8.1	
Men (> 50%)	11 (418/426)	0.03 (0.006, 0.05)	0.0009		13 (489/499)	-2.01 (-4.35, 0.14)	13.2		-1.84 (-3.44, -0.24)	2.5	
Study location				0.004				0.52			0.10
America	2 (180/184)	0.02 (-0.01, 0.06)	0.0005		4 (275/336)	-1.45 (-3.93, 1.03)	3.4		-0.29 (-1.05, 0.47)	0.0	
Asia	3 (117/108)	0.02 (-0.01, 0.05)	0.0004		3 (117/108)	0.19 (-5.10, 5.49)	12.4		1.09 (-3.21, 5.40)	10.3	
Europe	13 (282/270)	0.02 (-0.002, 0.04)	0.0007		17 (360/322)	-2.28 (-5.21, 0.66)	22.3		-2.54 (-4.87, -0.20)	4.0	
Latin America	8 (235/229)	0.12 (0.08, 0.16)	0.003		9 (243/236)	-2.89 (-6.30, 0.51)	11.0		-2.52 (-3.89, -1.14)	4.5	
Mg supplementation											
Formulation				0.01				0.12			0.31
Inorganic	14 (428/411)	0.08 (0.04, 0.12)	0.005		18 (456/440)	-3.52 (-5.75, -1.29)	9.9		-2.39 (-4.34, -0.43)	11.2	
Organic	12 (221/211)	0.02 (0.004, 0.04)	0.0005		15 (327/344)	-0.38 (-3.00, 2.23)	12.4		-1.32 (-2.54, -0.11)	1.8	
Dosage, mg/day				0.46				0.72			0.62
< 300	3 (64/62)	-0.004 (-0.04, 0.035)	0.0		3 (64/62)	-5.33 (-7.92, -2.74)	0.0		-3.34 (-6.74, 0.05)	4.9	
300-399	16 (520/520)	0.06 (0.03, 0.08)	0.002		20 (680/709)	-1.31 (-3.23, 0.60)	7.9		-1.47 (-2.54, -0.40)	2.1	
≥ 400	8 (232/211)	0.06 (0.03, 0.09)	0.001		11 (266/246)	-2.37 (-5.95, 1.21)	17.6		-1.67 (-4.41, 1.08)	13.9	
Duration, day				0.27				0.87			0.43
< 30	4 (52/39)	0.05 (0.04, 0.06)	0.0		8 (128/114)	-0.19 (-2.84, 2.45)	2.1		-0.23 (-2.92, 2.46)	7.7	
30-89	12 (283/282)	0.03 (-0.004, 0.06)	0.003		16 (360/332)	-2.82 (-5.43, -0.22)	16.8		-1.74 (-3.46, -0.01)	8.5	
≥ 90	13 (494/486)	0.07 (0.05, 0.10)	0.002		15 (645/666)	-0.76 (-2.77, 1.24)	4.8		-1.67 (-3.00, 0.34)	2.7	
Baseline Mg, mmol/L				0.005				0.21			0.90
Q1 (< 0.71)	6 (206/200)	0.15 (0.11, 0.18)	0.0004		6 (206/200)	-4.50 (-7.24, -1.76)	0.0		-5.05 (-9.12, -0.97)	0.0	
Q2 (0.72-0.82)	7 (139/137)	0.02 (-0.02, 0.05)	0.001		7 (139/137)	1.04 (-1.55, 3.62)	0.0		-0.28 (-5.65, 5.08)	0.0	
Q3 (0.83-0.88)	5 (143/124)	0.03 (0.02, 0.04)	0.0		5 (143/124)	-0.96 (-5.31, 3.40)	15.4		-0.80 (-5.10, 3.50)	0.0	
Q4 (≥ 0.88)	7 (355/360)	0.02 (-0.001, 0.04)	0.0		7 (355/360)	-3.70 (-5.47, 1.94)	0.0		-1.92 (-4.82, 0.98)	0.0	

Table 1. Stratified meta-analysis of Mg supplementation on serum Mg, SBP, and DBP from RCT data

Subgroups	Serum Mg, mmol/L				SBP, mmHg				DBP, mmHg		
	No. of studies *	WMD (95% CI)	τ^2, %	*P* **	No. of studies *	WMD (95% CI)	τ^2, %	*P* **	WMD (95% CI)	τ^2, %	*P* **
Design factors											
Prior BP status				0.26				0.79			0.59
Normotensive	15 (569/557)	0.06 (0.03, 0.10)	0.004		18 (703/746)	-1.78 (-3.33, -0.23)	3.7		-1.43 (-2.52, -0.35)	1.6	
Hypertensive	12 (247/236)	0.03 (0.02, 0.05)	0.0005		16 (307/271)	-2.16 (-5.71, 1.40)	32.4		-2.11 (-4.17, -0.05)	11.6	
Medication history †				0.78				0.11			0.72
Yes	5 (127/122)	0.06 (0.03, 0.10)	0.001		7 (136/131)	-5.69 (-10.37, -1.00)	20.0		-2.55 (-4.92, -0.19)	3.7	
No	10 (202/196)	0.05 (0.02, 0.07)	0.001		11 (240/208)	0.13 (-4.00, 4.25)	31.6		-1.52 (-4.12, 1.09)	13.7	
BP Measurements				0.26				0.58			0.74
Sphygmomanometer	11 (446/439)	0.04 (0.02, 0.06)	0.0006		14 (563/532)	-0.60 (-2.52, 1.33)	4.4		-1.69 (-3.28, -0.01)	5.1	
Automatic monitors	6 (161/151)	0.02 (-0.01, 0.05)	0.0006		9 (217/260)	-1.56 (-4.94, 1.83)	14.9		-1.21 (-3.16, 0.74)	4.6	
No. of BP measure				0.71				0.44			0.25
2 times	4 (111/115)	0.01 (-0.03, 0.06)	0.0012		5 (161/139)	-1.78 (-6.63, 3.08)	15.2		1.17 (-1.51, 3.84)	0.90	
3 times	5 (257/246)	0.04 (0.03, 0.06)	0.0001		7 (307/311)	-0.71 (-3.28, 1.87)	4.8		-2.04 (-4.17, 0.09)	3.9	
5 times	2 (16/15)	0.02 (-0.04, 0.08)	0.002		3 (23/23)	0.89 (-8.09, 9.86)	35.9		-1.80 (-3.76, 0.17)	0.0	
Position of BP measure				0.51				0.57			0.57
Sitting	8 (467/470)	0.08 (0.05, 0.11)	0.004		11 (554/559)	-3.44 (-5.69, -1.20)	6.6		-3.03 (-2.69, -0.60)	5.4	
Supine	11 (166/148)	0.02 (-0.002, 0.05)	0.001		13 (208/163)	0.79 (-3.15, 4.72)	32.7		-0.03 (-1.85, 1.79)	4.6	
Standing	6 (126/122)	0.004 (-0.03, 0.04)	0.0009		7 (137/106)	2.33 (-2.57, 7.22)	22.8		0.81 (-1.08, 2.70)	2.1	
Study design				0.07				0.88			0.08
Crossover	8 (263/265)	0.02 (-0.01, 0.05)	0.001		11 (333/337)	-1.65 (-4.39, 1.08)	8.0		-0.53 (-2.22, 1.15)	3.8	
Parallel	19 (552/529)	0.07 (0.04, 0.09)	0.002		23 (677/681)	-2.04 (-4.12, 0.04)	13.0		-2.42 (-3.60, -1.25)	3.3	
Trial quality factors											
Sample size				0.08				0.75			0.71
< 50	16 (241/219)	0.03 (0.008, 0.06)	0.002		20 (265/243)	-2.08 (-5.13, 0.97)	27.4		-1.61 (-3.44, 0.21)	10.1	
≥ 50	11 (574/575)	0.07 (0.05, 0.10)	0.002		14 (745/774)	-1.75 (-3.48, -0.008)	4.9		-2.01 (-3.28, -0.74)	2.9	
Randomization				0.86				0.30			0.26
Success	19 (648/632)	0.06 (0.03, 0.08)	0.003		25 (939/961)	-1.43 (-3.04, 0.19)	7.2		-1.50 (-2.71, 0.33)	4.9	
Failed	5 (143/138)	0.05 (-0.01, 0.11)	0.004		2 (30/16)	5.10 (-3.96, 14.17)	0.0		-4.28 (-7.19, -1.37)	0.0	
Dropout rate				0.65				0.002			0.04
< 10%	15 (588/578)	0.06 (0.03, 0.9)	0.003		19 (726/772)	-3.29 (-5.12, -1.47)	7.6		-2.63 (-3.92, -1.35)	4.5	

Table 1. Stratified meta-analysis of Mg supplementation on serum Mg, SBP, and DBP from RCT data

Subgroups	Serum Mg, mmol/L				SBP, mmHg				DBP, mmHg		
	No. of studies *	WMD (95% CI)	τ^2, %	*P* **	No. of studies *	WMD (95% CI)	τ^2, %	*P* **	WMD (95% CI)	τ^2, %	*P* **
≥ 10%	6 (111/106)	0.04 (0.005, 0.08)	0.001		6 (111/106)	5.30 (0.91, 9.69)	0.0		0.99 (-1.28, 3.25)	0.0	
Trial quality ††				0.33				0.02			0.02
High	18 (510/497)	0.06 (0.04, 0.09)	0.002		24 (643/658)	-3.37 (-5.34, -1.40)	11.7		-2.50 (-3.65, -1.36)	3.8	
Low	9 (306/296)	0.04 (0.02, 0.05)	0.0002		10 (367/360)	0.83 (-0.89, 2.56)	1.2		0.35 (-1.45, 2.15)	3.0	

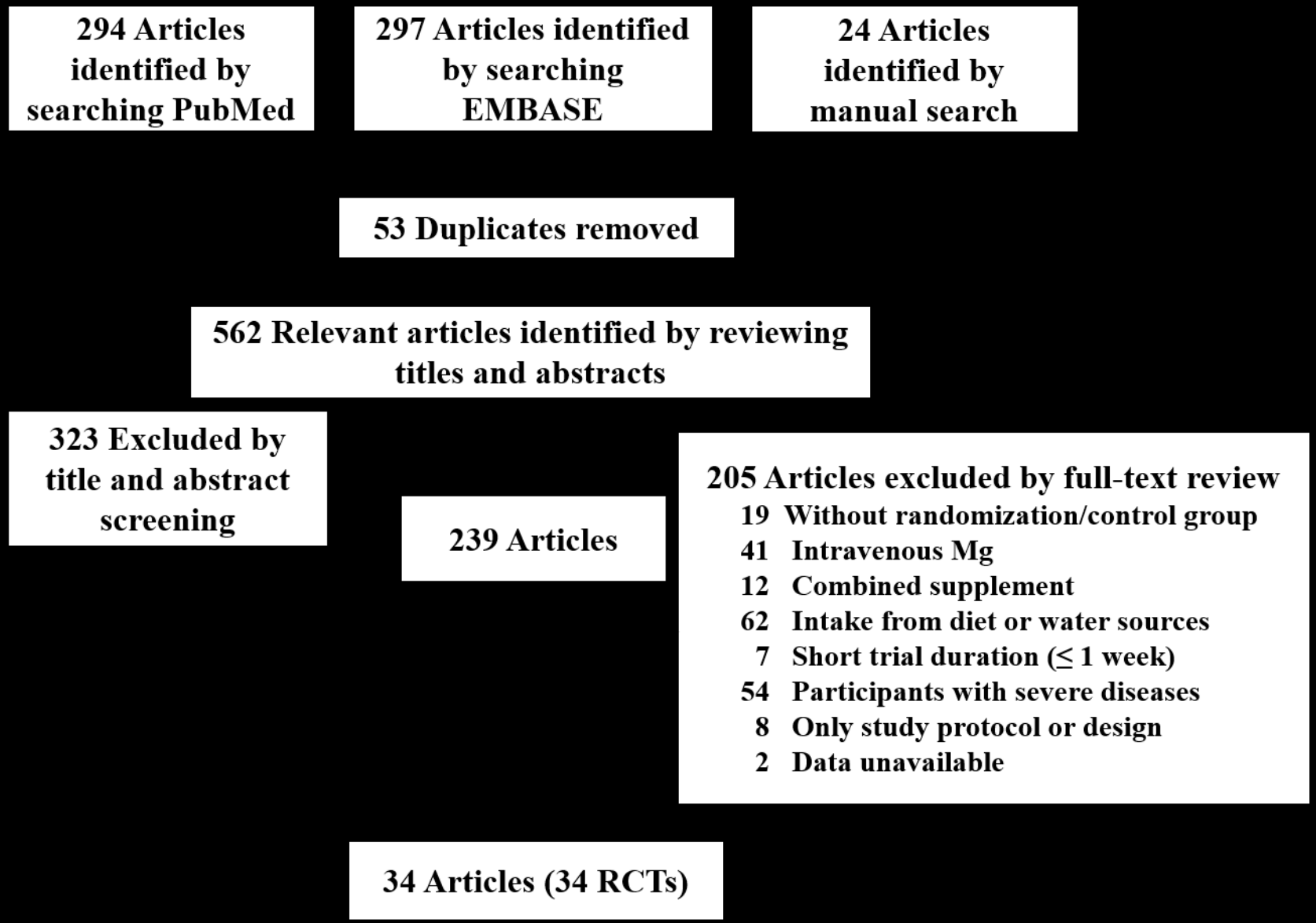
* Number of studies (total number of participants in Mg supplemental group/placebo group), ** *P* -values for interaction.

† Mediaction history represented for taking anti-hypertensive or anti-diabetic drugs during the period of study or off medication less than 1 month before entering the current study.

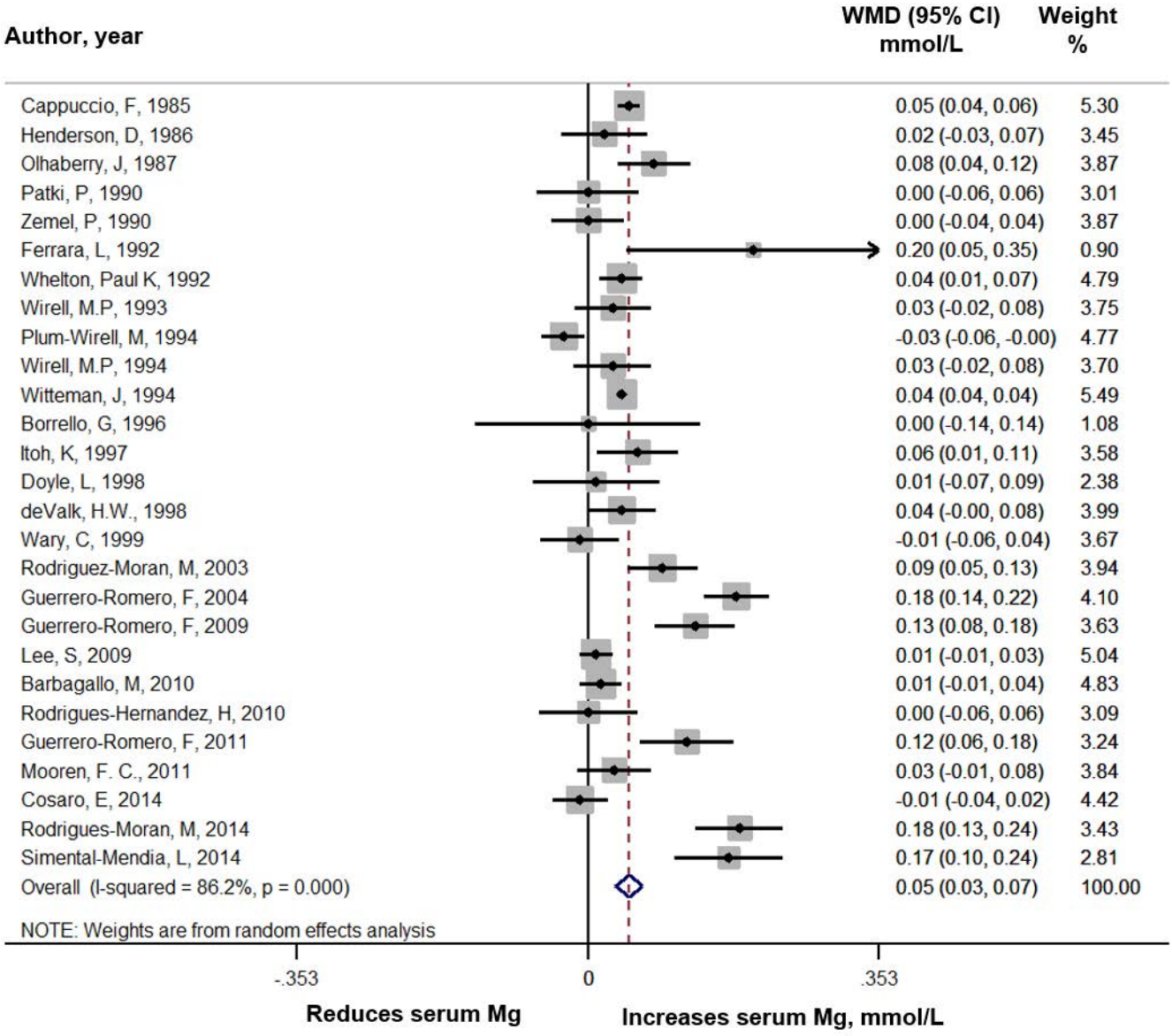
†† Trials quality were evaluated by Jadad score, low: ≤ 3, high: > 3.

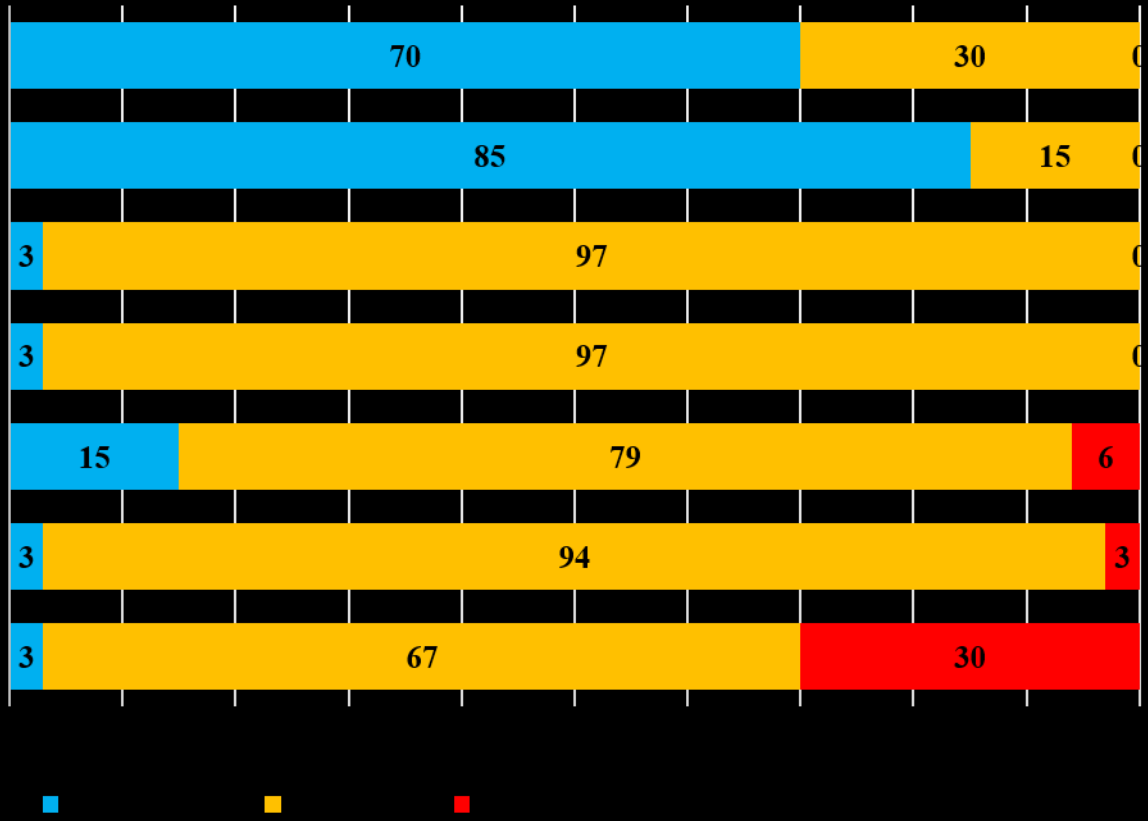
WMD: weighted mean difference, SBP/DBP: systolic/diastolic blood pressure, Q1-Q4: quartile 1 - quartile 4.

Meta-Analysis of Randomized Controlled Trials Assessing BP Lowering Effects by Oral Mg Supplementation



Supplemental figure 1. Flowchart for study selection


Author, year
WMD (95% CI) mmol/L
Weight %
Cappuccio, F, 1985
0.05 (0.04, 0.06)
5.30
Henderson, D, 1986
0.02 (-0.03, 0.07)
3.45
Olhaberry, J, 1987
0.08 (0.04, 0.12)
3.87
Patki, P, 1990
0.00 (-0.06, 0.06)
3.01
Zemel, P, 1990
0.00 (-0.04, 0.04)
3.87
Ferrara, L, 1992
0.20 (0.05, 0.35)
0.90
Whelton, Paul K, 1992
0.04 (0.01, 0.07)
4.79
Wirell, M.P, 1993
0.03 (-0.02, 0.08)
3.75
Plum-Wirell, M, 1994
-0.03 (-0.06, -0.00)
4.77
Wirell, M.P, 1994
0.03 (-0.02, 0.08)
3.70
Witteman, J, 1994
0.04 (0.04, 0.04)
5.49
Borrello, G, 1996
0.00 (-0.14, 0.14)
1.08
Itoh, K, 1997
0.06 (0.01, 0.11)
3.58
Doyle, L, 1998
0.01 (-0.07, 0.09)
2.38
deValk, H.W., 1998
0.04 (-0.00, 0.08)
3.99
Wary, C, 1999
-0.01 (-0.06, 0.04)
3.67
Rodriguez-Moran, M, 2003
0.09 (0.05, 0.13)
3.94
Guerrero-Romero, F, 2004
0.18 (0.14, 0.22)
4.10
Guerrero-Romero, F, 2009
0.13 (0.08, 0.18)
3.63
Lee, S, 2009
0.01 (-0.01, 0.03)
5.04
Barbagallo, M, 2010
0.01 (-0.01, 0.04)
4.83
Rodrigues-Hernandez, H, 2010
0.00 (-0.06, 0.06)
3.09
Guerrero-Romero, F, 2011
0.12 (0.06, 0.18)
3.24
Mooren, F. C., 2011
0.03 (-0.01, 0.08)
3.84
Cosaro, E, 2014
-0.01 (-0.04, 0.02)
4.42
Rodrigues-Moran, M, 2014
0.18 (0.13, 0.24)
3.43
Simental-Mendia, L, 2014
0.17 (0.10, 0.24)
2.81
Overall (I-squared = 86.2%, p = 0.000)
0.05 (0.03, 0.07)
100.00
NOTE: Weights are from random effects analysis
-.353
0
.353
Reduces serum Mg
Increases serum Mg, mmol/L


70
30
0
85
15
0
3
97
0
3
97
0
15
79
6
3
94
3
3
67
30

Supplemental Table 1. Characteristics of 34 articles included in the meta-analysis

Author, year	Country	Participants status	Total, N_t/N_p	Anti-HTN medication	Age, years	Sex, %women	Mg formulation	Dose, mg/day/ Duration, day	Crossover/ Measures of BP
Cappuccio, F, 1985	US	Mild to moderate hypertension	17, 9/8	Off medicine ≥2 month	Range: 33-66	Both, 47%	Mg asparate *	360/28	YES/Spygmomanometer
Henderson, D, 1986	Denmark	Hypertension	41, 21/20	NR	Mean: 62	Both, NR	MgO *	301/180	NO/NR
Olhaberry, J, 1987	Uruguay	Mild esential hypertension	40, 20/20	No medication	Range: 24-64	Female	$MgCl_2$ *	380.88/28	NO/Sphygmomanometer
Patki, P, 1990	India	Mild hypertension	37, 37/37	Off medicine ≥1 month	Mean: 49.9±7.6	Both, 78%	$MgCl_2$ *	480/56	YES/Spygmomanometer
Zemel, P, 1990	US	Mild hypertension	13, 7/6	Off medicine ≥3 months	Range: 20-69	Both, 14%	Mg asparate -HCl *	960/90	NO/Automatic BP monitor
Daly, N.M., 1990	Germany	Borderline hypertension	40, 20/20	No medication	Mean: 59	Both, 55%	MgO	500/84	NO/NR
Lind, L, 1991	Sweden	Hypertension	71, 49/22	No medication	Mean: 61	NR	Mg lactate Mg citrate	360/180	NO/Spygmomanometer
Ferrara, L, 1992	Italy	Mild to moderate hypertension	14, 7/7	No medication	Range: 40-60	Both, 43%	Mg pidolate *	360/180	NO/Automatic BP monitor
Whelton, Paul K, 1992	US	Healthy	461, 227/234	No medication	Range: 30-54	Both, 31%	NR *	360/180	YES/Sphygmomanometer
Paolisso, G., 1992	Italy	Lower arterial blood pressure	18, 9/9	Thiazide	Mean: 64±3	Both, 50%	Mg pidolate	379/56	NO/NR
Widman, L, 1993	Sweden	Mild hypertension	17, 17/17	Off medicine ≥4 months	Mean: 50±6	Both, 12%	$Mg(OH)_2$	360/21	YES/Sphygmomanometer
Wirell, M.P, 1993	Sweden	Mild to moderate hypertension	36, 18/18	Thiazide	Range: 29-62	Both, 47%	Mg asparate-HCl *	365/60	YES/NR

Supplemental Table 1. Characteristics of 34 articles included in the meta-analysis

Author, year	Country	Participants status	Total, N_t/N_p	Anti-HTN medication	Age, years	Sex, %women	Mg formulation	Dose, mg/day/ Duration, day	Crossover/ Measures of BP
Wirell, M.P, 1994	Sweden	Moderate hypertension	39, 21/18	Beta-block	Range: 26-69	NR	Mg asparate -HCl *	365/56	YES/Spygmomanometer
Plum-Wirell, M, 1994	Sweden	Mild to moderate untreated hypertention	39, 39/39	No medication	Range: 20-59	Both, 38%	Mg asparate-HCl *	365/60	YES/Spygmomanometer
Witteman, J, 1994	Belgium	Mild to moderate hypertension	91, 47/44	No medication	Range: 35-77	Female	Mg asparate-HCl *	485/180	NO/Sphygmomanometer
Purvis, John R, 1994	US	NIDDM	28, 28/28	Dietary control and hypoglycemic	Range: 28-84	Both, 86%	$MgCl_2$	384/42	YES/Automated BP mornitor
Borrello, G, 1996	Italy	Mild hypertension	83, 42/41	No medication	Mean: 42	Both, 64%	MgO *	238.32/84	NO/24-h BP, Ambulatory BP
Sanjuliani, F, 1996	Brazil	Mild to moderate hypertension	15, 15/15	NR	Range: 36-65	Both, 53%	MgO	600/21	YES/Automatic BP mornitor
Itoh, K, 1997	Japan	Healthy	33, 23/10	No medication	Mean: 65	Both, 67%	$Mg(OH)_2$ *	479.5/28	NO/Automatic BP mornitor
Sacks, Frank M, 1998	US	Healthy	48, 50/103	No medication	Mean: 39	Female	Mg lactate	336/112	NO/24-h BP, Ambulatory BP
deValk, H.W., 1998	Netherlands	T2DM	50, 25/25	Insulin and other anti-diabete medicine	Mean: 63	Both, 44%	Mg asparate-HCl *	360/90	NO/NR
Doyle, L, 1999	Ireland	Healthy	26, 13/13	No medication	Range: 20-28	Female	$Mg(OH)_2$ *	240/28	YES/Sphygmomanometer
Wary, C, 1999	Belgium	Healthy	30, 15/15	No medication	Range: 28-35	Male	Mg lactate *	288/30	NO/NR
Rodriguez-Moran, M, 2003	Mexico	T2DM and decreased serum Mg	63, 32/31	Glibenclamide	Mean: 57	NR	$MgCl_2$ *	450/112	NO/NR

Supplemental Table 1. Characteristics of 34 articles included in the meta-analysis

Author, year	Country	Participants status	Total, N_t/N_p	Anti-HTN medication	Age, years	Sex, %women	Mg formulation	Dose, mg/day/ Duration, day	Crossover/ Measures of BP
Guerrero-Romero, F, 2004	Mexico	Healthy	63, 32/31	No medication	Mean: 43	Both, NR	$MgCl_2$ *	300/84	NO/NR
Lee, S, 2009	South Korea	Healthy	155, 75/80	No medication	Range: 30-60	Both, 50%	MgO *	300/84	NO/Automated BP mornitor
Guerrero-Romero, F, 2009	Mexico	Diabetic hypertension & lower serum Mg	79, 40/39	Captopril	Range: 40-75	Both, 52%	$MgCl_2$ *	450/120	NO/Baumanometer & stethoscope
Barbagallo, M, 2010	Italy	Diabetic patients	60, 30/30	NR	Mean: 71.1±6.1	Both, 42%	Mg pidolate *	368/30	NO/Sphygmomanometer
Rodrigues-Hernandez, H, 2010	Mexico	Healthy	30, 20/18	No medication	Range: 30-65	Female	$MgCl_2$ *	450/120	NO/NR
Mooren, F. C., 2011	Germany	Healthy	47, 25/22	No medication	Range: 30-70	NR	Mg asparate-HCl *	365/180	NO/Sphygmomanometer
Guerrero-Romero, F, 2011	Mexico	Healthy	97, 49/48	No medication	Range: 40-65	Both, 41%	$MgCl_2$ *	450/90	NO/Sphygmomanometer
Cosaro, E, 2014	Italy	Healthy	14, 14/14	No medication	Range: 23-33	NR	Mg pidolate *	368/28	YES/Seminautomatic oscillometric device
Rodrigues-Moran, M, 2014	Mexico	Healthy	47, 24/23	No medication	Range: 20-60	Both, 66%	$MgCl_2$ *	382/120	NO/NR
Simental-Mendia, L, 2014	Mexico	New diagnosed prediabetes and hypomagnesemis	57, 29/28	NR	Range: 18-65	Both, 58%	$MgCl_2$ *	382/90	NO/NR

NIDDM, non-insulin dependent diabetes mellitus; BP, blood pressure; T2DM, type 2 diabete mellitus; NR, not reported; HTN, hypertension.

N_t: No. of participants in treatment group; N_p: No. of participants in placebo group. * Studies reported the serum Mg levels.