

High Blood Pressure & Cardiovascular Prevention

Impact of magnesium supplementation on blood pressure: an umbrella meta-analysis of randomized controlled trials

--Manuscript Draft--

Manuscript Number:	BPCP-D-23-00149
Full Title:	Impact of magnesium supplementation on blood pressure: an umbrella meta-analysis of randomized controlled trials
Article Type:	Review article
Abstract:	<p>Conflicting results on the effect of magnesium supplementation on blood pressure have been published in previous meta-analyses; hence, we conducted this umbrella meta-analysis of RCTs to provide a more robust conclusion on its effects. Four databases including PubMed, Scopus, EMBASE, and Web of Science were searched to find pertinent papers published on international scientific from inception up to Jun 2023. We utilized STATA version 17.0 to carry out all statistical analyses (Stata Corporation, College Station, TX, US). The random effects model was used to calculate the overall effect size ES and CI. 10 eligible meta-analysis papers with 8610 participants studied the influence of magnesium on SBP and DBP. The pooling of their effect sizes resulted in a significant reduction of SBP (ES= -1.25 mmHg; 95% CI: -1.98, -0.51, $p = 0.001$) and DBP (ES= -1.40 mmHg; 95% CI: -2.04, -0.75, $p = 0.000$) by magnesium supplementation. In subgroup analysis, a significant reduction in SBP and DBP was observed in magnesium intervention with dosage ≥ 400 mg/day (ES for SBP= -6.38 mmHg; ES for DBP= -3.71mmHg), as well as in studies with a treatment duration of ≥ 12 weeks (ES for SBP= -0.42 mmHg; ES for DBP= -0.45 mmHg). The findings of the present umbrella meta-analysis showed an overall decrease of SBP and DBP with magnesium supplementation, particularly at doses of ≥ 400 mg/day for ≥ 12 weeks.</p>

Impact of magnesium supplementation on blood pressure: an umbrella meta-analysis of randomized controlled trials

Kousalya Prabahar^a, Benjamin Hernández-Wolters^b, Hamed Kord-Varkaneh^{c,*}

^aDepartment of Pharmacy Practice, Faculty of Pharmacy, University of Tabuk, Tabuk, Saudi Arabia.

^bUniversity Center for Health Science, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico.

^c Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

* Address for correspondence: Hamed Kord-Varkaneh, Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran; email: hamedkordvarkaneh@sbmu.ac.ir

Short title: magnesium on blood pressure an umbrella review

Conflict of interest: The authors have no conflicts of interest to declare.

Funding: No funding was received for this study.

Abstract

Conflicting results on the effect of magnesium supplementation on blood pressure have been published in previous meta-analyses; hence, we conducted this umbrella meta-analysis of RCTs to provide a more robust conclusion on its effects. Four databases including PubMed, Scopus, EMBASE, and Web of Science were searched to find pertinent papers published on international scientific from inception up to Jun 2023. We utilized STATA version 17.0 to carry out all statistical analyses (Stata Corporation, College Station, TX, US). The random effects model was used to calculate the overall effect size ES and CI. 10 eligible meta-

analysis papers with 8610 participants studied the influence of magnesium on SBP and DBP. The pooling of their effect sizes resulted in a significant reduction of SBP (ES= -1.25 mmHg; 95% CI: -1.98, -0.51, p = 0.001) and DBP (ES= -1.40 mmHg; 95% CI: -2.04, -0.75, p = 0.000) by magnesium supplementation. In subgroup analysis, a significant reduction in SBP and DBP was observed in magnesium intervention with dosage ≥ 400 mg/day (ES for SBP= -6.38 mmHg; ES for DBP= -3.71 mmHg), as well as in studies with a treatment duration of ≥ 12 weeks (ES for SBP= -0.42 mmHg; ES for DBP= -0.45 mmHg). The findings of the present umbrella meta-analysis showed an overall decrease of SBP and DBP with magnesium supplementation, particularly at doses of ≥ 400 mg/day for ≥ 12 weeks.

Keywords: Magnesium, Blood pressure, Systematic review, Umbrella of meta-analysis.

Introduction

Systemic hypertension, a persistent elevation of the systemic arterial blood pressure (BP), is a highly prevalent condition and a major independent risk factor of mortality and cardiovascular disease [1]. Preventing and treating hypertension has become a significant factor in decreasing the risk and burden of various diseases, thus reducing disease-related mortality [2, 3]. However, inadequate management of BP still remains one of the greatest individual risk factors of all-cause mortality globally [4], and each 10 mmHg rise in average systolic blood pressure (SBP) has been previously associated with an increase in cardiovascular disease (CVD) and chronic kidney disease risk by up to 16% [5]. Dietary and lifestyle modifications play major role in managing BP [6, 7]. For this reason, the pressure-

lowering effect of natural supplements has been widely studied, and beneficial effects with minimal adverse effects have been discovered for many substances [3].

Magnesium is the fourth most common cation in the human body [8], and a deficient intake of magnesium has been associated with various diseases, including asthma, diabetes mellitus, hypertension, stroke, heart disease, hypertension, and even cancer [9] [10]. Therefore, magnesium has been proposed as a treatment for hypertension [11]. By inducing the formation of nitric oxide and prostacyclin [12], magnesium helps in modulating vasodilation, decreasing vascular tone and vascular reactivity [13]. Magnesium also possess anti-inflammatory and as antioxidant properties [14] and interacts with calcium [12], decreasing peripheral vascular resistance [15] and decreasing blood pressure [16].

Observational epidemiological studies have reported a negative association between dietary magnesium supplementation and BP [17], and various clinical trials have been conducted in the past years to study the effects of magnesium on BP, with inconsistent results published [16]. Even systematic reviews conducted on RCTs provided inconclusive results on the effects of magnesium on SBP and DBP. For instance, one meta-analysis reported a significant reduction in DBP and a non-significant reduction in SBP [18], while another meta-analysis reported that magnesium supplementation resulted in significant reduction of SBP and DBP [19], and a third meta-analysis reported only a slight decrease in BP [20]. In patients with type 2 diabetes mellitus a meta-analysis reported beneficial effect of magnesium on BP [21], while a second one showed a favorable effect on SBP but not on DBP [22]. We conducted this umbrella meta-analysis of RCTs to provide a clear evidence and conclusion on the effect of magnesium supplementation on blood pressure.

Methods

This study was implemented based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [23].

Search strategy and study selection

Four databases including PubMed, Scopus, EMBASE, and Web of Science were searched to find pertinent papers published on international scientific journals from inception up to June 2023. The search strategy was established using the following keywords and MeSH terms: (((("Magnesium"[Mesh]) OR "Magnesium"[tiab]))) AND (((((((Blood Pressure [Title/Abstract] OR Systolic Blood Pressure[Title/Abstract]) OR diastolic Blood Pressure[Title/Abstract]) OR "Blood Pressure"[Mesh]) OR SBP[Title/Abstract]) OR DBP[Title/Abstract]))) AND (((("systematic review" [Title/Abstract] OR "meta-analyses" [Title/Abstract] OR "meta-analysis" [Title/Abstract])))).

Inclusion and exclusion criteria

We included articles in the present umbrella meta-analysis according on PICO criteria: Population/Patients (P: subjects treated with magnesium); Intervention (I: magnesium); Comparison (C: control or placebo group); Outcome (O: SBP and DBP). Meta-analysis articles examining the effects of magnesium on blood pressure (SBP and DBP) in humans with reported effect sizes (ESs) and confidence intervals (CI), were included in the current umbrella meta-analysis. Moreover, observational studies, case reports, controlled clinical trials, prospective studies, studies with a ‘low quality’ score, and articles in languages other than English were excluded.

Methodological quality assessment and Grading of the evidence

Two independent researchers utilized the A Measurement Tool to Assess Systematic Reviews (AMSTAR)2 questionnaire to evaluate the methodological quality of eligible meta-analyses [24]. This tool contains 16 items that require referees to answer ‘Yes’, ‘Partial Yes’, ‘No’, or ‘No Meta-analysis’. The AMSTAR2 list was categorized into “high quality”, “moderate

quality”, “low quality”, and “critically low quality”. We appraised the general strength and quality of evidence using GRADE based on the Cochrane Handbook of systematic reviews of interventions [25].

Study selection and data extraction

Two independent investigators reviewed the papers to select those fulfilling the eligibility criteria and discrepancy was resolved by the corresponding author. The following items were extracted from the included articles: year of publication, first author’s name, study location, sample size, magnesium supplementation dosage, and effect sizes and CIs for SBP and DBP.

Data synthesis and statistical analysis

We utilized STATA version 17.0 to carry out all statistical analyses (Stata Corporation, College Station, TX, US). To calculate the overall ES and CIs, the random-effects model was used. Heterogeneity among studies was assessed using the I^2 statistic and Cochrane's Q-test, with a $p < 0.1$ or I^2 value $> 50\%$ regarded as significant. Subgroup analyses were conducted to detect potential sources of heterogeneity based on the reported median predetermined variables, namely duration of intervention and magnesium supplementation dosage. We applied sensitivity analyses to survey the influence of any particular effect size removal on the combined results. Formal Egger's tests and funnel plots visual checking were also performed to detect publication bias, with a P-value < 0.05 regarded as meaningful.

Results

Study characteristics

Figure 1 shows the flow diagram of the literature search process. 461 papers were recovered in the electronic database searches, out of which 172 were excluded for being duplications. After screening the titles and abstracts of the remaining 289 publications, 275 articles were removed. Ultimately, 10 meta-analyses published between 2002 and 2021 were included in the

umbrella meta-analysis, amounting to a total of 8610 participants [21, 22, 26-33]. Mean magnesium dose varied from 364 to 440 IU/day, and intervention duration ranged between 8.85 and 14.54 weeks. Detailed characteristics of the included meta-analyses are outlined in **Table 1**. Most of the included meta-analyses in this umbrella review were graded as having moderate to high quality; the results of the quality assessment of every article in each of the AMSTAR2 questionnaire items are presented in **Table 2**.

The effects of magnesium supplementation on systolic blood pressure

10 eligible review papers with 8610 participants studied the effect of magnesium on SBP. Pooling their effect sizes based on the random effects model, a significant reduction in SBP after magnesium supplementation was discovered (ES= -1.25 mmHg; 95% CI: -1.98, -0.51, $p = 0.001$) (**Fig. 2**). However, a significant heterogeneity among studies was detected ($I^2 = 92\%$, $p = 0.000$). In subgroup analysis, a significant reduction in systolic blood pressure was observed in magnesium intervention with doses ≥ 400 mg/day (ES= -6.38 mmHg; 95% CI: -11.56, -1.19, $p = 0.016$) and treatment duration ≥ 12 weeks (ES= -0.42 mmHg; 95% CI: -0.78, -0.06, $p = 0.020$) (**Supplementary Figure 1**).

The effects of magnesium supplementation on diastolic blood pressure

10 eligible review papers with 8610 participants scrutinized the influence of magnesium on DBP. The effect size pooling according to the random effects model discovered that magnesium supplementation significantly decreased DBP (ES= -1.40 mmHg; 95% CI: -2.04, -0.75, $p = 0.000$) (**Fig. 2**), with a significant heterogeneity among studies ($I^2 = 93\%$, $p = 0.000$). In subgroup analysis, a significant reduction in diastolic blood pressure was found in magnesium intervention with doses ≥ 400 mg/day (ES= -3.71 mmHg; 95% CI: -6.88, -0.53, $p = 0.022$) and treatment duration ≥ 12 weeks (ES= -0.45 mmHg; 95% CI: -0.76, -0.14, $p = 0.004$) (**Supplementary Figure 1**).

Sensitivity analysis and publication bias

After sensitivity analysis, no special arm was found to affect the combined effect size (Supplementary Figure 2). Egger's tests and visual inspection of the funnel plots showed no sign of publication bias (Figure 4).

Discussion

The present umbrella meta-analysis on the effect of magnesium supplementation on blood pressure summarized the results of 10 meta-analyses. The findings of this assessment support the evidence that magnesium supplementation lowers DBP and SBP in a statistically significant manner, although the effect size is small, hence, suggesting the potential use of magnesium as part of the dietary interventions for the management of hypertension. Although cost-utility analyses are lacking, magnesium supplementation could potentially reduce the economic costs of hypertension treatment. Sufficient evidence demonstrates the link between hypertension and various chronic diseases [34], but further investigations are warranted to study the effects of magnesium supplementation on other chronic diseases.

Magnesium is one of the most common minerals in the human body, with 99% of it distributed intracellularly [35]. The role of magnesium in reducing hypertension has been attributed to multiple mechanisms of action, including acting as a calcium channel blocker, competing with sodium binding sites on vascular smooth muscle cells, decreasing intracellular sodium and calcium, enhancing prostaglandin E, binding cooperatively with potassium, inducing vasodilation, improving endothelial dysfunction in diabetic and hypertensive patients [36]. Moreover, magnesium induces nitric oxide release from endothelial cells, which acts as vasoactive mediator and produces a synergistic effect with antihypertensive medications [37]. The effect of magnesium on osteopontin has also been proposed to be one of the mechanisms involved in inhibiting vascular calcification and reducing BP [38].

According to our umbrella meta-analysis, magnesium supplementation resulted in a statistically significant decrease in SBP (ES= -1.25 mmHg; 95% CI: -1.98, -0.51, p = 0.001) and DBP (ES= -1.40 mmHg; 95% CI: -2.04, -0.75, p = 0.000). Similar results have been obtained by several meta-analyses, including a meta-analysis of 11 RCTs conducted by Asbaghi et al. with magnesium doses ranging from 36.49 to 500 mg/day and intervention duration of 4 to 24 weeks, which reported a significant reduction of SBP and DBP [21], as well as one by Dibaba et al. which reported that administration of 365 to 450 mg/day of elemental magnesium resulted in a reduction of SBP by 4.18 mmHg and DBP by 2.27 mmHg [27], and other meta-analyses [39].

In contrast with our study results, Verma et al. reported that magnesium supplementation provides a moderate beneficial impact on SBP but not on DBP [22], which could be because their meta-analysis on hypertension included only four studies, with a high heterogeneity among those studies. Song et al. reported that magnesium supplementation did not provide beneficial effects on SBP and DBP [40], however, the study population of the meta-analysis included only patients with type 2 diabetes mellitus, which could be the reason for this conflicting result; moreover, the main focus of the study was the effect of magnesium on glycemic control rather than blood pressure.

According to The American Food and Nutrition Board, the recommended dietary magnesium intake for people aged 31-70 years is 420 mg/day for males and 320 mg/day for females [41].

In our subgroup analysis, a significant reduction in SBP and DBP was observed in magnesium supplementation with doses ≥ 400 mg/day and treatment duration ≥ 12 weeks. In line with our results, a meta-analysis conducted by Asbaghi et al. reported in their subgroup analysis that magnesium supplementation at a dose of >300 mg/day or with a duration of >12 weeks provided significant beneficial effects on both SBP and DBP [21]. In another meta-

analysis, magnesium supplementation of >370 mg/day resulted in SBP reduction by 0.66 mmHg and DBP reduction by 0.57 mmHg [30].

The reduction in BP due to magnesium supplementation could have beneficial effects on cardiovascular outcomes. A clinical trial reported that 0.8 to 2 mmHg reduction of SBP could help in decreasing the risks of coronary artery disease, stroke, and heart failure, with a 2 to 3 mmHg decrease of BP reducing the risk of stroke by up to 6 to 12% [42]. Hence, the reduction of BP by magnesium supplementation, although not enough to recommend magnesium as an antihypertensive monotherapy, could have clinical significance when used as a dietary supplement in addition to other antihypertensive medications in subjects with hypertension.

Strengths and limitations

To the best of our knowledge, this is the first umbrella meta-analysis to find the effect of magnesium supplementation on BP. Since our review included only meta-analyses of RCTs, bias was significantly reduced. In addition, Egger's test and visual inspection of the funnel plot revealed no publication bias.

However, our review is not without limitations. Significant heterogeneity was found among the included meta-analysis, and the dose and duration of magnesium interventions in patients with specific comorbidities were not reported. Thus, we recommend that future studies focus on the effects of magnesium supplementation on blood pressure in patients with comorbidities.

Conclusion

The findings of the present umbrella meta-analysis showed a small but statistically significant decrease of SBP and DBP with magnesium supplementation, with significant effects with doses ≥ 400 mg/day and duration ≥ 12 weeks. Although the reduction of BP by magnesium supplementation is not enough to recommend its use as monotherapy for hypertension, it

could have clinical significance when used as a dietary supplement in addition to other antihypertensive medications in patients with hypertension. Further studies are required to determine the effects of magnesium supplementation on BP in patients with comorbidities.

Acknowledgements: *None*

Compliance with Ethical Standards

- **Conflict of Interest:** None.
- **Funding:** None.
- **Ethical approval:** This article does not contain any studies with human participants or animals performed by any of the authors.
- **Informed consent:** Not applicable.

Conflict of interest: All authors report no conflict of interest.

References

1. Cooper RS, Amoah AG, Mensah GA. High Blood Pressure. Ethnicity & disease. 2003;13:48-52.
2. Oparil S, Weber MA. Hypertension: a companion to Brenner and Rector's the kidney. (No Title). 2005.
3. Brunström M, Carlberg B. Association of blood pressure lowering with mortality and cardiovascular disease across blood pressure levels: a systematic review and meta-analysis. JAMA internal medicine. 2018;178(1):28-36.
4. Collaborators GRF. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England). 2016;388(10053):1659.
5. Wan EYF, Yu EYT, Chin WY, Fong DYT, Choi EPH, Lam CLK. Association of blood pressure and risk of cardiovascular and chronic kidney disease in Hong Kong hypertensive patients. Hypertension. 2019;74(2):331-40.
6. Lee CJ, Kim JY, Shim E, Hong SH, Lee M, Jeon JY, et al. The effects of diet alone or in combination with exercise in patients with prehypertension and hypertension: a randomized controlled trial. Korean circulation journal. 2018;48(7):637-51.
7. Dickey RA, Janick JJ. Lifestyle modifications in the prevention and treatment of hypertension. Endocrine practice. 2001;7(5):392-9.
8. Fiorentini D, Cappadone C, Farruggia G, Prata C. Magnesium: biochemistry, nutrition, detection, and social impact of diseases linked to its deficiency. Nutrients. 2021;13(4):1136.

9. De Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. *Physiological reviews*. 2015.
10. Volpe SL. Magnesium in disease prevention and overall health. *Advances in nutrition*. 2013;4(3):378S-83S.
11. Houston M. The role of magnesium in hypertension and cardiovascular disease. *The Journal of Clinical Hypertension*. 2011;13(11):843-7.
12. Satake K, Lee JD, Shimizu H, Uzui H, Mitsuke Y, UEDA T, et al. Effects of magnesium on prostacyclin synthesis and intracellular free calcium concentration in vascular cells. 2004.
13. Landau R, Scott JA, Smiley RM. Magnesium- induced vasodilation in the dorsal hand vein*. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2004;111(5):446-51.
14. Patni N, Fatima M, Lamis A, Siddiqui SW, Ashok T, Muhammad A. Magnesium and Hypertension: Decoding Novel Anti-hypertensives. *Cureus*. 2022;14(6).
15. Feyh A, Bracero L, Lakhani HV, Santhanam P, Shapiro JI, Khitan Z, et al. Role of dietary components in modulating hypertension. *Journal of clinical & experimental cardiology*. 2016;7(4).
16. Rosanoff A. Magnesium supplements may enhance the effect of antihypertensive medications in stage 1 hypertensive subjects. *Magnesium research*. 2010;23(1):27-40.
17. Mizushima S, Cappuccio F, Nichols R, Elliott P. Dietary magnesium intake and blood pressure: a qualitative overview of the observational studies. *Journal of human hypertension*. 1998;12(7):447-53.
18. Dickinson HO, Nicolson D, Campbell F, Cook JV, Beyer FR, Ford GA, et al. Magnesium supplementation for the management of primary hypertension in adults. *Cochrane Database of Systematic Reviews*. 2006(3).
19. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. *European journal of clinical nutrition*. 2012;66(4):411-8.
20. Jee SH, Miller ER, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *American journal of hypertension*. 2002;15(8):691-6.
21. Asbaghi O, Hosseini R, Boozari B, Ghaedi E, Kashkooli S, Moradi S. The Effects of Magnesium Supplementation on Blood Pressure and Obesity Measure Among Type 2 Diabetes Patient: a Systematic Review and Meta-analysis of Randomized Controlled Trials. *Biol Trace Elem Res*. 2021 Feb;199(2):413-24.
22. Verma H, Garg R. Effect of magnesium supplementation on type 2 diabetes associated cardiovascular risk factors: a systematic review and meta-analysis. *Journal of human nutrition and dietetics : the official journal of the British Dietetic Association*. 2017 Oct;30(5):621-33.
23. Moher D, Shamseer L, Clarke M, Gherzi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*. 2015;4(1):1-9.
24. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *bmj*. 2017;358.
25. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj*. 2008;336(7650):924-6.
26. Zhao B, Deng H, Li B, Chen L, Zou F, Hu L, et al. Association of magnesium consumption with type 2 diabetes and glucose metabolism: A systematic review and pooled study with trial sequential analysis. *Diabetes Metab Res Rev*. 2020 Mar;36(3):e3243.

27. Dibaba DT, Xun P, Song Y, Rosanoff A, Shechter M, He K. The effect of magnesium supplementation on blood pressure in individuals with insulin resistance, prediabetes, or noncommunicable chronic diseases: a meta-analysis of randomized controlled trials. *The American journal of clinical nutrition*. 2017 Sep;106(3):921-9.
28. Zhang X, Li Y, Del Gobbo LC, Rosanoff A, Wang J, Zhang W, et al. Effects of Magnesium Supplementation on Blood Pressure: A Meta-Analysis of Randomized Double-Blind Placebo-Controlled Trials. *Hypertension*. 2016 Aug;68(2):324-33.
29. Rosanoff A, Plesset MR. Oral magnesium supplements decrease high blood pressure (SBP>155 mmHg) in hypertensive subjects on anti-hypertensive medications: a targeted meta-analysis. *Magnesium research*. 2013 Jul-Sep;26(3):93-9.
30. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. *Eur J Clin Nutr*. 2012 Apr;66(4):411-8.
31. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabetic medicine : a journal of the British Diabetic Association*. 2006 Oct;23(10):1050-6.
32. Dickinson HO, Nicolson DJ, Campbell F, Cook JV, Beyer FR, Ford GA, et al. Magnesium supplementation for the management of essential hypertension in adults. *The Cochrane database of systematic reviews*. 2006 Jul 19(3):Cd004640.
33. Jee SHA, Miller Iii ER, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: A meta-analysis of randomized clinical trials. *American journal of hypertension*. 2002;15(8):691-6.
34. Kokubo Y, Iwashima Y. Higher blood pressure as a risk factor for diseases other than stroke and ischemic heart disease. *Hypertension*. 2015;66(2):254-9.
35. Jahnke-Dechent W, Ketteler M. Magnesium basics. *Clinical kidney journal*. 2012;5(Suppl_1):i3-i14.
36. Guerrero-Romero F, Rodríguez-Morán M. The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial. *Journal of human hypertension*. 2009;23(4):245-51.
37. Sandoo A, Van Zanten JJV, Metsios GS, Carroll D, Kitas GD. The endothelium and its role in regulating vascular tone. *The open cardiovascular medicine journal*. 2010;4:302.
38. Mehansho H, Majeti S, Tzeghai G. Prevention of vascular calcification by magnesium and selected polyphenols. *Advances in Preventive Medicine*. 2021;2021:1-5.
39. Zhao B, Deng H, Li B, Chen L, Zou F, Hu L, et al. Association of magnesium consumption with type 2 diabetes and glucose metabolism: A systematic review and pooled study with trial sequential analysis. *Diabetes/metabolism research and reviews*. 2020;36(3):e3243.
40. Song Y, He K, Levitan E, Manson J, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta- analysis of randomized double- blind controlled trials. *Diabetic Medicine*. 2006;23(10):1050-6.
41. Intakes IoMSCotSEoDR. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. 1997.
42. Allhat O. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *Jama*. 2002;288(23):2998-3007.

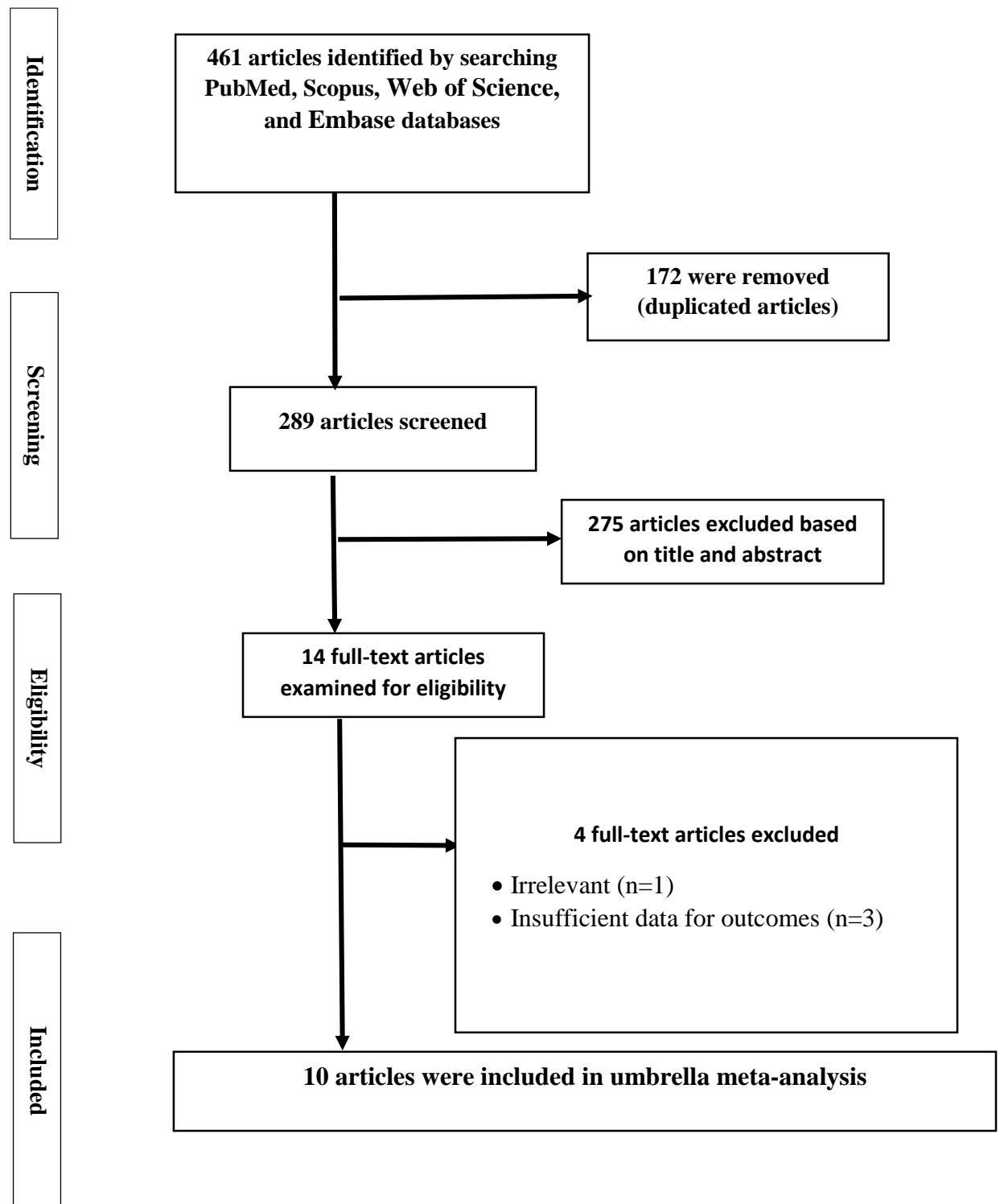


Figure1. Flow chart of the study selection process for the umbrella meta-analysis.

Figure 2. Forest plot of the umbrella review on the effects of magnesium intervention on systolic blood pressure.

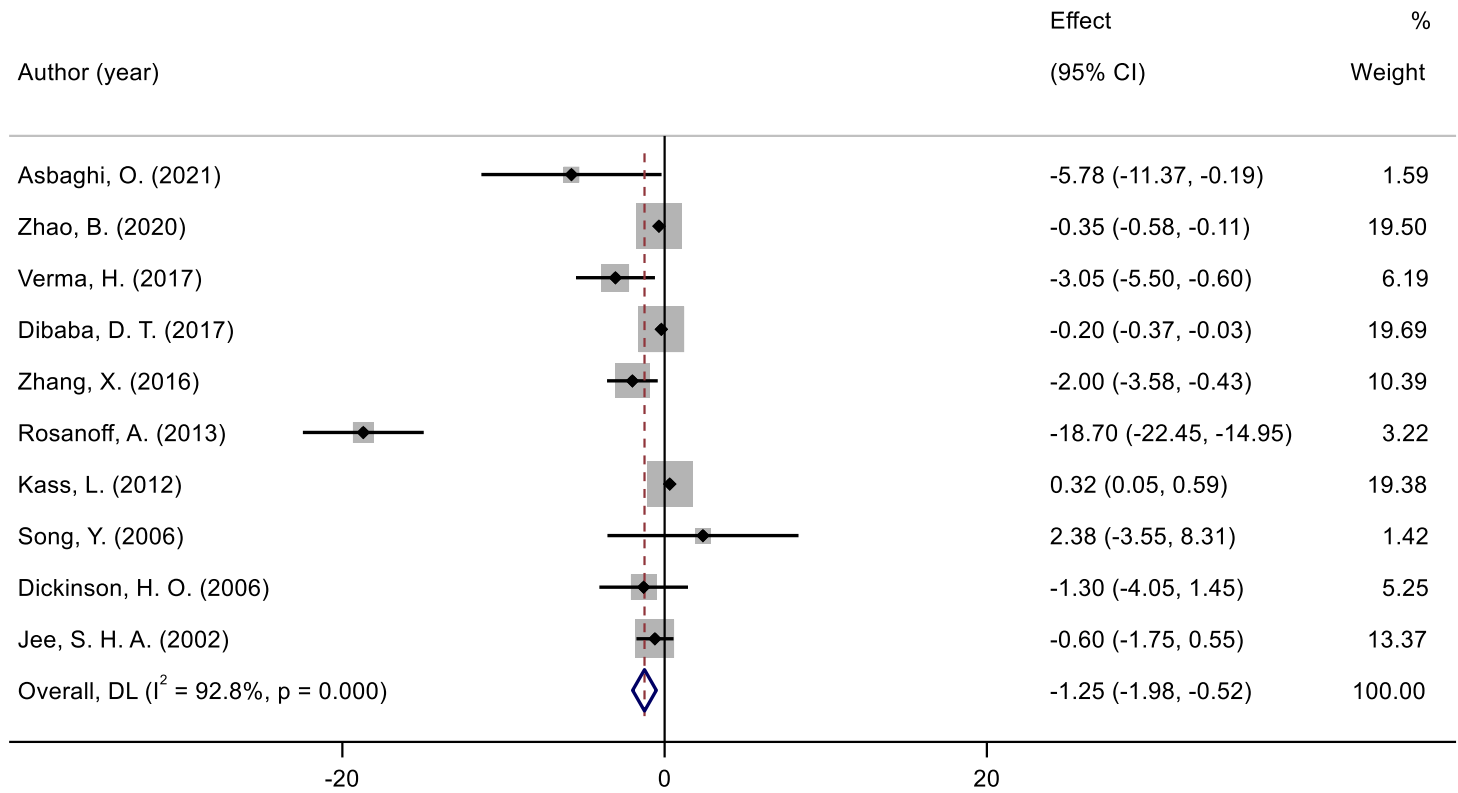


Figure 3. Forest plot of the umbrella review on the effects of magnesium intervention on diastolic blood pressure.

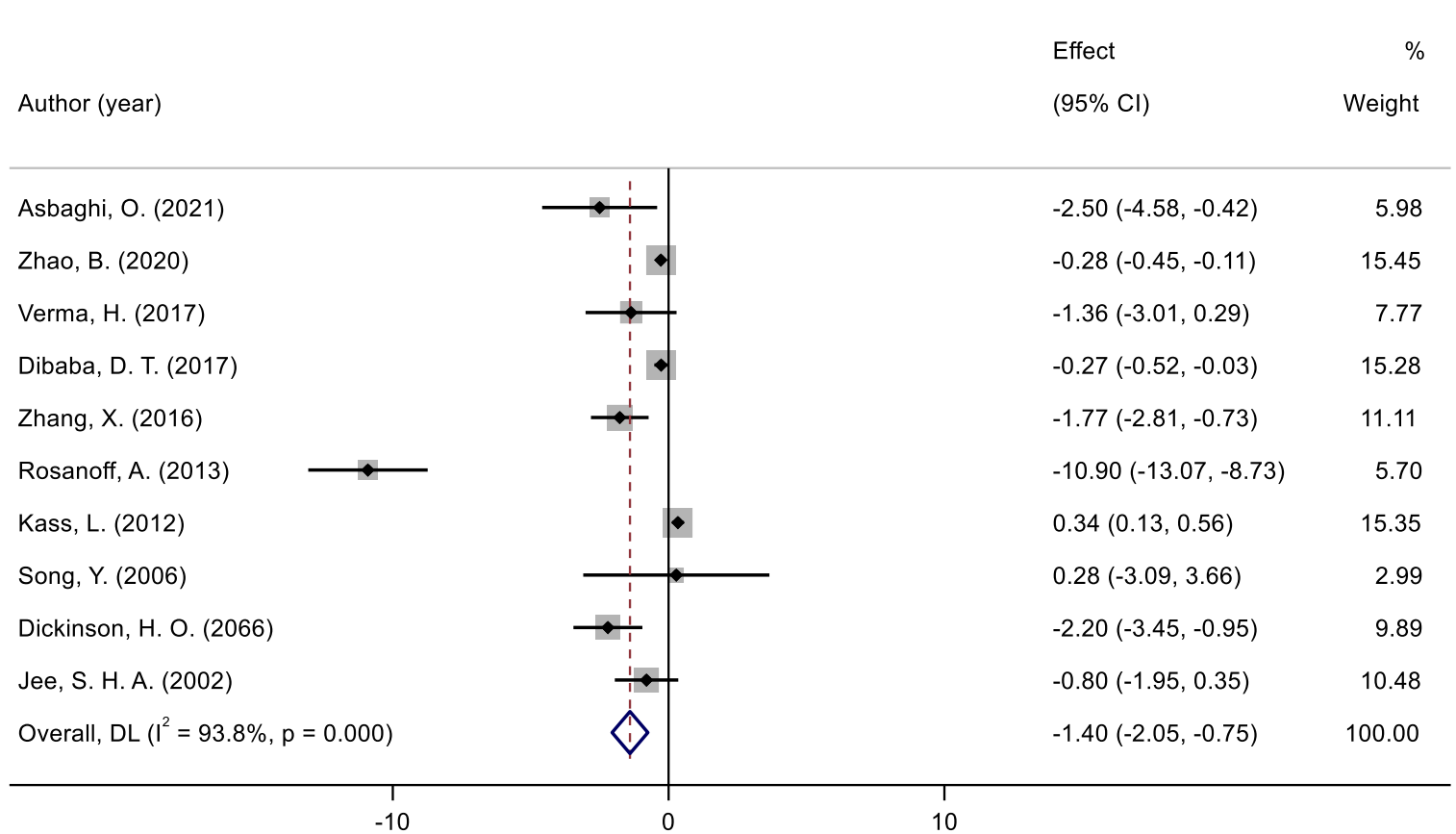
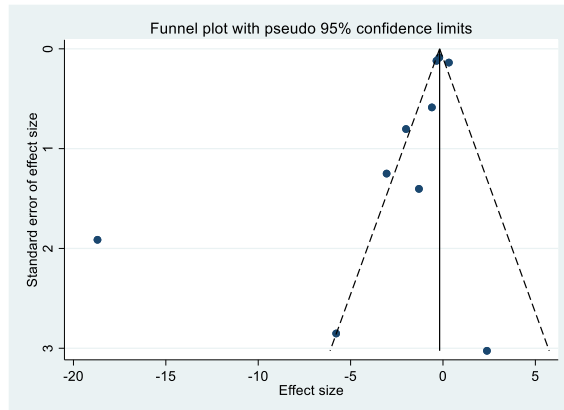


Figure 4. Funnel plot of the WMD versus the SE of the WMD.

Legend: WMD, weighted mean difference. CI, confidence interval. SE, standard error.

A) Systolic blood pressure (P=0.100)



B) Diastolic blood pressure (P = 0.052)

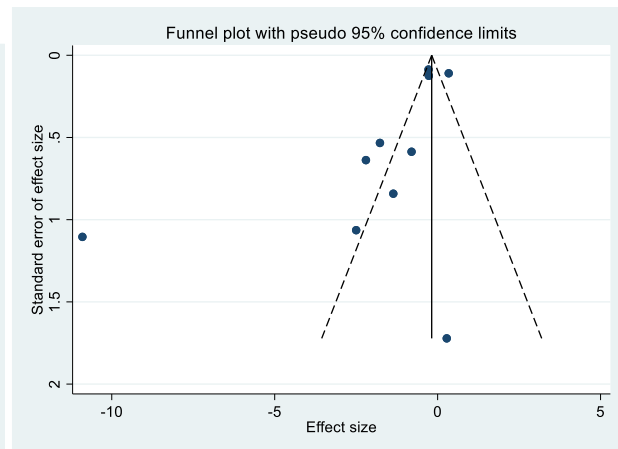


Table 1. Study characteristics of included studies

Citation (First author et al., year)	No. of Studies in Meta-analysis	Mean BMI	No. of Participants in Meta-analysis	Study duration (weeks)	Type of population	Mean age	Mean dosage (mg/day)	Outcomes
Asbaghi, O.,2021	7	28.33	357	11.42	Type 2 Diabetes Patient	59.75	364	SBP,DBP
Zhao, B.,2020	16	29.2	1105	13.25	Diffrent	48.14	383.18	SBP,DBP
Verma, H.,2017	19	28.2	1296	12.63	Diffrent	49.54	412	SBP,DBP
Dibaba, D. T.,2017	11	nr	543	14.54	Diffrent	54.85	401	SBP,DBP
Zhang, X.,2016	34	nr	1999	12.31	Diffrent	55.84	399	SBP,DBP
Rosanoff, A.,2013	7	nr	135	8.85	hypertensive subjects	nr	340	SBP,DBP
Kass, L.,2012	23	nr	1173	11.3	Diffrent	50.1	410	SBP,DBP
Song, Y.,2006	4	nr	237	12.5	Type 2 Diabetes Patient	59.41	440	SBP,DBP
Dickinson, H. O.,2006	12	nr	545	11	hypertensive subjects	54	413	SBP,DBP
Jee, S. H. A.,2002	20	nr	1220	12.95	Diffrent	52.2	443	SBP,DBP



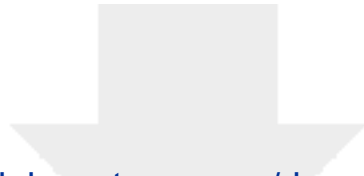
Click here to access/download
Supplementary Material
Supplementary Figure 1 edited.docx





Click here to access/download
Supplementary Material
Supplementary Figure 2.docx





[Click here to access/download](#)

Supplementary Material

Supplementary Table 1 edited.docx

