# Effect of magnesium supplementation on blood pressure: A meta-analysis

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SYSTEMATIC REVIEW

# Effect of magnesium supplementation on blood pressure: a meta-analysis

L Kass[1], J Weekes[1] and L Carpenter[2]

To date, there has been inconclusive evidence regarding the effect of magnesium supplements on blood pressure (BP). This meta-analysis was conducted to assess the effect of magnesium supplementation on BP and to establish the characteristics of trials showing the largest effect size. Primary outcome measures were systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of the follow-up period. One hundred and forty-one papers were identified, of which 22 trials with 23 sets of data ($n = 1173$), with 3 to 24 weeks of follow-up met the inclusion criteria, with a supplemented elemental magnesium range of 120–973 mg (mean dose 410 mg). 95% confidence intervals (CI) were calculated using DerSimonian and Laird's random-effects model, with effect size calculated using Hedges *G*. Combining all data, an overall effect of 0.36 and 0.32 for DBP and SBP, respectively, was observed (95% CI 0.27–0.44 for DBP and 0.23–0.41 for SBP), with a greater effect being seen for the intervention in crossover trials (DBP 0.47, SBP 0.51). Effect size increased in line with increased dosage. Although not all individual trials showed significance in BP reduction, combining all trials did show a decrease in SBP of 3–4 mm Hg and DBP of 2–3 mm Hg, which further increased with crossover designed trials and intake >370 mg/day. To conclude, magnesium supplementation appears to achieve a small but clinically significant reduction in BP, an effect worthy of future prospective large randomised trials using solid methodology.

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**Keywords:** hypertension; meta-analysis; supplementation; magnesium

## INTRODUCTION

Elevated blood pressure (BP) or hypertension is a major risk factor for mortality from cardiovascular and renal disease. Causes of essential hypertension include, but are not limited to, smoking, sedentary lifestyle, a diet high in sodium, and an inadequate intake of other minerals such as potassium, calcium and magnesium.[1]

It has been suggested that magnesium supplementation may decrease BP, as it acts as a calcium antagonist on smooth muscle tone, thus causing vasorelaxation.[2] There have been suggestions of an inverse relationship between daily dietary magnesium intake and BP.[3,4] There is also the possibility that individuals with dietary magnesium consumption in the higher quantiles are generally more health conscious and may take other steps to control BP. It should be considered, however, that the daily dietary intake of magnesium in the Western society has been declining from about 500 mg/day in the 1900s to a value closer to 175 mg/day,[5] increasing the likelihood of an individual being deficient in magnesium. This figure falls someway short of the current UK RNI outlined by the Department of Health[6] of 300 mg/day for men and 270 mg/day for women (12.35 and 11.1 mmol, respectively).

As hypertensives are usually advised to increase physical activity to improve BP and exercise causes increased excretion of magnesium in sweat and urine,[7] the authors set out to review the effect of magnesium on BP during exercise. There are no publications looking at the effect of magnesium intake on BP while undertaking physical activity or during the recovery period. Although regular exercise is advocated for hypertensive individuals, there can be concern that exercise may cause a transient increase in BP, negatively impacting an individual's BP. Both aerobic and resistance exercise can cause transient increases in BP, with resistance exercise often being perceived as having greater risk.[8] The introduction of magnesium through a supplement may enable the hypertensive to undertake an exercise programme at a greater intensity if BP is reduced through magnesium supplementation. Magnesium as a supplement has been shown to decrease BP in normotensives, yet is rarely considered as a supplement for elevated BP. Further, habitual dietary-magnesium intake is rarely assessed and no large randomised crossover studies have looked at baseline serum magnesium levels together with the impact of dietary or supplementary magnesium on BP. However, there is a focus in research among small trials on the effect of BP in various non-exercising individuals and this meta-analysis therefore sets out to review the general effect of magnesium on BP to enable future research into the effect of Mg on BP during exercise. Further, observation of the study designs used will help to influence the design of future research, allowing for more robust methodologies.

Some individual studies have shown significant reduction in both systolic (SBP) and diastolic blood pressure (DBP) with a magnesium intervention, although previous systematic reviews and meta-analyses have been less conclusive.[9–11] Burgess *et al.*[9] found no significant benefit of magnesium supplementation in hypertensive patients from a review of 12 treatment studies, and did not recommend magnesium as an antihypertensive agent. Dickinson *et al.*[10] reviewed 12 treatment studies of hypertensive patients and reported a small non-significant decrease in SBP of −1.3 mm Hg and a significant reduction of DBP of −2.2 mm Hg. Jee *et al.*[11] reported a small, non-significant reduction of

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−0.6 mm Hg SBP and −0.8 mm Hg DBP by analysing 20 treatment studies of hypertensive and normotensive individuals. However, a dose-dependent effect was also reported, with a reduction of −4.3 mm Hg SBP and −2.3 mm Hg DBP for every 240 mg/day (10 mmol) increase in supplemental magnesium. The variations in the dose-dependent relationships found in the above studies helped to rationalise the subgroup analysis of high and low magnesium dosage included in this meta-analysis.

The aim of this meta-analysis was to assess the effect of oral magnesium supplementation on the BP of both hypertensive and normotensive individuals and to establish the characteristics of trials associated with the greatest BP reductions.

## MATERIALS AND METHODS

### Article selection

Treatment studies published before July 2010 relating to the effects of magnesium supplementation on human BP were identified through a comprehensive search of MEDLINE and the Cochrane Library, using the keywords 'magnesium', 'supplementation', 'BP' and 'human'. Reference lists from the returned articles and previous systematic reviews were also searched. Relevant data were extracted by one investigator (JW); any articles containing data of an unclear or ambiguous nature were submitted to another investigator (LK); consensus was reached over whether to include these articles.

Twenty-two trials were included in the analysis, resulting in 23 sets of data, as a result of one trial producing two data sets. The dosage of magnesium ranged from 120 to 973 mg/day, with an average of 410 mg/day ± 179. Elemental magnesium was stratified into dosage $<370$ mg or $\geqslant 370$ mg/day. The majority of studies specified elemental magnesium dosages. In studies where elemental magnesium was not shown, the percentage of magnesium salt in the compound was used for the elemental magnesium. For magnesium oxide ($MgO^{-}$) 60% was used to calculate the elemental magnesium and 8.33% for magnesium chloride ($MgCl_2$).

The inclusion criteria were: (1) magnesium supplements as the only active intervention; (2) presence of a placebo or control group; (3) subjects over the age of 18; (4) random allocation of subjects to treatment conditions; and (5) parallel or crossover trial design. All criteria had to be met for inclusion into the study.

The primary outcome measures were SBP and DBP at the end of follow-up. Secondary outcome measures were total withdrawals from treatment and any adverse effects of treatment.

### Statistical analysis

For each trial, effect size was calculated using the Hedges *G* method[12] ($m^2-m^1$/s.d.$^2$). For randomised controlled trials, net change in BP was calculated as the mean difference (magnesium supplementation minus control) of the change in BP. For crossover trials, net change was calculated as the mean difference between the end of the magnesium supplementation and control or placebo periods. Standard error of the effect size was adjusted for crossover trials, as advised by Morris.[13] Repeated-measures designs can lead to errors in the exact variance, which underestimate the sampling variance. Where this correction can result in reduced accuracy of the meta-analysis, the degree of error is generally small and is therefore tolerated. Overall effect size estimates and 95% confidence intervals (CIs) were calculated using the DerSimonian and Laird's[14] random-effects model. The meta-analysis, Forest plots and Biggs funnel plots for both SBP and DBP were generated using STATA, version 11 (StataCorp LP, College Station, TX, USA).

## RESULTS

In total 141 potentially relevant articles were identified by the search strategy. Of these, 108 articles were excluded and 33 were electronically retrieved for further analysis. Exclusion criteria were: (1) combination of magnesium with other vitamins or minerals that can affect BP; (2) lack of a placebo or control group; (3) inadequate data being available to calculate the difference in BP change between groups; (4) subjects being $<18$ years of age; and (5) non-randomised allocation of subjects to treatment conditions.

From these, a further 11 articles were eliminated, leaving a total of 23 sets of data from 22 intervention trials. These trials included a total of 1173 individuals, with a sample size ranging from 13 to 155 participants. Every trial reported the sex of the subjects, with two only including males,[15,16] three only including females,[17–19] and the remaining 17 trials including both males and females. The total gender split of the subjects was 47% male and 53% female. The subjects were from 12 different countries (Brazil, Denmark, England, Finland, Holland, Ireland, Italy, Japan, Korea, Mexico, Sweden and USA). Thirteen trials were of parallel design, while 10 sets of data from nine trials were of crossover design. The mean age of individuals taking magnesium supplements in the trials was 50.1 years, while those on placebo treatment in the parallel trials had a mean age of 52 years. Subjects in three trials had non-insulin-dependent diabetes mellitus[20–22] and one trial observed individuals with insulin resistance.[15] Some or all of the subjects in six trials were receiving antihypertensive medication such as beta-blockers and diuretics. The other trials enrolled normotensive subjects, untreated hypertensive subjects or hypertensive subjects abstinent from treatment for a period of at least 1 month.

The duration of treatment with magnesium ranged from 3 to 24 weeks, with a mean duration of 11.3 weeks. The dose of elemental magnesium in the observed studies ranged from 120 mg/day (5 mmol) to 973 mg/day (40 mmol), with a mean dose of 410 mg/day (16.9 mmol). A total of seven different supplemental magnesium compounds were used ($MgO^{-}$, Mg aspartate, $MgCl_2$, $MgOH_2$, Mg lactate, Mg citrate, Mg pidolate). For 21 out of the 23 sets of data, trials were under double-blind conditions; the trial by Hattori *et al*.[23] was single blind, while no blinding was used by Kawano *et al*.[4] All studies used a placebo, aside from Kawano *et al*.,[4] which used baseline data and compared this with post-intervention results. Mean SBP on entry ranged from 110 to 173 mm Hg. Initial DBP ranged from 73 to 106.5 mm Hg for the subjects assigned to receive magnesium supplements.

Bias in the form of publication is difficult to avoid, but trials with a negative as well as a positive outcome were included in the meta-analysis to avoid this bias, as it is known that publication tends to favour positive outcomes. The quality of many of the included trials was poor and this may bias the results by way of an overestimation of the effect of treatment. Conversely, in this meta-analysis, it was seen that poorly designed trials may also bias the results against the supplement and its effect, as in the case of parallel designed trials.

### Analysis of the overall effect

Effect size for the meta-analysis for DBP was 0.36 and for SBP was 0.32, showing a similar effect for both measures (Figures 1 and 2). CIs at 95% were 0.23–0.41 for SBP and 0.27–0.44 for DBP. Heterogeneity for both cohorts was high ($I^2 = 82\%$ for DBP and 88% for SBP).

### Sub analysis–crossover vs non-crossover design

Stratification by crossover and non-crossover design was carried out.

When stratified by design of the trial, the effect estimates for SBP were 0.51 (CI 0.39–0.64) for crossover trials and 0.13 (CI 0.00–0.26) for non-crossover trials (Figure 3), and for DBP 0.47 (CI 0.35–0.59) for crossover trials and 0.23 (CI 0.10–0.36) for non-crossover trials (Figure 4).

In the DBP funnel plot (Figure 5) it can be seen that overall estimates of effect sizes in larger sample studies is quite diverse and spread quite widely at the top of the funnel, suggesting that only small studies showing negative results are more likely to be

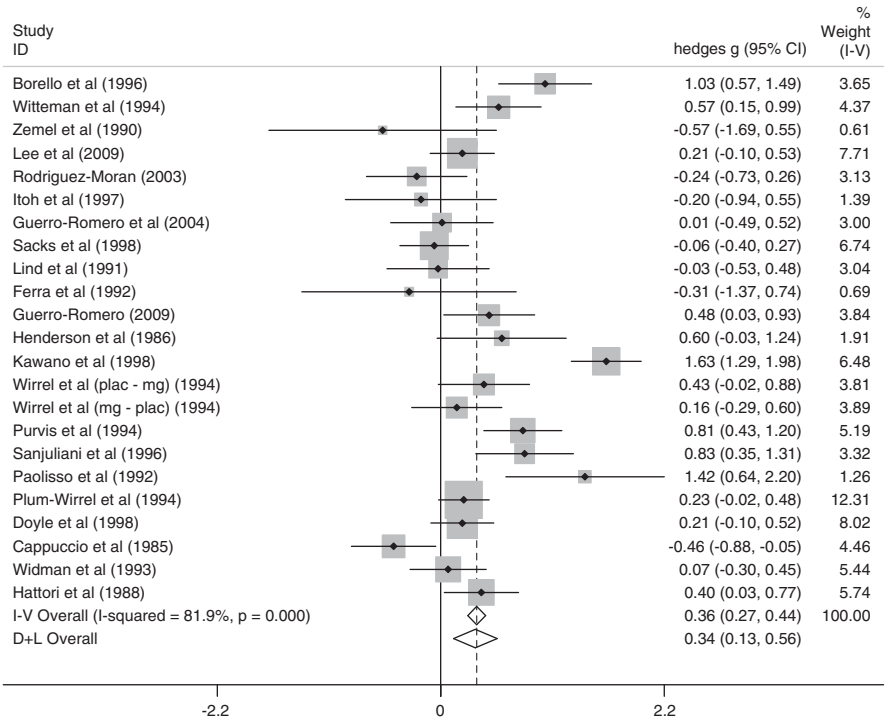


**Figure 1.** Forest plot for DBP.

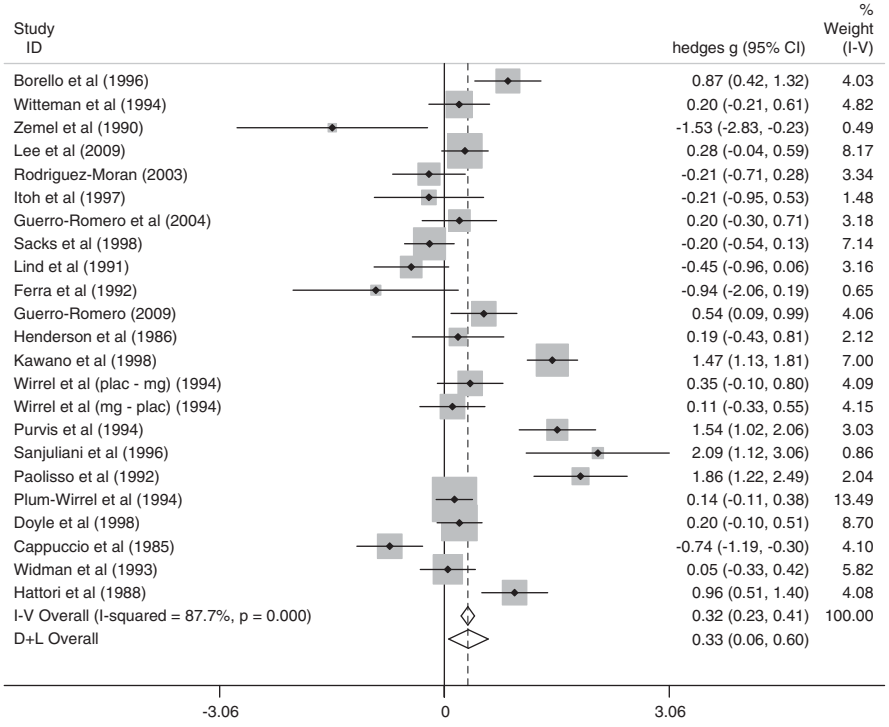


**Figure 2.** Forest plot for SBP.

published. For SBP (Figure 6) there seems to be a similar trend, but it can also be seen that there is a tendency for larger trials to fall within the left side of the funnel, around the 0 mark, suggesting that larger trials that show no effect are more likely to be published. From Figures 5 and 6 it can generally be seen that crossover trials show a more positive effect from the intervention.

### Subanalysis–dosage

The Committee on Medical Aspects of Food and Nutrition Policy[6] calculated a Reference Nutrient Intake (RNI) of 300 mg/day for adult males and 270 mg/day for adult females. None of the studies included in this meta-analysis had intakes between 300 and 370 mg and cohorts were all male; therefore two groups were

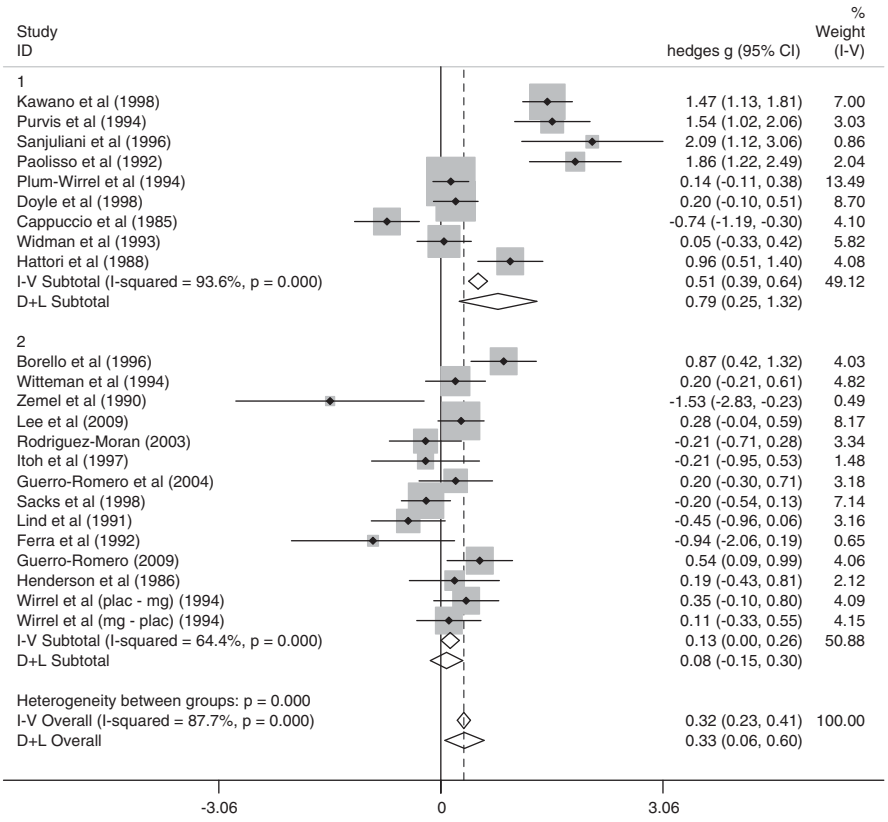


**Figure 3.** Forest plot for SBP by design. The top half (1) of the figure showing crossover designed studies; the lower half (2) shows non-crossover designed studies.

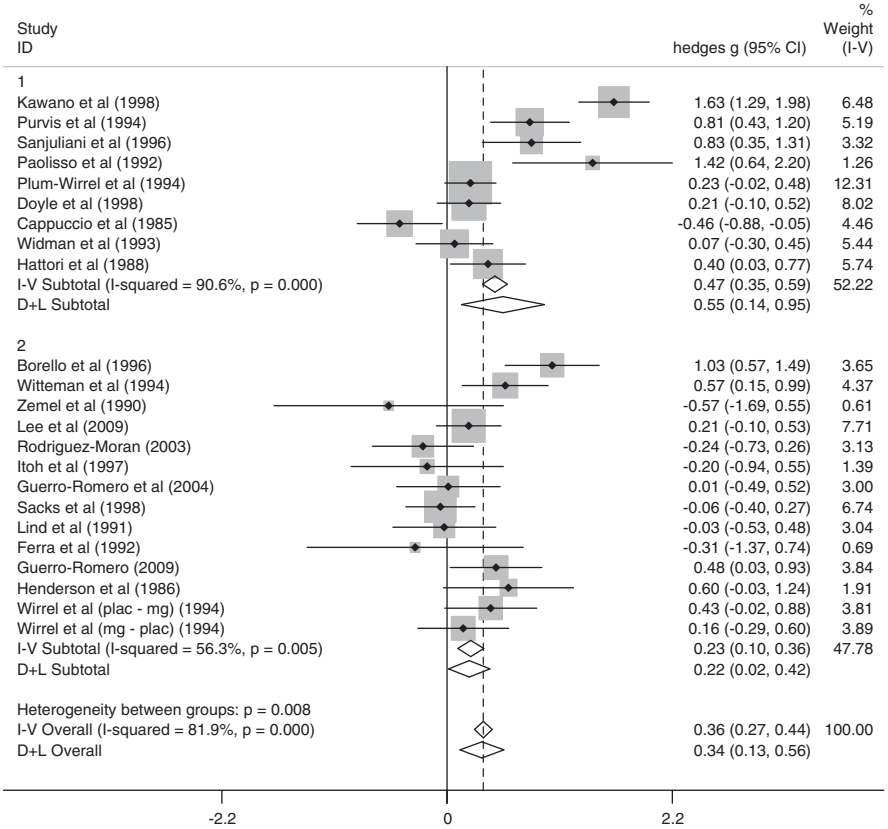


**Figure 4.** Forest plot for DBP by design. The top half (1) of the figure shows crossover designed studies; the lower half (2) shows non-crossover designed studies.

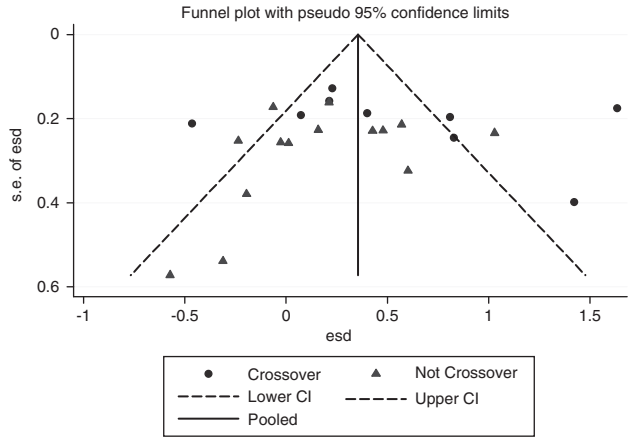


**Figure 5.** Funnel plot for DBP for all studies, coded for crossover and non-crossover design.

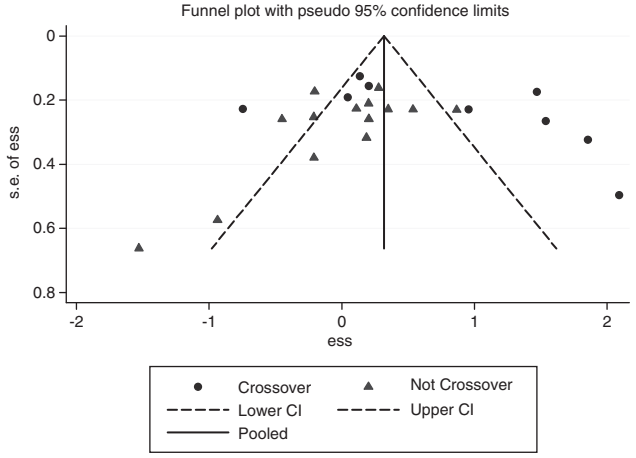


**Figure 6.** Funnel plot for SBP for all studies, coded for crossover and non-crossover design.

formed: one below and one above the RNI, with the division starting at the study with the nearest dosage above the RNI (370 mg). A subanalysis was then carried out dividing the dosage into $<370$ mg Mg/day and $\geqslant 370$ mg Mg/day, with results showing greater efficacy of magnesium supplementation at the higher dose (Figures 7 and 8). The $<370$ mg trials for SBP had an effect estimate of 0.14 (CI 0.03 to 0.25) and for DBP had an effect estimate of 0.21 (CI $-0.10$ to 0.31). The $\geqslant 370$ mg trials for SBP had an effect estimate of 0.72 (CI 0.56–0.89) and for DBP had an effect estimate of 0.66 (CI 0.51–0.82).

### Subanalysis–stratification by country

From the data analysed, no association could be found between country and effect size. Given the wide variation in publication origin and lack of information on the country of origin of subjects, no clinically relevant stratification by area could be made.

## DISCUSSION

This review of interventional epidemiological studies is suggestive of a negative association between magnesium supplementation and DBP and SBP, with a greater reduction being seen in SBP. The average reduction in BP based on an effect size of 0.36 for DBP and 0.32 for SBP translate to an actual reduction of 2–3 mm Hg for DBP and 3–4 mm Hg for SBP. At the lower dosage[24] the effect sizes for SBP and DBP were 0.87 and 1.03, respectively, whereas at the higher dosage[25] effect sizes were seen to be $-1.53$ and $-0.57$, although Zemel *et al.*'s[25] work was anomalous to other higher-dosage studies. The overall effect size for DBP was slightly higher than that for SBP. The majority of trials showed a reduction in BP, although significance was not always shown.

The Antihypertensive And Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT)[26] found, when comparing antihypertensive treatments, that a SBP reduction of between 0.8 and 2 mm Hg, depending on drug intervention, was clinically significant in reducing the incidence of coronary heart disease, heart failure and stroke. The clinical significance in the reductions found from this meta-analysis is potentially very important. The subanalysis discussed below allow for future research to realise the full potential of magnesium in lowering BP with appropriately designed trials.

### Dosage

When a subanalysis for dosage was carried out ($<370$ mg Mg and $\geqslant 370$ mg Mg/day), results for both SBP and DBP showed greater efficacy of magnesium supplementation at the higher dose. When the higher magnesium dosage was analysed a much higher effect size (DBP $= 0.66$ and SBP $= 0.70$; 95% CI 0.51–0.82 and 0.56–0.89 for DBP and SBP, respectively) was found. Those using $<370$ mg demonstrated high levels of variation. One anomaly for this was the study by Zemel *et al.*,[25] which used the highest dosage of 973 mg Mg/day but showed wide CI limits (DBP 95% CI $-1.69$ to 0.55, SBP $-2.83$ to $-0.23$) and a low effect size of $-0.57$ and $-1.53$ for DBP and SBP, respectively. This may be attributed to the small cohort size ($n = 13$) or to study design. However, dosage was not related to habitual dietary magnesium intake, which would affect the effect of supplementation, and no baseline measures of habitual magnesium intake were recorded in any of the studies. Further, no observations were made on the social–economic status of the cohorts, which would influence dietary intake and may bias the overall results. Only one study recorded serum magnesium levels, which the authors suggest would affect magnesium absorption from supplementation.

There was substantial heterogeneity between the findings of the trials for both DSP and SBP ($I^2 = 82$ and 88, respectively), which could be explained by random variation, the various population groups, the interventions or the methods used in the trials, and length of intervention. A more homogenous sample of studies may increase the effect size; although a random effects model was used, the difference between the studies was high.

### Crossover vs non-crossover design

Further subgroup analysis was carried out for study design (crossover vs non-crossover). For crossover trials the effect size increased substantially for both DBP and SBP when compared with the non-crossover trials, reinforcing the idea that paired data would have more robust results from the intervention than non-crossover, and that the effect from the intervention would be augmented.

Interestingly, the majority of crossover studies fell outside of the 95% confidence limits for SBP, which may be due to the different population groups between the studies or may be attributed to publication bias; however, effect size was larger in the crossover designed trials (SBP crossover 0.51, non-crossover 0.13; DBP crossover 0.47, non-crossover 0.23).

Trials were chosen to be as homogenous as possible, although some of the studies were of a lesser quality, with one failing to conceal allocation[4] and intra-subject variation for age, weight, clinical status and nationality.

A major limitation in most of the studies was lack of data on dietary intake, which would have had major implications for all studies. It would also have been beneficial if trials had looked at pre-trial serum magnesium levels and then looked at this again

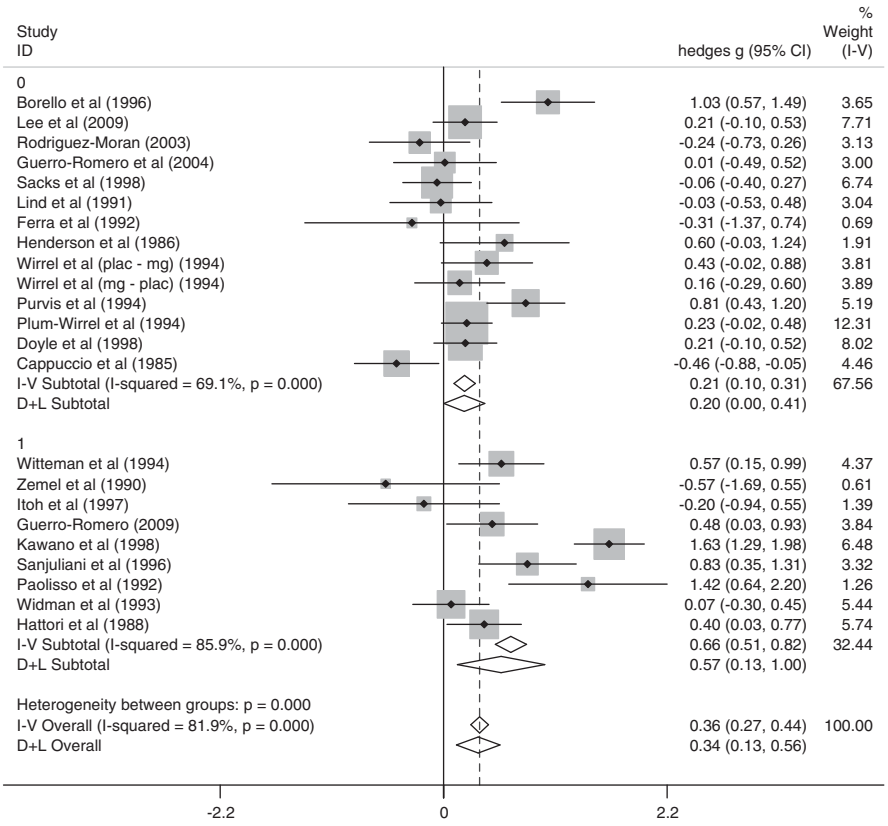


**Figure 7.** Forest Plot for DBP by dosage. The top half (0) of the figure shows $<370$ mg dosage magnesium; the lower half (1) shows $\geqslant 370$ mg dosage magnesium.

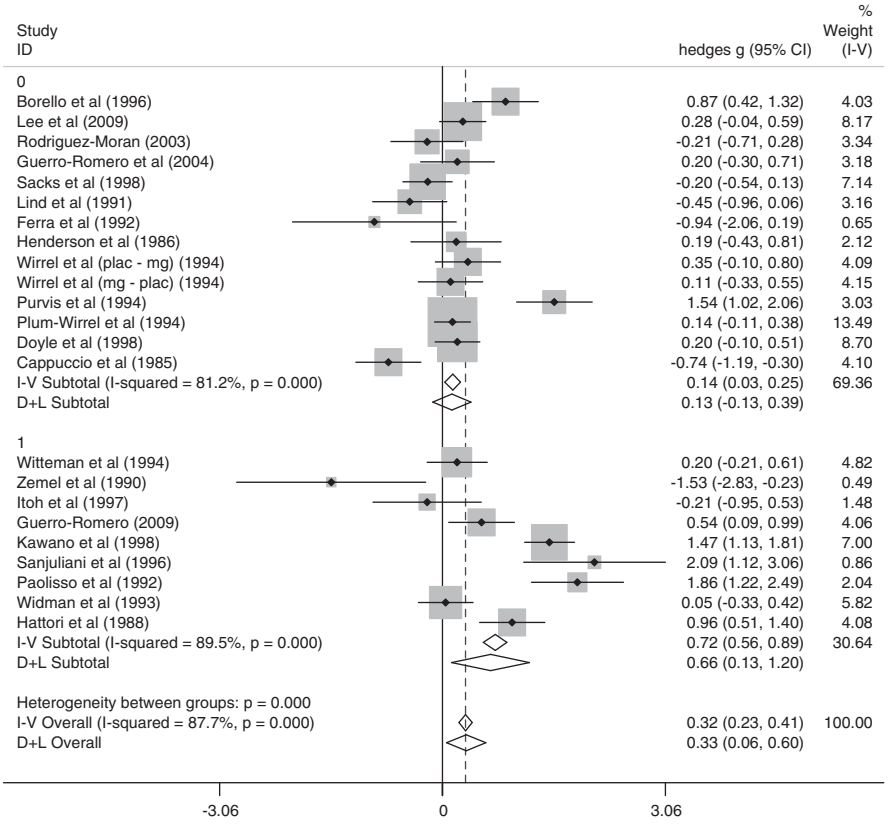


**Figure 8.** Forest plot for SBP by dosage. The top half (0) of the figure shows $<370$ mg dosage magnesium; the lower half (1) shows $\geqslant 370$ mg dosage magnesium.

after supplementation; this would also have given a better understanding of absorption over a range of magnesium intakes. Differences were seen between cross-over and non-crossover design and this would exaggerate inter-individual dietary habits in both design groups. Those who had the higher-magnesium diet may show less of a response to the supplement than those who had a lower intake, with a non-crossover design being more greatly affected by diet than a crossover design. To the best of the investigators' knowledge, only one systematic review has looked at dietary magnesium and BP,[27] and this concluded that there was a negative association between the two variables, although the authors attributed methodological problems of dietary data collection to this.

Of the 22 studies in this meta-analysis, 13 reported adverse effects from the intervention and placebo treatments,[4,15,16,18–22,28–32] six reported no adverse effects[24,33–38] and three did not report any information relating to adverse effects.[17,23,25] Of these studies, the adverse effects were largely either diarrhoea, or unspecific mild abdominal or bone pain. Only three studies reported serious adverse effects from the treatments that led to withdrawal from the investigations: Lind *et al*.[29] reported one case of visual impairment of a subject on magnesium treatment; Wirrel *et al*.[31] reported a myocardial infarction of a subject but did not specify the treatment that the subject was receiving; Plum-Wirrell *et al*.[32] reported a blood coagulation defect of one subject but also did not specify the treatment arm. Three subjects of Ferrara *et al*.[30] were also unable to complete the study due to an increase in BP.

All the trials analysed for this meta-analysis used magnesium supplements, and although the data had a high level of heterogeneity there was a reduction in BP, being more evident in the higher-dosage trials. Future research could potentially observe the effect of increased dietary magnesium intake to see if the results were correlated to similar amounts given as a supplement. Some studies have looked at magnesium and exercise in respect to performance and recovery parameters;[7,38] future research may investigate BP response alongside performance parameters.

In summary, this meta-analysis showed an overall reduction in SBP and DBP from magnesium supplementation. Studies had high heterogeneity, but the effect of treatment could still be seen. The average reduction in BP based on an effect size of 0.36 for DBP and 0.32 for SBP translates to an actual reduction of 2–3 mm Hg for DBP and 3–4 mm Hg for SBP. This could be strengthened by both crossover design and dosage $>370$ mg. Subanalysis for dosage showed greater efficacy of magnesium supplementation at the higher dose, with a higher effect size being seen. Those using $<370$ mg also demonstrated high levels of variation. Although these reductions are small, if optimised by the above suggestions, they could have a significant effect on BP, particularly on the pre-hypertensive population group. Further investigation may look at this effect during exercise and on pre-hypertensives who are encouraged to change their lifestyle and increase their physical activity level in order to maintain a normalised BP.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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