Magnesium supplementation for the management of primary hypertension in adults

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Abstract

Background
Epidemiological evidence on the effects of magnesium on blood pressure is inconsistent. Metabolic and experimental studies suggest that magnesium may have a role in the regulation of blood pressure.

Objective
To evaluate the effects of magnesium supplementation as treatment for primary hypertension in adults.

Search strategy
We searched the Cochrane Library, MEDLINE, EMBASE, Science Citation Index, ISI Proceedings, ClinicalTrials.gov, Current Controlled Trials, CAB abstracts, and reference lists of systematic reviews, meta-analyses and randomised controlled trials (RCTs) included in the review.

Selection criteria
Inclusion criteria were: 1) RCTs of a parallel or crossover design comparing oral magnesium supplementation with placebo, no treatment, or usual care; 2) treatment and follow-up ≥8 weeks; 3) participants over 18 years old, with raised systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥85 mmHg; 4) SBP and DBP reported at end of follow-up. We excluded trials where: participants were pregnant; received antihypertensive medication which changed during the study; or magnesium supplementation was combined with other interventions.

Data collection and analysis
Two reviewers independently abstracted data and assessed trial quality. Disagreements were resolved by discussion or a third reviewer. Random effects meta-analyses and sensitivity analyses were conducted.

Main results
Twelve RCTs (n=545) with eight to 26 weeks follow-up met our inclusion criteria. The results of the individual trials were heterogeneous. Combining all trials, participants receiving magnesium supplements as compared to control did not significantly reduce SBP (mean difference: -1.3 mmHg, 95% CI: -4.0 to 1.5, I²=67%), but did statistically significantly reduce DBP (mean difference: -2.2 mmHg, 95% CI: -3.4 to -0.9, I²=47%). Sensitivity analyses excluding poor quality trials yielded similar results. Sub-group analyses and meta-regression indicated that heterogeneity between trials could not be explained by dose of magnesium, baseline blood pressure or the proportion of males among the participants.

Reviewers’ conclusions
In view of the poor quality of included trials and the heterogeneity between trials, the evidence in favour of a causal association between magnesium supplementation and blood pressure reduction is weak and is probably due to bias. This is because poor quality studies generally tend to over-estimate the effects of treatment. Larger, longer duration and better quality double-blind placebo controlled trials are needed to assess the effect of magnesium supplementation on blood pressure and cardiovascular outcomes.

Synopsis
This review examined whether taking magnesium supplements could be recommended for treating adults with high blood pressure from no known cause. It reviewed 12 trials enrolling 545 people, which compared magnesium supplementation with a dummy drug (placebo) or no treatment, and measured blood pressure 8 weeks to 6 months later. The results of trials varied a lot: some trials found magnesium lowered blood pressure much more than placebo, while others found little difference between magnesium and placebo. On average, people receiving extra magnesium achieved slightly lower diastolic blood pressure at the end of trials. None of the studies reported any serious side effects of taking magnesium supplements. However, most included trials were of poor quality, so their results may not be reliable. The trials were not long enough or large enough to measure whether extra magnesium can reduce possible consequences of high blood pressure: death, heart attack or stroke. The review did not find robust evidence that oral magnesium supplementation reduces high blood pressure in adults. Larger, longer duration, better quality trials are needed to clarify whether magnesium supplementation can lower high blood pressure.

Background
High blood pressure, or hypertension, is associated with a variety of structural changes in the blood vessels and heart which can lead to cardiovascular disease, stroke and renal disease. It is one of the ten leading risk factors influencing the global burden of disease and is estimated to lead to over 7 million deaths each year, about 13% of the total deaths worldwide (WHO 2002). Reducing blood pressure levels is associated with significant reduction in cardiovascular and cerebrovascular morbidity and mortality (MacMahon 1990; PSC 2002). The most common form of hypertension, occurring in around 95% of all cases, is primary hypertension which is defined as high blood pressure with no identifiable cause (Brown 1997). Secondary hypertension is high blood pressure with an identifiable cause, e.g. renal disease or endocrine disturbances.

The epidemiological evidence about the effects of dietary magnesium intake on blood pressure is inconclusive (Burgess 1999; Ma 1995; Mizushima 1998). Although several studies suggest that higher levels of magnesium in the diet are associated with lower blood pressure, this association is not easy to interpret, firstly because of the difficulty in estimating accurately a person’s intake of magnesium and, secondly, because the amount of magnesium in diet is correlated with that of other nutrients that may modify blood pressure. Furthermore, conflicting results may be due to the effect of magnesium supplementation being influenced by dietary...
magnesium intake, type of medication, or level of hypertension. Although metabolic and experimental studies suggest that magnesium may have a role in the regulation of blood pressure, the mechanism by which magnesium deficiency might increase blood pressure is a matter of speculation (Buemi 2002). Studies in both animals and humans provide substantial evidence of a complex relationship between electrolytes: sodium, potassium, calcium and magnesium. Magnesium is a vasodilator when infused into veins and arteries (Terasawa 2001) and can cause a small but significant reduction in diastolic blood pressure (4/3 mmHg) in the short term (IMAGES 2004). Magnesium regulates the physical properties of cellular membranes and their permeability, and could therefore alter the permeability of cells for calcium and sodium, which is important in the development of hypertension (Singh 1989). It has also been hypothesised that an impairment in ionic metabolism may lead to an increase in intracellular calcium and a reduction in intracellular magnesium - characteristic features of hypertension - with a consequent alteration in sodium balance, which could raise blood pressure (Resnick 1999).

We performed a systematic review and the meta-analysis summarising the findings of randomised controlled trials of oral magnesium supplements on blood pressure. The systematic review of trials in hypertensive populations found no clear evidence of benefit of magnesium supplements and did not recommend it as a treatment for hypertension (Burgess 1999). The meta-analysis of 20 trials in both hypertensive and normotensive populations reported a small but non-significant reduction in blood pressure overall, but estimated a reduction in systolic blood pressure (SBP) of around 4.3 mmHg and a reduction in diastolic blood pressure (DBP) of around 2.3 mmHg for every 240 mg/day increase in magnesium (Jee 2002).

The aim of this review was to summarise the evidence about the benefits and harms of dietary magnesium supplementation for patients with primary hypertension, in order to inform decisions about recommendations for treatment. Ideally, we would assess the benefits and harms from the effects of the supplements on the risk of mortality and major cardiovascular outcomes - heart attack and stroke. However, as trials of nutritional supplements are usually small and short-term, these outcomes are rarely reported; we therefore concentrated on BP measurements, which are correlated with cardiovascular morbidity and mortality. We also summarised evidence about adverse effects, such as gastro-intestinal disturbances.

Results

Discussion

Effect of intervention

12 RCTs enrolling 545 participants, with between eight weeks and six months follow-up, met the review inclusion criteria. The trials were not designed to assess the effects of magnesium supplementation on mortality or cardiovascular events and only three trials reported such events. Meta-analysis of blood pressure outcomes showed that, overall, magnesium supplementation was associated with a small, statistically significant reduction in DBP but little change in SBP. However, as it is very unusual for an agent to lower DBP more than SBP (Law 2003), these findings for DBP should be interpreted with caution. Further, magnesium supplementation had little effect on SBP, even when the mean magnesium levels, which is not surprising as it is known that magnesium is poorly absorbed orally (BNF 2004).

Trials which are not blinded are more likely to report beneficial effects of the intervention than other trials (Schulz 1995). Nevertheless, a sensitivity analysis excluding trials which did not blind both participants and treatment providers showed similar results to the main analysis. Moreover, restriction of the analysis to the two trials which additionally blinded outcome assessors (Borrello 1996; Paolisso 1992) resulted in overall statistically significant net reductions in both SBP and DBP. This finding may not be generalizable, firstly because participants in these trials had higher mean baseline BP than those in most of the other trials and, secondly, because all participants in the trial of Paolisso 1992 had been receiving thiazide diuretics for over a year and may therefore have been suffering intracellular magnesium loss. Although these trials were triple blinded, they did not report adequate concealment of allocation, which has been shown to be associated with over-estimation of the effect of treatment (Schulz 1995).

There was heterogeneity between trials (I² = 62% and 47% for SBP and DBP respectively), which could reflect heterogeneity in either the patient populations, the interventions or the methods used in the trials. The possible modifying effects of dose of magnesium and initial blood pressure were evaluated by sub-group analysis, which showed no evidence that they influenced the effect of treatment. Hence it seems unlikely that either dose of magnesium or baseline blood pressure explains the heterogeneity.

Trials with 50% or fewer men showed a significantly greater net reduction in DBP in response to magnesium supplementation than other trials, but meta-regression showed no significant trend of the treatment effect with the percentage of male participants. The contrasting findings of the sub-group analysis and the meta-regression are partly because two trials (Paolisso 1992; Walker 2002) had exactly 50% men and the meta-regression did not require arbitrary assignment of these trials to one sub-group. The apparently significant difference in BP outcomes in the sub-group analysis between trials with a high percentage of male participants and others is likely to be a chance finding, as the pattern of results for DBP differed from that for SBP. Findings from multiple subgroup analyses can be misleading as subgroup analyses are observational by nature and not based on randomised comparisons (Cochrane Handbook).

Funnel plots showed little evidence of publication bias. Withdrawals were reported by treatment arm in eight trials enrolling 391 participants; both the rate of withdrawal for all causes and the rate of withdrawal due to adverse effects were similar in magnesium and control groups.

Adverse effects were reported by treatment arm in six trials enrolling 330 participants. The most commonly reported adverse effects were gastrointestinal symptoms. The reported frequency of all adverse events and of other adverse effects were similar in magnesium and control groups. Although two serious adverse events - a blood coagulation defect and a myocardial infarction - were reported in crossover trials, they cannot be ascribed to magnesium supplementation as the trials did not report which treatment the participants were receiving when these events occurred.

Previous findings

Our main findings - that magnesium supplementation has little effect on blood pressure - are consistent with those of a previous systematic review which did not include a meta-analysis (Burgess 1999).

A recent systematic review and meta-analysis of the effects of magnesium supplementation on blood pressure (Jee 2002) differed from ours in many aspects: it was not restricted to trials in hypertensive populations with at least 8 weeks follow-up and did not exclude trials with patients who had varied antihypertensive medications during the course of the trial. Although it included eight trials which we also included (Ferrara 1992; Henderson 1986; Kawano 1998; Lind 1991; Nowson 1989; Plum-Wirel 1994; Witteman 1994; Zemel 1990), it also included 12 trials which we excluded - six trials in normotensive populations (Dovey 1999; Itoh 1997; Purvis 1994; Sacks 1994; Salt 1998: TOPH 1992), four trials of less than eight weeks duration (Cappuccio 1985; Reyes 1984; Sanjuliani 1996; Widman 1993), one trial in which antihypertensive medication varied (Dyckner 1983) and one trial which was not randomised (Patki 1990). It excluded four trials which we included - two trials identified from searches of a database (CENTRAL) which Jee 2002 did not search (Borrello 1996; Paolisso 1992), one trial published after Jee 2002 completed their review (Walker 2002) and the trial of Wierl 1994. Furthermore, Jee 2002 analysed the difference between blood pressure at baseline and the end of the study (change scores) whereas we analysed blood pressure at the end of the study (final values), and Jee 2002 analysed ambulatory/home blood pressure from the study of Kawano 1998, whereas we analysed BP measured in clinic.
Nevertheless, the two reviews were consistent in finding that, overall, magnesium supplementation had little effect on the blood pressure of hypertensive people: Jee 2002 reported overall reductions in SBP (mean difference = -3.3 mmHg, 95% CI: -6.8 to 0.1) and in DBP (mean difference = -2.3 mmHg, 95% CI: -5.0 to 0.0), consistent with our findings of reductions in SBP (mean change = -1.3 mmHg, 95% CI: -4.0 to 1.5) and in DBP (mean difference = -2.2 mmHg, 95% CI: -3.4 to -0.9). The reviews were discordant in their explanation of differences between trials: Jee 2002 concluded that blood pressure reduction was significantly greater in participants with higher initial blood pressure, whereas we did not. If such an effect exists, the review of Jee 2002 is more likely than ours to detect it, as their review included trials with a wider range of initial blood pressure: our review was restricted to trials in hypertensive populations. Jee 2002 also concluded that blood pressure reduction was significantly greater in participants who received larger doses of magnesium (i.e. a dose-response), whereas we did not. The difference is largely due to the influence of a small trial (N=20) where the highest dose of magnesium (40 mmol/day, Zamul 1990). Baseline systolic blood pressure in this trial was 145 and 140 mmHg in the treatment and control groups, respectively, a difference which could easily have occurred by chance despite randomisation (p=0.5). This difference resulted in a substantial difference in the estimates of the effect of treatment made by Jee 2002 using change scores and made by us using final values (increases of 4 and 9 mmHg respectively), which was sufficient to change the conclusion regarding a possible dose-response. While it has been argued that it is better to use change scores than final values in a meta-analysis as they allow for differences between participants at baseline, the recommendation in the latest version of the Cochrane Reviewers' Handbook (Alderson 2003) is that: "Although sometimes used as a device to 'correct' for unecessary randomisation, this practice is not recommended." There are several reasons for this recommendation:

- in a meta-analysis of endpoint blood pressure, differences between groups at baseline tend to average out over the included trials,
- use of change scores involves two sources of measurement error, whereas use of final values involves only one,
- to exploit the extra precision gained by inclusion of additional cross-over trials, it is essential to analyse the final value rather than the change score as the former is likely to be more highly correlated within individuals and so lead to a more precise estimate of the treatment effect (Elbourne 2002).

Although epidemiological studies have reported an association between a higher magnesium intake and lower blood pressure in women (Acherio 1996; Keskelento 1988), we found no robust evidence that the effect of magnesium supplementation differed between men and women. While it is plausible that a biological mechanism specific to women may make them more susceptible to blood pressure reduction with magnesium supplementation than men, these epidemiological findings may have occurred by chance. The Dietary Approaches to Stop Hypertension (DASH) trial found a diet high in fruit and vegetables was effective in reducing blood pressure (Cooper 2000). While this diet was high in magnesium, it also high in other nutrients and low in fat and cholesterol, so it is difficult to identify the specific effective components.

Conclusions

Our meta-analysis demonstrated a small, statistically significant reduction in diastolic blood pressure and no reduction in systolic blood pressure with magnesium supplementation as compared to control. It found no evidence that magnesium supplementation is associated with adverse effects. However, for several reasons - the trials were of poor quality and had inconsistent results, magnesium supplementation resulted in little effect on systolic blood pressure and, although magnesium is known to be better absorbed orally, and it is unusual for an agent to lower DBP more than SBP (Law 2003) - we conclude that the evidence in favour of a causal association between magnesium supplementation and blood pressure reduction is weak. It is our opinion that, as poor quality studies generally tend to over-estimate the effects of treatment, the apparently significant reduction in diastolic blood pressure is most likely to be due to bias.

Even if increasing magnesium intake results in a reduction in diastolic blood pressure, this reduction is small, 2.2 mmHg, is not known to be sustained beyond 26 weeks and is not known to cause a decrease in morbidity and mortality. This is compared to the evidence for drugs, which singly result in average reductions of about 9.1 mmHg (95%CI: 8.8 to 9.3) in SBP and 5.5 mmHg (95%CI: 5.4 to 5.7) in DBP (Law 2003), are known to have sustained effects and to reduce morbidity and mortality. However, even small changes in blood pressure in large proportions of the population in a common condition such as hypertension could reduce adverse cardiovascular outcomes. Hence, if a clear sustained effect of magnesium supplementation on blood pressure were established, an increase in dietary magnesium at a population level could have important benefits.

Implications for research

More placebo controlled trials are warranted to clarify whether magnesium supplementation can reduce blood pressure in people with high blood pressure. These trials should be randomised, with adequate concealment of allocation of participants to treatment arms, and blinding of participants, treatment providers and outcome assessors. They should enrol a large number of participants and have long enough follow-up to allow detection of any meaningful long-term effects of magnesium supplementation. The question of whether the effect of magnesium supplementation on blood pressure varies with dose of magnesium, gender or baseline blood pressure should ideally be evaluated within such high quality RCTs, as comparisons between trials are likely to be confounded by other differences between trials.

References to studies included in this review

Borrello 1996 〈published data only〉


Ferrara 1992 〈published data only〉


Henderson 1986 〈published data only〉


Kawano 1998 〈published data only〉


Lind 1991 〈published data only〉


Nowson 2002 〈published data only〉


Paolisso 1992 〈published data only〉

Paolisso G, Marco G, Cozzolino D, Salvatore T, DAmore A, Lama D, Varricchio M, DOnofrio F. Chronic magnesium administration

Plum-Wirrel 1994 (published data only)

Walker 2002 (published data only)

Wirrel 1994 (published data only)

Wittteman 1994 (published data only)

Zemel 1990 (published data only)

* indicates the major publication for the study

References to studies excluded from this review

Appel 1995 (published data only)

Cappuccio 1985 (published data only)

Dyckner 1983 (published data only)

Geleijnse 1994 (published data only)


Hebert 1995 (published data only)

Hollis 1995 (published data only)

McCarron 1984 (published data only)

PatiK 1990 (published data only)

Reyes 1984 (published data only)

Sacks 1994 (published data only)

TOHP 1992 (published data only)
The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA 1992;267:1213-1220.

Widman 1993 (published data only)

Yamamoto 1995 (published data only)

Zoccali 2002 (published data only)
Zoccali C, MallamaF, Delfino D. Does calcium have a dual effect on arterial pressure? Response to 1,25 dihydroxy vitamin D3 and calcium supplements in essential hypertension. Journal of Hypertension 1987;5:267S-269S.

Additional references

Acherio 1996

Alderson 2003

Australian 1989

BNF 2004
British National Formulary 47. 2004.-.

Brown 1997

Bruce 1999

Buemi 2002
Burgess 1999

Cochrane Handbook

Conlin 2000

Curtin 2002

Dickerson 1994

Doherty 1999

Elbourne 2002


Higgins 2003

Higgins 2003

JNC VII 2003

Kawano 1998 (ii)

Kawano 1998 (ii)

Kawano 1998 (ii)


Singh 1989

Teragawa 2001

Thompson 2001

WHO 2002

Graphs

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

### Magnesium vs. control (parallel trials only)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>1 Systolic BP</td>
<td>9</td>
<td>389</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.27 [-4.23, 4.78]</td>
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<tr>
<td>2 Diastolic BP</td>
<td>9</td>
<td>389</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-2.01 [-4.13, 0.11]</td>
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### Magnesium vs. control (crossover trials only)

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<th>Effect size</th>
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<tr>
<td>1 Systolic BP</td>
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<td>282</td>
<td>MD (Random, 95% CI)</td>
<td>-3.53 [-5.53, -1.53]</td>
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<tr>
<td>2 Diastolic BP</td>
<td>3</td>
<td>282</td>
<td>MD (Random, 95% CI)</td>
<td>-2.02 [-3.07, -0.96]</td>
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### Magnesium vs. control (all trials, subgrouped by magnesium dose)

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<th>No. of participants</th>
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<tr>
<td>1 Systolic BP</td>
<td>12</td>
<td>671</td>
<td>MD (Random, 95% CI)</td>
<td>-1.26 [-3.99, 1.47]</td>
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<tr>
<td>1.1 Magnesium dose &lt;= 15 mmol/day</td>
<td>7</td>
<td>389</td>
<td>MD (Random, 95% CI)</td>
<td>-0.39 [-4.55, 3.78]</td>
</tr>
<tr>
<td>1.2 Magnesium dose &gt; 15 mmol/day</td>
<td>5</td>
<td>282</td>
<td>MD (Random, 95% CI)</td>
<td>-3.23 [-5.48, -0.98]</td>
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<tr>
<td>2 Diastolic BP</td>
<td>12</td>
<td>671</td>
<td>MD (Random, 95% CI)</td>
<td>-2.15 [-3.40, -0.90]</td>
</tr>
<tr>
<td>2.1 Magnesium dose &lt;= 15 mmol/day</td>
<td>7</td>
<td>389</td>
<td>MD (Random, 95% CI)</td>
<td>-1.98 [-3.86, -0.11]</td>
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<tr>
<td>2.2 Magnesium dose &gt; 15 mmol/day</td>
<td>5</td>
<td>282</td>
<td>MD (Random, 95% CI)</td>
<td>-2.08 [-3.29, -0.87]</td>
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### Magnesium vs. control (all trials - subgrouped by baseline blood pressure)

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<tr>
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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>1 Systolic BP</td>
<td>10</td>
<td>469</td>
<td>MD (Random, 95% CI)</td>
<td>-0.40 [-4.24, 3.45]</td>
</tr>
<tr>
<td>1.1 Baseline SBP &lt;=150 mmHg</td>
<td>5</td>
<td>278</td>
<td>MD (Random, 95% CI)</td>
<td>0.88 [-3.64, 5.40]</td>
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<tr>
<td>1.2 Baseline SBP &gt;150 mmHg</td>
<td>5</td>
<td>191</td>
<td>MD (Random, 95% CI)</td>
<td>-2.22 [-9.04, 4.61]</td>
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<tr>
<td>2 Diastolic BP</td>
<td>10</td>
<td>469</td>
<td>MD (Random, 95% CI)</td>
<td>-2.15 [-3.91, -0.39]</td>
</tr>
</tbody>
</table>
### 2.1 Baseline SBP <=150 mmHg
- **5** participants
- MD (Random, 95% CI) -1.62 [-3.57, 0.33]

### 2.2 Baseline SBP >150 mmHg
- **5** participants
- MD (Random, 95% CI) -2.93 [-6.19, 0.34]

**Magnesium vs. control (all trials - subgrouped by % male)**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
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</tr>
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<tr>
<td>1 Systolic BP</td>
<td>11</td>
<td>587</td>
<td>MD (Random, 95% CI)</td>
<td>-1.44 [-4.09, 1.20]</td>
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<tr>
<td>1.1 &lt;=50% male</td>
<td>4</td>
<td>228</td>
<td>MD (Random, 95% CI)</td>
<td>-5.34 [-8.17, -2.52]</td>
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<tr>
<td>1.2 &gt;50% male</td>
<td>7</td>
<td>359</td>
<td>MD (Random, 95% CI)</td>
<td>0.07 [-3.19, 3.34]</td>
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<tr>
<td>2 Diastolic BP</td>
<td>11</td>
<td>631</td>
<td>MD (Random, 95% CI)</td>
<td>-2.01 [-3.33, -0.70]</td>
</tr>
<tr>
<td>2.1 &lt;=50% male</td>
<td>4</td>
<td>228</td>
<td>MD (Random, 95% CI)</td>
<td>-4.75 [-6.47, -3.03]</td>
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<tr>
<td>2.2 &gt;50% male</td>
<td>7</td>
<td>403</td>
<td>MD (Random, 95% CI)</td>
<td>-1.32 [-2.34, -0.31]</td>
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**Magnesium vs. control (excluding poor quality trials)**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Systolic BP</td>
<td>10</td>
<td>456</td>
<td>MD (Random, 95% CI)</td>
<td>-0.40 [-4.11, 3.31]</td>
</tr>
<tr>
<td>1.1 Double blinded</td>
<td>8</td>
<td>355</td>
<td>MD (Random, 95% CI)</td>
<td>1.16 [-2.39, 4.70]</td>
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<tr>
<td>1.2 Triple blinded</td>
<td>2</td>
<td>101</td>
<td>MD (Random, 95% CI)</td>
<td>-6.88 [-10.12, -3.64]</td>
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<tr>
<td>2 Diastolic BP</td>
<td>10</td>
<td>456</td>
<td>MD (Random, 95% CI)</td>
<td>-1.94 [-3.59, -0.29]</td>
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<tr>
<td>2.1 Double blinded</td>
<td>8</td>
<td>355</td>
<td>MD (Random, 95% CI)</td>
<td>-1.32 [-2.60, -0.04]</td>
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<tr>
<td>2.2 Triple blinded</td>
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<td>101</td>
<td>MD (Random, 95% CI)</td>
<td>-5.71 [-8.02, -3.41]</td>
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</table>

**Magnesium vs. control: sensitivity analysis excl. trials not reporting SD of treatment effect**

<table>
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<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
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<tr>
<td>1 Systolic BP</td>
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<td>513</td>
<td>MD (Random, 95% CI)</td>
<td>-0.47 [-4.01, 3.07]</td>
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<tr>
<td>2 Diastolic BP</td>
<td>10</td>
<td>513</td>
<td>MD (Random, 95% CI)</td>
<td>-2.00 [-3.66, -0.34]</td>
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**Magnesium vs. control (sensitivity analysis without Paolisso)**

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<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Systolic BP</td>
<td>11</td>
<td>653</td>
<td>MD (Random, 95% CI)</td>
<td>-1.03 [-3.79, 1.74]</td>
</tr>
<tr>
<td>2 Diastolic BP</td>
<td>11</td>
<td>653</td>
<td>MD (Random, 95% CI)</td>
<td>-2.10 [-3.38, -0.82]</td>
</tr>
</tbody>
</table>

**Magnesium vs. control (parallel trials only)**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
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<tbody>
<tr>
<td>1 Withdrawal from treatment (all causes)</td>
<td>8</td>
<td>391</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.00 [-0.04, 0.03]</td>
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### Magnesium vs. control

<table>
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<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 All adverse effects</td>
<td>6</td>
<td>330</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>0.01 [-0.04, 0.06]</td>
</tr>
<tr>
<td>2 Gastro-intestinal adverse effects</td>
<td>3</td>
<td>245</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>3 Other adverse effects</td>
<td>4</td>
<td>229</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.00 [-0.07, 0.06]</td>
</tr>
</tbody>
</table>

### Magnesium vs. control for serum magnesium levels

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Serum magnesium</td>
<td>9</td>
<td>18</td>
<td>MD (Random, 95% CI)</td>
<td>-0.00 [-0.04, 0.04]</td>
</tr>
</tbody>
</table>