**MAGNESIUM AND HEALTH OUTCOMES: AN UMBRELLA REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSES OF OBSERVATIONAL AND INTERVENTION STUDIES**

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**ABSTRACT**

**Purpose:** To map and grade all health outcomes associated with Magnesium (Mg) intake using an umbrella review.

**Methods:** Umbrella review of systematic reviews with meta-analyses of observational studies and randomised controlled trials (RCTs) using placebo/no intervention as control group. We assessed meta-analyses of observational studies based on random-effects summary effect sizes and their P-values, 95% prediction intervals, heterogeneity, small-study effects and excess significance. For meta-analyses of RCTs, outcomes with a random effects P-value <0**.**005 and a high GRADE assessment, were classified as strong evidence.

**Results:** From 2,048 abstracts, 16 meta-analyses and 55 independent outcomes were included (36 in RCTs and 19 in observational studies). In RCTs of Mg versus placebo/no active treatment, 12 over 36 outcomes reported significant results (p<0.05). A strong evidence for decreased need for hospitalization in pregnancy and for decreased risk of frequency and intensity of migraine relapses in people with migraine was observed using the GRADE assessment. In observational studies, 9/19 outcomes were significant (p<0.05). However, only one outcome presented highly suggestive evidence (lower incidence of type 2 diabetes in people with higher Mg intake at baseline) and one suggestive (lower incidence of stroke associated with higher Mg intake at baseline).

**Conclusion:** Strong evidence according to the GRADE suggests that Mg supplementation can decrease the risk of hospitalization in pregnant women and reduce the intensity/frequency of migraine. Higher Mg intake is associated with a decreased risk of type 2 diabetes and stroke with highly suggestive and suggestive evidence, respectively, in observational studies.

**Key words:** magnesium; meta-analysis; pregnancy; diabetes; stroke; umbrella review.

**INTRODUCTION**

Magnesium (Mg) is a co-factor in more than 300 enzyme systems involved in several biochemical reactions, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation. [[1-4](#_ENREF_1)] In this regard, Mg is required for energy production, oxidative phosphorylation, and glycolysis.[[1](#_ENREF_1)] Mg is strongly involved in the structural development of bone and is required for the synthesis of nucleic acids and for the antioxidant glutathione.[[4](#_ENREF_4)] Finally, Mg plays a role in the transport of calcium and potassium ions across cell membranes, a fundamental process for nerve impulse conduction, muscle contraction, and heart function.[[5](#_ENREF_5)]

Even if Mg is largely distributed in plant and animal foods, some foods (such as green leafy vegetables, legumes, nuts, seeds, and whole grains) provide richer sources. [[6](#_ENREF_6)] However, dietary surveys of people in North America have reported that the intake of Mg is suboptimal and lower than recommended amounts. [[7](#_ENREF_7)] In particular, an analysis of data from the National Health and Nutrition Examination Survey (NHANES) found that the majority of Americans of all ages ingest less Mg from food than needed and only with supplementations can the American population reach the amount of Mg needed for good health.[[7](#_ENREF_7)]

Traditionally, Mg has been associated with better health outcomes, including lower risk of diabetes[[8](#_ENREF_8)], hypertension[[9](#_ENREF_9)], osteoporosis and fractures[[10](#_ENREF_10)], sarcopenia[[11](#_ENREF_11)] and frailty[[12](#_ENREF_12)], but the overall benefits of the use of Mg for diverse outcomes are still unclear. Therefore, we aimed to assess the strength and credibility of the evidence derived from systematic reviews with meta-analyses on Mg intake, with an umbrella review. We used the umbrella review methodology to combine evidence from a wide range of outcomes and populations, and we present results separately for observational studies and randomised controlled trials (RCTs).

**METHODS**

We conducted an umbrella review (i.e. an assessment of systematic reviews followed by meta-analyses done in a specific research topic).[[13](#_ENREF_13)] We searched the MEDLINE, Scopus, Embase databases from inception until 1st March 2018 with the following search terms: (Meta-Analysis[ptyp] OR metaanaly\*[tiab] OR meta-analy\*[tiab] OR Systematic review [ptyp] OR “systematic review” [tiab]) AND (magnesium [tiab]). In addition, we hand-searched the reference lists of eligible articles.

This review is recorded in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display\_record.php?ID=CRD42018092700).

***Inclusion/exclusion criteria***

We included formal systematic reviews with meta-analyses of longitudinal (prospective and case-control) studies that investigated the association of dietary magnesium (assessed through validated dietary questionnaires) with any health-related outcome (e.g. cardiovascular disease, cancer, death, diabetes or other metabolic diseases) or meta-analyses of randomized controlled trials (RCTs) vs. placebo/no intervention that investigated the association of magnesium (as oral supplementation) with any health-related outcome. Only papers written in English were considered.

Four authors (GC, GP, TB, SC) performed the primary screening of the title and abstract, by couples, independently. Disagreements were resolved through consensus with another independent author (JD). The full-texts of all potentially eligible articles were then retrieved by the same four authors and any disagreement was resolved with another independent author (NV).

Studies had to report the outcomes as odds ratio (OR), relative risk (RR), hazard ratio (HR), standardized mean differences (SMDs), weighted mean differences (WMDs) or mean differences (MDs).

Studies were excluded if: Mg was used in association with another medication/supplementation, i.e. double therapy (e.g. Mg plus calcium); use of Mg as laxative; use of Mg as intravenous agent; active control groups (e.g. a comparison between Mg and one antidepressant); cross-sectional studies; systematic reviews without meta-analysis; conference abstracts; animal or in vitro models.

***Data extraction***

Four independent investigators (GC, GP, TB, SC), extracted the following information for each meta-analysis, independently, in pairs: first author name; year of publication; the number of included studies and the total number of people included in the meta-analysis; the study population; the type of effect size used in the meta-analysis; the study design; the number of participants with and without events for each study. We finally extracted the information for doing the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[[14](#_ENREF_14)]

When more than one meta-analysis on the same research question using the same study design (observational or RCTs) was identified, the one with the largest number of included studies was selected.

***Quality of the meta-analyses***

We assessed the methodological quality of the included meta-analyses using AMSTAR.[[14](#_ENREF_14)] We categorized the overall AMSTAR score as high (8-11 items achieved), moderate (4-7 items) and low (0-3 items).[[14](#_ENREF_14)]

***Statistical analysis***

For each meta-analysis, we estimated the summary effect size and its 95% CI through both fixed and random-effects models.[[15](#_ENREF_15)] We also estimated the prediction interval and its 95% CI, which further accounts for between-study effects, and estimates the certainty of the association if a new study addresses that same association.[[16](#_ENREF_16),[17](#_ENREF_17)] In order to estimate whether any large (very precise) studies were available, for the largest (most precise) dataset of each meta-analysis, we calculated the standard error (SE) of the effect size. If the SE is less than 0**.**10 then the 95% confidence interval (CI) would be lower than 0**.**20 (which is less than the magnitude of a small effect size). Between-study inconsistency was estimated with the *I2* metric, with values > 50% indicative of high heterogeneity.[[18](#_ENREF_18)]

In addition, we calculated the evidence of small-study effects (i.e. whether small studies would have inflated effect sizes compared to larger studies). To this end, we used the regression asymmetry test.[[19](#_ENREF_19)] A p-value < 0**.**10 with more conservative effects in larger studies in random-effects meta-analysis was considered as indicative of small-study effects.[[20](#_ENREF_20)]

Finally, we applied the excess of significance test.[[21](#_ENREF_21)] Briefly, this test evaluates whether the number of studies with nominally significant results (i.e., with p < 0**.**05) among those included in a meta-analysis is too large based on the power that these data sets have to detect effects at α=0**.**05. The power estimate for each data set was calculated. The sum of the power estimates of each study provides the expected (E) number of data sets with nominal statistical significance. As described elsewhere, the number of expected ‘positive’ (i.e. statistically significant) data sets can be compared with the observed (O) number of statistically significant studies through a χ2-based test.[[21](#_ENREF_21)] The larger the difference between O and E, the higher the degree of excess significance.

We considered the effect size of the largest dataset and based on this we estimated the power of each constituent study with an algorithm using a non-central *t* distribution. Excess significance for each meta-analysis was considered whenever p < 0**.**10.

All the analyses were conducted with STATA 13.0.

***Grading the evidence***

For observational studies, using the criteria mentioned above, associations that presented nominally statistically significant random effects summary estimates (i.e. p < 0**.**05) were categorized into convincing, highly suggestive, suggestive, or weak evidence, following a grading scheme that has already been applied in various fields.[[22-29](#_ENREF_22)]

Criteria for class I (convincing) were the following: statistical significance with P<10−6, more than 1,000 cases (or >20,000 participants for continuous outcomes), the largest component study reported statistically significant effect (P<0**.**05); 95% prediction interval excluded the null; no large heterogeneity (I2 <50%), no evidence of small study effects (P>0**.**10) and excess significance bias (P>0**.**10); for class II (highly suggestive): statistical significance with P<10−6, more than 1,000 cases (or >20,000 participants for continuous outcomes), the largest component study reported statistically significant effect (P<0**.**05); for class III (suggestive): statistical significance with P<10−3, more than 1,000 cases (or >20,000 participants for continuous outcomes); for class IV (weak): the remaining statistically significant associations with P<0**.**05.

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a p-value <0**.**005 as the threshold for statistical significance, as recently proposed.[[30](#_ENREF_30),[31](#_ENREF_31)] The evidence of the RCTs was classified as follows: p<0.005 correspondend to high evidence; 0.005<p<0.01 moderate; all other outcomes having a p-value<0.05 as poor evidence. When the p-value for the random effect was <0**.**005, we further evaluated the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment.[[32](#_ENREF_32)] We also considered 95% prediction interval (excluding the null or not), the presence of large heterogeneity (I2 >50%), small study effects (P>0**.**10), and excess significance (P>0**.**10) as possible indicators of heterogeneity and bias in the available evidence.

**RESULTS**

***Literature review***

As shown in **Figure 1**, we identified 2,048 non-duplicated papers across three major databases. After applying the eligibility criteria, 95 publications were selected as potentially eligible and, among these, 16 meta-analyses [[33-48](#_ENREF_33)] (corresponding to 55 indipendent outcomes) were finally included in the present umbrella review.

***Meta-analyses of RCTs (vs. placebo/no treatment)***

As reported in **Supplementary** **Table 1**, the median number of RCT meta-analyses using placebo/no treatment for each outcome was 3 (range 2-34) with a median number of participants of 1,225 (range: 27 to 16,328).

Overall, 36 outcomes were included. Placebo was used in 23 outcomes (64%), followed by mixed control groups (placebo/no interventions/usual care) (13%). Twenty-three outcomes (64%) investigated the role of Mg in pregnant women, followed by diabetic or at high risk of diabetes participants (8 outcomes over 36).

Overall, 12 (33%) out of the 36 outcomes reported nominally significant summary results (p<0**.**05), with only 4 surving the application of a more stringent p value (p<0**.**005): lower diastolic blood pressure in mixed populations; reduction of frequency and intensity of migraine relapses in people with migraine; lower incidence of need for hospitalization in pregnant women.

In **Table 1**, we used the GRADE assessment for assessing the evidence regarding the use of Mg supplementations in RCTs in outcomes having a p-value <0.005. According to this evaluation, there was evidence that Mg supplementation (compared to placebo/no intervention) decreased the risk of frequency and intensity of migraine relapses in people with migraine and need for hospitalization in pregnant women, whilst the effect of Mg supplementation on diastolic blood pressure was only moderate, due to the large heterogeneity found for this outcome.

The study with the largest sample size of each database had a SE of less than 0**.**10 in only 6 outcomes over 36. The largest study was significant in 7/36 outcomes included. Heterogeneity among studies was generally low (I2<50% in 25/36 outcomes), with 19 having a I2=0%. Finally, evidence for excess statistical significance was present in three outcomes and small-study effects in two outcomes.

As reported in **Supplementary Table 2**, the median AMSTAR score for these meta-analyses was 7 (range: 5-9), indicating a moderate quality.

***Meta-analyses of observational studies***

As reported in **Supplementary** **Table 3**, the median number of studies in meta-analyses including observational studies for each outcome was 6 (range 3-32), the median number of participants was 108,424 (range 606 to 2,589,742), and the median number of cases was 7,741 (range 701 to 79,463).

All the meta-analyses included people from the general population (i.e. people without any specific inclusion criteria reflecting population-based studies), except one including patients with kidney failure followed by kidney transplant. Overall these meta-analyses included 19 outcomes, including a wide spectrum of medical disorders. Cardiometabolic diseases (i.e. cardiovascular diseases and their risk factors, including type 2 diabetes) were the most common outcomes investigated.

Using a p-value of 0.05, 9/19 (47%) of the outcomes included reported nominally significant summary results, with only two associations (i.e. the association between dietary and serum Mg with diabetes) surviving the application of the more stringent *P* value (*P* < 10−6).

The study with the largest sample size of each database had a SE of less than 0**.**10 in 11 outcomes and the largest study was significant in 9/19 outcomes. Heterogeneity among studies was low in 12/19, i.e. an I2 estimates <50%. Only one outcome reported a 95% prediction intervals excluding the null value. Evidence for excess statistical significance was present in 5/19 outcomes and small-study effects were seen in only two outcomes.

Using the above criteria, no outcome presented convincing evidence, one outcome presented highly suggestive evidence (class II: lower incidence of type 2 diabetes in people consuming more Mg) and one suggestive (class III: lower incidence of stroke associated with higher Mg intake at baseline). Weak evidence was found for 6/19 outcomes.

The median AMSTAR score was 5 (range: 4-8), which is moderate quality (**Supplementary Table 4**). However, the two outcomes having highly suggestive and suggestive evidence had a high quality of the evidence (AMSTAR= 7 for diabetes and 8 for stroke), respectivetly.

**DISCUSSION**

With this work, we provided a comprehensive overview of the reported associations between Mg and a wide range of health outcomes by incorporating evidence from meta-analyses of RCTs and observational studies. [[23](#_ENREF_23),[28](#_ENREF_28),[29](#_ENREF_29)] When analyzing the data from RCTs, there is a strong evidence that Mg supplementation is able to decrease the need for hospitalization in pregnant women and migraine relapses in people already affected by this condition. Finally, we found that higher dietary Mg intake was associated with a lower risk of type 2 diabetes and stroke in observational studies with highly suggestive and suggestive evidence, respectively.

The significant outcomes of intervention and observational studies included in this umbrella review are summarized in **Table 2**.

As main finding, we found that oral Mg supplementation is able to decrease the need of hospitalization in pregnant women. When compared to placebo, in fact, we observed that Mg led to 36 fewer hospitalizations per 1,000 pregnant women. This result is in line with the use of Mg sulfate, as suggested by several guidelines. Mg sulfate, in fact, is recommended for the prevention of eclampsia in women with severe pre-eclampsia in preference to other anticonvulsants [[21](#_ENREF_21)], suggesting that Mg is of particular importance in pregnancy. However, since the effect of Mg on pregnancy outcomes was heterogenous, as shown by the same Cochrane review[[36](#_ENREF_36)] from which this specific outcome was extracted, further studies are needed to explain the reasons for which Mg supplementation is able to decrease the need of hospitalization in pregnant women.

Furthemore, the effect of Mg on blood pressure remains unclear, despite this being a topic of great interest in nutritional science. Our umbrella review suggests that, when compared to placebo, Mg supplementation was able to decrease systolic and diastolic blood pressure by about 2 mmHg that is probably of limited clinical meaning. Similarly, higher dietary intake prevent the incidence of hypertension only with a weak evidence. Thus, the studies reporting a favorable effect on cardiometabolic outcomes, given by the effect of Mg on blood pressure, should probably consider other theories.

In observational studies, higher dietary Mg intake was associated with a lower risk of type 2 diabetes. In the meta-analysis including 32 studies (and 1,084,602 participants), people in the highest category of dietary Mg intake had a risk reduction of 28% compared to people having lower intake. Even if this finding was highly significant, it was characterized by a high heterogeneity, suggesting that some external factors can affect our results. From a pathophysiological point of view, low Mg intake could be associated with diabetes through several mechanisms. First, higher Mg intake is highly associated to other healthy lifestyle and dietary factors (e.g. cereal fibers [[29](#_ENREF_29)]) and it is consequently difficult to isolate the effect of Mg intake on diabetes risk from other dietary factors.[[49](#_ENREF_49)] Second, in animal models, intracellular Mg deficiency might result in dysfunction of tyrosine kinase activity during insulin signaling and glucose-induced insulin secretion consequently leading to impaired insulin sensitivity in insulin-sensitive tissues such as liver, muscle or fat. [[50](#_ENREF_50)] However, it should be noted that in RCTs when compared to placebo Mg supplementation was able to significantly improve only 2-hour oral glucose tolerance test in people at high risk of diabetes (and with a poor strength of evidence) and this finding was limited to only two studies. The effect of Mg supplementation in RCTs for the other metabolic outcomes (e.g. fasting plasma glucose, glycosylated hemoglobin or similar) was not significant, suggesting that we need more studies on this specific subject.

Our umbrella also suggest a role of Mg in neurological conditions. Taking into consideration the results of the RCTs, we reported that Mg supplementation was able to decrease migraine relapses in people already affected by this condition, with strong evidence according to GRADE. It is reported that Mg might prevent the waves of brain signaling (i.e. cortical spreading depression), which produces the visual and sensory changes that are the common forms of aura in migraine.[[51](#_ENREF_51)] Other works reported that Mg may decrease the release of pain transmitting chemicals in the brain, such as Substance P and glutamate.[[52](#_ENREF_52)] Finally, Mg might also prevent narrowing of brain blood vessels caused by the neurotransmitter serotonin.[[53](#_ENREF_53)] Even if these findings are limited to only a few RCTs (3 for frequency and 2 for intensity of migraine), they are of great clinical importance since migraine is a widely diffused condition in the general population.[[54](#_ENREF_54)] In observational studies, higher Mg intake, for example, significantly prevent the risk of stroke, with a suggestive evidence. The positive effect of dietary Mg on stroke can be justified by several factors including the effect of Mg on the prevention of diabetes (discussed before) and of hypertension even if the evidence regarding this latter is only weak, according to our investigation. In animal models, it seems that Mg protects neurons from glutamate-mediated necrosis[[55](#_ENREF_55)] and white matter tracts from prolonged ischemia.[[56](#_ENREF_56)]

The findings of our work should be interpreted within its limitations. First, we adopted evidence assessment criteria, which were based on already established tools for observation and interventional evidence.[[27](#_ENREF_27)] Although none of the components of these criteria provides definitive proof of lack of reliability, they cumulatively map the possibility that the results are susceptible to bias and uncertainty. Test for bias offer hints rather than conclusive evidence and are grossly underpowered when there are few studies in a meta-analysis (as in the majority of the outcomes assessed).[[57](#_ENREF_57)] We used an I2<50% as one of the criteria for class I evidence (convincing) in order to assign the best-evidence grade only to robust associations and without heterogeneity. However, I2 estimates can also carry substantial uncertainty[[58](#_ENREF_58)] and clinical heterogeneity may be substantial, even in the absence of statistical heterogeneity. In this regard, other important characteristics (such as mean follow-up in observational studies) were not reported possibly introducing other biases. Second, another limitation of the umbrella review approach is the use of existing meta-analyses. It is widely known that meta-analyses have important limitations[[59](#_ENREF_59)] and their results may also depend on choices made about what estimates to select from each primary study and how to represent them in the meta-analysis (e.g. in our umbrella review several meta-analyses did not report any information regarding the dosage of Mg and we excluded several studies if this criterion was not clear).[[60](#_ENREF_60)] In this regard, we finally observed that we were not able to summarize the findings regarding side effects observed in the RCTs, even if we have an important literature suggesting that the use of these supplementations is followed by some side effects such as diarrhea or other gastrointestinal conditions.[[61](#_ENREF_61)] Third, the RCTs included were generally small in size, representing a potential bias for this research.

In conclusion, in this umbrella review including 15 meta-analyses and 55 outcomes, we found that Mg supplementations were able to decrease, with strong evidence according to the GRADE, the intensity and frequency of migraine in people already affected by this condition and the risk of hospitalization in pregnant women. Moreover, higher Mg dietary intake significantly decreased the risk of type 2 diabetes and stroke with highly suggestive evidence. However, evidence for other clinical outcomes remains generally weak suggesting that further research is needed.

**ACKNOWLEDGMENTS**

**Conflict of interest**: Dr Koyanagi’s work was supported by the Miguel Servet contract financed by the CP13/00150 and PI15/00862 projects, integrated into the National R + D + I and funded by the ISCIII - General Branch Evaluation and Promotion of Health Research - and the European Regional Development Fund (ERDF-FEDER). Dr. Demurtas received a honorary consultance from Bayer. Dr Stubbs is supported by Health Education England and the National Institute for Health Research HEE/ NIHR ICA Programme Clinical Lectureship (ICA-CL-2017-03-001). BS is part supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King’s College Hospital NHS Foundation Trust. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. Dr Firth is supported by a Blackmores Institute Fellowship. The other authors declare no conflict of interest for this work.

**Funding source:** none

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