



# Hypomagnesaemia linked to depression: a systematic review and meta-analysis

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## Key words

hypomagnesaemia, magnesium, meta-analysis, depression.

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## Abstract

**Background:** The reported risk of depression in patients with hypomagnesaemia is controversial.

**Aim:** The objective of this meta-analysis was to assess the association between depression and hypomagnesaemia.

**Methods:** A literature search was performed using MEDLINE, EMBASE, Cochrane Database and clinicaltrials.gov from inception through October 2014. Studies that reported odds ratios, relative risks or hazard ratios comparing the risk of depression in patients with hypomagnesaemia were included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

**Results:** Six observational studies (three cohort studies, two cross-sectional studies and a case-control study) with a total of 19 137 patients were identified and included in the data analysis. The pooled RR of depression in patients with hypomagnesaemia was 1.34 (95% CI, 1.01–1.79,  $I^2 = 33\%$ ). The association between depression and hypomagnesaemia was marginally insignificant after the sensitivity analysis including only cohort and case-control studies, with a pooled RR of 1.38 (95% CI, 0.92–2.07,  $I^2 = 24\%$ ).

**Conclusion:** Our study demonstrates a potential association between hypomagnesaemia and depression. Further studies assessing the benefits of treatment of hypomagnesaemia in patients with depression are needed.

## Introduction

Depression is a common but serious disease affecting more than 151 million people worldwide.<sup>1</sup> Approximately 30% of all patients with depression attempt suicide, and half of them, unfortunately, die by suicide.<sup>2</sup> Despite antidepressant therapy, up to 50% of depressed patients fail to respond completely with treatment.<sup>3</sup>

Recent studies have emphasised the important role of trace elements in the function of the nervous system.<sup>4</sup> Magnesium is a coenzyme for more than 300 intracellular reactions,<sup>5</sup> and it has been proposed that hypomagnesaemia might be associated with significant adverse impacts on the central nervous system, leading to depression.<sup>4</sup> Thus, investigators have attempted to study this

inherent relationship. However, the results in prior studies of hypomagnesaemia and the risk of depression have been inconsistent. Several studies have shown an association between hypomagnesaemia and depression.<sup>6,7</sup> Conversely, a few studies have demonstrated no significant risk of depression in hypomagnesaemic individuals.<sup>1,8–10</sup>

The aim of this meta-analysis was to examine the association between depression and hypomagnesaemia.

## Methods

Two investigators (WC and CT) independently searched published studies indexed in MEDLINE, EMBASE, the Cochrane Database and clinicaltrials.gov from inception through October 2014. A manual search for additional relevant studies using references from retrieved articles

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**Table 1** Main characteristics of the studies included in this meta-analysis

	Young <i>et al.</i> <sup>10</sup>	Barragan-Rodriguez <i>et al.</i> <sup>8</sup>	Jacka <i>et al.</i> <sup>9</sup>	Jung <i>et al.</i> <sup>7</sup>	Camardese <i>et al.</i> <sup>6</sup>	Derom <i>et al.</i> <sup>18</sup>
Country	Canada	Mexico	Australia	Korea	Italy	Spain
Study design	Cohort study	Case-control study	Cross-sectional study	Cross-sectional study	Cohort study	Cohort study
Year	1996	2007	2009	2010	2012	2012
Total number	145	110 (55 cases and 55 age- and gender-matched control)	5708	112	123	12 939
Study sample	Medication-free ( $\geq 10$ day prior to study) major depressive disorder with Hamilton Depression Rating Scale (Ham-D) score $\geq 16$	Patients with type 2 DM, aged $\geq 65$ years	Community-dwelling healthy adult, aged 46–49 or 70–74 years	Healthy adult women without psychiatric disorder, aged 21–72 years	Outpatients during a major depressive episode ( $\geq 2$ major depressive episodes and no remission in former treatment trial)	University graduate
Exposure definition	Serum Ca/Mg $> 2.96$	Serum Mg $< 1.8$ mg/L	Decreased dietary Mg intake	Lowest tertile of serum magnesium	Baseline plasma magnesium level	The highest quintile of total magnesium intake (dietary Mg + supplemental Mg)
Exposure measurement	Serum Ca and magnesium measured prior to treatment	Serum magnesium	Self-administered food frequency questionnaires	Serum magnesium	Total plasma magnesium measured prior to treatment	Self-reported using semi-quantitative food frequency questionnaire
Outcome definition	Response to treatment: decrease in HAM-D score to $< 10$ and an overall decrease of $\geq 50\%$ from the original score	Depressive symptoms: a score $\geq 11$ in Yesavage scale	Case-level depression: a HADS-D score $\geq 8$	High risk of depressive mood disorder: Korean-HADS score $\geq 8$	Response to treatment: 50% decrease in total HAM-D score	Incident depression
Outcome ascertainment	Hamilton Depression Rating Scale assessed at 5 and 12 weeks after acute treatment phase	Structured interview using validated questionnaires (Yesavage scale)	Self-reported questionnaires using the Hospital Anxiety and Depression Scale (HADS)	Korean version of the Hospital Anxiety and Depression Scale (Korean-HADS)	Hamilton Depression Rating Scale measured 3 months after treatment	Self-reported, physician-made diagnosis of depression or self-reported use of antidepressant using questionnaires every 2 years
Adjusted OR or RR	OR for non-response: 1.19 (0.51–2.78)	1.79 (1.1–6.9)	1.16 (0.93–1.45)	3.92 (1.11–13.83)	3.41 (1.08–10.76)	1.11 (0.77–1.59)
Confounder adjusted	None	Age, gender duration of diabetes, HbA1c, concomitant physical illness, serum triglyceride, albumin, creatinine	Total energy intake, gender, age, waist-hip ratio, BMI, systolic blood pressure, education, income and health behaviour	Age, medical history of ischaemic heart disease	None	Age, sex, BMI, physical activity during leisure time, smoking status, marital status, number of children, employment status, self-perceived personality traits, alcohol and trans fatty acids intake, total energy intake, adherence to the Mediterranean dietary pattern
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 0 Outcome: 3	Selection: 4 Comparability: 2 Exposure: 3	Selection: 5 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 0 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

BMI, body mass index; Ca, calcium; DM, diabetes mellitus; HAM-D, The Hamilton Depression Rating Scale; HbA1c, glycated hemoglobin; Mg, magnesium; n/a, not available; OR, odds ratio; RR, risk ratio.

was also implemented. Conference abstracts and unpublished studies were excluded. Detailed search strategy is available in Appendix S1.

### Inclusion criteria

The inclusion criteria were as follows: (i) randomised controlled trials (RCT) or observational studies (cohort studies, case-control or cross-sectional) published as original studies to evaluate the risk of depression in patients with hypomagnesaemia; (ii) odds ratios, relative risks or hazard ratios with 95% confidence intervals (CI) were presented; and (iii) a reference group composed of participants who did not have hypomagnesaemia.

Study eligibility was independently determined by the two investigators noted above. Differing decisions were resolved by mutual consensus. The quality of each study was independently assessed by each individual investigator using the Newcastle-Ottawa quality assessment scale<sup>11</sup> for observational studies and Jadad quality assessment scale<sup>12</sup> for RCT.

### Data extraction

A standardised data collection form was used to extract the following information: last name of the first author, study design, year of study, country of origin, year of publication, sample size, characteristics of included participants, definition of depression, method used to diagnose hypomagnesaemia and adjusted effect estimates with 95% CI. The two investigators independently performed this data extraction.

### Statistical analysis

The Review Manager 5.2 software from Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird.<sup>13,14</sup> Given the high likelihood of between-study variances, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test. This statistic is complemented with the  $I^2$  statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of  $I^2$  of 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and >75% high heterogeneity.<sup>15,16</sup> The presence of publication bias was assessed by funnel plots of the logarithm of odds ratios versus their standard errors.<sup>17</sup>

## Results

Our search strategy yielded 2450 potentially relevant articles. There were 2274 articles excluded based on title and abstract for certainly not fulfilling inclusion criteria on the basis of the type of article, study design, population or outcome of interest. One hundred and seventy-six articles underwent full-length article review. One hundred and seventy articles were excluded (49 articles were not observational studies or RCT and 121 articles did not report the outcomes of interest). Six observational studies with a total of 19 137 patients were identified and included in the data analysis. Figure S1 outlines our search methodology and selection process.

### Risk of depression in hypomagnesaemic patients

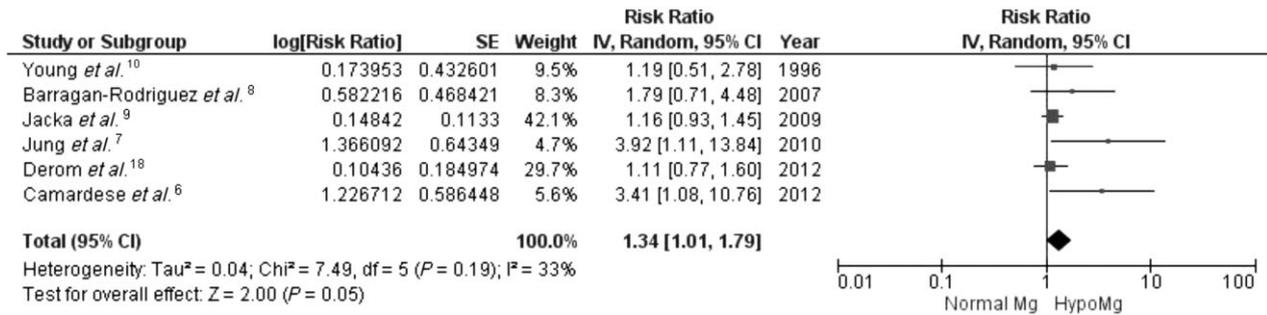
Six observational studies (three cohort studies, two cross-sectional studies and a case-control study) with a total of 19 137 patients were included in the data analysis for the risk of depression in patients with hypomagnesaemia. Table 1 describes the detailed characteristics and quality assessment of the included studies. The pooled risk ratio (RR) of depression in patients with hypomagnesaemia was 1.34 (95% CI, 1.01–1.79). The statistical heterogeneity was low with  $I^2$  of 33%. Figure 1 shows the forest plot of the included studies. The pooled RR of depression in patients with hypomagnesaemia became marginally insignificant with an RR of 1.38 (95% CI, 0.92–2.07,  $I^2 = 24%$ ) after the sensitivity analysis included only cohort and case-control studies, as shown in Figure 2.

### Evaluation of public bias

A funnel plot to evaluate publication bias for the risk of depression in patients with hypomagnesaemia was summarised in Figure S2. The plot was suggestive of a small publication bias in studies with positive correlation between depression and hypomagnesaemia.

## Discussion

Our meta-analysis results indicate a potential association between hypomagnesaemia and depression, with an overall 1.34-fold increased risk of hypomagnesaemia compared with those who did not have hypomagnesaemia with low level of heterogeneity. Despite marginal insignificance, the trend of this association still exists after sensitivity analysis with exclusion of cross-sectional studies.



**Figure 1** Forest plot of the included studies comparing risk of depression in patients who had hypomagnesaemia and those who did not; square data markers represent risk ratios (RR); horizontal lines, the 95% confidence interval (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. IV, inverse variance; SE, standard error.

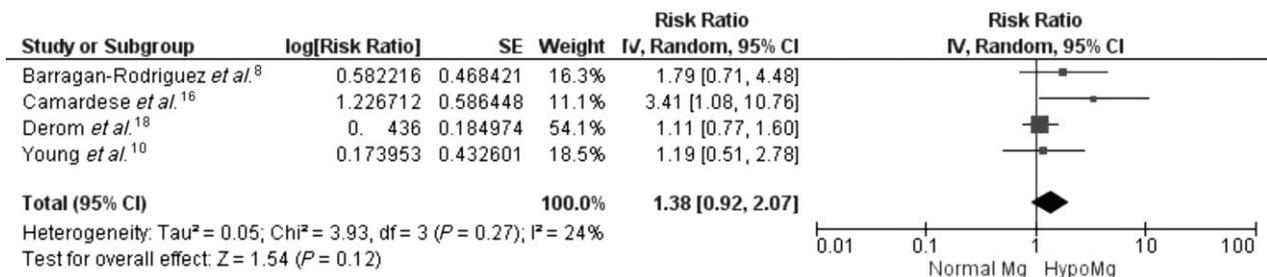
Physiologically, magnesium is a calcium antagonist and voltage-dependent blocker of N-methyl-D-aspartate (NMDA) channel, which plays an important role in calcium entry into the neuron.<sup>1,19</sup> High levels of calcium and glutamate in magnesium deficient environments may dysregulate neural synaptic function, especially in the hippocampus, leading to depression or other psychiatric illnesses.<sup>1</sup> Hypomagnesaemia can result in hypocalcaemia by lowering parathyroid hormone levels due to altered activation of the calcium-sensing receptor. A few mental health issues have been reported in patients with abnormal serum calcium in addition to hypomagnesaemia.<sup>20</sup> In animal models, magnesium has been shown to have antidepressant effects in mice,<sup>21</sup> as well as adjunctive effects with other treatments for depression.<sup>22</sup> Derom *et al.* recently provided an elegant review and showed that abnormalities in magnesium metabolism might be linked to depression.<sup>1</sup> Our meta-analysis confirmed the potential increase in risk of depression in patients with hypomagnesaemia.

Although almost all included studies were of moderate to high quality (as evaluated by Newcastle-Ottawa scale), there are a few limitations. First, there are small

statistical heterogeneities in the complete analysis. The potential sources of these heterogeneities include the variation for exposure definition (hypomagnesaemia), confounder-adjusted methods (e.g. age, obesity, medical comorbidities and psychotropic medication), follow-up duration and method for outcome ascertainment of depression. Second, the data on treatment response are limited. Thus, we were unable to assess the treatment effects of magnesium supplementation in depressed hypomagnesaemic patients. Lastly, this is a meta-analysis of observational studies with its inherent limitations. Therefore, our meta-analysis can at best demonstrate an association but not a causal relationship. Depression may also impede dietary intake and gastrointestinal function, potentially causing or contributing to hypomagnesaemia.

### Conclusion

Our study shows a potential association between hypomagnesaemia and depression. Further studies are required to investigate the treatment benefits for depression in patients with hypomagnesaemia.



**Figure 2** Forest plot of the sensitivity analysis including only cohort and case-control studies comparing risk of depression in patients who had hypomagnesaemia and those who did not; square data markers represent risk ratios (RR); horizontal lines, the 95% confidence interval (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. IV, inverse variance; SE, standard error.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Figure S1** Studies identification.

**Figure S2** Funnel plot of all studies included in the meta-analysis for the risk of depression in patients with hypomagnesaemia and those without hypomagnesaemia. RR, risk ratio; SE, standard error.

**Appendix S1** Literature search strategy for database: Ovid, MEDLINE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials.