

Review

Magnesium and mood disorders: systematic review and meta-analysis

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Background

Magnesium (Mg^{2+}) has received considerable attention with regards to its potential role in the pathophysiology of the mood disorders, but the available evidence seems inconclusive.

Aims

To review and quantitatively summarise the human literature on Mg^{2+} intake and Mg^{2+} blood levels in the mood disorders and the effects of Mg^{2+} supplements on mood.

Method

Systematic review and meta-analyses.

Results

Adherence to a Mg^{2+} -rich diet was negatively associated with depression in cross-sectional (odds ratio = 0.66) but not in prospective studies. Mg^{2+} levels in bodily fluids were on average higher in patients with a mood disorder (Hedge's g = 0.19), but only in patients treated with antidepressants and/or mood stabilisers. There was no evident association between Mg^{2+} levels and symptom severity. Mg^{2+} supplementation was associated with a decline in depressive symptoms in uncontrolled (g = -1.60) but not in placebo-controlled trials (g = -0.21).

Conclusion

Our results provide little evidence for the involvement of Mg^{2+} in the mood disorders.

Declaration of interest

None.

Keywords

Magnesium; depression; bipolar disorder; meta-analysis; systematic review.

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The trace element magnesium (Mg^{2+}) has an essential role in hundreds of enzymatic reactions.^{1,2} The Mg^{2+} in our bodies is derived from food such as cereals, nuts and (green) vegetables.^{3–5} Insufficient intake of Mg^{2+} can cause hypomagnesaemia (i.e. an Mg^{2+} level of <0.7 mmol/L).^{4,6–9} Hypomagnesaemia can also develop owing to the use of diuretics, defects in absorption or diarrhoea.^{1,5} About 2–15% of the general population has hypomagnesaemia. In some populations this percentage is even higher, e.g. it is 14–48% in patients with type 2 diabetes.¹⁰ Mg^{2+} deficiency may pose a risk to metabolic and cardiovascular health.^{11,12}

 Mg^{2+} and mental health

For over 50 years, the idea has existed that Mg^{2+} deficiency may also pose a risk to mental health,¹³ in particular with respect to (pathological) low mood.^{14–16} One hypothesis, which attempts to explain this association, is that Mg^{2+} deficiency affects brain chemistry, membrane fluidity and inflammation,^{1,17,18} all of which are associated with psychiatric illnesses¹⁹ and the response to antidepressants.¹⁷ Furthermore, Mg^{2+} may protect neurons against cell death owing to its regulating effects on calcium dynamics.¹ Mg^{2+} is also involved in the glutamatergic system, regulating learning, memory, neuroplasticity and perhaps antidepressant activity.²⁰

Animal studies

Some preclinical experiments have shown that Mg^{2+} deficiency is related to the functioning of limbic brain areas and to behaviour in rodents that some conceptualise as 'depression-like'.^{16,21} The administration of Mg^{2+} supplements,²² magnesium sulphate²³ and magnesium chloride²⁴ has been shown to alter this behaviour. However, owing to a lack of validity of the behavioural read-outs, the translational value of such experiments is questionable.^{25,26}

Human studies

There is a considerable amount of human data on the topic. Some studies evaluated whether the prevalence (cross-sectional) or the incidence (longitudinal) of depression differs as a function of dietary Mg^{2+} intake.^{27,28} Others have investigated Mg^{2+} in bodily fluids as a function of mood disorder status.^{29,30} Some experiments have also investigated whether Mg^{2+} supplementation can serve as an antidepressant.^{31,32}

Conflicting findings

However, the findings from these studies appear to be inconclusive,³³ and the two meta-analyses on the topic to date do not provide a high level of evidence either. Cheungpasitporn and colleagues³⁴ pooled data from three studies on blood Mg^{2+} levels with two studies on dietary Mg^{2+} intake and concluded from this heterogeneous pool of data that hypomagnesaemia is related to depression (odds ratio (OR) = 1.34). Li and colleagues³⁵ pooled nine cross-sectional and two prospective studies on dietary Mg^{2+} intake and found a relative risk of 0.81 for depressive symptoms in people who adhered to a diet high in Mg^{2+} . However, they did not differentiate between cross-sectional and longitudinal designs, leaving it open to interpretation whether dietary Mg^{2+} intake is a risk factor for depressive symptoms versus a concomitant phenomenon or a consequence of it.

The conflicting findings in this field may be attributable to moderators, such as the way in which dietary information is acquired or the blood component in which Mg^{2+} is measured (e.g. measurement methods and absolute values of Mg^{2+} are different for plasma and serum,³⁶ which may present an additional source of between-study heterogeneity in outcome). They may also stem from the differing methodological characteristics of individual studies

(e.g. sample size, participant characteristics, medication effects) or from general issues such as publication bias.

The current study

One way to provide a more definitive answer to the question of whether Mg^{2+} and mood disorders are related, as well as explaining the potential causes of heterogeneity in the findings, is to carry out a systematic review with meta- and moderator analyses covering the broad literature on this topic. We set out to present such analyses on the following associations: (a) mood disorder prevalence or incidence by dietary Mg^{2+} intake, (b) Mg^{2+} levels in bodily fluids by mood disorder status and severity, and (c) the effects of Mg^{2+} supplements on mood.

Method

This project was reported following the guidelines of PRISMA³⁷ and MOOSE.³⁸ PRISMA and MOOSE checklists can be found in Appendices 1 and 2, respectively. The review protocol is presented in appendix 3.

Search strategy

We searched PubMed, Web of Science, and Embase (from their commencement to 22 December 2017) for eligible papers using the following terms: (Magnesium OR Mg^*) AND (depression OR depress* OR affect* OR mood OR mania OR bipolar). The reference lists of identified articles were scrutinised, as were the references that were made to the two seminal papers on the topic^{14,15} (to which, at the date of our latest search, 65 and 5 references were made respectively).

Study selection

We included human studies that reported original findings on the following associations: (a) prevalence and/or incidence of depression as a function of dietary Mg^{2+} intake, (b) Mg^{2+} levels in bodily fluids/blood components as a function of mood disorder status and/or severity, and (c) changes in mood disorder status as a function of Mg^{2+} supplementation. Studies had to be published in peer-reviewed journals (including advance online publication) and written in English, French, German, Spanish or Dutch in order to be included.

In case of overlap among study samples, we excluded the study that reported on the fewest participants.

Data extraction

From each eligible article, we extracted data on a range of demographic, clinical and methodological variables, as well as raw numbers or effect-size estimates (with corresponding 95% confidence intervals) on the associations of interest. Data extraction is specified in Supplementary Table S1, available at <https://doi.org/10.1192/bjo.2018.22>. Authors of articles in which data necessary to our investigations were missing were contacted by e-mail to request these data.

Assessment of the eligibility of each publication and data extraction were performed independently by two of the authors. Cases of disagreement were resolved by discussion and consensus.

Quality assessment

The methodological quality of cross-sectional and case-control studies was assessed using the Newcastle-Ottawa scale,³⁹ and that of prospective studies was assessed using the method proposed by

Lievense *et al.*⁴⁰ The methodological quality of treatment trials was assessed using the method of evaluation of (randomised) trials provided by the US Department of Health and Human Services.⁴¹

Data analyses

Analyses were performed in STATA version 13.⁴² Associations were tested for statistical significance at a two-tailed confidence interval of 95%. Summary tables on characteristics of eligible papers were created.

Random-effects meta-analyses were used in all cases to pool the data. In case of binary outcomes (e.g. incidence of depression), we calculated the OR as an effect-size estimate. When continuous data served as the outcome and group membership as the predictor (e.g. Mg^{2+} concentrations in patients and healthy control participants), we calculated Hedge's g as the measure of effect. Associations between continuous variables (e.g. Mg^{2+} concentration and depression severity) were quantified using Pearson's r .

Heterogeneity in outcome was quantified using the I^2 measure and its statistical significance was assessed using the χ^2 statistic.⁴³ In cases of heterogeneity, moderator analyses were performed. Predictors of heterogeneity were, where applicable: the medium in which Mg^{2+} was determined, type of diagnosis, male/female ratio and mean age of the sample, type of medication, duration of follow-up, and the estimated methodological quality of the study. The sensitivity of our results was further tested by excluding each single study at a time.

Publication bias was assessed by means of visual inspection of funnel plots and Egger's test.⁴³ When evident, trim-and-fill procedures were applied to estimate pooled effect sizes while taking bias into account.⁴⁴

Results

We identified 4110 articles after duplicates were removed. Of these, 4053 articles were excluded, leaving 58 that reported on at least one of the associations of interest. The study selection process, from initial search to final selection, is presented in Figure 1. Table 1 and Supplementary Table 10 list the articles that were included in our meta-analyses^{14,15,27–32,45–94} and provide information on their characteristics.

Methodological quality of the included studies

In the online Supplementary Tables 2–9, we provide details on the quality assessment tools that we used. The assessment of study quality showed a high degree of agreement (~83% agreement; see the online supplement for more information) among two independent assessors (D.P. and M.M.). Item and total quality scores per eligible study are provided in Supplementary Tables 2–9. Methodological quality was not used as a criterion for inclusion or exclusion.

The overall methodological quality of the included studies was modest. In general, most studies applied valid statistical techniques, although statistical power was seldom reported. Methodological quality also was hampered by a lack of data on the representativeness of the sample, and drop-out and response rates. Most studies adjusted for confounding, ranging from almost absent adjustment to – in our view – thorough adjustment. Finally, for the treatment studies, no paper reported on the adequacy of randomisation and allocation concealment.

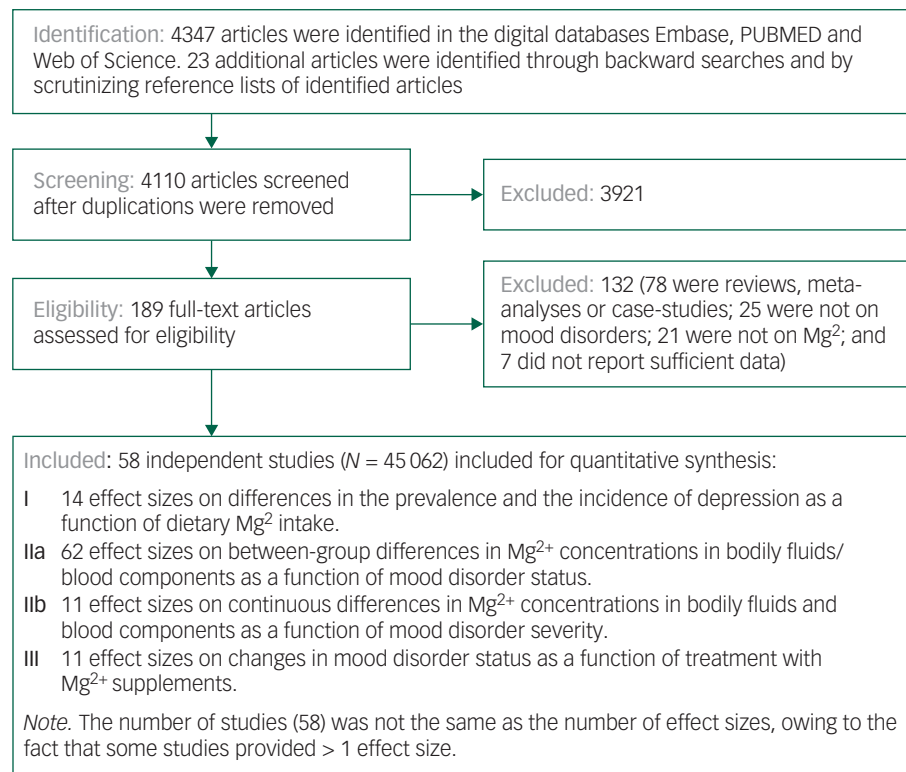


Fig. 1 Flowchart on identification, screening and inclusion of eligible articles.

Dietary Mg²⁺ and the prevalence or incidence of unipolar depression/depressive symptoms

Adherence to a diet high in Mg²⁺ was associated with a lower prevalence of depression in cross-sectional studies (OR (highest versus lowest category) = 0.66, 95% CI = 0.51–0.81; $P < 0.01$, $k = 12$, $n = 21\,927$), but not in longitudinal cohorts that assessed the incidence of new-onset depression (OR = 0.71, 95% CI = 0.40–1.02; $P = 0.10$, $k = 2$, $n = 18\,156$).

Between-study heterogeneity in outcome was present in the cross-sectional studies assessing the association between dietary Mg²⁺ intake and depression prevalence, as was evidence of publication bias (Figure 2A). Sample size was the only variable (Table 2) that was associated with between-study heterogeneity; smaller samples on average yielded stronger associations between dietary Mg²⁺ and mood disorder prevalence. The strength of this association, in terms of Spearman's rho (ρ), was 0.61. Correction for the presence of publication bias led to an attenuated, yet statistically significant, effect size estimate (OR = 0.84, 95% CI = 0.70–0.98).

Between-study heterogeneity and publication bias could not be assessed in the analysis of depression incidence owing to the small number of studies.

There were no studies which reported on the effects of dietary Mg²⁺ on symptoms of bipolar disorder.

Mg²⁺ levels in bodily fluids as a function of mood disorder status

Sixty-two effect-size estimates were found for Mg²⁺ levels in bodily fluids by mood disorder status. Pooling these data showed higher Mg²⁺ levels in patients with a mood disorder, relative to healthy controls ($g = 0.19$, 95% CI = 0.05–0.36; $P < 0.001$, $k = 62$, $n = 4433$).

There was between-study heterogeneity (Figure 2B). A large part of this was due to treatment status, as Mg²⁺ levels in bodily fluids were particularly high in patients who were treated with antidepressants and/or mood stabilisers ($P < 0.01$ for the difference between treated and untreated samples). In fact, Mg²⁺ levels of untreated patients were no different from those of controls. Diagnostic status was also associated with heterogeneity, as the differences between patients and controls were larger for samples composed of bipolar depressed patients (Figure 2B) relative to patients with depressive symptoms/major depression. No evident heterogeneity resulted from the medium in which Mg²⁺ levels were determined (e.g. plasma versus serum).

A significant association between sample size and effect-size estimate was observed, indicating that smaller samples on average yielded larger differences in Mg²⁺ concentrations between patients and controls ($\rho = -0.42$; Table 2). Egger's t -tests and funnel plots suggested the presence of publication bias. Correcting for this led to non-significant between-group differences overall.

Mg²⁺ levels and symptom severity

Pooling 11 effect-size estimates that reported on continuous associations between Mg²⁺ levels and scores on mood disorder severity scales showed no evident association between these variables. In some instances, heterogeneity in outcomes was observed. However, this remained unexplained in subgroup and sensitivity analyses (Figure 2C).

Changes in mood disorder status following treatment with Mg²⁺ supplements

Eleven studies showed that Mg²⁺ supplementation was associated with a decline in symptoms ($g = -0.44$, 95% CI = -0.68 to -0.20 ;

Table 1 Characteristics of the included studies. Studies are presented by year of publication and in alphabetical order

Author, year	Analysis ^a	N	Diagnosis ^b	Type of study	% Female	Mean age	Country
Nielsen ¹⁴	II	136	BD	C-S	N.K.	N.K.	Denmark
Malleson <i>et al</i> ¹⁵	II, IV ^c	14	MDD	TT	N.K.	N.K.	UK
Björum ⁴⁵	II, IV	60	Depression	TT with C-S	67	51	Denmark
Björum <i>et al</i> ⁴⁶	II, IV	68	Depression	TT with C-S	75	47	Denmark
Naylor <i>et al</i> ⁴⁷	II, IV	62	BD	TT with C-S	65	N.K.	UK
Herzberg & Herzberg ⁴⁸	II	119	MDD	C-S	41	32	Australia
Ramsey <i>et al</i> ⁴⁹	II, IV	83	BD, MDD	TT with C-S	27	N.K.	USA
Sengupta <i>et al</i> ⁵⁰	IV	131	BD, MDD	TT with C-S	48	N.K.	India
Strzyzewski <i>et al</i> ⁵⁰	II, IV ^c	46	BD, MDD	TT	57	37	Poland
Frazer <i>et al</i> ⁵¹	II, IV	194	BD, MDD	C-S	51	46	USA
Thakar <i>et al</i> ⁵²	IV	140	BD, MDD	C-S	57	40	Canada
Alexander <i>et al</i> ⁵³	IV	47	BD	C-S	53	34	Lebanon
Banki <i>et al</i> ⁵⁴	II, IV	34	MDD	C-S	100	42	Hungary
Linder <i>et al</i> ⁵⁵	II, IV	83	(rem) MDD	TT + C-S	50	53	Sweden
Kirov <i>et al</i> ⁵⁶	II, IV	319	BD, MDD	TT + C-S	N.K.	36	Bulgaria
Widmer <i>et al</i> ⁵⁷	II, IV	53	BD, MDD	TT + C-S	49	48	Switzerland
Widmer <i>et al</i> ⁵⁸	II, IV	101	BD, MDD	C-S	53	46	Switzerland
Young <i>et al</i> ⁵⁹	II	225	BD, MDD	C-S	61	37	Canada
Kamei <i>et al</i> ⁶⁰	II, IV	51	(rem) MDD	TT + C-S	35	38	Japan
Walker <i>et al</i> ⁶¹	III	71	Depression	TT	100	NK	UK
Levine <i>et al</i> ⁶²	II	29	BD, MDD	C-S	59	56	USA
De Souza <i>et al</i>	III	42	Depression	TT	100	32	UK
Zieba <i>et al</i> ⁶⁴	II	35	MDD	C-S	51	40	Poland
Imada <i>et al</i> ⁶⁵	II	101	BD, MDD	C-S	43	45	Japan
Sharkey <i>et al</i> ⁶⁶	I	279	Depression	C-S	100	~80	USA
Hornyak <i>et al</i> ⁶⁷	III	11	Depression	TT	55	47	Germany
Bhudia <i>et al</i> ³¹	III	273	Depression	TT	23	64	USA
Daini <i>et al</i> ⁶⁸	II, IV	162	MDD	C-S	24	32	Italy
Barragan-Rodriguez <i>et al</i> ⁶⁹	II	110	Depression	C-S	75	77	Mexico
Barragan-Rodriguez <i>et al</i> ⁷⁰	III	23	Depression	TT	52	68	Mexico
Iosifescu <i>et al</i> ⁷¹	II	29	MDD	TT	57	42	USA
Nechifor ⁷²	II	76	MDD	TT	~75	N.K.	Romania
Jacka <i>et al</i> ⁷⁷	I	5708	Depression	C-S	57	48	Norway
Rondanelli <i>et al</i> ⁷³	III	43	Depression	TT	63	78	Italy
Bae & Kim ⁷⁴	I, II	105	Depression	C-S	100	49	Rep. of Korea
Camardese <i>et al</i> ⁷⁵	II	123	MDD	C-S	54	48	Italy
Huang <i>et al</i> ⁷⁶	I, II	210	MDD	C-S	53	72	Taiwan
Jacka <i>et al</i> ⁷⁷	I	1023	MDD	C-S	100	51	Australia
Cubala <i>et al</i> ⁷⁸	II	40	MDD	C-S	58	32	Poland
Yary <i>et al</i> ⁷⁹	I	402	Depression	C-S	43	33	Malaysia
Büttner <i>et al</i> ⁸⁰	II	30	MDD	TT	43	46	Germany
Kim <i>et al</i> ⁸¹	I	849	Depression	C-S	100	15	Rep. of Korea
Miki <i>et al</i> ⁸²	I	2006	Depression	C-S	11	42	Japan
Misztak <i>et al</i> ⁸³	II	179	BD	C-S	61	45	Poland
Rajizadeh <i>et al</i> ⁸⁴	II	650	Depression	C-S	70	34	Iran
Styczeń <i>et al</i> ³⁰	II	164	MDD	C-S	75	N.K.	Poland
Tarleton & Littenberg ⁸⁵	I	8894	Depression	C-S	53	46	USA
Fard <i>et al</i> ⁸⁶	III	95	Depression	TT	100	28	Iran
Gu <i>et al</i> ⁸⁷	II	329	MDD	PROS + C-S	37	60	China
Martinez-Gonzalez <i>et al</i> ⁸⁸	I	15 836	MDD	PROS	59	38	Spain
Rubio-López <i>et al</i> ⁸⁹	I	710	Depression	C-S	52	8	Spain
Yary <i>et al</i> ²⁸	I	2320	Depression	PROS + C-S	0	53	Finland
Bambling <i>et al</i> ⁹⁰	III	12	MDD	TT	66	49	Australia
Mehdi <i>et al</i> ⁹¹	II, III	12	MDD	TT	75	47	USA
Miyake <i>et al</i> ⁹²	I	1745	Depression	C-S	100	31	Japan
Rajizadeh <i>et al</i> ⁹²	III	60	Depression	TT	73	32	Iran
Szkup <i>et al</i> ⁹³	II	198	Depression	C-S	100	56	Poland
Tarleton <i>et al</i> ⁹⁴	III	112	Depression	TT	62	53	USA

ADs, antidepressants; BD, bipolar disorder; C-S, cross-sectional; MDD, major depressive disorder; PROS, prospective; REM, remitted; TT, treatment trial.

a. This column indicates in which meta-analysis the study in the corresponding row was included:

I Dietary Mg²⁺ in relation to mood disorder prevalence and incidence; **II** Mg²⁺ in bodily fluids of patients and healthy control subjects or Mg²⁺ in relation to symptom severity; **III** Mg²⁺ supplements as an antidepressant; **IV** additional analyses ([1] differences in Mg²⁺ levels in bodily fluids between patients with mood v. other psychiatric disorders, [2] pre-post treatment (with antidepressants and/or mood stabilisers) differences in Mg²⁺ levels in bodily fluids, and [3] Mg²⁺ ATPase in erythrocytes or platelets; see Results section).

b. We distinguish depression from MDD here. Depression refers to self-reported symptoms, MDD to the diagnosed syndrome.

c. This study reported on changes in Mg²⁺ levels over the course of treatment in a single patient sample only.

$P < 0.01$, $k = 11$, $n = 714$). This effect was restricted to uncontrolled studies ($g = -1.62$, 95% CI = -2.81 to -0.40) and was not observed in placebo-controlled studies ($g = -0.22$, 95% CI = -0.48 – 0.17 ; Figure 2D). The difference between effect-size estimates for controlled versus uncontrolled studies was significant. The remaining

heterogeneity could not be explained by the specified moderators or publication bias (Figure 2D; Table 2).

Dosage of Mg²⁺ supplementation (range 225–4000 mg) and number of weeks of treatment (range 1–12) were unrelated to outcome.

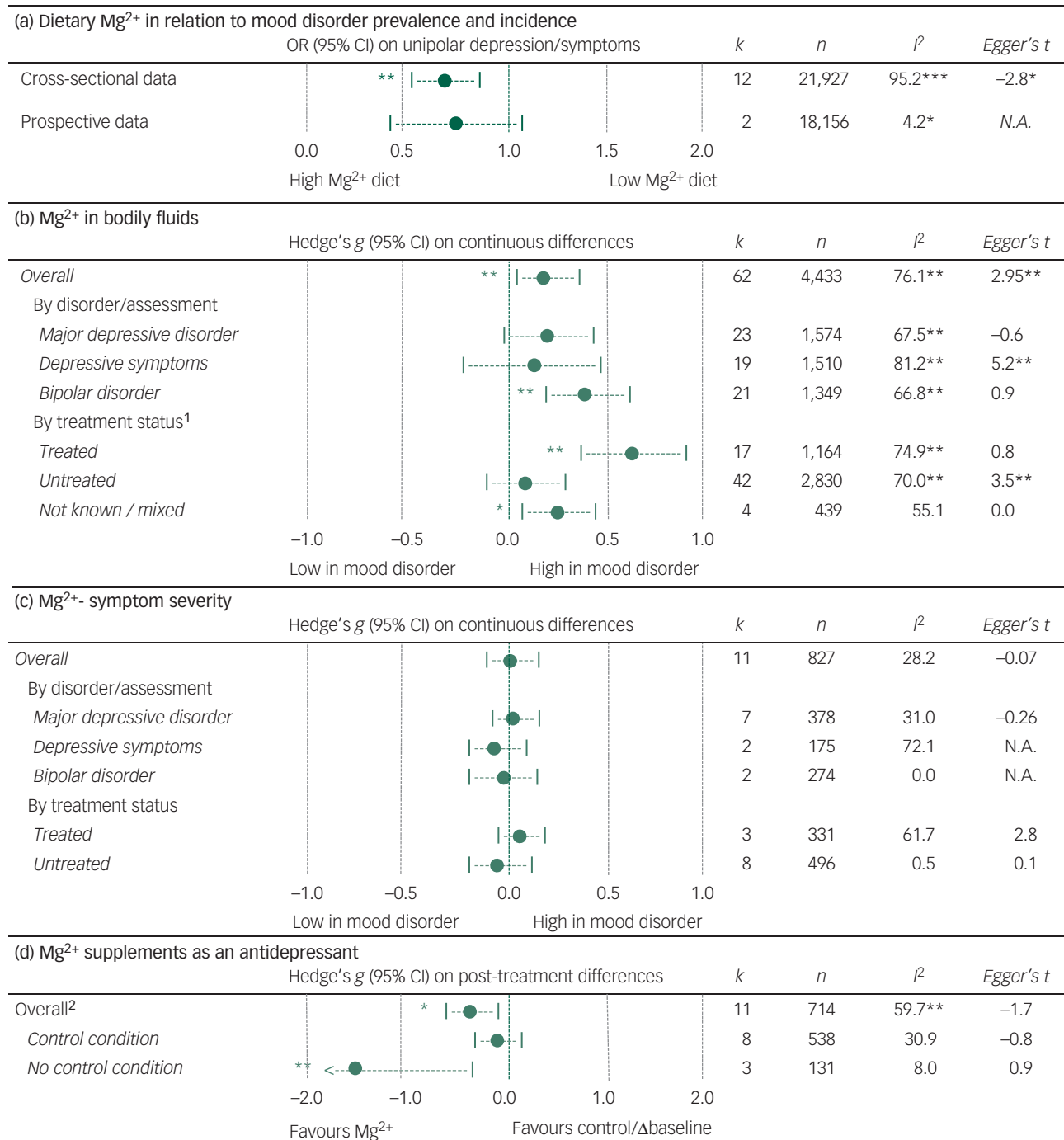


Fig. 2 Results of the meta-analyses, heterogeneity, and publication bias assessment. **A:** dietary Mg²⁺ intake was associated with prevalence of depression but not with incidence of depression. **B:** patients with mood disorders on average had higher levels of Mg²⁺, and this effect was driven by treatment status. **C:** Non-significant associations between the amount of Mg²⁺ in bodily fluids and mood disorder severity. **E:** Change in mood disorder symptoms over the course of treatment with Mg²⁺ supplements. **1:** The effect-size estimate for differences in Mg²⁺ between patients with a mood disorder and healthy control subjects was significantly different for treated v. non-treated patients. **2:** The effect-size estimate for changes in mood disorder symptoms was statistically significantly different at *P* < 0.01 when comparing studies that applied a (placebo) control v. those studies that compared pre- v. post-treatment scores.

N.A., not applicable (because <3 estimates were available).

Note. Results provided in parts **B** and **C** were not driven by the type of bodily fluid in which Mg²⁺ was measured.

Table 2 Meta-regression coefficients and standard error on the relation between study characteristics and effect-size estimates, separately for the different indicators that are in use to operationalise the hypothesis of Mg^{2+} involvement in mood disorders

	Dietary Mg^{2+} ^a <i>k</i> = 12 <i>n</i> = 21 927	Fluid Mg^{2+} ^b <i>k</i> = 62 <i>n</i> = 4433	Fluid Mg^{2+} ^c <i>k</i> = 11 <i>n</i> = 827	Mg^{2+} treatment <i>k</i> = 11 <i>n</i> = 714
Year	−0.007 (0.055)	0.008 (0.009)	0.005 (0.008)	0.015 (0.039)
<i>N</i>	0.0001 (0.001)*	−0.005 (0.001)**	0.001 (0.001)	0.002 (0.003)
Age of the sample	−0.009 (0.008)	−0.001 (0.010)	0.001 (0.006)	0.004 (0.014)
% Female	−0.003 (0.007)	−0.002 (0.004)	−0.002 (0.003)	0.016 (0.013)
Methodological quality	−0.046 (0.165)	0.001 (0.061)	−0.014 (0.073)	−0.377 (0.695)
Treatment weeks	N.A.	N.A.	N.A.	−0.082 (0.073)

N.A., not applicable.
 In order to aid with interpretation, we include a synopsis. Sample size was positively associated with the effect-size estimates in dietary studies; this indicates that smaller samples on average yielded stronger associations between dietary Mg^{2+} and depression prevalence (the strength of this association in terms of Spearman's rho (ρ) was 0.61). Sample size was negatively associated with the effect-size estimates in studies investigating differences in Mg^{2+} in bodily fluids between patients and healthy control subjects. This means that smaller samples on average yielded larger differences (the strength of this association was $\rho = -0.42$).
 a. Results are presented for cross-sectional data only. There were only two prospective studies available and hence separate meta-regression analyses were not possible. Results from the analyses were no different when the prospective studies were pooled with the cross-sectional.
 b. Mean differences in bodily fluid Mg^{2+} levels between patients with a mood disorder and healthy control subjects.
 c. Continuous differences in bodily fluid Mg^{2+} levels as a function of mood disorder symptom severity.
 * $P < 0.05$; ** $P < 0.01$.

Additional analyses

Three meta-analyses were performed which were not *a priori* defined but driven by the data that we encountered.

The first analysis explored between-group differences in Mg^{2+} levels in bodily fluids between patients with mood disorders versus other psychiatric disorders. Pooling 11 associations ($n = 508$) showed little evidence for the existence of such an association ($g = -0.07$, 95% CI = -0.47 – 0.33 ; $P = 0.47$).

The second analysis quantified pre–post treatment (with antidepressants and/or mood stabilisers) changes in Mg^{2+} levels in bodily fluids. A total of 17 effect-size estimates on this association ($n = 223$) showed no evidence for the existence of such changes ($g = -0.09$, 95% CI = -0.27 – 0.10 ; $P = 0.36$).

Finally, we pooled 13 effect-size estimates from three studies ($n = 545$) on between-group differences in Mg^{2+} -ATPase (the enzyme that mediates the transport of Mg^{2+} across the cell membrane).^{1,95} We found higher Mg^{2+} -ATPase activity in patients with depression relative to controls ($g = 0.69$, 95% CI = 0.42 – 0.93 ; $P < 0.001$).

Discussion

We quantitatively pooled the available human data on the involvement of Mg^{2+} in the pathophysiology of mood disorders. A summary and discussion of our results is presented below, arranged by the type of association investigated.

Dietary Mg^{2+} and the prevalence and incidence of mood disorders

We found that adherence to a diet high in Mg^{2+} was negatively associated with prevalence of depression in cross-sectional studies. Note that all studies investigated associations with major depression or depressive symptoms, but not bipolar disorder. This suggests that dietary Mg^{2+} intake may play a part in the pathology of depression. However, the cross-sectional design of these studies precludes any causal association or conclusions being made regarding the direction of the effect.

Furthermore, the sources of heterogeneity that we observed weaken the rationale for this association. Considerable between-study heterogeneity in outcome was observed, and sample size was the only variable which moderated this heterogeneity; studies that included fewer subjects tended to report a stronger association between dietary Mg^{2+} and prevalence of depression. We found

evidence of publication bias when we used formal tests to assess this bias, which is in keeping with this small-study effect.⁹⁶

The belief in an association between dietary Mg^{2+} intake and depression may be further weakened by the lack of a significant association between dietary Mg^{2+} intake and the incidence of depression in longitudinal studies (epidemiological cohorts). However, the number of longitudinal studies was limited, and not only was the point estimate for the effect from these studies rather similar to the pooled estimate for cross-sectional studies (ORs of 0.71 and 0.66, respectively), but their confidence intervals were also widely overlapping. This, together with the observation of between-study heterogeneity, leaves it open to debate on whether the effect is sufficiently strong as to be clinically relevant.

A lack of statistical evidence for the existence of an association in longitudinal studies could suggest reverse causation, i.e. in the depressed state, the likelihood of adhering to a diet low in Mg^{2+} may be increased. This is in line with evidence which demonstrates that mood disorders set the stage for a low-quality diet, which by extension is low in Mg^{2+} .^{5,97,98} Additionally, the evidence indicating that the quality of the diet may cause – *de novo* – depression is suggestive, but limited and not fully consistent.⁹⁹ On the other hand, the results from two recent randomised trials^{100,101} suggest that dietary advice may alleviate depressive symptoms in patients who already are depressed, although it may be questioned whether this effect is solely due to a change of diet or to other factors such as selective expectancies.¹⁰²

Mg^{2+} levels in bodily fluids as a function of mood disorder status

Against expectations, we found higher Mg^{2+} levels in bodily fluids in patients with a mood disorder relative to healthy control subjects. This effect was moderated by treatment status; Mg^{2+} levels were high in patients treated with antidepressants and/or mood stabilisers and were not so in untreated patients. Perhaps this observation reflects the hypothesis that an increase in Mg^{2+} may underlie the clinical efficacy of (fast-acting) antidepressants.¹⁷ However, alternative explanations may account for this finding. Dehydration for instance is one; antidepressants and mood stabilisers decrease renal water reabsorption,¹⁰³ which can lead to dehydration, a common side-effect of antidepressants.¹⁰⁴ This may result in artificially high concentrations of trace elements. Other potential confounding factors are presented below.

Notwithstanding the lack of a clear and single explanation for the higher levels of Mg^{2+} in treated patients, the similar Mg^{2+}

levels in untreated patients and healthy control subjects suggest little involvement of (peripheral) Mg^{2+} in the pathophysiology of mood disorders.

Changes in mood following treatment with Mg^{2+} supplements

In line with expectations, we found that treatment with Mg^{2+} supplements was associated with a decline in depressive symptoms. This effect was moderated by study type. The supposed therapeutic efficacy of Mg^{2+} supplements on mood was only observed in uncontrolled studies; in controlled studies, they did not have a superior effect compared with placebo. Therefore, the effect of Mg^{2+} supplements on mood may merely represent a placebo effect. This finding does not corroborate the hypothesis that Mg^{2+} affects the pathophysiology of mood disorders.^{17,19}

Additional analyses

We performed three additional meta-analyses that were driven by the data that we encountered. The first of these showed no group differences in Mg^{2+} levels in bodily fluids in patients with mood disorders versus patients with other psychiatric disorders. The second provided no evidence for differences in Mg^{2+} levels pre- and post-treatment with an antidepressant and/or mood stabiliser. Finally, Mg^{2+} -ATPase, the enzyme that mediates the transport of Mg^{2+} across the cell membrane,^{1,94} showed higher activity in patients relative to healthy controls. The effect size of this association was large, but it was derived from only three studies.

We will not discuss these findings further given the limited number of studies and their exploratory nature.

Comparison with previous meta-analyses

Our findings stand out from two previous meta-analyses in that our analysis included a more comprehensive collection of articles, which were pooled by type of association.

Cheungpasitporn *et al.*³⁴ pooled data from three studies on blood Mg^{2+} levels and two studies on dietary Mg^{2+} intake and concluded that hypomagnesaemia was related to depression. Our results are not in line with their conclusion. This discrepancy may be due to the heterogeneous nature of the studies pooled by Cheungpasitporn *et al.*³⁴ Furthermore, we do not speak in terms of *hypomagnesemia*, because the data do not allow that. As mentioned previously, hypomagnesemia refers to <0.7 mmol Mg^{2+} /L blood,⁹ and the included studies on Mg^{2+} in blood do not report on this; they report on continuous values instead. Additionally, information on hypomagnesemia cannot be estimated from diet. Hence, Cheungpasitporn *et al.*³⁴ probably refer to low levels of Mg^{2+} when using the term *hypomagnesemia*.

Our findings from cross-sectional dietary data are similar to those reported by Li *et al.*³⁵ What we add is the crucial separation between cross-sectional and prospective data. As we have shown, results from these two types of data are clearly distinct, with evidence for an association between dietary Mg^{2+} and depression in cross-sectional but not prospective studies.

Limitations

Our results should be interpreted in light of the following limitations, many of which relate to measurement error and confounding. In the case of confounding, it is likely that in our meta-analyses we overestimated the strength of associations. By contrast, with regards to measurement error, it is more likely that the effect-size estimates we reported on the associations of interest are an underestimation of

the true effect. In extreme cases, measurement error may even have led to a lack of construct validity and an inability to assess certain associations.

Most studies that we reviewed were observational in nature, except for some treatment studies; therefore, our results may have been affected by residual confounding. For example, Mg^{2+} is derived from diet,^{3,4} and diet is influenced by income-related disparities^{97,105} and many other such variables. Each of these variables may have effects on the outcome that are difficult to distinguish from the effects of Mg^{2+} intake. Another limitation related to the dietary data was that only one single assessment of dietary practices was applied in each of the included studies. One single assessment may not be enough to capture dietary habits and the dietary changes that may have occurred. Finally, the investigators of the included studies calculated the Mg^{2+} in nutrients in order to reach an overall Mg^{2+} estimate and in doing so ignored a relevant source of dietary Mg^{2+} ; tap and bottled water.¹⁰⁶

The Mg^{2+} measurements in bodily fluids, as they were performed in the included studies, were also limited. First, they were all taken in peripheral tissues, while the pathophysiology of the mood disorders is believed to reside in the brain. Although positive correlations have been reported between central and peripheral Mg^{2+} parameters, there clearly is not a one-to-one relationship between them.^{107,108} Furthermore, the included studies extracted isolated Mg^{2+} parameters (e.g. Mg^{2+} levels from blood serum). This is a limitation because Mg^{2+} levels and receptor systems interact and as such probably define biological outcome; single measurements may simply not be rigorous or elaborate enough, and as such the findings in this field of study may lack construct validity.

A general limitation is that the mood disorders are highly heterogeneous, whereas in the included studies they were not conceptualised as such. Perhaps, subtypes of mood disorders exist in which Mg^{2+} plays an important part, and this is overlooked when broad disorders are included and presented as if they were the same outcome variable. Finally, the populations under study were largely Caucasian, sample sizes were generally quite small and follow-up periods were relatively short.

Future work

Future studies could assess multiple dietary and Mg^{2+} parameters at multiple time points and define their potential interacting effect on mood disorder incidence, course and subtype while accounting for time-related changes in other variables such as body mass index. Such an investigation would aid construct validity by reducing the potential influence of measurement error. Moreover, the study of Mg^{2+} and the mood disorders could use a certain amount of control, for instance in the form of randomly assigned long-term dietary interventions. This may reduce the potential influence of residual confounding on outcome. Ideally, such studies would be based on validated animal models and specific knowledge of the potential underlying mechanisms.

Conclusion

The question of interest here was whether Mg^{2+} is involved in the pathophysiology of the mood disorders. This association seems plausible, yet the results of our analyses by and large do not provide compelling evidence for the involvement of Mg^{2+} in mood disorders. Although this conclusion is based on the largest and most comprehensive body of human data to date, there are methodological and practical limitations that may have hindered valid assessment of the associations of interest. Future studies should aim to reduce confounding and measurement error in

order to increase knowledge on the potential role of Mg^{2+} in the pathophysiology of the mood disorders.

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Supplementary material

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- 108 Morris ME. Brain and CSF magnesium concentrations during magnesium deficit in animals and humans: neurological symptoms. *Magnes Res* 1992; **5**(4): 303–13.

Appendices

Appendix 1 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and appendix
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made.	5 and appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5 and appendix
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis.	4 and 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies).	4 and appendix
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5, 6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	Table 1 and appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4 and appendix

(Continued)

(Continued)			
Section/topic	#	Checklist item	Reported on page #
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6,7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6,7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4 and appendix
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression; see Item 16).	6
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review-level (e.g. incomplete retrieval of identified research, reporting bias).	7, 8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7,8
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review.	1

Appendix 2 MOOSE checklist

Criteria	Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include	
✓ Problem definition	There is a considerable amount of human data on the topic. Some studies evaluated whether the prevalence (in cross-sectional studies) or the incidence of depression (in longitudinal cohorts) differs as a function of dietary Mg ²⁺ intake. Others have investigated Mg ²⁺ in bodily fluids as a function of mood disorder status. Some experiments also have investigated whether Mg ²⁺ supplementation can serve as an antidepressant. However, the findings from these studies appear to be inconclusive and the 2 meta-analyses on the topic to date do not provide a high level of evidence either.
✓ Hypothesis statement	Mg ²⁺ deficiency also poses a risk to mental health, in particular to a (pathological) low mood
✓ Description of study outcomes	(I) the prevalence and incidence of depression (II) Mg ²⁺ levels by mood disorder status/severity, and (III) improvement in mood
✓ Type of exposure or intervention used	(I) dietary Mg ²⁺ intake, (II) mood disorder status/severity, and (III) Mg ²⁺ supplements
✓ Type of study designs used	Case-control studies, cross-sectional studies, prospective studies, treatment trials, randomised controlled trials
✓ Study population	No restriction applied
Reporting of search strategy should include	
✓ Qualifications of searchers	The credentials of the investigators are indicated at the title page
✓ Search strategy, including time period included in the synthesis and keywords	Systematic searches in PubMed, Web of Science (WoS) and Embase (from their commencement to 22 December 2017)
✓ Databases and registries searched	PubMed, WoS, and Embase
✓ Search software used, name and version, including special features	WoS 2017
✓ Use of hand searching	Bibliographies of the retrieved papers (only the included studies) were hand searched for additional references and backward searches were performed regarding the two first papers on the topic
✓ List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the PRISMA flow chart including reasons for exclusions
✓ Method of addressing articles published in languages other than English	Papers had to be written in English, French, German, Spanish or Dutch in order to be included. All articles however were written in English
✓ Method of handling abstracts and unpublished studies	We contacted a number of authors for full report of relevant unpublished studies in case we found an abstract and no paper
✓ Description of any contact with authors	We contacted authors of relevant articles for necessary information in case that was not provided in the article
Reporting of methods should include	
✓ Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the paper
✓ Rationale for the selection and coding of data	A data extraction sheet was developed (available on request). Data extracted were related to bibliographic details of included study, method of identification of the study, Characteristics of cases/ controls, outcomes and quality assessment

(Continued)

(Continued)		
Criteria	Brief description of how the criteria were handled in the meta-analysis	
✓	Assessment of confounding	We conducted sensitivity analyses where possible and relevant by requesting results by type of diagnosis, type of blood compartment in which Mg was measured, and type of study.
✓	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	The methodological quality of cross-sectional- and case-control studies was assessed using the Newcastle–Ottawa scale and that of prospective studies using the method proposed by Lieveense <i>et al.</i> The methodological quality of treatment trials was assessed using the method of evaluation of (randomised) trials provided by the US Department of Health and Human services. Study quality was related to outcome as a continuous moderator.
✓	Assessment of heterogeneity	We used the I^2 and Q values to assess heterogeneity
✓	Description of statistical methods in sufficient detail to be replicated	We mentioned type of analysis we used (random-effects meta-analysis and subgroup meta-analysis) and type of software we used (STATA)
✓	Provision of appropriate tables and graphics	We included a PRISMA flow chart to show the method of studies identification, Table 1 shows characteristics of included studies, Table 2 provides the results from moderator analyses. Figure 2 provides the main results, and those by subgroup.
Reporting of results should include		
✓	Graph summarising individual study estimates and overall estimate	Not provided. The number of studies was so large that a forest plot would not be interpretable
✓	Table giving descriptive information for each study included	Table 1 and Supplementary Table 10
✓	Results of sensitivity testing	Figure 2
✓	Indication of statistical uncertainty of findings	95% CI intervals were presented around point estimates for all analyses together with I^2 and Q values
Reporting of discussion should include		
✓	Quantitative assessment of bias	All analyses are discussed in light of bias and limitations.
✓	Justification for exclusion	This is presented in detail in the flow-chart and the result section
✓	Assessment of quality of included studies	Quality of the studies was related to outcome in all analyses
Reporting of conclusions should include		
✓	Consideration of alternative explanations for observed results	We emphasise alternative explanations for our results (reverse causation, confounders and measurement error)
✓	Generalisation of the conclusions	We reported the fact that almost all of the studies were on participants of Caucasian descent
✓	Guidelines for future research	We suggest future work with lower potential for confounding and measurement error
✓	Disclosure of funding source	No funding was required for conducting this review

Appendix 3 Study protocol

Working title of the project

Magnesium and disorders of mood: a systematic review with meta-analyses

Review question(s)

1. Does mood disorder prevalence or incidence vary by dietary Mg^{2+} intake.
2. Do Mg^{2+} levels in bodily fluids vary by mood disorder status and severity.
3. Does Mg^{2+} supplementation have an effect on mood.

Searches

We conducted comprehensive searches in three major databases: PubMed, Web of Science, and Embase through December 2017. We used the following terms: (Magnesium OR Mg^*) AND (depression OR depress* OR affect* OR mood OR mania OR bipolar).

The reference-lists of identified articles were scrutinised, as were the references that were made to the 2 seminal papers on the topic (Nielsen, 1964 and Malleon, Frizel, and Marks, 1968) to which, at the date of our latest search, 65 and 5 references were made respectively).

Nielsen J. Serum and erythrocyte magnesium in patients with manic states during lithium treatment. *Acta Psychiatr Scand* 1964; 40(2): 190–6.

Malleon A, Frizel D, Marks V. Ionized and total plasma calcium and magnesium before and after modified ECT. *Br J Psychiatry* 1968; 114(510): 631–33.

Types of study to be included

1. Cross-sectional or prospective studies or randomised controlled trials on the relation between dietary Mg^{2+} intake and the prevalence or incidence of a mood disorder (unipolar or bipolar depression of any kind).
2. Cross-sectional or prospective studies or randomised controlled trials on Mg^{2+} levels in bodily fluids as a function of mood disorder status and severity.
3. Open- or blinded trials (random and non-random, including one-group pre-post designs) reporting on the effects of Mg^{2+} supplementation on any type of mood outcome (e.g. self- and clinician rated questionnaires, diagnosis).

Condition or domain being studied

Psychiatry; mood disorders (unipolar or bipolar depression of any kind).

Participants/population

No restrictions

Intervention(s), exposure(s)

1. Dietary Mg^{2+} intake as measured by a food frequency questionnaire, recall, or diary.
2. Mood disorder status versus healthy control status including gradations in this defined by severity.
3. Mg^{2+} supplementation on any type and any dose.

Comparator(s)/ control

1. High versus low Dietary Mg^{2+} intake of any kind (e.g. continuous, highest quartile versus lowest quartile).
2. Healthy control condition.
3. Placebo (blinded and non-blinded), active control condition (blinded and non-blinded), pre-post measurement in a single group.

Outcome(s)

Primary outcomes (ABS).

- Question 1. Prevalence and incidence of mood disorders.
- Question 2. Blood levels (in any blood component/bodily fluid) of Mg^{2+} .
- Question 3. Changes in mood of any type.

Secondary outcomes. Not applicable

Data extraction

Two of the authors (Danny Phelan and Marc Molendijk) independently screened titles and abstracts of potentially eligible articles. When indicated, this was followed by a review of the full texts of potentially candidate papers. Any type of disagreement with regard to inclusion was resolved by consensus after discussion with a third author.

Risk of bias (quality) assessment

The Newcastle-Ottawa Scale (NOS) cohort version (Wells *et al*, 2016) was used to assess the methodological quality of the included cross-sectional studies on the association between dietary Mg^{2+} intake and the prevalence of mood disorders.

The prospective cohort studies on the relation between dietary Mg^{2+} intake and the incidence of mood disorders were assessed regarding their methodological quality by using the method proposed by Lieveense *et al* (2002).

The NOS case-control version (Wells *et al*, 2016) was used to assess the methodological quality of the included cross-sectional studies on the association between abnormalities in Mg^{2+} levels in blood components/bodily fluids as a function of mood disorder status.

Methodological quality of treatment trials on changes in mood over the course of Mg^{2+} supplementation was assessed by means of the method of evaluation of (randomised) trials provided by the US Department of Health and Human services (2016).

Lieveense AM, Bierma-Zeinstra SMA, Verhagen AP, Van Baar ME, Verhaar JAN, Koes BW. Influence of obesity on the development of osteoarthritis of the hip: a systematic review. *Rheumatol*, 2000; 41(10): 1155–62.

The US Department of Health and Human services, National Heart, Lung and Blood Institute <http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/rct>.

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2013). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2009. Epub Available from: <http://www.ohri.ca>.

Strategy for data synthesis

Quantitative synthesis will be performed by means of random-effects meta-analyses performed in STATA version 13 (2013).

StataCorp LP. (2013). Stata Statistical Software: Release 13-statistical software. College Station, TX.

Analysis of subgroups or subsets

To examine the potential source of heterogeneity across studies, the following sensitivity analyses (per question) were conducted:

- Question 1. Analyses by study type (cross-sectional / prospective studies / randomised controlled trials)
- Question 2. Analyses by disorder (major depressive disorder / depressive symptoms / bipolar disorder / mania), treatment status (antidepressants / electroconvulsive therapy / untreated / not known), blood component / bodily fluid (plasma / serum / urine / cerebrospinal fluid).
- Question 3. Analyses by disorder (major depressive disorder / depressive symptoms / bipolar disorder / mania), control condition (yes / no).

Sources of heterogeneity were also investigated by means of meta-regression analyses with sample size, average age of the sample, female percentage of the sample and methodological quality of the study as predictor. For the third question we also regressed number of weeks of treatment and Mg^{2+} on outcome.

Organisational affiliation of the review

None

Anticipated or actual start date

July 2016

Anticipated completion date

December 2017

Funding sources/sponsors

The review and meta-analyses were supported by a Leiden University research appointment (Marc Molendijk).

Language

English

Country

The Netherlands

Subject index terms

Depression, mood, bipolar disorder, mania, trace-elements, magnesium, Mg^{2+} , diet, review, meta-analysis

