Review article

Magnesium and depression: a systematic review

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Introduction: The incidence of depression is increasing worldwide. Much is still unknown about the possible role of magnesium in depression prevention and treatment. Magnesium has an effect on biological and transduction pathways implicated in the pathophysiology of depression. The possible role of magnesium in depression prevention and treatment remains unclear.
Objectives: We systematically reviewed the possible links between magnesium and depression in humans.
Methods: Twenty-one cross-sectional studies, three intervention trials, one prospective study, one case only study, and one case series study were included based on specific selection criteria.
Results: A higher intake of dietary magnesium seems to be associated with lower depression symptoms though reverse causality cannot be excluded. The results assessing the association between blood and cerebrospinal fluid magnesium and depression are inconclusive.
Discussion: Magnesium seems to be effective in the treatment of depression but data are scarce and incongruous. Disturbance in magnesium metabolism might be related to depression. Oral magnesium supplementation may prevent depression and might be used as an adjunctive therapy. However, more interventional and prospective studies are needed in order to further evaluate the benefits of magnesium intake and supplementation for depression.

Keywords: Depression, Major depression, Magnesium, Review

Introduction

Mental disorders are one of the most burdensome diseases due to their high prevalence, early age of onset, and their resulting severe disabilities.[1] Specifically, depression affects about 151 million people worldwide[2] and is the most prevalent mental disorder in young adults.[3] Magnesium is the second most predominant intracellular cation and plays a role in over 300 enzymatic reactions.[4,5] Dietary magnesium intake is insufficient in most populations.[6–8] Studies show that an inadequate intake of magnesium can lead to different health problems such as hypertension,[9] cardiovascular disease,[10] and type 2 diabetes.[9,11] It is likely that it might be also related to depression.[12] Magnesium has an effect on biological and transduction pathways implicated in the pathophysiology of depression.[13] Magnesium is a natural calcium antagonist and a voltage-dependant blocker of the *N*-methyl-D-aspartate (NMDA) channel, which plays a role in the entrance of calcium into the neuron.[14,15] By regulating this entry, magnesium may acquire neuroprotective properties and it is likely to protect the neuron against cell death.[16,17] High levels of calcium ions and glutamate with insufficient magnesium, especially in the hippocampus, may deregulate brain cell synaptic function contributing to depression or other mood disorders.[18]

Animal studies show that magnesium induces antidepressant effects in mice[19] and that it is useful as an adjunctive therapy for depression.[20,21] Studies investigating the relationship between serum/plasma magnesium and depression are inconsistent and evidence about magnesium intake and depression in human is scarce (see below).

The present study summarizes background information on magnesium and depression and systematically reviews the possible links between both in cross-sectional and intervention studies. We also suggest directions for future research.

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Background of the issue

Depression

Lots of epidemiological studies have been realized about the prevalence of major depression but experience indicates to be careful while comparing international major depression prevalence.[22] The point prevalence of mayor depression is around 5.3% (interquartile range: 3.6–6.5%).[23] This prevalence varies according to the country and there is a tendency for it to increase, particularly in adolescents.[24] Aalto-Setala *et al.*[2] report a point prevalence rate of depression of 10.8% among a non-clinical sample of 20–24-year-olds. Moreover, lifetime risk of depression reaches 21.4% at world level.[25,26]

Clinical depression has unfavorable effects on physical health, relationships, and cognitive performance.[27] Recent evidence demonstrates that depression is a predictor of mortality.[28] Among the most common symptoms of depression are: anhedonia, psychomotor difficulties, excessive guilt of hopelessness, and disturbances of appetite or weight.[29] Depression is a multifactorial disease influenced by genetic, hormonal, immunological, biochemical, and neurodegenerative factors, and also by environmental factors such as nutrients and diet.[30] Lots of studies have demonstrated the role of folate,[31–33] fish consumption, and omega-3 fatty acids,[34,35] and vitamin B6 and B12[31,33] in the etiology of depression.

Magnesium

Magnesium is the second most predominant intracellular cation and it is an important cofactor in over 300 enzymatic reactions.[4,5] Furthermore, magnesium has a crucial role in ATP-generating and ATP-utilizing reactions, thus also in the facilitation of transphosphorylation reactions that are indispensable to cell activation and deactivation.[5,36,37] Magnesium regulates energy metabolism and production, DNA and RNA synthesis and structure, cell growth, cytoskeletal function, membrane structure, and ion homeostasis.[36,38] Magnesium is also a natural calcium antagonist and a voltage-dependent blocker of the NMDA channel, which plays a role in the entrance of calcium into the neuron.[14,15] By regulating this entry, magnesium may acquire a neuroprotective property and is likely to protect the neuron against cell death.[16]

The Recommended Dietary Allowance (RDA) of magnesium for men between 31 and 50 years old is 420 mg (17.4 mmol)/day and for women of the same age, it is 320 mg (13.3 mmol)/day.[39] In many Western countries, magnesium intake from dietary sources is insufficient.[6–8] Particularly, evidence show that 68% of the American adults consume less than the American RDA of magnesium with 19% having an intake of less than 50% of the RDA.[6] In a French population (35–60 years old), the overall mean dietary intake is around 369 ± 106 mg/day in men and 280 ± 84 mg/day in women. Seventy-seven percent of women and 72 percent of men have dietary magnesium intakes lower than the RDA. Moreover, 23% of women and 18% of men consume less than 2/3 of these RDA.[40] This can be problematic as inadequate intake of magnesium is linked to different health problems such as hypertension,[9] cardiovascular disease,[10] and type 2 diabetes.[9,11]

Animal studies show that a magnesium-deficient diet enhances depression- and anxiety-related behaviour in mice.[41] Magnesium also induces antidepressant- and anxiolytic-like effects in mice.[19] Magnesium chloride administration has similar pharmacological effects as antidepressants at a preclinical level and thus may potentiate the effectiveness of antidepressant components in therapy of human depression.[20] Similarly, magnesium sulfate improves post-traumatic depression and anxiety in rats.[21] However, it must be borne in mind that there are important differences between experimental models of depression in mice and rats and human depression. With regard to humans, interventional case studies show that magnesium may be useful in the treatment of depression.[42,43]

Materials and methods

Search strategy

We conducted a systematic bibliographic review by searching in PubMed database – without any limit regarding date of publication – for case only, series, cross-sectional, prospective observational studies, and intervention trials specifying the following search terms [magnesium], [magnesium intake], and [magnesium supplements] hedged with [depression] and [affective disorders] and [relative risk] or [case-control] or [odds-ratio] or [follow-up] or [incidence] or [cohort] or [cross-sectional] or [trial] or [experimental]. We obtained additional published studies by hand-searching the key publications and reviews for references.

Selection criteria

We included studies that investigated the relationship between magnesium and depression in human adults and that were published in English. The principal exposure measure included magnesium and we took depression as the outcome. We excluded reviews, comments, letters, abstracts, animal studies, studies in which depression was not one of the outcome variables (we only took into account major depression and unipolar depression, not bipolar disorder), and reports which took into account electrolytes in general without evaluating the specific role of magnesium. The selected papers used RDC (research diagnostic criteria),[44–48] DSM-III-R,[49–55] DSM-IV,[56–58] or

ICD-9[59] criteria for major depression diagnosis. To measure symptoms and severity of depression they used scales such as the Hospital Anxiety and Depression Scale (HADS),[12,60] Yesavage and Brink score,[61,62] Montgomery Asberg (MA) Depression Rating Scale,[63] Beck depression inventory,[63,64] Hamilton Rating Scale for Depression (HAM-D),[44,50,57,65] Association for Methodology and Documentation in Psychiatry (AMDP)-depression rating scale,[52–54] Manual for the Assessment and Documentation of Psychopathology (MADP)-depression rating scale,[55] Clinical Global Impression scale,[49] Schedule for Affective Disorders and Schizophrenia-lifetime version (SADS-L),[45,46,48] and the Comprehensive Psychopathological Rating Scale (CPRS),[47] or questionnaires such as the Menstrual Health Questionnaire (MHQ)[66] and the Moos questionnaire.[66] Fig. 1 shows the flowchart indicating how we selected pertinent studies. A total of 189 were obtained through PubMed research, of which 174 were excluded because they did not match our selection criteria. Of these, we reviewed the full texts of 15 articles of which one was excluded because it used as exposure an extract containing many other elements in addition to magnesium wherefore it was impossible to distinguish if the observed effects were due to magnesium or to the other components. Furthermore, 13 relevant cross-matching references were retained for analysis. In this paper, we thus reviewed a total of 27 studies.

Results

Among the 27 final epidemiological articles selected for analysis, 21 were exclusively cross-sectional studies,[12,44–57,59–61,63,65,67] three were intervention trials,[62,64,66] one was a prospective study,[58] one was a case only study,[68] and one was a case series study.[69] Only four of these studies examined the effect of magnesium administration in the treatment of major depression. Two were interventional trials[62,65] and two were case studies.[68,69] All the other studies investigated the effect of magnesium in the prevention of depression.[12,44–57,59–61,63–64,67] All subjects included were adults and studies were conducted in the USA, Canada, Mexico, Japan, Korea, Australia, Italia, Spain, Bulgaria, United Kingdom, Poland, Sweden, and Switzerland. Cross-sectional studies analyzed blood or cerebrospinal fluid (CSF) magnesium in

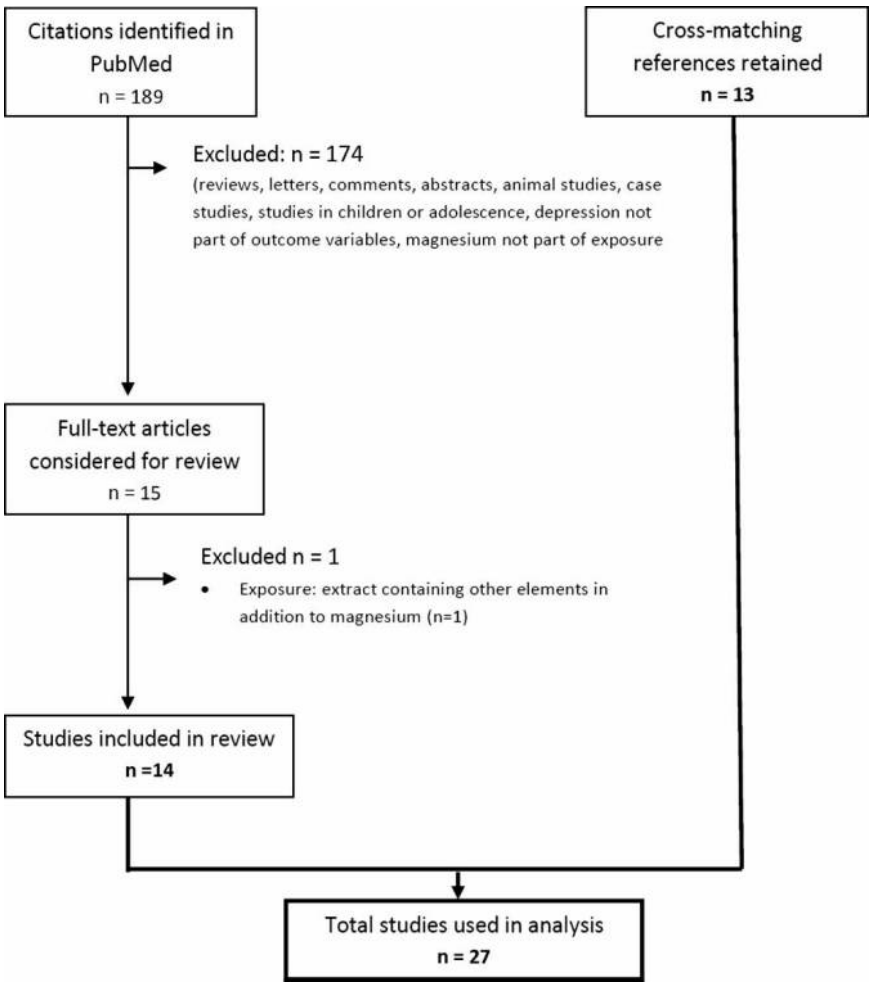

Figure 1 Flowchart of the identification and selection of relevant studies.

depressed patients and one study examined if magnesium intake was related to depression. Two intervention trials examined if magnesium was useful to reduce depressive symptoms and one determined if magnesium during cardiac surgery was neuroprotective. The only prospective study aimed to evaluate the association between magnesium intake and depression incidence in a cohort of 12 939 Spanish university graduates initially free of depression. The case only study and the case series study described the improvement of depressive state after magnesium supplementation. Methodological details and results of the analyzed studies are summarized in Tables 1–4.

CSF magnesium in patients with depression

Little information is known about CSF magnesium in patients with depression. Two cross-sectional studies carried out in adults in the USA found no differences in magnesium CSF between patients with depression and control subjects.[45,49] However, when depression patients were combined with adjustment disorder patients, they had significantly lower mean CSF magnesium levels than patients with schizophrenia and control subjects taken together.[49] Finally, a study conducted in Finland[51] including 14 patients with depression and 15 normal subjects indicated that CSF calcium/magnesium (Ca/Mg) ratios were higher in patients with depression compared to controls, whereas CSF magnesium and CSF Ca/Mg ratios were not correlated with severity of depression.

Blood magnesium in patients with depression

Considerable interest has been shown in the possible role of altered magnesium metabolism in depression. Of the 21 cross-sectional studies included in the methodological part of this review, 19 investigated blood magnesium levels in patients with depression and healthy adults. Among them, seven studies (one in depressed and non-depressed diabetic subjects[61] and five in depressed and healthy subjects without medical illness[46,51,54,57,63] and one in major depressive patients[65]) investigated associations between serum magnesium and depression severity. Findings are contradictory. The study in diabetic patients[61] showed a strong association between hypomagnesemia and depression score while the results of Hasey *et al.*[63] and Widmer *et al.*[54] indicated a significant positive relationship between serum magnesium concentrations and depression severity. Finally, four other studies found no correlations between both.[46,51,57,65]

Results on serum/plasma magnesium levels in patients with depression are conflicting. Several studies have shown that high serum/plasma magnesium levels were associated with depression.[44,47,52–56] However, in one of these studies these differences were only significant in men,[52] in another one only in patients with longstanding but not with acute depression,[47] and in a third one differences were only found for total plasma magnesium levels but not for concentrations of ultrafiltrable magnesium.[44] On the contrary, magnesium levels have also been reported as being lower in patients with depression compared to controls.[57,59,61] Similarly, a study in 16 patients with depression and 12 normal subjects found lower total plasma magnesium levels among patients, but no differences in ionized magnesium levels.[67] Jung *et al.*[60] assessed serum magnesium levels in 112 healthy adult women without psychiatric disorders and observed that women in the lowest tertile of serum magnesium levels had a higher risk of developing depressive mood disorder. Finally, other authors[48] mentioned no differences in serum magnesium levels between subjects with depression and controls.

Most of the results obtained with regard to erythrocyte magnesium levels showed that they were higher in patients with depression compared to controls.[44,52–55] It has to be mentioned that in one study those differences were only found in men[52] and in another one only when patients with depression were compared to non-hospitalized healthy controls but not when they were compared to hospitalized healthy controls.[44] However, in one Japanese study[50] erythrocyte magnesium concentrations did not differ between subjects with major depression and healthy controls.

Serum Ca/Mg ratios

Few studies have examined serum Ca/Mg ratios in patients with depression and results of those that have been conducted are conflicting. A Korean study[60] carried out in 112 healthy women showed that women in the middle tertile of serum Ca/Mg ratio had significantly lower scores on depression and a lower risk of developing a depressive disorder than those of the highest tertile. Similarly, Levine *et al.*[51] showed higher serum Ca/Mg ratio in patients with depression. However, no differences were found in a Canadian study.[48]

Magnesium, neuroprotectant used in the treatment of depression?

As mentioned in the Introduction, magnesium plays an important role in brain metabolism. A single-institution randomized, blinded, placebo-controlled clinical trial was conducted in 2006 to evaluate whether magnesium was neuroprotective in patients undergoing cardiac surgery.[64] Three hundred and fifty patients undergoing elective coronary artery bypass grafting, valve surgery, or both took part in the study. They received either magnesium sulfate during the operation and for 24 hours thereafter (magnesium group) or no intervention (placebo group).

Table 1 Cross-sectional studies ($n = 20$)

Author, (year), [ref] country	Patients	Treatment/drug-free period before intervention	Controls	Exposure	Confounders	Results
Banki *et al.* (1985),[49] USA	41 female psychiatric patients (19–67 yrs) recently hospitalized (divided into 3 groups): MD, schizophrenic disorder, adjustment disorder	No major psychotropic medication for ≥2 wks, free from Li for ≥6 mo.	15 female patients with only peripheral illness (26–59 yrs)	CSF Mg (LB, AAS)	/	CSF Mg heterogeneous among groups (F = 1.68, df = 1.52). Depressed + adjustment disorder: significantly lower mean CSF Mg levels >< control + schizophrenic groups (F = 9.69, df = 1.52; $P < 0.005$). After exclusion of patients who had made suicide attempts: difference insignificant.
Barragan-Rodríguez *et al.* (2007),[61] Mexico	55 type 2 diabetic patients (≥ 65 yrs) with newly diagnosed depression (40 women, 15 men)	Not mentioned	55 age- and gender-matched diabetic controls (≥65 yrs) without depressive symptoms (43 women, 12 men)	Serum Mg (colorimetric method)	Age, duration of diabetes, HbA1c, concomitant physical illnesses, serum triglycerides, albumin, and creatinine levels, and gender	Serum Mg levels significantly lower among depressive than control diabetic subjects (0.74 ± 0.25 vs. 0.86 ± 0.29 mmol/l, $P = 0.02$). Bivariate analysis: strong association between hypomagnesemia and depression score (OR = 2.5; 95% CI 1.02–6.17). Association remained significant in the adjusted logistic regression analysis (OR = 1.79; 95%, CI = 1.1–6.9, $P = 0.03$).
Camardese *et al.* (2012),[65] Italy	123 outpatients during a major depressive episode (at least two major depressive episodes and no remission in the former treatment trial) 56 men and 67 women (mean age: 48 yrs)			Total plasma Mg (colorimetric assay)	Age and gender	No association between plasma Mg levels and psychopathological severity. Magnesium levels were a predictor of response to treatment (OR = 32.50; 95% CI = 1.10–957.19, $P = 0.04$)
Frazer *et al.* (1983),[44] USA	Patients with affective disorders but without medical disorders (58 women, 58 men, ≥19 yrs) divided into 3 groups: UP, BP, manic	Patients drug-free for ≥ 9 d and controls for ≥ 2 wks before taking blood	42 women, 37 men, 42 women ≥19 yrs, no medical disorders, divided into 2 groups: non-hospitalized, hospitalized	Plasma and erythrocyte Mg (AAS)	Demographic variables in multiple comparisons	Plasma Mg significantly higher in depressed patients than in hospitalized healthy controls ($P < 0.005$) but concentrations of ultrafiltrable Mg did not differ. Erythrocyte Mg concentrations were significantly higher in depressed patients than in non-hospitalized healthy controls ($P < 0.001$) but this difference was not seen between the depressives and the hospitalized healthy controls.

Continued

Table 1 *Continued*

Author, (year), [ref] country	Patients	Treatment/drug-free period before intervention	Controls	Exposure	Confounders	Results
Frizel *et al.* (1969),[67] UK	16 depressive patients (9 women, 7 men; mean age 52.3 yrs)	Majority treated by convulsive therapy, 3 by tryptophan	12 normal subjects without depressive illness	Total and ionized plasma Mg (fluorimetric method, 8-hydroxyquinoline-5-sulphonic acid)	/	No differences in ionized Mg between groups. Total plasma Mg significantly lower in depressed patients.
George *et al.* (1994),[45] USA	173 affectively-ill inpatients (95 men, 78 women; mean age: 39.9 yrs) divided into 3 groups: UP, BP I and BP II	No active substance abuse within past 2 yrs	59 healthy volunteers (22 men, 37 women; mean age 30.5)	CSF Mg (LB, AAS)	/	No significant differences between group means of CSF Mg between controls and UP patients. No significant differences between controls and patients when a separate analysis was done taking gender into account. No correlation between CSF Mg levels and rating scales of depression on the day of the lumbar puncture.
Hasey *et al.* (1993),[63] Canada	13 UP patients (6 men, 7 women), mean age: 52.4 yrs	All free of Li treatment, 10 subjects without treatment ≥ 5 d	/	Serum Mg (spectrophotometry)	/	Serum Mg concentrations correlate positively and significantly with depression severity ($r = 0.63$, $n = 11$, $P < 0.04$).
Imada *et al.* (2002),[56] Japan	71 in-patients and out-patients with mood disorder [17 with BP I (mean age: 39.9 yrs), 15 with BP II (mean age: 48.3 yrs) and 22 with MD (mean age: 48.3 yrs)], 42 men, 29 women	Almost all BP and 60% of MD were taken psychotropic drugs	30 sex- and age-matched healthy subjects (16 men, 14 women; mean age 43.1 yrs) without psychiatric disease	Serum Mg (photometric method using the xylidyl blue method)	/	Mean serum Mg levels significantly higher in the MD group ($P < 0.01$) compared to levels in control group.
Jacka *et al.* (2009),[12] Australia	5708 community dwelling healthy adults (2461 men, 3247 women) 46–49 or 70–74 yrs	/	/	Dietary Mg intake (169 item FFQ)	Total energy intake, gender, age group, waist–hip ratio, body mass index, blood pressure, income, education, physical activity, current smoking and alcohol use	Inverse association between standardized energy-adjusted Mg intake and standardized depression scores not confounded by age, gender, body habitus or blood pressure ($\beta = -0.16$, 95% CI = −0.22 to – 0.11). Association was attenuated after adjustment for socioeconomic and lifestyle variables, but remained statistically significant ($\beta = -0.11$, 95% CI = −0.16 to – 0.05). Standardized Mg intake was also related to case-level depression (OR = 0.70, 95%, CI = 0.56–0.88), although association attenuated when adjusted for socioeconomic and lifestyle factors (OR = 0.86, 95% CI = 0.69–1.08).

Joffe *et al.* (1996),[46] Canada	135 consecutive outpatients with UP non-psychotic MD (41 men, 94 women), 39.1 yrs	Medication free for ≥ 2 wks, no Li for ≥ 6 wks	/	Serum Mg (for methods see Joffe and Singer, 1990)[83]	/	No significant correlation between serum Mg levels and severity of depression.
Jung *et al.* (2010),[60] Korea	112 healthy adult women without psychiatric disorders, 21–72 yrs	/	/	Serum Ca and Mg (automatic analytical instrument) and Ca/Mg ratio	Age, BMI, menopausal status, physical activity, smoking status, alcohol use, hypertension, diabetes, ischemic heart disease	Women in the middle tertile of serum Ca/Mg ratio: significantly lower scores of depression ($P = 0.004$) and a lower OR for the risk of depressive disorder (OR = 0.31, 95% CI = 0.10–0.93) than those in the highest tertile. The OR for the risk of depressive mood disorder was higher in women in the lowest tertile of serum Mg than in those in the highest tertile (OR = 3.92, 95% CI = 1.11–13.83).
Kamei *et al.* (1998),[50] Japan	31 patients MD (in active phase: 10 men, 2 women, mean age 42.8 yrs; in remission: 13 men, 6 women, mean age 36.6 ± 13.3 yrs)	Active phase: never received AD, subjects in remission: Li carbonate or AD (2 wks – 12 mo)	20 healthy participants (10 men, 10 women, mean age 36.1 yrs)	Erythrocyte Mg (AAS)	/	No differences in Mg concentrations between the 3 groups. No differences were indicated by the paired t-test in erythrocyte Mg concentrations between active and remission phase.
Kirov *et al.* (1990),[59] Bulgaria	37 patients (15 schizophrenic, 10 depressed, 6 manic and 6 persenile Alzheimer's disease patients), 18–60 yrs	Some of them Li or neuroleptics	303 blood donors, 18–60 yrs	Plasma Mg (AAS)	/	Depressed patients: lower plasma Mg levels than healthy volunteers.
Levine *et al.* (1999),[51] USA	14 acutely depressed and recently hospitalized patients (2 men, 12 women, 35–70 yrs): 12 with MD and 2 with BP	No medications for ≥ 7 d	15 normal subjects (10 men, 4 women, 20–80 yrs)	CSF and serum Ca and Mg (LB, colorimetric determination)	/	CSF and serum Ca/Mg ratios higher in research group than in controls (ANOVA test: df: 1.27; $F = 4.26$; $P = 0.04$; df = 1.27; $F = 14.7$; $P = 0.007$, respectively). CSF and serum Mg, and CSF and serum Ca/Mg ratios not correlated with severity of depression. Mann–Whitney *U* test: higher serum Ca/Mg ratio ($P = 0.001$) and tendency toward a higher CSF Ca/Mg ratio in depressed patients compared with controls ($P = 0.1$).

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Table 1 ***Continued***

Author, (year), [ref] country	Patients	Treatment/drug-free period before intervention	Controls	Exposure	Confounders	Results
Linder *et al.* (1989),[47] Sweden	56 patients (30 women, 26 men) divided into 2 groups: First group: 32 hospitalized patients with acute MD studied during the acute phase and 26 of them were also studied after clinical improvement, 1 to 12 mo after the first study. Second group: 24 outpatients with longstanding depression	19 of 24 outpatients with longstanding history of depression treated with Li for 3–21 yrs. No washout period, patients continued on prescribed medication during study.	27 healthy volunteers (14 women, 13 men, 26–63 yrs), mainly students and staff from the hospital	Plasma, serum, and mean diurnal (24-h) Mg (AAS)	/	Higher morning levels of serum Mg during longstanding (0.94 ± 0.03) but not during acute depression (0.75 ± 0.03) compared with controls (0.69 ± 0.02, $P < 0.001$). Similar differences noted for the diurnal mean of serum Mg.
Widmer *et al.* (1992),[52] Switzerland	20 depressive patients classified into UP or BP (9 men, 11 women; mean age: 46.2 yrs for UP, 57.0 yrs for BP)	Drug-free for ≥ 2 wks	33 healthy controls chosen from the hospital staff and matched for sex and age with patients (18 men and 15 women; mean age: 43.7 yrs)	Erythrocyte and plasma Mg (AAS)	/	Male drug-free UP patients: higher erythrocyte Mg levels than male controls ($P < 0.0003$). The female UP did not differ from female controls for erythrocyte Mg level. Plasma Mg levels higher in male UP compared with male controls ($P < 0.005$). The female UP did not differ from female controls for plasma Mg level.
Widmer *et al.* (1993),[53] Switzerland	34 depressed patients (13 men, 21 women, mean age: 46.0 yrs), classified into UP ($n = 23$), BP (or manic-depressives, $n = 6$), and dysthemics (or neurotics, $n = 5$	Drug free ≥ 2 wks, controls: no medication	35 healthy controls (20 men, 15 women, mean age: 42.0 yrs) chosen from the hospital staff.	Erythrocyte and plasma Mg (AAS)	/	Higher plasma and erythrocyte Mg concentrations in patients than in controls (+12%, $P < 0.0001$ and +14%, $P < 0.0001$, respectively).
Widmer *et al.* (1995),[54] Switzerland	53 depressed in-patients (20 men, 33 women; mean age: 48.3 yrs) classified into UP or BP	Drug free for ≥ 2 wks, never received Li therapy, controls: no medication	48 healthy controls (27 men and 21 women; mean age: 43.0 yrs) chosen from the hospital staff	Erythrocyte and plasma Mg and plasma-ultrafiltrable Mg (AAG)	/	High and very significant increase in erythrocyte Mg for both male (13%, $P < 0.0004$) and female patients (11%, $P < 0.0003$) compared with control values. In contrast, only in male patients, plasma Mg was significantly higher (11.7%, $P < 0.001$) than in controls. Only a small difference between patients and controls for plasma-ultrafiltrable Mg. There is a positive relationship between erythrocyte Mg levels and the severity of depression in MD patients.

Widmer *et al.* (1998),[55] Switzerland	88 depression inpatients (61 women, mean age: 50.1 yrs, 27 men; mean age: 48.3 yrs)	Drug free for ≥ 2 wks, never received Li therapy	61 sex- and age-matched healthy controls (28 men, mean age: 44.5 yrs and 33 women; mean age: 43.2 yrs) chosen from the hospital staff.	Erythrocyte and plasma Mg (AAS)	/	Female and male patients: higher erythrocyte ($P < 0.001$ and $P < 0.001$, respectively) and plasma ($P < 0.005$ and $P < 0.003$, respectively) Mg contents than control subjects.
Young *et al.* (1996),[48] Canada	145 MD patients (45 men, 100 women; mean age: 37.1 yrs)	Medication-free for ≥10 d	80 controls (42 men, 38 women) divided into 2 groups : BP outpatients disorder and outpatients with diagnosis other than mood disorder	Serum Mg and Ca/Mg ratio (method not mentioned)	/	Across groups: no statistical differences between MD group and control group with respect to Mg levels and Ca/Mg ratio.
Zieba *et al.* (2000),[57] Poland	19 UP MD patients (mean age: 42.2 yrs)	No information	16 healthy volunteers (mean age: 37.0 yrs)	Serum Mg levels (flame AAS)	/	No significant correlation between serum Mg levels and severity of depression. Serum Mg concentrations in depressed group significantly lower (by 0%) than in control group (t = 2.759 (33), $P = 0.0094$).

Yrs: years; MD: major depression; wks: weeks; Li: lithium; mo: months; CSF: cerebrospinal fluid; Mg: magnesium; LB: lumbar puncture; AAS: atomic absorption spectrophotometry; OR: odds ratio; CI: confidence interval; UP: unipolar, BP: bipolar; d: day(s); FFQ: food frequency questionnaire; Ca: calcium; BMI: body mass index; AD: antidepressants; h: hour.

Depression was evaluated preoperatively and 3 months postoperatively by depression inventories. Depression inventory scores were generally better 3 months postoperatively than before cardiac surgery; this could be due to familiarity with test procedures during retesting. In addition, changes were similar between groups which made the authors conclude that magnesium did not influence depression symptomatology 3 months after operation.

With regard to the role of magnesium in the treatment of depression, two interventional studies have been conducted in humans[62,66] with different results. In a randomized, active control equivalent trial with newly diagnosed depressed elderly with type 2 diabetes and hypomagnesemia, allocated to receive either 50 ml of magnesium chloride or imipramine 50 mg daily during 12 weeks, Barragan-Rodriguez *et al.*[62] reported that serum magnesium and depression score were similar in both groups at baseline. In this study, depression scores decreased in both groups and there were no significant differences between both, which led the authors to conclude that oral magnesium supplementation (using magnesium chloride) was as effective as imipramine at 50 mg daily in reducing depression symptoms in depressed elderly type 2 diabetics with hypomagnesemia. However, magnesium supplementation was not shown to improve depressive symptoms in a randomized, double-blind, placebo-controlled, crossover study including 38 American women suffering from premenstrual symptoms.[66]

Magnesium supplementation in the treatment of depression – case studies

One case study conducted by Enya *et al.*[68] described how after the second day of intravenous magnesium supplementation, the depressive state of a 69-year-old woman improved dramatically. In addition, Eby and Eby[69] described four cases of two men and two women aged between 23 and 59 years old, with a previous diagnosis of depression and previously treated with antidepressants, whose depression symptoms were reduced or even disappeared after magnesium treatment.

Magnesium intake and prevalence of depression

Magnesium intake has been shown to be inadequate in many countries. Moreover, as mentioned before, magnesium is essential for a good brain functioning. However, surprisingly few studies have examined the association of magnesium intake and depression in humans. To the best of our knowledge, only one cross-sectional epidemiological study has been carried out in humans.[12] The study took place in Western Norway, where 5708 adult subjects were recruited from the Hordaland health study (conducted

Table 2 Experimental trials/interventions ($n = 3$)

Author, (year) [ref], country	Study design	Sample population	Drug-free period before intervention	Intervention	Control	Duration	Outcome results
Barragán-Rodríguez *et al.* (2008),[62] Mexico	Randomized, active control equivalent trial	23 elderly (≥ 60 yrs) with type 2 diabetes, hypomagnesemia, and newly diagnosed depression	No previous or current treatment with AD	50 ml of $MgCl_2$ 5% solution (equivalent to 450 mg of elemental Mg), $n = 12$	Imipramine 50 mg daily during 12 weeks, $n = 11$	12 weeks	Baseline: no differences in serum Mg levels between $MgCl_2$ group (1.3 ± 0.04 mg/dl) and imipramine group (1.4 ± 0.04 mg/dl, $P = 0.09$), nor in depression scores (17.9 ± 3.9 and 16.1 ± 4.5 point, respectively, $P = 0.34$). At the end of follow-up the Yasavage and Brink scores significantly decreased in both groups ($P < 0.005$) without significant differences in the scores between groups (11.4 ± 3.8 and 10.9 ± 4.3 point, respectively, $P = 0.27$). Serum Mg levels were significantly higher in the group with $MgCl_2$ (2.1 ± 0.08 mg/dl) than in subjects with imipramine (1.5 ± 0.07 mg/dl, $P < 0.0005$).
Bhudia *et al.* (2006),[64] USA	Randomized, blinded, placebo-controlled	350 patients undergoing elective coronary artery bypass grafting, valve surgery, or both (270 men, 80 women), mean age: 64 yrs	/	Mg sulfate to increase plasma levels $1\frac{1}{2}$ to 2 times normal during cardiopulmonary bypass (= Mg group; $n = 174$: 133 men, 41 women)	Placebo ($n = 176$: 137 men, 39 women)	20 months	Depression inventory scores were generally better 3 months postoperatively than preoperatively with few changes between groups ($P > 0.6$).
Walker *et al.* (1998),[66] USA	Randomized, double-blind, placebo-controlled, cross over	38 volunteer women suffering from premenstrual symptoms, 18–50 yrs	/	1 Mg tablet per day	1 placebo tablet per day	4 menstrual cycles (2 cycles intervention, 2 cycles placebo)	No significant differences in depression symptoms between Mg and placebo supplementation after 1 and 2 months.

Yrs: years; AD: antidepressants; $MgCl_2$: magnesium chloride; Mg: magnesium.

Table 3 Prospective studies ($n = 1$)

Author, (year) [ref], country	Sample population	Follow-up	Confounders	Exposure	Outcome	Outcome Results
Derom *et al.* (2012),[58] Spain	12 939 University graduates (Seguimiento Universidad de Navarra: 5503 men, 7636 women), mean age: 37.6 ± 11.7 yrs	5.8 ± 2.4 yrs	Baseline BMI, physical activity during leisure time, smoking status, marital status, number of children, employment status, self-perceived personality traits, alcohol and TFA intakes, total energy intake, adherence to the MDP	Dietary Mg intake and total Mg intake (= dietary Mg + supplemental Mg)	Incident depression (self-reported, physician-made diagnosis of depression, or self-reported use of AD)	Higher Mg intake (total Mg or dietary Mg) was not associated with lower depression risk.

Yrs: years; BMI: body mass index; TFA: trans fatty acids, MDP: mediterranean dietary pattern; Mg: magnesium, AD: antidepressants.

Table 4 Case only and series studies ($n = 2$)

Author, (year) [ref], country	Sample population	Clinical characteristics	Laboratory data	Treatment	Results
Enya *et al.* (2004),[68] Japan	1 woman 69 yrs	Headache, joint pain of bilateral knees, sleeplessness, paresthesia in extremities. Psychiatrist diagnostic of depressive state.	Serum electrolyte levels: Na 143 mEq/l, K 3.2 mEq/l, Cl 103 mEq/l, Ca 8.6 mg/l, and Mg 0.7 mg/l Serum pH: 7.45	Spironolactone, oral magnesium oxide, and magnesium sulfate potassium chloride sup.	On the 2nd day of i.v. magnesium supplementation, the patient's depressive state improved dramatically.
Eby *et al.* (2006),[69] USA	4 cases: 2 men 40 and 59 yrs 2 women 23 and 35 yrs	Depression, anxiety, insomnia. Treated previously with antidepressants.		Glycinate or taurinate of magnesium.	Sleep was restored, depression was greatly reduced or disappeared, anxiety disappeared.

Yrs: years.

from 1997 to 1999). Dietary intakes were evaluated through self-administered food frequency questionnaires and symptoms of depression were self-reported using the Hospital Anxiety and Depression Scale. Findings indicate an inverse association between magnesium intake and depressive symptoms. This association persisted after adjustments for age, gender, anthropometric characteristics, blood pressure, socioeconomic status, and lifestyle factors.

Magnesium and the incidence of depression

To be better protected against reverse causality bias, a longitudinal study was conducted to evaluate the effect of magnesium intake (dietary magnesium and total magnesium) on depression occurrence among 12 939 Spanish university graduates initially free of depression (Seguimiento Universidad de Navarra Cohort Study). Total magnesium intake (dietary and supplemental magnesium) and dietary magnesium intake were assessed with a validated, semiquantitative food frequency questionnaire, and incident depression was ascertained through the use of antidepressive drugs and/or through self-reports of a new clinical diagnosis of depression by a medical doctor. Results suggested that higher magnesium intake was not related to a lower risk of developing repression. However, intakes of magnesium were not very low among participants even among those in the lowest category of intake. It is still possible that at extremely low levels of magnesium intake an increased risk of developing depression might occur.

Discussion

Twenty-seven studies (21 cross-sectional studies, 3 intervention trials, one prospective study, one case only study, and one case series study) were included in this systematic review. In general, total calcium and magnesium concentrations in the CSF are relatively stable even when changes occur in their serum levels.[70] These findings suggest that estimating calcium and magnesium levels may be more precise

in CSF than in their respective blood levels.[51] Two cross-sectional studies found no differences in CSF magnesium levels between patients with depression and controls.[45,49] Furthermore Levine *et al.*[51] indicated that CSF magnesium was not correlated to severity of depression in a population of Finland. Magnesium concentrations are normally higher in CSF than in plasma (CSF: 1.2 mmmol/l, plasma: 0.9 mmol/l) due to the active transport of magnesium across the blood–brain barrier.[71] The lack of significant differences in CSF magnesium levels between patients with depression and healthy controls observed in the above-mentioned studies might be explained by the fact that during magnesium deficiency, CSF concentrations go down but this decline lags behind and is less pronounced than changes that might be seen in plasma.[72] Prolonged magnesium supplementation only slightly increases CSF magnesium concentrations in rats.[73]

A potential efficacy of oral magnesium in the prevention of depression or as an adjunct in its treatment should not be surprising if we bear in mind that magnesium deficiency has been related to the pathogenesis of neuropathologies such as depression.[42,74] Magnesium ions in normal conditions block calcium entrance through the NMDA receptor channel.[15] Magnesium deficiency may destruct neurons by causing the opening of NMDA-coupled calcium channels producing an excessive intra-neuronal mitochondrial concentration of calcium, which may activate calcium-dependent enzymes that are normally repressed. This in turn results in a series of mechanisms such as cytoskeletal breakdown, failure to generate ATP and production of free radicals, all leading to neuronal death. It is worth noting that L-glutamate, although being the principal excitatory neurotransmitter in the brain and being vital for neuronal transaction, is harmful for neurons when presented in excess.[16,75] Too many calcium ions and glutamate with insufficient magnesium, especially in the hippocampus, may deregulate brain cell synaptic function inducing depression or other mood disorders.[18]

It is not clear as to whether serum/plasma magnesium concentrations are related to severity of depressive symptoms. Even if all patients were free of drug treatment during the assessment, some studies found a positive correlation between both,[54,63] some a negative correlation,[61] and most of them no correlation.[46,51,57,65] Studies determining serum/plasma magnesium levels in depressed patients have reached different conclusions. Some authors reported higher magnesium concentrations in patients with depression compared to controls.[44,47,52–56] It has to be mentioned that results of one study are true only for men,[52] in another one only in patients with longstanding but not with acute depression,[47] and in a third one only for total plasma magnesium but not for ultrafiltrable magnesium.[44] However, magnesium serum/plasma concentrations have also been found to be lower in patients with depression,[57,59,61,67] with one of these studies finding this difference only in total plasma but not in ionized magnesium levels.[67] Another study observed no differences in magnesium serum/plasma concentrations between depressed and control subjects.[48] Furthermore, women with low levels of serum magnesium seemed to have a greater risk of developing depression.[60] These discrepancies in the results might be explained by the lack of information on socio-demographic factors, differences in mean age and sex distribution between patients and controls, and methodological differences between the studies. Methodology diversity includes differences in patient population, e.g. inpatients[44] versus outpatients,[48] or acute[55] and chronic patients.[47] Another possible explanation might be the blood sampling procedures and techniques varying from one study to another. Furthermore, some authors evaluated ultrafiltrable[44,54] and ionized magnesium levels,[67] whereas other ones took into account total serum/plasma magnesium concentrations.[59,63] Studies have shown no[44,67] or poor differences[54] when it comes to ultrafiltrable or ionized magnesium levels, which may suggest that there is no major perturbation when it comes to free serum magnesium levels in patients with depression.[54] A limitation of cross-sectional studies evaluating plasma/serum magnesium levels is that 99% of total magnesium is intracellular. By consequence, measured plasma magnesium levels often do not reflect total body magnesium content and can produce misleading results.[76] Clinical troubles are generally more influenced by tissue magnesium levels rather than blood magnesium concentrations. Therefore, correlating symptoms to plasma magnesium levels is often very difficult.[77] In addition, magnesium homeostasis and metabolism depend on dietary intake, gut absorption, renal regulation,[78] as well as on endocrine parameters.[13] Plasma and intracellular magnesium may also depend on seasonal variations, ethnic origin, or genetic factors.[79,80] A final important limitation that could explain contradictory results found in the above-mentioned studies is the potential effect of psychotropic medication (such as antidepressants and lithium) on serum/plasma magnesium levels.[81] Whereas most of the studies have included medication-free patients with depression, three of them did not.[47,56,59] This may be an additional alternative explanation for some of the observed inconsistencies.

As mentioned before, 99% of total body magnesium is intracellular,[77] which makes assessing magnesium levels in erythrocytes more reliable. The few results obtained with regard to erythrocyte magnesium levels showed that magnesium levels were higher in

patients with depression compared to controls.[44,52–55] In one study those differences were only found in men[52] and in another one only when patients with depression were compared to non-hospitalized healthy controls but not when they were compared to hospitalized healthy controls.[44] Nevertheless, no differences were found in a Japanese study[50] including 21 patients with depression and 20 healthy participants. Additionally to the above-mentioned limitations, we may add – similarly as in serum and plasma – that one of the mechanisms of action of antidepressants is an increase of intracellular magnesium.[82] Nechifor[82] reported, for example, that erythrocyte magnesium increased after the use of psychotropic drugs. However, except from the patients with depression in remission phase of Kamei *et al.*,[50] all patients were drug-free before starting the study.

Hypercalcemia[83,84] and hypomagnesemia[61] have been associated with depressive symptoms and treatment of disturbed electrolyte metabolism may temporarily improve psychiatric symptomatology.[83] Women in the middle tertile of serum Ca/Mg ratio presented lower depression scores and a lower risk of developing depression in a Korean study conducted in 2010.[60] Similarly, Levine *et al.*[51] described higher CSF and serum Ca/Mg ratio in patients with depression compared to controls, whereas other authors observed no differences.[48] All patients were medication-free in the three studies. The contradictory findings observed may be attributed to increased stress that some participants with acute depression might have undergone and which may have elevated their Ca/Mg ratio.[51] This would leave to the conclusion that depression is more related to a disturbance in electrolyte metabolism rather than to an elevation or decrease in levels of a specific electrolyte.

Let us also emphasize that all of the above-discussed studies were based on cross-sectional designs. A potential source of bias in cross-sectional studies is reverse causation bias. It cannot be inferred whether hypomagnesemia may lead to depression or whether depressive symptoms are inducing hypomagnesemia. Furthermore, selection bias cannot be ruled out completely. In this case for example, selection bias[55] and volunteer bias[45] might be observed in some studies. Inconsistencies in the above-discussed studies might also arise because most of the latter ones did not consider major confounders such as age, obesity or other medical diseases, or conditions. To conclude, the determination of the sample size is crucial to find statistical significance and to detect small differences. Inadequate sample size may explain why apparently important clinical results are not statistically significant.[85] Of the 21 cross-sectional studies included in the analysis, four had a small total sample size ($n < 60$)[49,50,52,57] and three a very small sample size ($n < 30$).[51,63,67] Small sample sizes increase random variability between subjects and may be an explication for inconsistent results in different studies.

Interventional studies are thus needed in order to demonstrate with more accuracy a cause–effect relationship. However, data emerging from interventional studies are scarce and contradictory. It has been observed that magnesium did not influence depressive symptoms 3 months after cardiac surgery in a randomized, blinded, placebo-controlled trial. In this study, patients randomized to the magnesium group received 780 mg (32 mmol) of $MgSO_4$ in 100 ml of normal saline intravenously over 15 minutes during anesthesia induction, followed by 3160 mg (120 mmol) in 100 ml of normal saline over 24 hours. Plasma magnesium levels were increased to between 3.6 and 4.8 $mgdl^{-1}$. Patients randomized to the placebo group received normal saline intravenously in the cardiopulmonary bypass circuit (CPB) and over 24 hours.[64] Interestingly, magnesium supplementation has not been shown to improve depressive symptoms in a randomized, double-blind, placebo-controlled, crossover study in women with premenstrual symptoms. Here, 200 mg of magnesium oxide (MgO) with 100 mg of amino acids were administered per day to each participant of the 'magnesium group' during two menstrual cycles whereas the other group received one placebo tablet per day. At the start of the third menstrual cycle, the daily supplement was crossed over for each volunteer until the end of the fourth cycle.[66] Nevertheless, in another study, where newly diagnosed depressive elderly patients with type 2 diabetes and hypomagnesemia were randomly allocated to receive either Imipramine 50 mg daily or 50 ml of $MgCl_2$ 5% solution equivalent to 450 mg of elemental magnesium during 12 weeks, oral magnesium supplementation seemed to be as effective as Imipramine at 50 mg/day to reduce depressive symptoms.[62] It is worth noting that results of these three studies cannot be compared because of their different nature, study design, and study population. Furthermore, in the study of Walker *et al.*[66] women only suffered mild premenstrual symptoms, which might explain the lack of significant results. Bhudia *et al.*[64] included only a fraction of the centre's cardiac surgical population. Generalizing their results to the population at large might thus induce errors. Finally, even if Barragan-Rodriguez *et al.*[62] did not include a placebo control group, comparing two active treatment groups is an effective way for evaluating the efficacy of a therapy without ethical implications.[86,87] Their results are consistent with findings from case studies reporting that oral magnesium treatment is as an adjunctive therapy for treating major depression.[42,43] Here again, a limit worth mentioning is that sample sizes were relatively small in two

studies ($n = 23$[62] and $n = 38$[66]). Even if magnesium is known to be important in health and plays a role in the pathophysiology of depression, little investigation has been conducted to analyze relationships between magnesium intake and depression. To the best of our knowledge, only one epidemiological study in humans suggested an inverse association between magnesium intake and depression severity.[12] It remains to be clarified that the cross-sectional design of this study does not permit the determination of any causality or establish the true direction of the relationship. A poor quality diet might be the cause but also the consequence of depression. However, the sample is large and the study included men and women as well as middle-aged and older participants. A study that has taken into account causality is the longitudinal study of Derom *et al.*[58] investigating the relationship between magnesium intake and the risk of developing depression. Authors could not find any significant relationship suggesting that higher magnesium intake was not related to lower depression risk in a cohort of educated, middle-aged healthy adults. However, as magnesium intake levels were not extremely low among the participants, it is possible that a higher incidence of depression might be found in populations with lower levels of magnesium intake (such as elderly people).

Conclusion

The global burden of disease attributed to major depression is huge and it is growing. Magnesium is important in cell growth and it is involved in biological pathways implicated in depression. Magnesium deficiency may destruct neurons and deregulate brain cell synaptic function inducing depression or other mood disorders. In animal studies, results on the relationship between magnesium and depression are more congruent than those in humans and have shown that magnesium-deficient diet enhances depression-related behavior in mice and that magnesium induces anti-depressant effects in mice. As there are important differences between animal models of depression and human depression, it is also important to explore associations between magnesium intake and depressive symptoms in human studies, which was the objective of this review. Studies investigating the relationship between serum/plasma magnesium and depression throughout the years have advanced discrepant results. It is yet unclear whether blood or CSF magnesium concentrations and Ca/Mg ratio are higher, lower, or equal in patients with depression compared to healthy subjects. To what extent magnesium could be useful in the treatment and prevention of depression deserves further investigation. Even if interventional case studies have suggested that magnesium is useful in the treatment of depression, more experimental trials are needed to confirm those conclusions. Up to date, only two studies have investigated the relationship between magnesium intake and depression. One cross-sectional study found an inverse association whereas a prospective study could not find any effect of magnesium intake on depression risk.

Recognizing, treating, and, most of all, preventing depression are important issues and the possible role of magnesium deficiency in depression may have important public health and treatment implications that should be further investigated. More interventional and prospective studies including large samples and longer follow-up periods are thus needed in order to investigate any potential cause–effect relationship between magnesium and depression. Future research should specifically focus on the effect of oral magnesium supplementation and dietary intake in the treatment and on the development of depression, which remains poorly investigated at this time.

References

1 Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl R, Kessler RC, Demler O, *et al.* Cross-national comparisons of the prevalences and correlates of mental disorders. Bull World Health Organ 2000;78:413–26.
2 Aalto-Setala T, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Lonnqvist J. One-month prevalence of depression and other DSM-IV disorders among young adults. Psychol Med 2001;31:791–801.
3 World Health Organization. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008.
4 Sanders GT, Huijgen HJ, Sanders R. Magnesium in disease: a review with special emphasis on the serum ionized magnesium. Clin Chem Lab Med 1999;37:1011–33.
5 Touyz RM. Magnesium in clinical medicine. Front Biosci 2004; 9:1278–93.
6 King DE, Mainous AG, Geesey ME, Woolson RF. Dietary magnesium and C-reactive protein levels. J Am Coll Nutr 2005;24: 166–71.
7 Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of US adults. J Nutr 2003;133:2879–82.
8 Dolega-Cieszkowski JH, Bobyn JP, Whiting SJ. Dietary intakes of Canadians in the 1990s using population-weighted data derived from the provincial nutrition surveys. Appl Physiol Nutr Metab 2006;31:753–58.
9 Song YQ, Sesso HD, Manson JE, Cook NR, Buring JE, Liu SM. Dietary magnesium intake and risk of incident hypertension among middle-aged and older US women in a 10-year follow-up study. Am J Cardiol 2006;98:1616–21.
10 Song YQ, Manson JE, Cook NR, Albert CM, Buring JE, Liu SM. Dietary magnesium intake and risk of cardiovascular disease among women. Am J Cardiol 2005;96:1135–41.
11 Song YQ, Manson JE, Buring JE, Liu SM. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. Diabetes Care 2004;27:59–65.
12 Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. Austr NZ J Psychiatry 2009;43:45–52.
13 Murck H. Magnesium and affective disorders. Nutr Neurosci 2002;5:375–89.
14 Iseri L, Franch J. Magnesium: nature's physiologic calcium blocker. Am Heart J 1984;108:188–93.
15 Bresink I, Danysz W, Parsons CG, Mutschler E. Different binding affinities of NMDA receptor-channel blockers in various brain-regions – indication of NMDA receptor heterogeneity. Neuropharmacology 1995;34:533–40.

16 Gillessen T, Budd S, Lipton S. Excitatiory amino acid neurotoxicity. In: Alzheimer C (ed.) Molecular and cellular biology of neuroprotection in the CNS series: advances in experimental medicine and biology, Vol. 513. New York: Kluwer Academic/Plenum Publishers; 2002. p. 3–40.
17 Sobolevskii AI, Khodorov BI. Blocker studies of the functional architecture of the NMDA receptor channel. Neurosci Behav Physiol 2002;32:157–71.
18 Durlach D, Bac P. Mechanisms of action on the nervous system in magnesium deficiency and dementia. In: Yasui M, Strong MJ, Ota K, Verity MA (eds.) Mineral and metal neurotoxicology. New York: CRC Press; 1997.
19 Poleszak E, Szewczyk B, Kedzierska E, Wlaz P, Pilc A, Nowak G. Antidepressant- and anxiolytic-like activity of magnesium in mice. Pharmacol Biochem Behav 2004;78:7–12.
20 Cardoso CC, Lobato KR, Binfare RW, Ferreira PK, Rosa AO, Santos AR, *et al.* Evidence for the involvement of the monoaminergic system in the antidepressant-like effect of magnesium. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:235–42.
21 Fromm L, Heath DL, Vink R, Nimmo AJ. Magnesium attenuates post-traumatic depression/anxiety following diffuse traumatic brain injury in rats. J Am Coll Nutr 2004;23:529S–33S.
22 Patten SB. International differences in major depression prevalence: What do they mean? J Clin Epidemiol 2003;56:711–16.
23 Eaton WW, Martins SS, Nestadt G, Bienvenu OJ, Clarke D, Alexandre P. The burden of mental disorders. Epidemiol Rev 2008;30:1–14.
24 Alonso J, Bruffaerts R, Gabilondo A, Haro JM, Kovess V, Vilagut G, *et al.* Depression. European Commission Task Force on major and chronic diseases of DG SANCO's Health Information Strand. Report 2007. Luxemburg 2008. p. 101–16.
25 Kessler RC, Angermeyer M, Anthony JC, de Graaf R, Demyttenaere K, Gasquet I, *et al.* Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 2007;6:168–76.
26 Gabilondo A, Rojas-Farreras S, Vilagut G, Haro JM, Fernandez A, Pinto-Meza A, *et al.* Epidemiology of major depressive episode in a southern European country: results from the ESEMeD-Spain project. J Affect Disord 2010;120:76–85.
27 Nutt D. Anxiety and depression: individual entities or two sides of the same coin? Int J Psychiatry Clin Pract 2004;8:19–24.
28 Mykletun A, Bjerkeset O, Overland S, Prince M, Dewey M, Stewart R. Levels of anxiety and depression as predictors of mortality: the HUNT study. Br J Psychiatry 2009;195:118–25.
29 American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
30 Jacka F, Berk M. Food for thought. Acta Neuropsychiatry 2007;19:321–23.
31 Sanchez-Villegas A, Doreste J, Schlatter J, Pla J, Bes-Rastrollo M, Martinez-Gonzalez MA. Association between folate, vitamin B-6 and vitamin B-12 intake and depression in the SUN cohort study. J Hum Nutr Diet 2009;22:122–33.
32 Tolmunen T, Hintikka J, Ruusunen A, Voutilainen S, Tanskanen A, Valkonen VP, *et al.* Dietary folate and the risk of depression in Finnish middle-aged men – a prospective follow-up study. Psychother Psychosom 2004;73:334–39.
33 Skarupski KA, Tangney C, Li H, Ouyang BC, Evans DA, Morris MC. Longitudinal association of vitamin B-6, folate, and vitamin B-12 with depressive symptoms among older adults over time. Am J Clin Nutr 2010;92:330–35.
34 Sanchez-Villegas A, Henriquez P, Figueiras A, Ortuno F, Lahortiga F, Martinez-Gonzalez MA. Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. Eur J Nutr 2007;46:337–46.
35 Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamaki H, *et al.* Fish consumption and depressive symptoms in the general population in Finland. Psychiatr Serv 2001;52:529–31.
36 Saris NEL, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium – an update on physiological, clinical and analytical aspects. Clin Chim Acta 2000;294:1–26.
37 Shechter M. Does magnesium have a role in the treatment of patients with coronary artery disease? Am J Cardiovasc Drugs 2003;3:231–39.
38 Wolf FI, Trapani V. Cell (patho) physiology of magnesium. Clin Sci 2008;114:27–35.
39 Food and Nutrition Board IoM. Magnesium. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997. p. 190–249.
40 Galan P, Preziosi P, Durlach V, Valeix P, Ribas L, Bouzid D, *et al.* Dietary magnesium intake in a French adult population. Magnesium Res 1997;10:321–28.
41 Singewald N, Sinner C, Hetzenauer A, Sartori SB, Murck H. Magnesium-deficient diet alters depression- and anxiety-related behavior in mice - influence of desipramine and Hypericum perforatum extract. Neuropharmacology 2004;47:1189–97.
42 Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. Med Hypotheses 2006;67:362–70.
43 Enya M, Kanoh Y, Mune T, Ishizawa M, Sarui H, Yamamoto M, *et al.* Depressive state and paresthesia dramatically improved by intravenous $MgSO_4$ in Gitelman's syndrome. Internal Med 2004;43:410–14.
44 Frazer A, Ramsey TA, Swann A, Bowden C, Brunswick D, Garver D, *et al.* Plasma and erythrocyte electrolytes in affective disorders. J Affect Disord 1983;5:103–13.
45 George MS, Rosenstein D, Rubinow DR, Kling MA, Post RM. CSF magnesium in affective disorder: lack of correlation with clinical course of treatment. Psychiatry Res 1994;51:139–46.
46 Joffe RT, Levitt AJ, Young LT. The thyroid, magnesium and calcium in major depression. Biol Psychiatry 1996;40:428–29.
47 Linder J, Brismar K, Beck-Friis J, Sääf J, Wetterberg L. Ca and Mg in affective disorders: difference between plasma and serum in relation to symptoms. Acta Psychiat Scand 1989;80:527–37.
48 Young LT, Robb JC, Levitt AJ, Cooke RG, Joffe RT. Serum Mg2+ and Ca2+/Mg2+ ratio in major depressive disorder. Neuropsychobiology 1996;34:26–8.
49 Banki CM, Vojnik M, Papp Z, Balla KZ, Arato M. Cerebrospinal-fluid magnesium and calcium related to amine metabolites, diagnosis, and suicide attempts. Biol Psychiatry 1985;20:163–71.
50 Kamei K, Tabata O, Muneoka K, Muraoka SI, Tomiyoshi R, Takigawa M. Electrolytes in erythrocytes of patients with depressive disorders. Psychiatry Clin Neurosci 1998;52:529–33.
51 Levine J, Stein D, Rapoport A, Kurtzman L. High serum and cerebrospinal fluid Ca/Mg ratio in recently hospitalized acutely depressed patients. Neuropsychobiology 1999;39:63–70.
52 Widmer J, Bovier P, Karege F, Raffin Y, Hilleret H, Gaillard JM, *et al.* Evolution of blood magnesium, sodium and potassium in depressed-patients followed for 3 months. Neuropsychobiology 1992;26:173–79.
53 Widmer J, Stella N, Raffin Y, Bovier P, Gaillard JM, Hilleret H, *et al.* Blood magnesium, potassium, sodium, calcium and cortisol in drug-free depressed patients. Magnesium Res 1993;6:33–41.
54 Widmer J, Henrotte JG, Raffin Y, Bovier P, Hilleret H, Gaillard JM. Relationship between erythrocyte magnesium, plasma electrolytes and cortisol, and intensity of symptoms in major depressed patients. J Affect Disord 1995;34:201–9.
55 Widmer J, Henrotte JG, Raffin Y, Mouthon D, Chollet D, Stepanian R, *et al.* Relationship between blood magnesium and psychomotor retardation in drug-free patients with major depression. Eur Psychiatry 1998;13:90–7.
56 Imada Y, Yoshioka SI, Ueda T, Katayama S, Kuno Y, Kawahara R. Relationships between serum magnesium levels and clinical background factors in patients with mood disorders. Psychiatry Clin Neurosci 2002;56:509–14.
57 Zieba A, Kata R, Dudek D, Schlegel-Zawadzka M, Nowak G. Serum trace elements in animal models and human depression: Part III. Magnesium. Relationship with copper. Hum Psychopharm Clin 2000;15:631–5.
58 Derom ML, Martinez-Gonzalez MA, Sayon-Orea Mdel C, Bes-Rastrollo M, Beunza JJ, Sanchez-Villegas A. Magnesium intake is not related to depression risk in Spanish university graduates. J Nutr 2012;142:1053–9.
59 Kirov GK, Tsachev KN. Magnesium, schizophrenia and manic-depressive disease. Neuropsychobiology 1990;23:79–81.
60 Jung KI, Ock SM, Chung JH, Song CH. Associations of Serum Ca and Mg Levels with Mental Health in Adult Women Without Psychiatric Disorders. Biol Trace Elem Res 2010;133:153–61.
61 Barragan-Rodriguez L, Rodriguez-Moran M, Guerrero-Romero F. Depressive symptoms and hypomagnesemia in older diabetic subjects. Arch Med Res 2007;38:752–56.
62 Barragan-Rodriguez L, Rodriguez-Moran M, Guerrero-Romero F. Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. Magnesium Res 2008;21:218–23.

63 Hasey GM, Dalessandro E, Cooke RG, Warsh JJ. The interface between thyroid-activity, magnesium, and depression: a pilot study. Biol Psychiatry 1993;33:133–5.
64 Bhudia SK, Cosgrove DM, Naugle RI, Rajeswaran J, Lam BK, Walton E, *et al.* Magnesium as a neuroprotectant in cardiac surgery: a randomized clinical trial. J Thorac Cardiov Sur 2006;131:853–61.
65 Camardese G, De Risio L, Pizi G, Mattioli B, Buccelletti F, Serrani R, *et al.* Plasma magnesium levels and treatment outcome in depressed patients. Nutr Neurosci 2012; 15:78–84.
66 Walker AF, De Souza MC, Vickers MF, Abeyasekera S, Collins ML, Trinca LA. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. J Womens Health 1998;7:1157–65.
67 Frizel D, Coppen A, Marks V. Plasma magnesium and calcium in depression. Br J Psychiatry 1969;115:1375–77.
68 Enya M, Kanoh Y, Mune T, Ishizawa M, Sarui H, Yamamoto M, *et al.* Depressive state and paresthesia dramatically improved by intravenous $MgSO_4$ in Gitelman's syndrome. Intern Med 2004;43:410–14.
69 Eby & Eby. Rapid recovery from major depression using magnesium treatment. Med Hypotheses 2006;67:362–70.
70 Jimerson DC, Post RM, Carman JS, van Kammen DP, Wood JW, Goodwin FK, *et al.* CSF Calcium – clinical correlates in affective-illness and schizophrenia. Biol Psychiatry 1979;14:37–51.
71 Ebel H, Gunther T. Magnesium metabolism – a review. J Clin Chem Clin Biol 1980;18:257–70.
72 Morris ME. Brain and CSF magnesium concentrations during magnesium deficit in animals and humans: neurological symptoms. Magnesium Res 1992;5:303–13.
73 Schain RJ. Cerebrospinal fluid and serum cation levels. Arch Neurol 1964;11:330–33.
74 Daini S, Tonioni F, Barra A, Lai C, Lacerenza R, Sgambato A, *et al.* Serum magnesium profile in heroin addicts: according to psychiatric comorbidity. Magnesium Res 2006;19:162–66.
75 Mark LP, Prost RW, Ulmer JL, Smith MM, Daniels DL, Strottman JM, *et al.* Pictorial review of glutamate excitotoxicity: Fundamental concepts for neuroimaging. Am J Neuroradiol 2001;22:1813–24.
76 Mann J, Truswwell AS. Essentials of human nutrition. New York: Oxford University Press; 2002.
77 Gullestad L, Dolva LO, Waage A, Falch D, Fagerthun H, Kjekshus J. Magnesium-deficiency diagnosed by an intravenous loading test. Scand J Clin Lab Inv 1992;52:245–53.
78 Golf SW, Riediger H, Matthes S, Kuhn D, Graef V, Temme H, *et al.* Homeostasis of magnesium in men after oral supplementation – results of a placebo controlled blind-study. Magnesium-Bulletin 1990;12:144–48.
79 Touitou Y, Touitou C, Bogdan A, Beck H, Reinberg A. Serum magnesium circadian-rhythm in human adults with respect to age, sex and mental status. Clin Chim Acta 1978;87:35–41.
80 Henrotte JG. Genetic regulation of blood and tissue magnesium content in mammals. Magnesium 1988;7:306–14.
81 Jabotinsky-Rubin K, Durst R, Levitin LA, Moscovich DG, Silver H, Lerner J, *et al.* Effects of haloperidol on human plasma magnesium. J Psychiatry Res 1993;27:155–59.
82 Nechifor M. Magnesium in major depression. Magnesium Res 2009;22:163S–166S.
83 Hewer W, Stark HW. Psychiatric disorders in elderly patients caused by disturbed calcium metabolism. Fortschritte Der Neurologie Psychiatrie 2010;78:161–67.
84 Tanaka M, Yamazaki S, Hayashino Y, Fukuhara S, Akiba T, Saito A, *et al.* Hypercalcaemia is associated with poor mental health in haemodialysis patients: results from Japan DOPPS. Nephrol Dial Transpl 2007;22:1658–64.
85 Jekel JF, Katz DL, Joann GE. Sample size, randomization, and probability theory. In: Jekel JF, Katz DL, Joann GE (eds.) Epidemiology, biostatics, and preventive medicine. 3d ed. Philadelphia: Saunders Elseviers; 2007. p. 197–212.
86 Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments - Part 2: Practical issues and specific cases. Ann Intern Med 2000;133: 464–70.
87 Reynolds T. The ethics of placebo-controlled trials. Ann Intern Med 2000;133:491–492.