Magnesium intake and depression: the SUN cohort

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Abstract. Objective. A higher magnesium intake may reduce the risk of depression. We analyzed this association in the SUN Mediterranean cohort with an expanded sample size (n = 15,836) and a long follow-up (median = 10.2 y). Methods. We followed 9,289 women (age = 34.8, SD = 10.4) and 6,547 men (age = 42.8, SD = 13.1) initially free of any history of depression for a new-onset of medically diagnosed depression (maximum follow-up = 15.9 y). All participants in this cohort were university educated. We systematically reviewed previous studies relating magnesium to depression. Results. We observed 837 incident cases of depression during 147,915 person-years of follow-up in the SUN cohort. No significant association of magnesium intake with the risk of depression was found, with a fully-adjusted hazard ratio = 0.85 (95% confidence interval = 0.60-1.22, for fifth versus first quintile). When we used a more restrictive definition for depression (both a medical diagnosis and habitual use of antidepressants), this HR was 0.63 (0.35-1.14). No significant association was found in our systematic review. Conclusion. No conclusive evidence for an association between magnesium dietary intake and depression incidence was found. Further longitudinal studies with a larger sample size and a better assessment of confounders and of depression cases are needed to try to identify potential protection against depression by magnesium.

Key words: mood disorders, dietary patterns, mediterranean diet, nutritional epidemiology

Major unipolar depressive disorder or depression is the most frequent type of mood disorder worldwide. Depression is one of the most commonly diagnosed psychiatric conditions, with a high lifetime prevalence. It represents a relapsing condition associated with severely impaired quality of life, high sanitary and pharmacological costs, a heavy burden of personal and familial suffering, frequent comorbidities, increased risk of suicide, and higher risk of all-cause mortality. The yearly prevalence of major depressive disorder is approximately 7% in Europe, with wide between-country variability and a life-time prevalence of 13% [1, 2]. In this context, preventive approaches are needed to appropriately address the control of depressive disorders as they represent a priority for public health. Although depression seems to be a multifactorial disease, nutritional factors might be a contributing or component cause for the development of depression and therefore, changes

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Magnesium intake and depression of dietary habits may constitute an interesting possibility for the prevention of depression [3-5]. The scientific report of the 2015 US Dietary Guidelines Advisory Committee considered that the available evidence on the role of nutrition in the risk of depression was limited, and that the protective dietary patterns associated with reduced risk of depression are those patterns emphasizing seafood, vegetables, fruits and nuts [6]. Some of these foods, especially green leafy vegetables, legumes, nuts, seeds, and whole grains, are good sources of magnesium, and, thus, magnesium may represent an interesting nutrient for the prevention of depression [7]. Moreover, dietary magnesium intake is insufficient in most populations [8]. Alterations in magnesium regulate neurobiological pathways implicated in the pathophysiology of depressive illness, and impaired magnesium homeostasis has been suggested to be associated with affective disorders and depression in particular [7]. Magnesium inhibits presynaptic excitatory amino acids such as glutamate, blocks voltage-dependent calcium channels, and it blocks N-methyl-D-aspartate (NDMA) receptors. The emerging NMDA hypothesis of depression holds that the pathogenesis of depression may arise from stressors inducing excessive NMDAR activity. A variety of stressors has been considered such as glucocorticoids, inflammatory stimuli, oxidative stress, hyperhomocysteinemia and, in particular, magnesium deficiency [9].

Furthermore, magnesium might be involved in the etiology of depression because it is implicated in biological and transduction pathways related to the genesis of depression, including its action as a blocker of the NMDA channel where it blocks the entry of calcium in the neuron and may thus prevent cell death. Magnesium intake has also been inversely associated with inflammatory biomarkers and associated with a reduction in the release of ACTH. Rodent models have supported a role for magnesium in the prevention of depression, and magnesium has been used as an adjunctive treatment for this condition [7, 10].

However, the specific role of magnesium in human depression remains unclear. [7] Over the decades, only small studies with cross-sectional designs analyzed the association findings and reported contradictory results [7, 10]. More recently, a longitudinal study (the SUN project) with a large sample size (n = 12,939) and long follow-up (median = 6.3 y) failed to find any conclusive association [11]. A more recent study involving a smaller cohort (n = 2320) with a longer follow-up (21.3 y), did find a non-linear inverse association [12]. We conducted a longitudinal study in the context of a dynamic cohort of young and highly-educated adults, the SUN project, to assess this association with an expanded follow-up and a larger sample size than our previous assessment [11]. We also conducted a systematic review of the literature on magnesium intake and the risk of depression.

Methods and material and

Study population

The SUN project comprises a multipurpose, prospective, and dynamic cohort of young adult, university graduates conducted in Spain. The SUN Project study methods have been previously published in detail [13, 14]. The recruitment of participants started in 1999, and it is permanently open. Mailed questionnaires are used to gather baseline characteristics and information on changes in diet, lifestyles and new medical diagnoses of disease every two years. All participants included in the SUN cohort met the requirement that they had completed university studies. Thus, better control of confounding by education-related variables is achieved, which makes the interpretation of the results easier and adds validity to the high-quality self-reported information derived from their questionnaires. In addition >50% of volunteers are health professionals themselves.

The database for the SUN cohort included 22,476 volunteers as of December 2015. After the exclusion of recently recruited participants (n = 1028) because we included only volunteers with a minimum of a two-year follow up, and also excluding participants with any previous history of depression at baseline (n = 2251) or who were outside predefined intake limits (800-4000 kcal/d in males and 500-3500 kcal/d in females) for total energy intake (n = 2020), we had follow-up information on 15,836 participants initially free of depression, with mean age at baseline: 38.1 years (SD: 12.2) and 57.8% women. Participants not retained in the study (n = 1341) were not included in any of our analyses. Our retention rate was therefore 92%. We defined retention rate as the ratio of participants who completed at least one follow-up questionnaire, within a period of two
years (allowing nine extra months to account for delays) after each biennial questionnaire, from all of the participants who had completed the initial questionnaire. Each participant was followed up, for up to 15.9 years, having seven possible periods of biennial follow-up. Participants who reported a medical diagnosis of depression more than once during the total study period, were included in the analyses for their first diagnosis of depression only, but not thereafter.

This study was conducted according to the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the University of Navarra. The completion of the self-administered questionnaire was considered to imply informed consent. Our Institutional Review Board specifically approved this consent process.

**Assessment of depression (exposure)**

Incident cases of depression were assessed in each biennial follow-up questionnaire (from Q2, i.e. two-year follow-up questionnaire to Q14, i.e. 14-year follow-up questionnaire). Participants were asked to provide their diagnosis date in each questionnaire. Information on physician-diagnosed depression was therefore updated biennially (Q_2-Q_14). Thus, we defined as an incident case of depression any participant who responded affirmatively to the question “Have you ever been diagnosed with depression by a medical doctor?” and who was free of depression at baseline. Self-reported medical diagnosis of depression was validated in a subset of the SUN cohort by using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, as the gold standard (27). The percentage of confirmed depression cases was 74.2% (95% CI: 63.3%, 85.1%), and the percentage of confirmed non-depression cases was 81.1% (95% CI: 69.1%, 92.9%). The results of this validation study were the content of a previous, specific publication [15].

**Assessment of other variables**

Dietary magnesium intake was assessed with a 136-item validated food frequency questionnaire [11]. The baseline questionnaire of the SUN cohort [13, 14] collected a rich array of information on socio-demographic variables, including marital status, anthropometric characteristics, lifestyle and health related habits, including adherence to a Mediterranean-type diet, smoking habits, total energy intake, alcohol intake, and medical history. Time spent on physical activities was estimated by the information obtained from the questionnaires. Time (in hours/week) spent in different physical activities such as walking, gardening, running, cycling or playing different outdoors sports or activities was obtained as self-reported data at baseline, with a validated questionnaire [16].

Adherence to the Mediterranean diet (MedDiet) was assessed by using the MedDiet score proposed by Bach et al. [17]. Fiber consumption, body mass index (BMI), and comorbidity information (e.g., prevalence/history of cancer, diabetes, or cardiovascular disease) were collected in the baseline questionnaire. Participants also answered questions about personality and behavior, such as their levels of competitiveness, anxiety, and dependence, using Likert scales with values in the range of 0-10.

**Statistical analyses**

For each participant we computed person-years of follow-up, from the date of returning the baseline questionnaire to the date of depression diagnosis, death, or to the date of returning the last follow-up questionnaire, whichever came first. Cox regression models (proportional hazards models) were fitted to assess the relationship between magnesium intake (quintiles) and the risk of new-onset depression. We estimated hazard ratios (HR) and their 95% confidence intervals (CI) across the four upper quintiles, using the lowest quintile as the reference category. We adjusted a first model for sex and age. Subsequently, we fitted a multivariable model (model 1) additionally adjusted for smoking, self-perceived personality traits and total energy intake. In another fully-adjusted model (model 2), we additionally adjusted for BMI, physical activity, marital status, employment status, alcohol intake, trans-fat intake and adherence to the MedDiet. We repeated all these analyses using an alternative definition of incident cases of depression, with the requirement of fulfilling two criteria: a self-reported medical diagnosis of depression and the habitual use of antidepressants.

We conducted several sensitivity analyses to test the robustness of our findings in different scenarios, namely, by adding magnesium intake from supplements, additionally adjust for recruitment year for the cohort, using age as the
underlying time variable, conducting stratified analyses by sex and age, removing early cases (two-year follow-up questionnaire), removing late cases (occurring ≥ nine years of follow-up) and using as exposure the residuals of magnesium regressed on total energy intake. All P values are two-tailed and statistical significance was set at P < 0.05.

We used STATA 12.0 for all analyses.

Results

From the 15,836 participants included in the analyses accruing 147,915 person-years, 837 participants reported medically-diagnosed depression during the study period. Table 1 shows the distribution of baseline characteristics of the participants according to quintiles of magnesium intake. Participants with higher magnesium intake were slightly older, with a lower BMI and considerable higher energy expenditure in physical activity, less likely to be active smokers, and drank more alcohol. Their total energy intake was considerably higher and they had higher intakes of both trans-fat and omega-3 fatty acids.

The association between magnesium intake and the risk of depression onset is shown in Table 2. Magnesium intake was not associated with the risk of developing depression, with fully-adjusted HR: 0.85 (95% CI: 0.60-1.22) after adjusting for known potential confounders. Also, an adjusted HR was estimated after a multivariable analysis but including only cases that met a more stringent definition (both medical diagnosis and usual treatment with anti-depressants), and our findings were also inconclusive. The inverse association remained statistically non-significant, HR: 0.63 (95% CI: 0.35-1.14).

Figure 1 shows a graphical display of the results of different sensitivity analyses, under different

Table 1. Baseline characteristics of participants in the SUN cohort according to quintiles of magnesium intake. Means (standard deviations) or percentages.
Table 2. Relative risks (hazard ratios, HR) with 95% confidence intervals) of incident depression according to quintiles of magnesium intake during 9.3 years of mean follow-up in 15,836 participants in the SUN cohort (1999-2015).

<table>
<thead>
<tr>
<th>Quintiles of magnesium intake</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using all cases with a medical diagnosis</td>
<td>3168</td>
<td>3167</td>
<td>3167</td>
<td>3167</td>
<td>3167</td>
</tr>
<tr>
<td>Magnesium intake (mg/d)</td>
<td>&lt;311</td>
<td>311-371</td>
<td>372-428</td>
<td>429-505</td>
<td>&gt;505</td>
</tr>
<tr>
<td>Cases of depression</td>
<td>160</td>
<td>184</td>
<td>155</td>
<td>177</td>
<td>161</td>
</tr>
<tr>
<td>Person-years</td>
<td>29644</td>
<td>29661</td>
<td>29956</td>
<td>29737</td>
<td>28917</td>
</tr>
<tr>
<td>Age-, sex-adjusted HR</td>
<td>1 (ref.)</td>
<td>1.12 (0.91-1.39)</td>
<td>0.94 (0.75-1.17)</td>
<td>1.06 (0.86-1.31)</td>
<td>0.99 (0.79-1.23)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (ref.)</td>
<td>1.03 (0.83-1.30)</td>
<td>0.83 (0.64-1.07)</td>
<td>0.89 (0.68-1.17)</td>
<td>0.80 (0.58-1.09)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (ref.)</td>
<td>1.06 (0.85-1.34)</td>
<td>0.86 (0.66-1.12)</td>
<td>0.94 (0.70-1.27)</td>
<td>0.85 (0.60-1.22)</td>
</tr>
</tbody>
</table>

| Using only cases with both diagnosis and treatment | 3007 | 2992 | 3002 | 2999 | 3028 |
| Magnesium intake (mg/d) | <311 | 311-371 | 372-428 | 429-505 | >505 |
| Cases of depression* | 57 | 64 | 52 | 62 | 60 |
| Person-years | 28473 | 28459 | 28681 | 28562 | 27954 |
| Age-, sex-adjusted HR | 1 (ref.) | 1.11 (0.77-1.58) | 0.88 (0.60-1.28) | 1.02 (0.71-1.46) | 0.96 (0.66-1.38) |
| Model 1 | 1 (ref.) | 0.94 (0.64-1.37) | 0.68 (0.44-1.04) | 0.70 (0.44-1.11) | 0.60 (0.35-1.02) |
| Model 2 | 1 (ref.) | 0.94 (0.64-1.39) | 0.68 (0.43-1.06) | 0.71 (0.43-1.17) | 0.63 (0.35-1.14) |

*Both a validated self-reported medical diagnosis and the habitual use of anti-depressants were required to be adjudicated as cases.

Model 1 Adjusted for sex, age, smoking, self-perceived personality traits and total energy intake
Model 2 Adj. for age, sex, BMI, leisure-time physical activity, smoking, marital status, employment status, self-perceived personality traits, alcohol, trans-fat intake, total energy intake and adherence to the MedDiet

**Figure 1.** Sensitivity analyses for the comparison (hazard ratios, 95% confidence intervals) of the incidence rates of depression for the highest versus the lowest quintile of magnesium intake.
assumptions, for the hazard ratio of the fifth versus the first quintile of magnesium intake. In none of these analyses were the results statistically significant. We did not find significant results when, instead of quintiles, we used quartiles or tertiles to build the groups of magnesium intake.

Discussion

In our population of young and healthy university graduates, we did not find any evidence to support that a higher magnesium intake might be associated with a decreased risk of depression. However, our point estimates for the hazard ratios were lower (i.e. farther from the null) when we used a more stringent case definition for depression. The possibility of non-differential misclassification bias would be reduced when the case definition has an increased specificity, and if a true inverse association were present, it would be more apparent when using a highly specific definition [18]. In fact, our findings might be compatible with an inverse association of lower magnitude, but our study may be too underpowered to detect such an effect. The statistical power of our study, for example, to detect a 20% relative reduction in risk between extreme quintiles would be only 53%. Therefore, a type 2 error cannot be discarded in our results. Larger cohorts are needed with a sample size at least two-fold greater than ours.

It is well known than magnesium deficiency is highly prevalent and that magnesium has been reported to present inverse associations with hypertension, type 2 diabetes, stroke and coronary heart disease. These conditions may share common pathophysiological pathways with depression. But two available systematic reviews on magnesium and depression [7, 10] reported diverse conclusions. Derom et al. [7] in their non-quantitative systematic review concluded that oral magnesium supplementation may prevent depression and might be used as an adjunctive therapy; however, their conclusion was mainly null, because they reported that most studies were small, cross-sectional and prone to bias, therefore the available data for a preventative effect of magnesium on depression were scarce and incongruous. In a more recent quantitative review with meta-analysis, Cheungpasitporn et al. [10] concluded that a potential association between hypomagnesaemia and depression was supported by the pooling of six epidemiological studies. However, these authors reported that two of the studies that they considered [19, 20] were cross-sectional in design, and reverse causality bias could not be excluded. However, another study that they included was also cross-sectional [21] as acknowledged by the very authors of the original study in their paper (“our results are based on cross-sectional analysis”) [21]. This leaves only three true prospective studies [11, 22, 23] to be included in the Cheungpasitporn quantitative meta-analysis, and the results would be a non-significant relative risk of depression of 1.30 (95% CI: 0.66-2.54) using a random-effects model (this computation has been reproduced by us, after excluding cross-sectional studies and is available on request). Therefore, that meta-analysis did not support a direct association between hypomagnesaemia and the risk of depression. Consequently, Cheungpasitporn et al. [10] were right in highlighting that “the association between depression and hypomagnesaemia was marginally insignificant after the sensitivity analysis, including only cohort and case–control studies, with a pooled RR of 1.38 (95% CI, 0.92–2.07, I2 = 24%)”.

We conducted an updated systematic review of published papers on magnesium and depression as of June 2016. We identified 2,114 articles using the databases EMBASE, PubMed and Web of Science. We excluded 2,018 articles after reading their title and abstract. Ninety six articles were selected for full-text review. Sixty of these articles were excluded for different reasons (21 did not report on magnesium, 25 did not report on mood disorders, 11 were reviews or case studies and two did not report sufficient data). Finally, we assessed and analyzed 36 studies. Most results of these studies (53 conclusions or different analyses, because some articles included several analyses) were based on cross-sectional designs. Among these 53 analyses, most conclusions were null (no association), 16 conclusions supported an inverse association (lower magnesium levels associated with a higher depression risk), and 10 conclusions supported a direct association (higher magnesium levels associated with higher risk of depression). Most of these studies had a very small sample size. However, among these 53 analyses, we identified five large cross-sectional studies: in their fully-adjusted analyses, one of them supported a direct association (low magnesium associated with a lower risk, but only in older subjects) [24],
one supported a null association [19], and other three supported an inverse association [24-26].

We identified six longitudinal prospective studies on magnesium and depression. Two of them were conducted among initially depressed subjects [22, 23], and four of them (including the updated assessment in the SUN cohort) were conducted among initially non-depressed subjects, as it is methodologically correct for etiological studies [11, 12, 27, 28]. The random-effects meta-analysis of these four studies yielded a pooled relative risk of 0.62 (95% CI: 0.36-1.08), with sufficient evidence of heterogeneity (I² = 77%). Therefore, there is some suggestion of an inverse association, but there is no definitive or significant evidence for a protection by magnesium against depression.

The Kuopio cohort study [12] is important because it has high methodological quality and a long follow-up period (>20 years). It found a significant inverse association in contrast with our current results from the SUN cohort. However, the sample size in the Kuopio cohort was considerably smaller (n = 2320) and the association was only present for the intermediate category of magnesium intake, namely for the second tertile versus the lowest tertile (HR: 0.49, 95% CI: 0.25-0.95), but not for the highest versus the lowest tertile (0.60; 0.28-1.27). Therefore, the evidence does not support a linear inverse association.

In contrast, we did find in the SUN cohort strong inverse associations between better adherence to high-quality dietary patterns and the risk of depression [29]. This should be included with the present findings, because this contrast further supports the notion that it seems more logical to use the approach of dietary patterns in nutritional epidemiology instead of focusing on only one nutrient. It would be overly optimistic to think that the effect of a single nutrient could be so strong as to obtain clinically relevant changes in the incidence of disease. On the contrary, many nutrients act synergistically in an overall dietary pattern to show a stronger effect [6, 30, 31]. With this in mind, magnesium can be one of the elements present as part of a healthy dietary pattern, which may contribute to decreasing the risk of developing depression. This is supported by the relatively high correlations observed between healthy dietary patterns being inversely associated with depression risk [29, 32-37] and the intake of magnesium. These correlations in the SUN cohort were 0.43 for the MedDiet pattern, 0.20 for the pro-vegetarian dietary pattern and 0.60 for the Alternative Healthy Eating Index. These three patterns showed strong inverse associations with the risk of developing depression in the SUN cohort [29].

Our study has several limitations to be considered when interpreting our findings. A methodological limitation is the potential recall error associated with self-reported data for onset or diagnosis of depression. Also, as the design of our cohort recruits only highly educated participants, and mostly all Caucasian, it could have introduced a selection bias, and further studies should be done in a representative sample of subjects, to be able to generalize our findings. However, this is a highly educated and cooperative cohort, and we have evidence of the high quality and validity of the self-reported data provided by our participants. In fact several validation studies have been done to confirm the high quality of the self-reported data of our participants [38-43]. Another potential weakness of our study is the lack of information on depression severity and also that we did not adjust our estimates for baseline family history of depression, consequently there is a possibility for measurement error and for uncontrolled confounding related to family factors that we cannot account for.

Despite these limitations, the SUN study is the largest prospective cohort study that has assessed, to our knowledge, this association.

In summary, our results do not confirm that a higher intake of magnesium may significantly reduce the future development of depression. Notwithstanding, some important studies did find inverse associations. These and the potential effect of magnesium on depression deserve further research. Further longitudinal studies with a large sample size, sufficiently long follow-up and a better assessment of potential confounding factors, including a thorough assessment of baseline parental factors, are needed.

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