Magnesium Intake Is Not Related to Depression Risk in Spanish University Graduates

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Abstract

Magnesium is the second most predominant intracellular cation and it is an important cofactor in over 300 enzymatic reactions. It is a calcium antagonist and a voltage-dependant blocker of the N-methyl-D-aspartate channel, which plays a role in the entrance of calcium into the neuron. Other mechanisms also add biological plausibility to neuro-protective properties for magnesium, including an inverse association with major depression. A higher magnesium intake has been related to lower depressive symptoms. However, epidemiological evidence on this issue is scarce. Our aim was to prospectively evaluate the association between dietary magnesium intake and depression incidence in a cohort of 12,939 Spanish university graduates initially free of depression (Seguimiento Universidad de Navarra Cohort Study). Total magnesium intake was assessed with a validated, semiquantitative FFQ and incident depression was ascertained through self-reports of a new clinical diagnosis of depression done by a medical doctor and/or the habitual use of antidepressive drugs. The self-report was validated against the Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria in a subsample of the cohort. Cox regression models were used to obtain HR of incident depression during follow-up according to baseline quintiles of magnesium intake using the lowest quintile as the reference category. After a median follow-up of 6.3 y, 737 new cases of depression were identified. No association between magnesium intake and depression was found, with multivariate-adjusted HR = 1 (reference), 1.00 (95% CI: 0.78–1.27), 1.00 (0.76–1.31), 0.95 (0.70–1.30), and 1.11 (0.77–1.59) for increasing categories (quintiles 1–5) of total magnesium intake. No dose-response relationship was found (P-trend = 0.59). Results were robust through different sensitivity analyses, including nutrient density or residual models. In conclusion, our findings do not suggest an inverse association between magnesium intake and depressive disorder.


Introduction

Unipolar depression affects ~151 million people worldwide and it is, according to the WHO, the third leading cause of Disability Adjusted Life Years (1). It is estimated that ~10–21% of men and 20% of women in Europe suffer from a major depressive episode once in their lifetime (2,3). As for Spain, lifetime prevalence is ~10.6% (4). It is well-established knowledge that depression has adverse effects on global health (5). Given this menacing effect, it is extremely important to find useful treatments and investigate effective preventive methods for depression.

Various factors play a role in the etiology of depression, such as personal, genetic, hormonal, immunological, biochemical, neurodegenerative, and environmental factors. For example, physical activity, nutrients, foods, and overall dietary patterns have been reported to be associated with depression (6). In fact, both cross-sectional (7) and prospective cohort studies (8) have suggested inverse associations for folate dietary intake. Longitudinal studies have also found inverse associations for dietary intake of vitamins B-6 and B-12 (9) or (n-3) fatty acids (10,11) but direct associations for other nutrients such as trans fatty acids (TFA) (12).

Magnesium is the second most predominant intracellular cation and is an important cofactor in over 300 enzymatic reactions. Some evidence suggests that alterations in magnesium regulate neurobiological pathways implicated in the pathophysiology of depressive illness (13) and that impaired magnesium homeostasis is associated with affective disorders and depression in particular (14,15). Magnesium has a crucial role...
in ATP-generating and ATP-utilizing reactions and thus also in the facilitation of transphosphorylation reactions that are indispensable to cell activation and deactivation. Magnesium regulates energy metabolism and production, DNA and RNA synthesis and structure, cell growth, cytoskeletal function, membrane structure, and ion homeostasis. Magnesium is also a natural calcium antagonist and a voltage-dependant blocker of the N-methyl-D-aspartate channel, which plays a role in the entrance of calcium into the neuron. By regulating this entry, magnesium may acquire a neuroprotective property and is likely to protect the neuron against cell death. Furthermore, in animal models, a magnesium-deficient diet increases depression-related behavior (16). Similarly, magnesium intake has been reported to have antidepressant effects in mice (17). Case studies in humans also have suggested that magnesium might be effective in the treatment of depression (18,19). Moreover, magnesium supplementation relieves depressive symptoms in depressed elderly type 2 diabetics showing hypomagnesemia (20).

However, evidence from epidemiological studies investigating associations between magnesium intake and depression in adults is scarce. To the best of our knowledge, only one cross-sectional study has appraised this hypothesis. The study included 5708 participants (aged 46–49 or 70–74 y) from the Hordaland Health Study (Western Norway) and found an inverse association between magnesium intake and depressive symptoms (15). Given the little empirical research available, assessing the relationship between magnesium intake and incident depression in humans is of paramount importance, especially when magnesium intake has decreased over the years, probably because of a higher ingestion of refined and processed foods (21). In Spain, ~26.33% of men and 38.53% of women have magnesium intakes less than two-thirds of the RDA (22).

The aim of our study was to prospectively assess the association between magnesium intake and the incidence of depression in a Mediterranean cohort study. As far as we know, no longitudinal study has ever evaluated the effect of magnesium intake on depression occurrence among adults.

**Methods**

**Study participants.** This research is part of the Seguimiento Universidad de Navarra (SUN) Project that was designed in 1998 with the collaboration of some investigators from the Harvard School of Public Health, adapting the methods previously used by large cohorts such as the Nurses’ Health Study and the Health Professionals’ Follow-up Study (23). The SUN project is a dynamic cohort (i.e., with permanently open recruitment). All participants are university graduates. Participants were recruited through collaborations with some Spanish universities and their alumni associations (e.g., Universidad de Navarra Alumni Association) and with some professional associations (e.g., associations of Pharmacists, Nurses, Physicians, and Dentists from some Spanish provinces). These organizations provided lists of potential candidates to receive the invitation and sent invitation letters to their members. No stratification by age, sex, or socioeconomic status was done. The study was designed to identify associations between lifestyle habits such as diet and several diseases, including depression (24). Study methods were previously published in detail elsewhere (23,24). Baseline assessment and follow-up information is gathered through postal or Web-based questionnaires every 2 y.

By October 2010, 19,576 participants had been recruited. We excluded participants lost to follow-up (n = 2114). We also excluded 1675 participants with energy intake outside the predefined limits (<66 kcal/d or >4000 kcal/d in men and <500 kcal/d or >3500 kcal/d in women) (25) and 1233 participants with a history of cancer or cardiovascular disease at baseline. Participants were classified as having cardiovascular disease at baseline if they reported at least one of the following conditions: myocardial infarction, stroke, atrial fibrillation, paroxysmal tachycardia, coronary artery bypass, heart failure, aortic aneurism, pulmonary embolism, or peripheral venous thrombosis. Another 1615 participants using antidepressant medication or presenting depression at baseline were also excluded. Finally, 12,939 participants initially free of depression, cardiovascular disease, and cancer were included in the analysis (Supplemental Fig. 1). The retention rate was 89.2%.

The Institutional Review Board of the University of Navarra approved the study protocol. Voluntary completion of the baseline questionnaire was considered to imply informed consent.

**Exposure assessment.** Dietary exposures were ascertained through a 136-item, semiquantitative FFQ previously validated in Spain (26) and recently reevaluated (27,28). Nutrient scores were calculated as frequency × nutrient composition of specified portion size where frequencies were measured in 9 categories (≥6/d, 4–6/d, 2–3/d, 1/d, 5–6/wk, 2–4/wk, 1/wk, 1–3/mo, never, or almost never) for each food item. Nutrient intake scores are computed using ad hoc computer software specifically developed for this aim. A trained dietician updated the nutrient data bank using the latest available information included in the food composition tables for Spain (29,30). The FFQ also contained additional questions about vitamins and mineral supplements, such as magnesium, and another section for patterns of consumption that are more typical of the Mediterranean diet (23).

Dietary magnesium was calculated from magnesium-rich foods. Total magnesium intake was computed as the sum of dietary magnesium and magnesium intake derived from supplements (25). Finally, these continuous variables were categorized into quintiles. A subsample in our cohort showed good reproducibility for assessing magnesium intake. Pearson correlation coefficients were 0.69 (<1 y between responses) and 0.65 (≥1 y between responses) (28).

**Assessment of other variables.** The baseline assessment gathered information with regard to sociodemographic (e.g., sex, age, marital status, and employment status), anthropometric (weight and height), lifestyle and health-related habits (e.g., smoking status and physical activity during leisure time), psychological (e.g., self-perceived personality traits such as anxiety, competitiveness, and psychological dependence) characteristics, and medical history variables (e.g., prevalence of chronic diseases and medication use). The validity of self-reported weight and BMI in the SUN Project was previously documented in a subsample of this cohort (31). We assessed the participation and time spent in 17 activities by using a physical activity questionnaire previously validated in Spain (32). To quantify the volume of activity during leisure time, the time spent in each activity in hours each week is multiplied by its typical energy expenditure, expressed in metabolic equivalent tasks (MET), then summed over all activities to yield a MET·h/wk score for each participant (33). Adherence to the Mediterranean dietary pattern (MDP) was appraised according to the score created by Trichopoulou et al. (34,35). We categorized this score into 3 groups (low adherence from 0 to 2, moderate adherence from 3 to 5, and high adherence from 6 to 9).

**Outcome assessment.** The participants were defined as having incident depression when they were free of depression and antidepressant treatment at baseline and positively responded to the question “Have you ever been diagnosed as having depression by a medical doctor?” during follow-up or when they reported the habitual use of antidepressant drugs in any of the follow-up questionnaires. Antidepressant use was ascertained through an open question in which the participants reported their medication utilization. A self-reported, physician-made diagnosis of depression has demonstrated acceptable validity in the validation study conducted in a subsample of our cohort by means of the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders (4th edition) as the criterion standard applied by experienced psychiatrists unaware of the answers to the questionnaires. The estimated sensitivity and specificity were 0.37 and 0.96, respectively (36).

**Statistical analysis.** Cox proportional hazards multivariate models were fit to assess the association between baseline magnesium intake
(total and dietary) and the incidence of depression during the follow-up period. HR and their 95% CI were calculated with the lowest quintile of total and dietary magnesium intake designated as the reference category. Tests of linear trend across increasing categories were conducted by assigning the medians to each category; this variable was treated as continuous. Exit time was defined as age at diagnosis of depression for cases, or age when completing the last follow-up questionnaire or age at death (whichever occurred first) for participants who did not develop depression.

In the Cox regression analyses, we fitted a crude (univariate) model, an age-adjusted and sex-adjusted model, and a multivariate-adjusted model. Potential confounders included in this last model were: baseline BMI (kg/m², continuous), physical activity during leisure time (MET-h/wk, continuous), smoking status (never, past, current, missing), marital status (single, married, widowed, separated, other), number of children (none, 1 child, 2 children, 3 children, >3 children), employment status (unemployed, part-time employed, full-time employed, student, housewife, retired, missing), self-perceived personality traits such as competitiveness, anxiety, and psychological dependence (continuous, score from 0 to 10), alcohol and TFA intakes (g/d, continuous), total energy intake (kcal/d, continuous), and adherence to the MDP (low, moderate, high).

We conducted ancillary sensitivity analyses and repeated all the statistical models after: 1) excluding early cases of incident depression (cases reported within the first 2 y of follow-up); 2) excluding participants who reported taking antidepressant drugs but not having a physician’s diagnosis of depression; 3) excluding late cases of depression (reported after ≥8 y of follow-up); 4) excluding very late cases of depression (reported after ≥10 y of follow-up); and 5) using the nutrient density (magnesium/100 kcal) or the residual model (residuals of a regression with total caloric intake as the independent variable and absolute magnesium intake as the dependent variable) (25); both the nutrient density and the residual models were adjusted for total energy intake and all other potential confounders. We finally analyzed interactions between sex and magnesium intake and conducted further sensitivity analyses by stratifying our sample by sex (men and women).

All P values were 2-tailed and significance was set at P < 0.05. Values in the text are mean ± SD unless otherwise noted.

Results

We evaluated 5303 men and 7636 women. The age of participants at recruitment was 37.6 ± 11.7 y. The total magnesium intake was 416 ± 124 mg/d (median = 404 mg/d) and the follow-up was 5.8 ± 2.4 y (median = 6.3 y). Participants belonging to the highest levels of total magnesium intake (Q5) were more likely to be women, older, more physically active, never smokers, and have higher alcohol intakes (Table 1). Not surprisingly, total energy intake increased according to higher levels of magnesium intake. The adherence to the MDP was minimal in the lowest quintile of magnesium intake (Q1). Despite the significance of some statistical tests (due to large sample size), absolute differences in levels of personality traits (competitiveness, anxiety, and psychological dependence), marital status, and total number of children did not vary according to levels of magnesium intake.

Overall, 737 new cases of depression were identified during the follow-up period (243 cases in men and 494 in women). No association between total magnesium intake and depression incidence was observed (Table 2). Participants with the lowest intake (first quintile, Q1) were considered to comprise the reference category. For successive quintiles (2nd to 5th) of total magnesium intake, we found multivariate-adjusted HR = 1 (reference), 1.00 (95% CI: 0.78–1.27), 1.00 (0.76–1.31), 0.95 (0.70–1.30), and 1.11 (0.77–1.59) for depression, respectively. No dose-response relationship was found (P-trend = 0.59).

Although magnesium intake from supplements represented only a small amount of the total magnesium intake by our participants, similar analyses were also conducted to assess the possible role of dietary magnesium after excluding magnesium from supplements (Table 2, bottom). There was no association between dietary magnesium intake and incident depression.

Supplementary sensitivity analyses were conducted to control for possible sources of bias in the estimation of the association between total magnesium intake and the risk of depression (Table 3). When cases of depression reported within the first 2 y of follow-up (early cases) were excluded from the analyses, total magnesium intake was not related to depression risk, with multivariate-adjusted HR = 1.33 (95% CI: 0.83–2.13) for the 5th quintile and HR = 1.04 (95% CI: 0.70–1.37) for the 4th quintile compared to the lowest quintile. The linear trend across increasing categories was not significant (P-trend = 0.13). Results did not change when participants who reported taking antidepressant drugs without a physician’s diagnosis of depression were excluded with multivariate-adjusted HR = 1.22 (95% CI: 0.80–1.86) for Q5 compared with Q1. Furthermore, neither significant increment nor decrement in depression risk was found when we excluded late cases of depression (reported after ≥8 y or after ≥10 y of follow-up). We also repeated the analyses after stratifying the sample by sex and reran the fully adjusted analyses after applying the nutrient density or the residual models (Table 3, bottom rows). No association between magnesium intake and depression was found in any of these analyses.

Discussion

As far as we know, this is the first large prospective cohort study that investigated the association between magnesium intake and depression incidence in humans. We found that higher magnesium intake was not associated with lower depression risk among Spanish university graduates followed-up for a median time period of longer than 6 y.

Epidemiologic literature relating magnesium intake and depression is scarce. Most studies about this issue have been carried out in animals. Malnutrition by magnesium depletion induces depression-like behavior in rats (16). Other animal studies have shown that oral magnesium administration led to antidepressant effects (17). It is not well established whether plasma magnesium is higher or lower in depressive patients. Contradictory results have been reported. Some case studies in humans have reported that magnesium intake might be useful in the treatment of depression (18,19). An interventional study performed in depressive diabetic patients showed that magnesium chloride was able to improve their depressive symptoms (20). On the contrary, 2 other studies reported that magnesium did not relieve depressive symptoms in postmenopausal women (37) nor did it influence depressive symptomatology in patients undergoing cardiopulmonary bypass (38). However, the results of the above-mentioned studies cannot be compared with our findings because of the differences in methodology and evaluation.

To the best of our knowledge, only one cross-sectional epidemiologic study in humans has assessed how magnesium intake influences depression. In that final sample of 5708 community-dwelling individuals aged 46–49 or 70–74 years from Western Norway, findings suggested an inverse relationship between magnesium intake and depressive symptoms (15). Their findings were in contrast with our results, although exposure and outcome assessment were similar in the Norwegian study to those used in

Conclusion
better protected against reverse causality bias. The sizable number of incident cases observed in our cohort allowed us to also conduct a diversity of sensitivity analyses; in one of them, we excluded early cases (those diagnosed during the first 2 y) to obtain results better protected against the possibility of reverse causality. The results remained nonsignificant in those analyses.

Different reasons might be addressed to explain the lack of association between magnesium intake and depression incidence in our study. First of all, magnesium is likely to provide only a weak inverse association with depression risk. Even if we carried out our cohort. Dietary intakes were evaluated by a self-administered, optically readable FFQ of 169 food items and symptoms of depression were self-reported using the Hospital Anxiety and Depression Scale. Nevertheless, the cross-sectional nature of that study represents a limitation to causal inferences (15). A poor-quality diet and thus lower magnesium intake levels might have been the result of depressive symptoms and not the cause. Our longitudinal design with a median follow-up time of 6.3 y was better protected against reverse causality bias. The sizable number of cases allowed us to also conduct a diversity of sensitivity analyses; in one of them, we excluded early cases (those diagnosed during the first 2 y) to obtain results better protected against the possibility of reverse causality. The results remained nonsignificant in those analyses.

Different reasons might be addressed to explain the lack of association between magnesium intake and depression incidence in our study. First of all, magnesium is likely to provide only a weak inverse association with depression risk. Even if we carried out a number of sensitivity analyses, the results remained nonsignificant. One possible explanation is that magnesium intake levels might be influenced by depressive symptoms, which could lead to a reverse causality bias. However, our study was designed to minimize such bias by including a large number of cases, a median follow-up time of 6.3 years, and a longitudinal design. Despite these efforts, the results remained nonsignificant in the sensitivity analyses.

### Table 1: Characteristics of participants according to quintiles of total magnesium intake

<table>
<thead>
<tr>
<th>Quintiles of magnesium intake</th>
<th>Values (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>2587</td>
</tr>
<tr>
<td>Q2–Q4</td>
<td>2588</td>
</tr>
<tr>
<td>Q5</td>
<td>2587</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>2587</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % men</td>
<td>44.0</td>
</tr>
<tr>
<td>Age at baseline, y</td>
<td>37.7 ± 11.7</td>
</tr>
<tr>
<td>Baseline BMI, kg/m²</td>
<td>23.7 ± 3.6</td>
</tr>
<tr>
<td>Physical activity during leisure time, MET-h/wk</td>
<td>17.2 ± 18.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>44.0</td>
</tr>
<tr>
<td>Number of children</td>
<td>1.0 ± 1.4</td>
</tr>
<tr>
<td>Unemployment</td>
<td>4.1</td>
</tr>
<tr>
<td>Personality scores, range = 0–10</td>
<td>6.9 ± 1.8</td>
</tr>
<tr>
<td>Competitiveness</td>
<td>6.0 ± 2.3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.8 ± 3.0</td>
</tr>
<tr>
<td>Psychological dependence</td>
<td>5.7 ± 8.8</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>TFA, g/d</td>
<td>1670 ± 395</td>
</tr>
<tr>
<td>Total energy intake, kcal/d</td>
<td>3.0 ± 1.1</td>
</tr>
<tr>
<td>Total magnesium intake, mg/d</td>
<td>262 ± 46</td>
</tr>
</tbody>
</table>

1 Values are mean ± SD unless otherwise stated. MDP, Mediterranean dietary pattern; MET, metabolic equivalent task; Q, quintile; TFA, trans fatty acids.

### Table 2: Associations between total and dietary magnesium intakes (Q1–Q5) and risk of depression in adults

<table>
<thead>
<tr>
<th>Total magnesium intake</th>
<th>Q1 (ref)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2587</td>
<td>2588</td>
<td>2589</td>
<td>2588</td>
<td>2587</td>
<td></td>
</tr>
<tr>
<td>Median, mg/d</td>
<td>273</td>
<td>346</td>
<td>404</td>
<td>469</td>
<td>576</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>14,283</td>
<td>14,098</td>
<td>13,388</td>
<td>13,030</td>
<td>14,117</td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>153</td>
<td>152</td>
<td>151</td>
<td>138</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>1 (ref)</td>
<td>0.99 (0.79–1.25)</td>
<td>0.96 (0.77–1.21)</td>
<td>0.92 (0.73–1.16)</td>
<td>1.05 (0.83–1.32)</td>
<td>0.87</td>
</tr>
<tr>
<td>Model 1 (95% CI)</td>
<td>1 (ref)</td>
<td>0.99 (0.79–1.24)</td>
<td>0.95 (0.76–1.19)</td>
<td>0.90 (0.71–1.14)</td>
<td>1.01 (0.80–1.27)</td>
<td>0.87</td>
</tr>
<tr>
<td>Model 2 (95% CI)</td>
<td>1 (ref)</td>
<td>1.00 (0.78–1.27)</td>
<td>1.00 (0.76–1.31)</td>
<td>0.95 (0.70–1.30)</td>
<td>1.11 (0.77–1.59)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary magnesium intake</th>
<th>Median, mg/d</th>
<th>Q1 (ref)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>271</td>
<td>344</td>
<td>401</td>
<td>465</td>
<td>570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>1 (ref)</td>
<td>1.03 (0.83–1.29)</td>
<td>0.97 (0.77–1.21)</td>
<td>1.01 (0.80–1.26)</td>
<td>0.98 (0.77–1.24)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Model 1 (95% CI)</td>
<td>1 (ref)</td>
<td>1.03 (0.82–1.29)</td>
<td>0.95 (0.76–1.20)</td>
<td>0.99 (0.79–1.24)</td>
<td>0.95 (0.75–1.20)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Model 2 (95% CI)</td>
<td>1 (ref)</td>
<td>1.03 (0.81–1.32)</td>
<td>0.98 (0.75–1.30)</td>
<td>1.04 (0.76–1.41)</td>
<td>1.01 (0.70–1.47)</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

1 HR estimated with Cox regression and 95% CI. If the CI includes 1.00, the results are not significant (2-tailed P > 0.05). Model 1: adjusted for age in years (continuous) and sex. Model 2: model 1 additionally adjusted for BMI (kg/m², continuous), leisure time physical activity (MET-h/wk, continuous), smoking (non, former, current, and missing value), marital status (single, married, widowed, separated, other), number of children (0, 1, 2, 3, >3), employment status (unemployed, part time, full time, student, housewife, retired, missing value), self-perceived personality traits (competitiveness, anxiety, and dependence; ordinal, 0–10), alcohol and TFA intake (g/d), total energy intake (kcal/d), and adherence to the MDP (3 categories). MDP, Mediterranean dietary pattern; Q, quintile; ref, reference; TFA, trans fatty acids.
out our research in a large cohort sample, our sample size could be underpowered to detect a significant reduced risk of developing depression caused by magnesium intake if the true inverse association were only weak. As an example, if we wanted to show a RR of 0.9 to achieve a power of 80% for a 95% CI and thus to find significant results, we would need to reach a number of 28,807 individuals in each quintile, which would yield a total sample size of 144,035 participants.

A second possible reason is that magnesium absorption depends not only on magnesium intake but also on its bioavailability (39). For instance, vitamins B-6 (40) and D (21) stimulate magnesium absorption. One would suppose that magnesium and some vitamin intake as a whole might have had a greater effect on reducing depression risk.

It should also be noted that magnesium is not an isolated element. Interactions between different food components need to be taken into account to examine the contribution of a nutrient to disease risk. In this way, dietary patterns might have a greater effect on a specific disease than individual food elements. Interactions between different food components need to be taken into account to examine the contribution of a nutrient to disease risk. In this way, dietary patterns might have a greater effect on a specific disease than individual food elements.

Finally, in our participants, even among those classified in the lowest quintile of magnesium intake, intakes were not very low, with mean intakes >250 mg/d for the lowest quintile. Even if those values appear slightly below the Spanish dietary reference intakes (44), they were not so low as to expect a substantially increased risk of depression. It is possible that the increased risk may appear at only very low levels of intake and the prevalence of extremely low intake of magnesium might have been almost negligible in our cohort. In addition, most of our participants were young and healthy. Because magnesium deficit is more prevalent in the elderly, we cannot rule out the possibility that lower magnesium intake is associated with depression among older participants. Further investigation in this field is necessary to support this assumption.

Two possible limitations of our study need to be addressed: the quality of nutritional assessment and the accuracy of magnesium intake. FFQ are known to contain a certain degree of measurement error, which might have affected our results. Nevertheless, the semiquantitative FFQ used in this project was previously validated in Spain (26) and recently revalidated (27,28). The case ascertainment of clinical depression was based on self-reports. This is another limitation that we acknowledge. A social desirability bias could have led to a misreport of depression diagnosis. This might have biased (supposedly toward the null) the reported associations if participants with depression and low magnesium intake were more likely to under-report depression than those with moderate or high levels of magnesium intake. Notwithstanding, several previous cohort studies of highly educated participants have demonstrated the validity of self-reported depression. Specifically, our validation study (36) found a very high specificity (0.96) for the self-reported diagnosis of depres-
sion, which implies an underestimation, and consequently a low sensitivity, rather than an overestimation of true cases of incident depression.

A final possible caveat might be inherent to residual confounding because of the possibility that some confounding variables were measured imperfectly or with some error. Additionally, some unknown or unmeasured confounders related to lifestyle might also have biased our reported results. For instance, some potential confounders related to psychological characteristics have not been collected for the SUN Project, such as family history of depressive disorders, loneliness, social network of participants, or use of illicit drugs. The lack of control for these potential confounders warrants caution in the interpretation of our reported results.

The strengths of our study are also worth stating, such as the long period of follow-up, our large sample size, a high response rate, the existence of published validation studies of our methods, and the adjustment for a sizeable number of potential confounders. The prospective design of our study increases the ability to provide scientific evidence and makes it possible to avoid recall bias and reverse causality. Furthermore, our participants' high level of education and their interest for health increases the internal validity and quality of information obtained through self-administered questionnaires. A final important strength worth citing is the robustness of our findings in different sensitivity scenarios.

In conclusion, our data suggest that higher dietary and total magnesium intakes are not associated with a lower risk of developing depression in a cohort of educated, middle-aged, healthy adults. Our findings are, however, compatible with the possibility that magnesium supplementation might ameliorate depression symptoms in already depressed patients or might be inversely associated with depression risk in other populations such as diabetics or elderly individuals.

The neurobiological mechanisms behind the possible reduced depression risk from high levels of magnesium intake are still not perfectly understood and deserve further attention. Additional cohort studies in older participants and with a wider between-subject variability in magnesium intake are needed to investigate this association.

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Literature Cited


