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Magnesium Intake and Risk of Amyotrophic Lateral Sclerosis: Results From Five Large Cohort Studies

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Abstract

Objective—A low magnesium intake has been suggested to be associated with amyotrophic lateral sclerosis (ALS) in pathological and case-control studies, but prospective studies in humans are lacking.

Methods—The relation between dietary intake of magnesium and ALS risk was explored in five large prospective cohort studies [the Nurses' Health Study, the Health Professionals Follow-up Study, the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort Study, and the National Institutes of Health – AARP Diet and Health Study], comprising over 1,050,000 men and women contributing 1,093 cases of ALS during a mean of 15 years of follow-up. Cox proportional hazards models were used within each cohort, and cohort-specific estimates were subsequently pooled using a random-effects model.

Results—Dietary magnesium intake was not associated with ALS risk, relative risk 1.07, 95% confidence interval: 0.88– 1.31 comparing the highest quintile of intake with the lowest.

Conclusions—This finding does not support a protective effect of magnesium intake on ALS risk. Further analyses should explore magnesium intake in combination with heavy metal exposure and genetic variants affecting magnesium absorption.

Keywords

amyotrophic lateral sclerosis; motor neuron disease; longitudinal cohort studies; epidemiology; magnesium

Introduction

Many Americans are deficient in magnesium and do not reach the Recommended Dietary Allowance (1, 2). The cause of Amyotrophic Lateral Sclerosis (ALS) is largely unknown, and there is no effective treatment to date. One possible risk factor for ALS is a low magnesium intake, which has been suspected since the 1970's when low levels of magnesium and calcium were found in the soil in areas with high ALS incidence (3). Since then, a lower magnesium content in bones and ligaments has been found in post mortem analyses of ALS patients compared to controls (4), and a high magnesium intake has been reported to be modestly associated with a lower risk of ALS in a case-control study (5). However, it is still unclear whether magnesium plays a role in ALS development as magnesium supplementation did not affect survival in ALS mice models (6), and there are no prospective studies on magnesium intake on ALS risk in humans..

We therefore explored the association of dietary intake of magnesium and ALS risk in five large cohorts including over 1,050,000 men and women contributing 1093 cases of ALS during a mean of 15 years of follow-up.

Materials and Methods

Study population

The study population comprised the participants in five large cohorts: the Nurses' Health Study (NHS) (7), the Health Professionals Follow-up Study (HPFS) (8), the Cancer Prevention Study II Nutrition Cohort (CPS-IIN) (9), the Multiethnic Cohort Study (MEC) (10), and the National Institutes of Health – AARP Diet and Health Study (NIH-AARP) (11). All studies have been approved by the institutional review board of the institution where the study was conducted.

Ascertainment of ALS

Follow-up of ALS in the CPS-IIN, MEC, and NIH-AARP was through a search of the National Death Index. Vital status of the participants in these studies was determined by automated linkage with the National Death Index. The underlying and contributing causes of death were coded according to the International Classification of Diseases, Ninth Revision. All individuals with code 335.2 (motor neuron disease) listed as the underlying or contributing cause of death were considered to have had ALS. In a previous study (12), it was found that ALS was the primary diagnosis listed on death certificates in the majority of instances where code 335.2 was listed as a cause or contributory cause of death (12).

In NHS and HPFS, incident ALS was also documented. In each biennial follow-up questionnaire, participants were asked to report a specific list of medically diagnosed conditions (initially not including ALS) and "any other major illness." ALS was added to the list of specific conditions on the NHS questionnaires in 1992 onwards and on the HPFS questionnaires in 2000 onwards. We requested permission for release of relevant medical records from participants who reported a diagnosis of ALS on the open question on major illnesses or on the specific question. Because of the rapidly progressive nature of the disease (median survival 1.5 to 3 years)(13–15), many participants with ALS died before we could send the release request for medical records, so the request was sent to the closest family member. After obtaining permission, we asked the treating neurologists to complete a questionnaire to confirm the diagnosis of ALS and to rate the certainty of the diagnosis (definite, probable, or possible). Starting in 2004 the questionnaire was modified to include the El Escorial criteria. The final confirmation for our study purposes was made by a neurologist with experience in ALS diagnosis based on the review of medical records. We relied on the diagnosis made by the treating neurologist if the information in the medical

record was insufficient or if it could not be obtained. Only participants with definite and probable ALS are included as cases in the primary analyses. When we were unable to confirm (i.e., obtain a copy of the medical record or the neurologist's questionnaire) incident self-reported ALS, we classified the participant as having 'possible ALS' and excluded him or her from the primary analysis unless death occurred during follow-up and ALS was listed on the death certificate.

Assessment of Magnesium intake

A separate validated food frequency questionnaire (FFQ) was used for each cohort, assessing the average food consumption over the previous year (7–11, 16). Diet was assessed every four years in NHS and HPFS, in 1992 and 1999 in CPS-IIN and at baseline in MEC and NIHAARP. Dietary intake of magnesium was calculated by multiplying the frequency at which each food was consumed by the magnesium content of the specified portion size. Magnesium intake from magnesium supplements and multivitamins was available in NHS and HPFS. Magnesium intake from multivitamins was available in NIH-AARP and MEC, but no information on magnesium supplements was available in CPS-IIN. A validation and reproducibility study in HPFS show a correlation coefficient by FFQ and two one-week diet records of 0.73 for magnesium (17). Further, the validity of magnesium intake in the NHS is indirectly supported by the finding of a significant inverse association between magnesium intake and sudden cardiac death (18).

Statistical analyses

All analyses were conducted separately within each cohort. Baseline dietary magnesium intake was divided into cohort-specific quintiles. Energy adjustment was performed using the residual method (19) and participants with log-transformed energy intake greater than 3 standard deviations from the study-specific mean were excluded ($n=47,335$, 4.4%). In sub-analyses, we calculated the cumulative average of energy-adjusted magnesium intake in the NHS and HPFS (20). Person-time was calculated as the date of return of the questionnaire until the date of first onset of ALS symptoms (HPFS, NHS), death from ALS or any other cause, or end of follow-up. The end of follow-up was December 2008 in NHS, HPFS, December 2006 in CPS-IIN, and December 2007 in NIH-AARP and MEC. Because of the long duration of follow-up in NHS, we split the person-time and cases into two uncorrelated segments in NHS: 1980–1994 and 1994–2008. In accordance with the underlying theory of survival analysis, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same persons (21). Thus, pooling the estimates from the two time periods is equivalent to using a single time period but takes advantage of the updated exposure assessment in 1994.

Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (CI) for categories of magnesium intake in each cohort in relation to ALS. We stratified the Cox models by age in single years to obtain better age adjustment. We evaluated potential confounders correlated with ALS or magnesium intake, and adjusted for sex, smoking (never smoked, pack-years: <10, 10–20, 20–30, 30–40, >40), education level (<high school, high school, >high school), body mass index (underweight, normal weight, overweight, obese), physical activity level (low, medium, high), vitamin E from food and supplements (in quintiles), alcohol intake (0, 0.1–5, 5.1–15, 15.1–30, >30 grams/day), and diabetes diagnosis at baseline. The association between smoking and ALS (22) and vitamin E and ALS (23) in these cohorts has previously been reported. The log relative risk from each cohort was weighted by the inverse of its variance, and the weighted log relative risks were then pooled using a random-effects model (24).

Calcium is suspected to be involved in ALS pathogenesis and may compete with magnesium for absorption and membrane binding (25). However, since calcium intake was positively correlated with magnesium intake (correlation coefficients ranging from 0.63 in HPFS to 0.83 in CPS-IIN), we adjusted for calcium in a sensitivity analysis (in quintiles), but not in the main model. We also evaluated effect measure modification between magnesium and ALS by calcium intake (≤ 600 , > 600 mg/day), by alcohol intake (≤ 7 , > 7 grams/day), and by smoking (never, past, current). In additional sensitivity analyses, we excluded diuretics users since some diuretics can cause magnesium depletion (26). Further, we excluded the first four years of follow-up to minimize the possibility of including participants with ALS symptoms at the time of completing the baseline questionnaire.

In total, we identified 1,093 cases of ALS among 13,370,713 person-years contributed by 1,053,389 men and women. Analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Characteristics of the study population are reported in Table 1. Men had a higher intake of magnesium than women; the mean dietary magnesium intake in all studies combined was 339 mg for men and 288 mg for women (Recommended Dietary Allowance is 420 for men and 320 for women) (1). Participants with a higher intake of magnesium tended to have a higher physical activity level, smoke less, and have higher intakes of vitamin E and calcium (Table 2). The distribution of the characteristics in Table 2 was similar across the cohorts.

Overall, there was no association between dietary magnesium intake and ALS risk (multivariable adjusted RR 1.07, 95% CI: 0.88, 1.31) comparing the highest quintile to the lowest in the pooled analyses (Table 3). Results were similar across cohorts (data not shown) and among men and women (men: RR 1.10, 95% CI: 0.85, 1.41; women: RR 1.08, 95% CI: 0.71, 1.64).

Information on magnesium supplement use was available in the NHS and HPFS cohorts, where it was uncommon (4% in NHS, 1.5% in HPFS). In addition, magnesium intake from multivitamins was available in NHS, HPFS, MEC and NIH-AARP. When including magnesium from multivitamin supplement and magnesium supplement use in analyses in NHS, HPFS, MEC and NIH-AARP, results were similar: RR 0.99, 95% CI: 0.74, 1.32, compared to when magnesium supplement use was not included in analysis: RR 1.06, 95% CI: 0.80, 1.40, comparing the highest quintile of magnesium intake with the lowest. When adjusting for calcium in the model, results were similar to main results (RR 1.10, 95% CI: 0.88, 1.38). Results were also similar after using updated magnesium intakes in NHS and HPFS (data not shown). When looking more closely at a low dietary magnesium intake, we found that intakes in the lowest 5% were not associated with risk of ALS: RR 1.00, 95% CI: 0.76, 1.31, comparing with intakes in the highest 5%. Further, no significant deviation from linearity was detected when cubic spline transformations were used (P for deviation from linearity = 0.49).

In sub analyses, we excluded diabetes patients and results remained similar (RR 1.10, 95% CI: 0.89, 1.34). In addition, we excluded diuretics users in NHS and HPFS and results were very similar to main analyses (data not shown). Further, we excluded the first four years of ALS cases, and similar results were obtained; multivariate RR 1.13, 95% CI: 0.90, 1.41 for the highest compared to the lowest intake of dietary magnesium. Lastly, we found no indication that the association between dietary magnesium intake and ALS risk was modified by calcium, alcohol or smoking.

Discussion

In this pooled analysis of five large populations-based prospective cohorts, we found that dietary magnesium intake was not associated with ALS risk. Our study benefits from a large sample size and a prospective design, minimizing potential recall bias. Additionally, the ALS cases included in this study are likely from a whole range of ALS cases and there is no selection bias that is present in case-control studies when cases are recruited from ALS tertiary-care centers (27, 28). In our study, we used ALS mortality as a proxy for ALS incidence in the CPS-IIN, MEC, and NIH-AARP cohorts and this may introduce some misclassification of outcome. Still, this bias is likely modest because median survival of ALS patients after diagnosis is relatively short (1.5–3 years) (13) and death certificates have been estimated to accurately identify 70–90% of cases of ALS or motor neuron diseases (29, 30), making mortality a reasonable substitute for incidence. Another limitation is that magnesium intake in MEC and NIH-AARP was assessed at baseline only, and thus does not account for changes in dietary intake during the follow-up. However, the consistency of results in these cohorts with those obtained in NHS and HPFS where dietary information was updated and validated (17), suggests that bias from this source is likely to be modest. There is likely misclassification of exposure due to the measurement of magnesium intake by FFQ's, not capturing all foods containing magnesium. This misclassification can lead to underestimation of an association between diet and disease risk. Another potential limitation was that information on magnesium supplementation was only available in the HPFS and NHS cohorts. However, this bias is likely small since magnesium supplementation use was rare. In addition, as in all observational studies, there might be unmeasured confounding by unknown predictors of ALS.

To our knowledge, this is the first prospective study on magnesium intake and ALS risk. In a previous case-control study (n=107 ALS cases) a high magnesium intake was associated with a modest and non-significant decrease in ALS risk (5). In a SOD-1 mouse model of familial ALS, magnesium supplementation did not affect disease onset or survival (6), but intriguingly, magnesium supplementation protected neurons from damage in a Parkinson Disease (PD) rat model (31). Also, mutations in genes affecting the TRPM6 or TRPM7 channels can cause poor magnesium absorption (32, 33), and mutations in the *TRPM7* gene have been reported in ALS patients (34). Finally, the results of previous studies suggest that exposure to lead is a risk factor for ALS (35, 36), and since lead can substitute magnesium in important biological processes and cause protein misfolding and inflammation (37), it remains possible that magnesium deficiency increases ALS risk in the presence of lead or other heavy metals. In summary, in this large longitudinal study, we found no association between magnesium intake and ALS risk. This result does not support the hypothesis that magnesium intake is a major determinant of ALS risk. On the other hand, a possible role of magnesium deficiency as a risk factor for ALS in individuals who are genetically vulnerable or exposed to heavy metals cannot be excluded.

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Table 1

Cohorts Included in the Pooled Analysis of Dietary Magnesium Intake and Amyotrophic Lateral Sclerosis Risk.

Study	Start of follow-up	End of follow-up	Mean age at baseline	Baseline cohort size *	No. of ALS cases	Dietary Magnesium median, mg/day (20–80%)
HPFS (men)	1986	2008	54.8	49,753	63	323 (242–422)
NHS (women)	1980	2008	46.8	92,218	101	275 (206–357)
CPS-IIIN	1992	2006				
Men			64.2	77,462	126	243 (177–324)
Women			62.2	88,221	95	201 (142–272)
MEC	1993–1997	2007				
Men			60.3	92,408	83	341 (232–499)
Women			59.7	113,506	57	301 (203–448)
NIH – AARP	1995–1996	2007				
Men			61.8	323,628	384	328 (239–444)
Women			61.4	216,193	184	276 (198–377)
Total				1,053,389	1093	

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; CPS-IIIN, Cancer Prevention Study II Nutrition Cohort; MEC, Multiethnic Cohort study; NIH, National Institutes of Health; ALS, amyotrophic lateral sclerosis.

* Cohort size after applying study-specific exclusions and excluding participants with log-transformed energy intake values beyond 3 standard deviations from the study-specific mean.

Age-adjusted Characteristics of Study Participants at Baseline According to Dietary Magnesium Intake in the Five Cohort Studies.

Table 2

	Quintile of Dietary Magnesium Intake*				
	Q1	Q2	Q3	Q4	Q5
Sex, % men [‡]	39.0	46.6	52.0	57.1	63.0
Age, mean (SD) [‡]	59.9 (8.1)	59.9 (8.1)	59.9 (8.1)	59.9 (8.1)	59.9 (8.1)
Body mass index, mean (SD)	26.3 (5.1)	26.3 (4.8)	26.3 (4.8)	26.3 (4.8)	26.6 (4.9)
Current smokers, %	15.2	13.8	13.3	12.9	14.0
Education > high school, %	69.0	73.0	74.5	74.9	73.0
High level of physical activity, %	20.0	23.6	26.3	29.1	34.0
Vitamin E including supplements (mg/day), mean (SD)	57.3 (107.5)	64.9 (111.5)	69.6 (114.7)	74.1 (116.7)	83.6 (123.8)
Dietary calcium intake (mg/day), mean (SD)	395.0 (158.9)	574.5 (194.6)	719.7 (241.7)	898.3 (306.0)	1292.4 (537.1)
Alcohol intake (g/day), mean (SD)	6.7 (18.9)	8.2 (19.3)	9.5 (20.6)	10.9 (23.2)	15.6 (37.0)
Diabetes diagnosis at baseline	7.6	7.6	7.9	8.5	10.0

Abbreviations: CI, confidence interval; RR, relative risk.

* Cohort-specific quintiles

[‡]Values are not age-adjusted

Pooled Relative Risk of Amyotrophic Lateral Sclerosis by Dietary Magnesium Intake in Data from Five Cohort Studies.

Table 3

Quintile of Dietary Magnesium Intake						
	Q1	Q2	Q3	Q4	Q5	P_{trend} P^* heterogeneity
No. of cases	196	217	200	249	231	
Person-years	2,650,850	2,674,366	2,678,717	2,682,194	2,684,586	
Age-adjusted RR (95% CI) [†]	Reference	0.99 (0.75–1.32)	0.95 (0.78–1.16)	1.13 (0.89–1.44)	1.04 (0.86–1.26)	0.45
Multivariate RR (95% CI) [‡]	Reference	1.02 (0.78–1.33)	0.98 (0.80–1.21)	1.21 (0.96–1.52)	1.07 (0.88–1.31)	0.48

Abbreviations: CI, confidence interval; RR, relative risk.

* P-values for the tests of heterogeneity between studies were calculated using the Q statistic.

[†] Adjusted for age and sex.

[‡] Adjusted for age, sex, smoking status, energy intake, body mass index, physical activity, education level, alcohol intake, dietary intake and supplement use of vitamin E, dietary intake of calcium, and diabetes diagnosis at baseline.