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Dietary Magnesium Intake Is Inversely Associated with Mortality in Adults at High Cardiovascular Disease Risk[1–3]

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Abstract

The relation between dietary magnesium intake and cardiovascular disease (CVD) or mortality was evaluated in several prospective studies, but few of them have assessed the risk of all-cause mortality, which has never been evaluated in Mediterranean adults at high cardiovascular risk. The aim of this study was to assess the association between magnesium intake and CVD and mortality risk in a Mediterranean population at high cardiovascular risk with high average magnesium intake. The present study included 7216 men and women aged 55–80 y from the PREDIMED (Prevención con Dieta Mediterránea) study, a randomized clinical trial. Participants were assigned to 1 of 2 Mediterranean diets (supplemented with nuts or olive oil) or to a control diet (advice on a low-fat diet). Mortality was ascertained by linkage to the National Death Index and medical records. We fitted multivariable-adjusted Cox regressions to assess associations between baseline energy-adjusted tertiles of magnesium intake and relative risk of CVD and mortality. Multivariable analyses with generalized estimating equation models were used to assess the associations between yearly repeated measurements of magnesium intake and mortality. After a median follow-up of 4.8 y, 323 total deaths, 81 cardiovascular deaths, 130 cancer deaths, and 277 cardiovascular events occurred. Energy-adjusted baseline magnesium intake was inversely associated with cardiovascular, cancer, and all-cause mortality. Compared with lower consumers, individuals in the highest tertile of magnesium intake had a 34% reduction in mortality risk (HR: 0.66; 95% CI: 0.45, 0.95; $P < 0.01$). Dietary magnesium intake was inversely associated with mortality risk in Mediterranean individuals at high risk of CVD. This trial was registered at controlled-trials.com as ISRCTN35739639. J. Nutr. 144: 55–60, 2014.

Introduction

Magnesium is an essential mineral for the human body, acting as a coenzyme in different ATP-dependent reactions and in the production and transport of energy and proteins (1). The major food sources of magnesium are vegetables, fruits, legumes, nuts, soy products, and whole grains. Some evidence suggests that high dietary magnesium intake plays a protective role not only in cardiovascular risk factors, such as diabetes mellitus (2),

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[3] Supplemental Appendix is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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hypertension (3), and metabolic syndrome (4), but also in cardiovascular disease (CVD)[20] (5).

A meta-analysis evaluating the association between magnesium and the risk of cardiovascular events demonstrated that both dietary and serum magnesium were inversely related with the risk of total CVD events (6). Similarly, inverse associations between dietary magnesium intake and risk of stroke or ischemic heart disease were also demonstrated in 2 other recent meta-analyses (7,8).

Prospective studies have also been made into the relation between magnesium and cardiovascular and cancer mortality. Some suggest inverse associations (9,10) between magnesium intake and cardiovascular mortality, but others have found no significant associations (4,11,12). Two prospective studies have evaluated the association between dietary magnesium intake and cancer death (11,12). Finally, an inverse association between dietary or plasma magnesium concentrations and sudden cardiac death was reported recently (13), and serum magnesium has also been inversely associated with cardiovascular, cancer, and all-cause mortality in middle-aged men (14).

Although some studies have shown that dietary magnesium intake is inversely related to CVDs and mortality, very few have evaluated the risk of all-cause mortality (11), and these associations have not been evaluated previously in Mediterranean individuals.

We hypothesized that dietary magnesium intake is inversely associated with CVDs and mortality. Therefore, the main aim of the present study was to assess the association between dietary magnesium intake and the risk of CVD (a composite including stroke, myocardial infarction, and cardiovascular death) and cardiovascular, cancer, and all-cause mortality in Mediterranean individuals at high risk of CVD and with a high average magnesium intake.

Materials and Methods

Study population. The PREDIMED (Prevención con Dieta Mediterránea) study is a multicenter, randomized, parallel-group clinical trial conducted in Spain. Details of the cohort, design of the study, and methods were described previously (15–18). The study was registered at controlled-trials.com as ISRCTN35739639 (19). A complete list of the PREDIMED investigators is listed in the **Supplemental Appendix**. The study included men (aged 55–80 y) and women (aged 60–80 y) who were free of CVD at enrollment but at high CVD risk. The inclusion criteria for the participants in the trial were having type 2 diabetes mellitus or three or more of the following cardiovascular risk factors: *1)* family history of premature CVD; *2)* overweight or obesity; *3)* current smoking; *4)* hypertension; *5)* hypercholesterolemia; and *6)* low HDL-cholesterol. The exclusion criteria included the following: *1)* presence of BMI $\geq$ 40 kg/m^2; *2)* alcohol or drug abuse; *3)* any severe chronic illness; and *4)* allergy or intolerance to olive oil or nuts. The study included 7447 participants who were randomly assigned to 1 of 2 Mediterranean diets (MedDiets) [supplemented with either extra-virgin olive oil (EVOO) or mixed nuts] or to a control diet (advice on a low-fat diet). All participants included in the study provided written informed consent according to a protocol approved by the institutional review boards of the recruiting centers. In the present study, we analyzed data as in an observational prospective cohort.

Assessment of magnesium intake and other covariates. Dietary magnesium intake was assessed by a validated baseline 137-item FFQ completed by trained dieticians (20). We used Spanish food composition tables to estimate energy and nutrient intake (21,22). Reproducibility and validity of the FFQ for dietary magnesium intake estimated by the Pearson's correlation coefficient (r) was 0.71, and the intraclass correlation coefficients for reproducibility and validity were 0.83 and 0.67, respectively ($P < 0.001$). At baseline, we administered several questionnaires about history of illnesses, medication use, lifestyle variables, and educational achievement. The validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire was used to assess physical activity (23). If participants were being treated with antidiabetic, cholesterol-lowering, or antihypertensive agents, or if they had been diagnosed previously, they were considered to be diabetic, hypercholesterolemic, or hypertensive, respectively. Anthropometric and blood pressure measurements were taken by trained personnel. We used calibrated scales and a wall-mounted stadiometer to measure weight and height, respectively, with participants in light clothing and no shoes. Waist circumference was measured midway between the lowest rib and the iliac using an anthropometric tape. We used a validated oscillometer (HEM705CP; Omron) to measure blood pressure in triplicate with a 5-min interval between each measurement, and we recorded the mean of these three values.

Ascertainment of CVD and mortality. For the present analysis, we used the following endpoints: *1)* a composite of cardiovascular events (myocardial infarction, stroke, and death from cardiovascular causes); and *2)* cardiovascular, cancer, and all-cause mortality. The endpoint adjudication committee, whose members were unaware of treatment allocation, updated information on these endpoints once a year. The committee used different sources of information: *1)* yearly questionnaires and examinations for all participants; *2)* family physicians; *3)* yearly review of medical records; and *4)* linkage to the National Death Index. Medical records of deceased participants were requested, and the endpoint adjudication committee determined the cause of death.

Statistical analyses. ANOVA or the Pearson's χ^2 tests were used to compare the quantitative or categorical baseline characteristics of the study participants, respectively, across baseline energy-adjusted tertiles of magnesium intake. The results were expressed as means $\pm$ SEs or percentages.

Follow-up time was calculated as the difference between the date of the cardiovascular event, death, or end of follow-up (the date of the last visit or the last recorded clinical event of participants who were still alive) and the date of recruitment.

Multivariate Cox regression models were fitted to estimate the hazard ratios (HRs) and 95% CIs of the cardiovascular events and cardiovascular, cancer, and all-cause mortality. We stratified all analyses by the recruitment center. The first multivariate model was adjusted for sex, age (years), and intervention group. The second model was also adjusted for the following covariates: *1)* BMI; *2)* smoking status (never, former, current smoker); *3)* leisure time physical activity [metabolic equivalent task (MET)-min/d, MET, 1 MET-min is approximately equivalent to 1 kcal, METs-min/d); *4)* educational level (illiterate/primary education, secondary education, academic/graduate); *5)* prevalence of hypertension (yes/no); *6)* prevalence of diabetes (yes/no); *7)* prevalence of hypercholesterolemia (yes/no); *8)* family history of coronary heart disease (CHD) (no, yes before 55 y, yes after 55 y); *9)* use of aspirin (yes/no); *10)* use of oral antidiabetic medication (yes/no); *11)* use of antihypertensive medication (yes/no); *12)* use of hypocholesterolemic medication (yes/no); and *13)* alcohol intake (continuous, adding a quadratic term). A third model was adjusted for the total of dietary fiber and calcium intake. When myocardial infarction and stroke were used as the outcomes of the analysis, the models were adjusted for the same potential confounders used in model 2. We also separated the analysis by intervention group. We assigned the median value to each tertile of magnesium intake and used it as a continuous variable to assess linear trend tests in various models. During the follow-up, we obtained information on magnesium intake yearly. We repeated the analysis using generalized estimating equations to evaluate the association between repeated measurements of energy-adjusted magnesium intake and mortality. For each 1-y period, the exposure indicator we used was the average magnesium intake of all repeated measurements from baseline to the beginning of that yearly period.

The level of significance for all statistical tests was $P < 0.05$ for bilateral contrast. Analyses were performed using SPSS statistical software (version 19; SPSS).

[20] Abbreviations used: CVD, cardiovascular disease; EVOO, extra-virgin olive oil; MedDiet, Mediterranean Diet; MET, metabolic equivalent task.

Results

For the present analysis, we excluded those participants with high or low energy intake (<500 or >3500 kcal/d for women; <800 or >4000 kcal/d for men) and those with incomplete dietary data at baseline (n = 78). As a result, a total of 7216 participants were included. There were no significant interactions between dietary magnesium intake and sex, alcohol intake, smoking status, or the use of medication.

The baseline characteristics of study participants according to baseline energy-adjusted tertiles of dietary magnesium are shown in **Table 1**. The participants in the highest tertile of dietary magnesium intake were mainly women, had lower body weight, were more physically active, and were less likely to smoke or drink alcohol. These participants also had intakes of dietary fiber and calcium. The mean intake of magnesium in the lowest and the highest energy-adjusted tertile, respectively, was 318 and 454 mg/d.

The median follow-up time of the study was 4.8 y; after this period, 323 total deaths, 81 cardiovascular deaths, 130 cancer deaths, and 277 cardiovascular events occurred (**Table 2**). Of the total deaths, 145 were in the lower energy-adjusted tertile of magnesium intake and 78 in the upper tertile.

Table 2 shows the HRs and 95% CIs for CVD and mortality according to baseline energy-adjusted tertiles of magnesium intake. After adjusting for potential confounders (model 2), those participants with the highest magnesium intake had 37% less risk of all-cause mortality (HR: 0.63; 95% CI: 0.46, 0.86; P-trend < 0.01) than those participants in the lower tertile. Magnesium intake was also inversely associated with cardiovascular and cancer mortality. The respective multivariable HRs in model 2 for the highest energy-adjusted tertile of magnesium intake were 0.53 [95% CI: 0.28, 0.99 (P-trend = 0.06)] and 0.55 [95% CI: 0.33, 0.91 (P-trend = 0.04)]. Additional adjustment for total intake of dietary fiber and calcium intake (model 3) did not appreciably alter these results [HR for all-cause mortality for the highest compared with the lowest tertile: 0.66 (95% CI: 0.45, 0.95); HR for cardiovascular mortality: 0.41 (95% CI: 0.19, 0.88); HR for cancer mortality: 0.63 (95% CI: 0.35, 1.15)]. To exclude the potential bias effect of those individuals

TABLE 1 Baseline characteristics of study participants according to energy-adjusted tertiles of dietary magnesium intake[1]

	Baseline energy-adjusted tertiles of magnesium intake			
Variable	1 (n = 2405)	2 (n = 2406)	3 (n = 2405)	P values[2]
Median magnesium intake, *mg/d*	312	341	442	
Age, *y*	67 ± 6	67 ± 6	67 ± 6	0.05
Men, *% (n)*	54.2 (1303)	38.7 (932)	34.8 (836)	<0.01
BMI, *kg/m²*	30.0 ± 3.70	29.9 ± 3.86	29.9 ± 4.00	0.54
Weight, *kg*	78.2 ± 11.9	76.2 ± 12.1	75.8 ± 11.7	<0.01
Leisure-time energy expenditure in physical activity, *MET-min/d*	225 ± 227	224 ± 226	244 ± 262	<0.01
Smoking status, *% (n)*				<0.01
Never	53.6 (1290)	63.6 (1530)	67.3 (1619)	
Current	18.9 (454)	12.4 (299)	10.4 (251)	
Former	27.5 (661)	24.0 (577)	22.2 (535)	
Educational level, *% (n)*				0.15
Illiterate/primary education	76.8 (1847)	78.3 (1885)	77.8 (1872)	
Secondary education	16.5 (396)	14.8 (355)	14.3 (345)	
Academic/graduate	6.7 (162)	6.9 (166)	7.8 (188)	
Prevalence of diabetes, *% (n)*	46.2 (1111)	49.5 (1191)	50.9 (1225)	<0.01
Prevalence of hypertension, *% (n)*	83.1 (1998)	83.6 (2011)	81.5 (1961)	0.14
Prevalence of hypercholesterolemia, *% (n)*	68.8 (1654)	72.5 (1745)	75.4 (1813)	<0.01
Family history of myocardial infarction, *% (n)*	19.5 (468)	23.4 (563)	24.1 (580)	<0.01
Medication use, *% (n)*				
Aspirin	21.3 (512)	21.9 (527)	23.9 (574)	0.08
Oral antidiabetic drugs	29.6 (712)	33.7 (812)	33.2 (799)	<0.01
Antihypertensive drugs	72.9 (1753)	74.1 (1784)	71.1 (1711)	0.06
Statins	37.2 (894)	40.4 (972)	43.2 (1038)	<0.01
Total energy intake, *kcal/d*	2340 ± 565	2110 ± 496	2260 ± 542	<0.01
Magnesium intake, *mg/d*	318 ± 73.0	347 ± 67.8	454 ± 102	<0.01
Alcohol intake, *g/d*	12.1 ± 17.9	6.97 ± 11.7	5.94 ± 10.6	<0.01
Total protein, *g/d*	86.9 ± 20.9	88.1 ± 19.4	98.9 ± 21.6	<0.01
Total carbohydrates, *g/d*	240 ± 78.9	218 ± 66.4	244 ± 71.4	<0.01
Total fat, *g/d*	105 ± 28.0	92.8 ± 26.0	93.9 ± 29.0	<0.01
Saturated fat, *g/d*	26.9 ± 8.84	23.8 ± 7.67	23.7 ± 8.45	<0.01
Monounsaturated fat, *g/d*	53.3 ± 14.9	46.2 ± 14.2	44.9 ± 15.2	<0.01
Polyunsaturated fat, *g/d*	15.8 ± 6.4	14.6 ± 5.90	16.2 ± 7.26	<0.01
Total fiber, *g/d*	20.4 ± 5.55	23.0 ± 5.57	32.3 ± 9.19	<0.01
Calcium intake, *mg/d*	890 ± 306	1010 ± 321	1190 ± 375	<0.01

[1] Values are means ± SEs or percentages (*n*). MET, metabolic equivalent task.

[2] P values for comparisons across baseline energy-adjusted magnesium intake (Pearson χ^2 test for categorical variables or one-factor analysis of variance for continuous variable) as appropriate.

TABLE 2 Hazard ratios and 95% CIs for cardiovascular event and mortality according to tertiles of magnesium intake[1]

	Baseline energy-adjusted tertiles of dietary magnesium intake, HR (95% CI)			
	1 (low) (n = 2405)	2 (n = 2406)	3 (high) (n = 2405)	P-trend
Major event[2]				
Median magnesium intake, *mg/d*	312	341	442	
Cardiovascular event, *% (n)*	4.6 (111)	3.8 (91)	3.1 (75)	
Crude model	1 (Reference)	0.86 (0.65, 1.14)	0.73 (0.54, 0.98)	0.04
Multivariable model 1[3]	1 (Reference)	0.96 (0.72, 1.28)	0.80 (0.59, 1.09)	0.15
Multivariable model 2[4]	1 (Reference)	0.92 (0.68, 1.23)	0.83 (0.60, 1.14)	0.27
Cardiovascular mortality				
Cardiovascular death, *% (n)*	1.7 (40)	1.0 (23)	0.7 (18)	
Crude model	1 (Reference)	0.60 (0.36, 1.01)	0.49 (0.28, 0.85)	0.02
Multivariable model 1	1 (Reference)	0.70 (0.41, 1.18)	0.51 (0.28, 0.95)	0.04
Multivariable model 2	1 (Reference)	0.67 (0.39, 1.16)	0.53 (0.28, 0.99)	0.06
Cancer death				
Cancer death, *% (n)*	2.6 (63)	1.5 (37)	1.2 (30)	
Crude model	1 (Reference)	0.62 (0.42, 0.94)	0.52 (0.34, 0.81)	0.01
Multivariable model 1	1 (Reference)	0.67 (0.44, 1.02)	0.57 (0.35, 0.91)	0.04
Multivariable model 2	1 (Reference)	0.65 (0.42, 1.01)	0.55 (0.33, 0.91)	0.04
All-cause mortality				
All causes of death, *% (n)*	6.0 (145)	4.2 (100)	3.2 (78)	
Crude model	1 (Reference)	0.73 (0.57, 0.94)	0.59 (0.45, 0.78)	<0.01
Multivariable model 1	1 (Reference)	0.79 (0.61, 1.03)	0.64 (0.48, 0.86)	<0.01
Multivariable model 2	1 (Reference)	0.77 (0.59, 1.01)	0.63 (0.46, 0.86)	<0.01

[1] Cox regression models were used to assess the risk of mortality by tertiles of dietary magnesium intake (mg/d).
[2] Major event was a composite of myocardial infarction, stroke, and death from cardiovascular causes.
[3] Multivariable model 1 was adjusted for age in years, sex, and intervention group.
[4] Model 2 was also adjusted for body mass index (kg/m^2), smoking status (never, former, current smoker), educational level (illiterate/primary education, secondary education, academic/graduate), leisure time physical activity (metabolic equivalent task-min/d), prevalence of diabetes (yes/no), prevalence of hypertension (yes/no), prevalence of hypercholesterolemia (yes/no), family history of coronary heart disease (no, yes before 55 y, yes after 55 y), use of aspirin (yes/no), use of antihypertensive medication (yes/no), use of oral antidiabetic medication (yes/no), use of hypocholesterolemic medication (yes/no), alcohol intake (continuous, adding a quadratic term). All models were stratified by recruitment center. Extremes of total energy intake were excluded.

who took magnesium supplements and multivitamins, we conducted a sensitivity analysis from which they were excluded (seven individuals from the total population, 0.09%), and the results did not change.

After adjusting for all potential confounders included in the previous model 2, the HRs for baseline dietary magnesium intake and major cardiovascular event were 0.83 (95% CI: 0.6, 1.14; P-trend = 0.27) and 0.62 (95% CI: 0.36, 1.06; P-trend = 0.08) when we analyzed only the risk of myocardial infarction. Neither was any association found when we analyzed the risk of stroke (HR: 1.10; 95% CI: 0.70, 1.74; P-trend = 0.64).

When we separated the analysis by intervention group, we observed a significant reduction in the risk of all-cause mortality in those individuals in the highest tertile of magnesium consumption and assigned to the control low-fat diet (HR: 0.42; 95% CI: 0.22, 0.78; P-trend < 0.01). There were no associations for those who were assigned to the MedDiet with nuts and EVOO. Compared with the individuals in the lowest tertile of magnesium intake, we observed a significant reduction in the risk of cardiovascular mortality in the individuals in the highest tertile of magnesium intake and assigned to the MedDiet supplemented with nuts (HR: 0.27; 95% CI: 0.08, 0.87; P-trend = 0.04). No associations were observed for the other intervention groups and other outcomes (major event and cancer death).

When we used generalized estimating equations to assess the association between yearly updated measurements of energy-adjusted magnesium and all-cause mortality, we observed a fully-adjusted RR of 0.70 (95% CI: 0.52, 0.95), but the linear trend test was nonsignificant (P-trend = 0.32). The analysis to assess the relation between magnesium intake and cardiovascular mortality and cancer mortality showed a fully-adjusted RR of 0.77 (95% CI: 0.40, 1.48) and 0.50 (95% CI: 0.30, 0.83), respectively. The linear trend tests were also nonsignificant (P-trend = 0.91 and 0.12, respectively).

Discussion

In this prospective study of Mediterranean individuals at high risk of CVD, an inverse association was found between dietary magnesium intake and risk of mortality. No significant associations were observed between magnesium intake and major cardiovascular events. When we evaluated the repeated measurements of magnesium intake over time, we found a reduction in the RR of all-cause and cancer mortality in those individuals in the higher tertile of magnesium intake compared with those in the lower tertile.

There were no associations between baseline magnesium intake and mortality in participants in the highest tertile of magnesium intake in either of the MedDiet groups (supplemented with EVOO or nuts). However, a significant association was found in those randomly assigned to a low-fat control diet; they were advised to reduce the intake of all sources of fat. The lower magnesium intake in this group, then, probably resulted in a stronger inverse association between magnesium intake and mortality. In fact, previous evidence has suggested an inverse relation between marginal-to-moderate dietary magnesium deficiency and several chronic diseases (24).

A meta-analysis of 532,979 participants from 19 studies has shown that the pooled RR of total CVD events was 15% and 33% lower in the highest category of dietary magnesium and

serum magnesium, respectively, than in the lowest (6). Results were similar for ischemic stroke in another meta-analysis of seven prospective studies with 241,378 participants (7). Significant associations between circulating magnesium and CVD events were shown by the most recent meta-analysis, which also associated dietary magnesium with 22% lower risk of ischemic heart disease and showed an inverse significant association between dietary magnesium and fatal ischemic heart disease up to a threshold of ~250 mg/d compared with higher intakes (8). The findings of these meta-analyses consistently showed inverse associations between magnesium intake or status and cardiovascular events. However, in the present study of the PREDIMED cohort, we have not demonstrated a significantly decreased risk in the composite of cardiovascular events.

To the best of our knowledge, five previous prospective studies have directly assessed the associations between magnesium intake and the risk of cardiovascular death with diverging results (4,9–11,13). In agreement with our results, a decreased risk in mortality by CVD and sudden cardiac death was found in the women of the Japan Collaborative Cohort and the Nurses' Health Study, respectively (10,13). Conversely, a nonsignificant inverse association was found for fatal CHD in the men of the Health Professional Follow-Up Study cohort (9), and a nonsignificant effect was also found between dietary magnesium and cardiovascular death in the Women's Health Study and the Cohort of Swedish Men (4,11). The mean intake of magnesium in the lowest categories in these studies was apparently adequate for healthy individuals but probably not for individuals at high cardiovascular risk, such as those in the PREDIMED study (24).

Only 2 prospective studies—the Cohort of Swedish Men and the EPIC-Heidelberg Study—have assessed the association between dietary magnesium intake and cancer mortality. Neither of them showed any associations (11,12), so our study is the first to find a significant inverse association between dietary magnesium intake and cancer mortality in individuals at high cardiovascular risk. However, middle-aged men with higher serum magnesium concentrations had a 50% lower risk of cancer death than those in the lower quartile of serum magnesium intake (14). Magnesium is involved in several biochemical reactions modulating cell proliferation, differentiation, and apoptosis (25). It was also shown to play a key role in genetic stability and DNA synthesis (26), and supplemental magnesium was shown to reduce the incidence of cancer, possibly by means of inhibition of *c-myc* oncogene expression in cancer cells (27,28). Intake of magnesium was also reported to reduce insulin resistance and the risk of type 2 diabetes, which is a potential risk factor for cancer (29).

Finally, only one prospective study has related dietary magnesium intake and all-cause mortality. The results of this study concluded that there was no significant association between magnesium intake and all-cause mortality in the men of the Cohort of Swedish Men (11). However, in agreement with our results, there was a 60% reduction in all-cause mortality in individuals with a high concentration of serum magnesium compared with those in the reference category (14). In our study, we also found a significant reduction in the risk of all-cause mortality. It should be mentioned that the enrollment conditions of the present study—i.e., individuals at high cardiovascular risk, most of whom are overweight or obese and who apparently have increased requirements of dietary magnesium—have contributed to the positive associations observed between magnesium intake and disease or mortality. Moreover, magnesium deficiency, through exacerbating chronic inflammatory stress, may play a role in the onset of such chronic diseases as atherosclerosis, hypertension, osteoporosis, diabetes mellitus, and cancer (24).

There may be several explanations for these associations. In particular, hypertension is a strong risk factor for CVD, and it is known that magnesium can lower blood pressure (30). Also, magnesium intake may inhibit platelet aggregation, modulate inflammation, and improve endothelial function. All of these mechanisms can have a beneficial effect on lowering the risk of CVD and death (5,31).

We acknowledge that magnesium is an isolated nutrient, and it is important to investigate the associations between the whole diet and health. However, to establish appropriate dietary patterns, it is essential to know which nutrients and food play an important role in the target pathologies, in this case CVD and mortality.

Several potential limitations of our study deserve comment. First, the present results may not be extrapolatable to the general population because the study was conducted in participants with a high risk of CVD. Second, there is the possibility of residual confounding, especially of dietary fiber or other nutrients. To prevent this from happening, we adjusted the analysis for possible confounders. The FFQ may also lead to the misclassification of magnesium intake despite having been validated and providing a reasonable reflection of dietary intake (20). Finally, given the observational nature of the study, it is not possible to firmly establish a cause-and-effect relation of the variables studied. Conversely, the strengths of our study are that the sample studied is large, the follow-up relatively long, and the ascertainment of mortality accurate.

In conclusion, the findings from this prospective study suggest an inverse association between dietary magnesium intake and cardiovascular, cancer, and all-cause mortality. Additional studies in different populations should confirm these results.

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