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## Dietary magnesium intake and fracture risk: data from a large prospective study

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### Abstract

Research considering the relationship between dietary Mg and osteoporosis as well as fractures are sparse and conflicting. We therefore aimed to investigate Mg intake and the onset of fractures in a large cohort of American men and women involved in the Osteoarthritis Initiative over a follow-up period of 8 years. Dietary Mg intake (including that derived from supplementation) was evaluated through a FFQ at baseline and categorised using sex-specific quintiles (Q); osteoporotic fractures were evaluated through self-reported history. Overall, 3765 participants (1577 men; 2071 women) with a mean age of 60.6 (SD 9.1) years were included. During follow-up, 560 individuals (198 men and 368 women) developed a new fracture. After adjusting for fourteen potential confounders at baseline and taking those with lower Mg intake as reference (Q1), men (hazard ratio (HR) 0.47; 95% CI 0.21, 1.00,  $P=0.05$ ) and women (HR 0.38; 95% CI 0.17, 0.82,  $P=0.01$ ) in the highest quintile reported a significantly lower risk for fracture. Women meeting the recommended Mg intake were at a 27% decreased risk for future fractures. In conclusion, higher dietary Mg intake has a protective effect on future osteoporotic fractures, especially in women with a high risk for knee osteoarthritis. Those women meeting the recommended Mg intake appear to be at a lower risk for fractures.

**Key words:** Magnesium: Fractures: Osteoporosis: Epidemiology

Mg is the fourth most abundant cation in the body and plays a pivotal role in many of its functions, being involved in more than 300 enzymatic reactions<sup>(1,2)</sup>.

Several observational studies have demonstrated that low Mg intake is associated with a higher risk for several CVD and metabolic diseases, including coronary artery disease<sup>(3)</sup>, hypertension<sup>(4)</sup>, the metabolic syndrome<sup>(5)</sup> and diabetes<sup>(6)</sup>.

Although about 60% of total Mg is stored in the bone<sup>(7)</sup>, the role of this cation in bone diseases and osteoporosis is still unclear. In a recent systematic review and meta-analysis, higher dietary Mg intake was not associated with decreased fracture risk in prospective studies<sup>(8)</sup>. In the largest prospective study included in this meta-analysis<sup>(9)</sup>, the authors found that Mg intake higher than the RDA resulted in a higher risk for

fractures, probably related to more physical activity and falls<sup>(9)</sup>. A similar result was obtained by another large study in Swedish people<sup>(10)</sup>.

These findings are, however, surprising as in cross-sectional studies there was a significant association between higher Mg intake and bone mineral density (BMD)<sup>(8)</sup>. The beneficial role of Mg in inflammation<sup>(11)</sup> and oxidative stress<sup>(12)</sup>, two remarkable risk factors for osteoporosis, is well-known. Moreover, Mg is contained in green vegetables, nuts, cereals and other components of a Mediterranean diet that seems to have an important protective effect on bone fractures in women<sup>(13)</sup>.

Because of these conflicting results, we aimed to investigate the effect of higher Mg intakes on the onset of fractures in a large cohort of American men and women involved

**Abbreviations:** HR, hazard ratio; OAI, Osteoarthritis Initiative.

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in the Osteoarthritis Initiative (OAI) over a follow-up period of 8 years.

## Methods

### Data source and subjects

Data were obtained from subjects enrolled in the OAI database, which is available for public access at <http://www.oai.ucsf.edu/>. Specific data sets used are those recorded during baseline and screening evaluations (V00) and those from each database reporting data on fractures until 96 months from baseline (V10). All participants in this study were recruited as part of the ongoing, publicly and privately funded, multicentre, and longitudinal OAI study. Patients at a high risk for knee osteoarthritis were recruited from four clinical sites in the USA (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006.

All of the participants provided written informed consent. The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco.

### Exposure

Dietary Mg intake was obtained through a FFQ recorded during the baseline visit of the OAI. As this questionnaire included data on Mg supplementation, this intake was also calculated. Mg intakes were computed as residuals from the regression model, with total energetic intake as the independent variable (residual method)<sup>(14)</sup>. The entire cohort was divided into quintiles (Q) of Mg intake according to sex using 205, 269, 323 and 398 mg/d for men and 190, 251, 306 and 373 mg/d for women.

### Outcomes

The presence of fractures at baseline and during follow-up was obtained through self-reported history of fractures at the most common sites for osteoporotic fractures, that is, the hip, spine and the forearm. As the hip, spine and the forearm are the most common sites of osteoporotic fractures, these outcomes were initially evaluated separately; although, for convergence problems, analyses for the hip ( $n$  44) and spine ( $n$  77) were not reliable.

### Covariates

A number of variables were identified from the OAI data set to explore the relationship between dietary Mg intake and incident fractures. These included the following: (1) race defined as 'whites' *v.* others; (2) smoking habits as 'previous/current' *v.* never; (3) educational level categorised as 'college' *v.* others; (4) yearly income as < or  $\geq$ \$50 000 and missing data; (5) BMI, measured by a trained nurse; (6) comorbidities assessed using the modified Charlson co-morbidity score, with higher scores indicating an increased severity of conditions<sup>(15)</sup>; (7) daily intake of vitamin D, Ca, K (from food and from supplements) and total energy intake; and (8) physical activity, evaluated

using the Physical Activity Scale for the Elderly, a validated scale for assessing the physical activity level in the elderly. The scale covers twelve different activities including walking, sports and housework, and is scored from 0 upwards, without a maximum score<sup>(16)</sup>. Moreover, data regarding the use of drugs positively affecting bone (teriparatide, bisphosphonates and hormones) were also recorded.

### Statistical analyses

As Mg intake was significantly different between men and women, as was the incidence of fractures during follow-up ( $P < 0.0001$  for both comparisons), and as the interaction between dietary Mg intake and sex in predicting fracture onset at follow-up was significant ( $P_{\text{for interaction}} = 0.04$ ), all findings are reported by sex.

For continuous variables, normal distributions were tested using the Kolmogorov–Smirnov test. The data are shown as means and standard deviations for quantitative measures, and as frequency and percentages for all discrete variables by dietary Mg intake at baseline. For continuous variables, differences between the means of the covariates by quintiles of dietary Mg intake were analysed using an ANOVA; the  $\chi^2$  test was applied for discrete variables. Bonferroni correction was used in all analyses. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch's ANOVA was used.

Multivariate Cox regression models were studied using total Mg intake (sum of Mg from supplements and from foods) at baseline as exposure, categorised as quintiles and as outcome incident fractures at follow-up. Factors that reached a statistical significance between participants with osteoarthritis and those without or significantly associated with depressive symptomatology at follow-up (considering  $P < 0.05$  as statistically significant) were included. Multicollinearity among covariates was assessed using variance inflation factor, with a cut-off value of 2 as a reason for exclusion, but no variable was excluded owing to this reason. Data of Cox regression analysis were reported as hazard ratios (HR) with their 95% CI. A similar analysis was run modelling total Mg intake as a continuous variable.

All analyses were performed using SPSS 21.0 for Windows (SPSS Inc.). All statistical tests were two-tailed and statistical significance was assumed for  $P < 0.05$ .

## Results

### Study participants

At baseline, among 4796 potentially eligible individuals, 243 reported unreliable data in the FFQ (i.e. <2092 kJ (<500 kcal) or >20 920 kJ (>5000 kcal)), 788 had a fracture at baseline, and 117 were lost at follow-up (i.e. did not have the first follow-up visit), leaving 3765 participants eligible for this research.

### Baseline analyses

Overall, 3765 participants (1577 men; 2071 women) with a mean age of 60.6 (SD 9.1) (range: 45–79) years were eligible for

**Table 1.** Participants' characteristics by baseline magnesium intake in men (Mean values and standard deviations; numbers and percentages)

	Q1 (n 316)		Q2 (n 314)		Q3 (n 316)		Q4 (n 315)		Q5 (n 316)		P*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Mg from diet (mg/d)	149	38	200	45	235	46	292	48	419	92	<0.0001
Mg from supplementation (mg/d)	13	29	38	45	61	45	65	45	69	43	<0.0001
Total Mg intake (mg/d)	161	34	239	18	299	16	359	22	491	87	<0.0001
Age (years)	60.0	9.7	59.3	9.4	60.5	9.4	62.2	9.7	60.9	9.4	0.002
Nutritional parameters											
Energy intake (kJ/d)	4431	1339	5569	1590	6335	1816	7297	1937	9519	2690	<0.0001
Energy intake (kcal/d)	1059	320	1331	380	1514	434	1744	463	2275	643	<0.0001
Ca intake (mg/d)	539	300	762	371	903	388	1078	463	1372	506	<0.0001
K (mg/d)	1556	432	2076	513	2421	537	2965	592	4059	974	<0.0001
Vitamin D intake (mg/d)	147	129	289	193	397	192	455	210	538	242	<0.0001
Alcohol intake (% of energy)	6.8	9.1	6.8	8.2	6.4	8.1	5.8	6.8	4.9	5.7	0.005
BMI (kg/m <sup>2</sup> )	29.2	4.3	29.2	3.9	28.7	4.1	28.4	4.0	28.6	4.2	0.05
Demographics											
White race											
n	239		265		286		272		265		0.005
%	76		84		91		87		84		
Smoking (previous/current)											
n	159		165		154		160		163		1.00
%	51		53		49		51		52		
College											
n	118		120		112		116		112		0.56
%	37		38		36		37		35		
Yearly income (<\$50 000)											
n	207		231		230		224		218		0.69
%	68		75		74		73		70		
PASE (points)	171	84	182	79	174	89	174	88	186	94	0.13
Medical conditions and medications											
Charlson co-morbidity score	0.43	0.89	0.41	0.90	0.41	0.89	0.42	0.93	0.43	0.98	1.00
Hormones											
n	2		4		6		7		4		0.30
%	0.6		1.3		1.9		2.2		1.3		
Bisphosphonates											
n	2		7		3		7		5		0.38
%	0.6		2.2		1.0		2.2		1.6		

Q, quintile; PASE, Physical activity Scale for Elderly.

\* P values were calculated using the ANOVA for continuous and  $\chi^2$  test for categorical ones, respectively. Bonferroni correction was applied for all comparisons.

inclusion in the current study. The mean intake of Mg was 295 (SD 116) mg/d, with 53 (SD 47) mg derived from oral supplementation. Only 27.0% of the whole cohort reached correspondent RDA (i.e. 420 mg for men and 320 for women, respectively)<sup>(17)</sup>.

The baseline characteristics by dietary Mg intake and by sex are summarised in Tables 1 and 2. Independent of sex, those with higher Mg intake were more significantly old, white and had a significantly higher energy intake including a higher dietary intake of micronutrients (K, Ca and vitamin D), but they consumed a significantly lower amount of alcohol than participants with lower Mg intake. Conversely, no significant differences emerged regarding the physical activity level and presence of comorbidities. Finally, men with higher Mg intake were significantly leaner than those consuming less Mg (Table 1). In women, individuals consuming more Mg were also more likely to be prescribed bisphosphonates than those consuming less Mg, although this difference did not reach significance ( $P=0.06$ ). In the sample as a whole, only four participants used teriparatide, which may be due to the fact that people who already had a diagnosis of fractures were excluded.

### Follow-up analyses and incident fracture onset

After a mean period of 6.2 years, 560 individuals (198 men and 362 women) developed a new fracture. As shown in Table 3, men (Q5 20; 95% CI 13, 27 *v.* Q1 27; 95% CI 18, 36; Fig. 1(a)) and women (Q5 27; 95% CI 20, 34 *v.* Q1 31; 95% CI 23, 39; Fig. 1(b)) with higher Mg intake reported a significantly lower incidence of fractures compared with those having a lower Mg intake.

After adjusting for fourteen potential confounders at baseline and taking those with lower Mg intake as reference (i.e. those in Q1), men (HR 0.47; 95% CI 0.21, 1.00,  $P=0.05$ ) and women (HR 0.38; 95% CI 0.17, 0.82,  $P=0.01$ ) in the fifth quintile reported a significantly lower risk for fracture (Table 3). As height is a better predictor than BMI for fractures<sup>(18)</sup>, in a secondary analysis, we introduced height in the fully adjusted model. Compared with subjects having a lower Mg intake, men in the fifth quintile reported a non-significant association with incident fractures (HR 0.75; 95% CI 0.45, 1.25,  $P=0.75$ ), whereas women with the highest Mg intake reported a significantly reduced risk for fractures (HR 0.47; 95% CI 0.33, 0.68,  $P<0.0001$ ).

**Table 2.** Participants' characteristics by baseline magnesium intake in women (Mean values and standard deviations; numbers and percentages)

	Q1 (n 414)		Q2 (n 411)		Q3 (n 421)		Q4 (n 414)		Q5 (n 411)		P*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Mg from diet (mg/d)	134	34	179	46	207	43	262	42	371	45	<0.0001
Mg from supplementation (mg/d)	9	23	43	46	71	41	45	40	83	35	<0.0001
Total Mg intake (mg/d)	144	34	225	17	281	15	338	19	454	76	<0.0001
Age (years)	59.2	8.7	60.0	8.9	61.4	8.7	61.1	8.9	61.3	8.9	0.01
<b>Nutritional parameters</b>											
Energy intake (kJ/d)	3753	1100	4556	1510	4987	1473	5971	1682	7544	2247	<0.0001
Energy intake (kcal/d)	897	263	1089	361	1192	352	1427	402	1803	537	<0.0001
Ca intake (mg/d)	771	465	1036	479	1266	460	1477	497	1722	547	<0.0001
K (mg/d)	1408	400	4867	517	2145	492	2675	542	3689	833	<0.0001
Vitamin D intake (mg/d)	164	137	336	199	476	198	536	202	631	207	<0.0001
Alcohol intake (g/d)	4.1	7.1	3.8	6.4	3.8	5.7	3.5	5.7	2.7	4.4	0.007
BMI (kg/m <sup>2</sup> )	29.0	5.2	28.7	5.2	28.7	5.69	28.3	5.2	28.3	5.2	0.28
<b>Demographics</b>											
<b>White race</b>											
n	284		294		322		329		315		<0.0001
%	69		72		77		80		77		
<b>Smoking (previous/current)</b>											
n	218		236		235		225		226		0.79
%	53		28		56		55		55		
<b>College</b>											
n	100		101		108		104		109		0.44
%	24		25		26		25		27		
<b>Yearly income (&lt;\$50 000)</b>											
n	206		212		226		234		210		0.29
%	52		54		56		59		54		
PASE (points)	147	76	155	747	152	78	157	79	155	76	0.37
<b>Medical conditions and medications</b>											
Charlson co-morbidity score	0.36	0.89	0.37	0.82	0.35	0.76	0.35	0.74	0.35	0.71	0.99
<b>Hormones</b>											
n	5		7		8		11		6		0.47
%	1.4		2.0		2.2		2.9		1.7		
<b>Bisphosphonates</b>											
n	54		61		86		73		76		0.06
%	13.1		14.8		20.5		17.7		18.6		

Q, quintile; PASE, Physical activity Scale for Elderly.

\* P values were calculated using the ANOVA for continuous variables and the  $\chi^2$  test for categorical ones, respectively. Bonferroni correction was applied for all comparisons.

When divided by the RDA, only women reaching the RDA for Mg had a significant reduction in fracture risk of 27% (95% CI 0.51, 0.98,  $P=0.04$ ).

On the contrary, total Mg intake, modelled as continuous variable, was not associated with any decreased risk for having fracture at follow-up (for 10 mg increase in Mg intake: HR 1.00; 95% CI 0.97, 1.03,  $P=0.99$  in men and HR 0.99; 95% CI 0.96, 1.02,  $P=0.55$  in women).

## Discussion

In this study, higher dietary Mg intake was associated with a significant reduction in fracture risk over 8 years of follow-up. Those having the highest Mg intake, in fact, reported a significant reduction of in fracture risk of 53% in men and of 62% in women, after adjusting for fourteen potential baseline confounders. However, the association between Mg intake and the onset of fractures seems to be stronger in women as only women reaching the RDA showed a significantly lower risk for fractures and only in women, after adjusting for height, did the association between Mg intake and fractures remain significant.

As shown at baseline, the prevalence of low Mg intake is very high, as only a quarter of the participants of OAI reported sufficient intake of Mg. These data are in line with other studies showing a prevalence of Mg intakes lower than RDA reaching 75%<sup>(19,20)</sup>. Low Mg intake seems to predispose people to several medical conditions including metabolic diseases<sup>(5,6)</sup>, CVD<sup>(3,4)</sup> and musculoskeletal diseases (e.g. sarcopenia)<sup>(21)</sup>.

Conversely, the data on Mg intake and fracture/osteoporosis risk are less clear. As mentioned in the 'Introduction' section, several studies and a recent meta-analysis reported contrasting findings on the association between Mg intake and fractures<sup>(9,10)</sup>. Our research is, to the best of our knowledge, the first reporting a clear and significant association between higher Mg intake and reduction in fractures in both sexes.

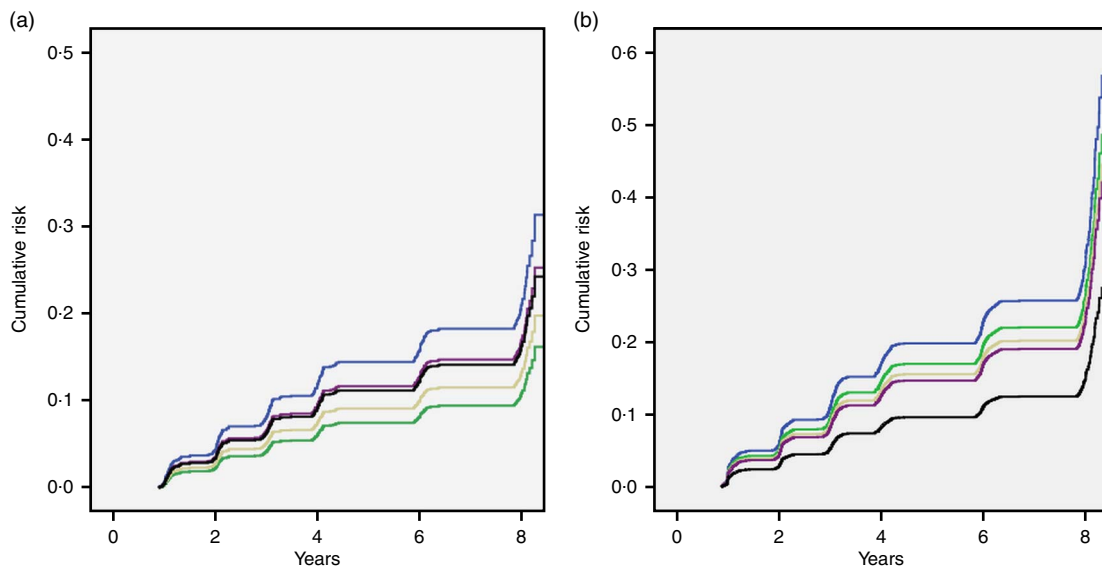
Several explanations support a role for Mg in preventing osteoporosis and fractures. First, Mg seems to be of relevance in bone health, positively affecting the function of osteoblasts and osteoclasts, and modulating Ca homeostasis, through a regulation of calcitriol and the parathyroid hormone<sup>(22)</sup>. Moreover, Mg stabilises amorphous Ca phosphate, slowing its transformation to hydroxyapatite<sup>(23)</sup> and making

**Table 3.** Association between baseline magnesium intake and incident fractures (Hazard ratios (HR) and 95% confidence intervals)

Mg intake	Men							Women						
	Cases	Subjects	Incidence rate		HR*	95% CI	P	Cases	Subjects	Incidence rate		HR*	95% CI	P
			Rate	95% CI						Rate	95% CI			
Q1	42	316	27	18, 36	1	Ref.		78	414	31	23, 39	1	Ref.	
Q2	26	314	13	9, 18	0.53	0.31, 0.90	0.02	73	411	30	22, 38	0.77	0.52, 1.14	0.20
Q3	34	316	18	10, 25	0.56	0.33, 0.97	0.04	74	421	28	20, 36	0.62	0.39, 0.99	0.05
Q4	44	315	22	15, 29	0.65	0.36, 1.17	0.15	76	414	36	25, 47	0.56	0.32, 0.98	0.04
Q5	52	316	20	13, 27	0.47	0.21, 1.00	0.05	61	411	27	20, 34	0.38	0.17, 0.82	0.01

Q, quintile; Ref, referent value.

\* Fully adjusted hazard ratios included as covariates: age (as continuous); total energy intake (as continuous); race (white v. others); BMI (as continuous); education (college v. others); smoking habits (current v. previous/never); yearly income ( $\geq$  v.  $<$  \$50 000 or missing data); Charlson co-morbidity index; use of drugs affecting positively bone (bisphosphonates, hormones, teriparatide); Ca intake (mg/d); K (mg/d); vitamin D intake (mg/d); alcohol intake (% of total energy intake); Physical Activity Scale for the Elderly (as continuous).



**Fig. 1.** Cumulative risk for any fracture at follow-up by magnesium intake at baseline in men (a) and women (b). Q, quintile; —, Q1; —, Q2; —, Q3; —, Q4; —, Q5.

bones stronger. In osteoporotic women, low Mg and high hydroxyapatite content has been more commonly shown in the trabecular bone<sup>(24)</sup>.

Other effects, however, could contribute to the positive role of Mg on bone. First, Mg has an anti-inflammatory action<sup>(25)</sup> and inflammation is a chronic condition leading to osteoporosis and fractures<sup>(26)</sup>. Second, Mg seems to be an essential element supporting muscular strength<sup>(21,27)</sup> and consequently reduces the risk for falls and finally fractures.

The effect of Mg on fractures was more important in women than in men. It is known that women, particularly after menopause, have a decreased intake of micronutrients than men<sup>(28)</sup> making them more sensitive to the consequences of nutritional deficiencies. Curiously, the other investigations regarding Mg and fractures were made in women, whereas the data in men are reported only by two studies showing no association between Mg intake and fractures<sup>(29,30)</sup>. However, more research is needed to understand why the association between Mg and fractures is less consistent in men.

The findings of our study should be interpreted within its limitations. First, dietary Mg intake was estimated only at baseline. Therefore, we cannot know if the changes in dietary patterns could affect our results. Second, the information regarding fractures and other medical conditions were only self-reported. Even if several studies<sup>(31,32)</sup> reported that for major osteoporotic fractures the accuracy of self-reported fractures is as accurate as radiological records, we cannot exclude an underestimation of some non-clinical fractures, such as vertebral ones. Third, no data on BMD assessments are available and this could introduce another bias in our findings. Fourth, we were not able to run analyses for specific fracture sites due to a likely lack of power for these analyses. Finally, the OAI included participants with knee osteoarthritis or those at a high risk for this condition. Thus, a selection bias cannot be excluded and the generalisability of our findings in other contexts should be verified. Conversely, among the strengths of our work, we can include the large sample size of men and women as well as the long follow-up period of observation.



In conclusion, higher dietary Mg intake has a protective effect on bone osteoporotic fractures, particularly in women, suggesting an important role of this mineral in osteoporosis and fractures. Further randomised controlled trials are needed to understand the possible role of Mg in delaying fractures.

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N. V. and M. N. analysed the data; B. S., M. S. and J. D. wrote the manuscript; A. V. and S. M. revised the manuscript. All authors approved the final version of this manuscript.

None of the authors has any conflicts of interest to declare.

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