

Magnesium intake, bone mineral density, and fractures: results from the Women's Health Initiative Observational Study¹⁻⁴

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ABSTRACT

Background: Magnesium is a necessary component of bone, but its relation to osteoporotic fractures is unclear.

Objective: We examined magnesium intake as a risk factor for osteoporotic fractures and altered bone mineral density (BMD).

Design: This prospective cohort study included 73,684 postmenopausal women enrolled in the Women's Health Initiative Observational Study. Total daily magnesium intake was estimated from baseline food-frequency questionnaires plus supplements. Hip fractures were confirmed by a medical record review; other fractures were identified by self-report. A baseline BMD analysis was performed in 4778 participants.

Results: Baseline hip BMD was 3% higher ($P < 0.001$), and whole-body BMD was 2% higher ($P < 0.001$), in women who consumed >422.5 compared with <206.5 mg Mg/d. However, the incidence and RR of hip and total fractures did not differ across quintiles of magnesium. In contrast, risk of lower-arm or wrist fractures increased with higher magnesium intake [multivariate-adjusted HRs of 1.15 (95% CI: 1.01, 1.32) and 1.23 (95% CI: 1.07, 1.42) for quintiles 4 and 5, respectively, compared with quintile 1; P -trend = 0.002]. In addition, women with the highest magnesium intakes were more physically active and at increased risk of falls [HR for quintile 4: 1.11 (95% CI: 1.06, 1.16); HR for quintile 5: 1.15 (95% CI: 1.10, 1.20); P -trend < 0.001].

Conclusions: Lower magnesium intake is associated with lower BMD of the hip and whole body, but this result does not translate into increased risk of fractures. A magnesium consumption slightly greater than the Recommended Dietary Allowance is associated with increased lower-arm and wrist fractures that are possibly related to more physical activity and falls. This trial was registered at clinicaltrials.gov as NCT00000611. *Am J Clin Nutr* 2014;99:926-33.

INTRODUCTION

Low magnesium intake has been implicated in neuromuscular disorders, hypertension, cardiac arrhythmias, mitral valve prolapse, atherogenesis, insulin resistance, eclampsia, and disordered bone metabolism (1, 2). Interest in the latter has arisen because magnesium intake may be a modifiable risk factor for fracture and osteoporosis.

Magnesium depletion has been associated with decreased osteoblastic and osteoclastic activity, osteopenia, bone fragility (3, 4), vitamin D resistance or reduction (4-7), and parathyroid hormone resistance (8) or reduction (6). In postmenopausal

women, low magnesium intake has been correlated with more rapid bone loss or lower bone mineral density (BMD)⁵ (9-11). In the Framingham Heart Study, although no longitudinal association was shown between magnesium intake and BMD over 4 y, a 2% higher trochanteric BMD was noted for every 100 mg Mg consumed by women at baseline (9). Supplementation with magnesium has resulted in improvement in BMD or a reduction in bone-turnover markers in some human trials (12), but other trials have shown no benefit (9, 13-15). These data suggest that magnesium intake might favorably alter BMD, but the relation to fracture outcomes is unclear.

Although magnesium deficiency has been shown to be deleterious to skeletal health, intake of amounts greater than the Recommended Dietary Allowance (RDA) may potentially pose risks. The RDA of magnesium for women was raised from 280 to 320 mg/d by the National Academy of Science in 1997 (16). Magnesium excess (5-10 times nutrient requirements) in rats

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⁵ Abbreviations used: BMD, bone mineral density; CAD, coronary artery disease; FFQ, food-frequency questionnaire; HT, hormone therapy; MET, metabolic equivalent task; RDA, Recommended Dietary Allowance; WHI, Women's Health Initiative.

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had no effect on BMD in shorter-term studies (17) but lowered BMD in longer-term studies (18). There have been reports from human studies of bone lesions and lower BMD in cases of acute exposure to high-dose magnesium (19–22), but to our knowledge, there are no data on chronic exposure to excess magnesium intake in relation to BMD and fracture risk. This prospective cohort study examined the role of magnesium intake as an independent risk factor for altered BMD and fracture of the hip, forearm and wrist, and total fractures after accounting for important covariates in postmenopausal women enrolled in the Women's Health Initiative (WHI) Observational Study.

SUBJECTS AND METHODS

Study group

The WHI Observational Study is a prospective cohort study that is based on 40 clinical centers throughout the United States. A total of 93,676 postmenopausal women aged 50–79 y (mean: 64 y) were enrolled between 1994 and 1998. These women completed screening and enrollment questionnaires by a self-report, interview, physical examination, and blood specimen collection as previously described (23). Procedures followed were in accordance with ethical standards of institutional review boards of all participating institutions. From this sample, a sample of 73,684 participants with no missing data on magnesium or other model covariates was selected for all analyses.

Outcome ascertainment

Baseline BMD at the hip, posterior-anterior spine, and total body was measured in a subgroup of 6108 women who participated in the WHI Observational Study BMD Cohort. Three clinical centers participated (Pittsburgh, PA; Birmingham, AL; and Phoenix and Tucson, AZ). These clinics were chosen to provide maximum racial and ethnic diversity and, hence, were not representative of the WHI as a whole. BMD was obtained by using dual-energy X-ray absorptiometry with a Hologic QDR densitometer (Hologic Inc). Technicians were trained and certified by the University of California, San Francisco, Bone Density Coordinating Center. Standard protocols for positioning and analysis, routine spine and hip phantoms, and a random-sample review were used. Hardware and software changes were centralized, and calibration phantoms, which were scanned across instruments and clinical sites, were in close agreement (interscanner variability <1.5% for the spine, <4.8% for the hip, and <1.7% for linearity) (24, 25).

Questionnaires were sent to subjects annually to report hospitalizations and other clinical outcomes, including incident falls, hip, lower-arm and wrist, and other fractures. Proxy interviews regarding health outcomes were conducted for women who were unable to attend clinic visits or deceased (26). A fall history was obtained by asking about the number of times the participant fell or landed on the ground (excluding sporting activities) in the past year. The falls outcome variable for this analysis was based on a participant reporting ≥ 2 falls in the past year. All hip fractures were verified by review of an X-ray, MRI, or operative reports by centrally trained and blinded physician adjudicators at each clinical center. Lower-arm and wrist fractures were self-reported. Total fractures were defined as all reported clinical fractures other than those of the ribs, sternum, skull or face, fingers, toes, and

cervical vertebrae. WHI Clinical Trial data showed the validity of self-reports because 71% of self-reported single-site fractures were subsequently confirmed by a physician review (27).

Exposure ascertainment

Total daily magnesium intake included dietary and supplemental sources (ie, magnesium from dietary supplements or medications). Baseline dietary magnesium was ascertained via a modified food-frequency questionnaire (FFQ) as previously described (28). Current supplements and medications were directly observed by an interviewer at baseline clinic visits and coded into Medispan database (First DataBank Inc). A standardized interviewer-administered form was used to collect information on supplement ingredients, frequency (pills/wk) and duration (mo and y) of use for each supplement. Only supplements used ≥ 1 time/wk were recorded (29). Nutrient intakes were estimated from the FFQ by using a database derived from the University of Minnesota's Nutrition Coordinating Center (Minnesota Nutrition Data System for Research, version 30) (30). Magnesium-intake estimates from the FFQ and means from 8-d food-intake records correlated well, with Pearson's correlation coefficients of 0.68 for energy-adjusted intake and 0.61 for unadjusted intake (28).

Other covariates

Covariates included age (50–59, 60–69, and 70–79 y), race-ethnicity, parental history of fracture, personal fracture at ≥ 55 y of age, BMI, history of coronary artery disease (CAD; defined as a history of angina or myocardial infarction), treated diabetes, self-reported health, hormone therapy (HT) use, alcohol intake, total calcium intake, current and past smoking, and physical activity in metabolic equivalent tasks (METs) per week. Physical activity was assessed by using a detailed questionnaire that asked about the number of minutes per week spent walking outside the home and the frequency and duration of recreational activities, which were classified by using standardized codes of the energy expenditure associated with activities in METs (31). Calcium intake and alcohol consumption were estimated from the FFQ. Weight measured to the nearest 0.1 kg and height measured to the nearest 0.1 cm per protocol were used to generate BMI (in kg/m^2), which was stratified into < 25 and ≥ 25 .

Statistical analysis

Data on magnesium intake and all included covariates were available for 73,684 women. In the primary analysis, the cohort was stratified by quintiles of daily magnesium intake. A series of linear models were run to look at baseline BMD by modeling BMD at each site as a function of quintiles of magnesium intake 1) in an unadjusted model and 2) in a model adjusted for all of the previously mentioned covariates. Least-squares means and 95% CIs are presented. In addition, a second set of models that evaluated baseline BMD at each site as a function of a linear trend of magnesium were run with *P*-linear trend values presented.

The RR of fracture was estimated for each quintile and compared with magnesium intake in the lowest quintile. Proportional hazards models were fit for each outcome by modeling the outcome of interest as a function of quintiles of magnesium intake. Models were initially adjusted for age and then further adjusted for all covariates. To examine the effect of missing data,

we reran our age-adjusted model on a full set of 89,547 participants who had both outcome and magnesium data. Because results were nearly identical, results are presented for the final sample that contained no missing data with event totals, annualized percentages, and HRs with 95% CIs. As with BMD models, a second model to evaluate the linear trend on each fracture site was run with corresponding *P*-trend values presented. *P* = 0.05 was set a priori to determine significant differences between groups.

In addition to main-effect models, we examined whether the effect of magnesium on hip, lower-arm and wrist, and total fractures was modified by baseline characteristics, including age, HT, history of CAD, history of fracture at ≥ 55 of age, BMI, physical activity, total calcium intake, total potassium intake, and total vitamin D intake. For each subgroup analysis, HRs for fracture or fall were computed for each category of the subgroup, as well as corresponding interaction model to evaluate the interaction between the subgroup and linear trend over magnesium groups. We also used this method to test for interaction with use of magnesium supplements or magnesium-containing medications. SAS software (version 8.2; SAS Institute Inc) was used in all analyses.

RESULTS

Descriptive data

The 73,684 women included in this analysis accrued 563,231 person-years of follow-up. The mean age of enrollees was 63 y. Approximately 85% of the cohort was white. Approximately one-half of enrollees had never smoked, and 40% of enrollees had never used HT. Approximately 58% of women had BMI ≥ 25 , and 40% of women denied walking for exercise.

Characteristics of women enrolled in the WHI Observational Study and their stratification by quintiles of magnesium intake are summarized in **Table 1**. Women in the highest quintile of magnesium intake tended to be thinner, reported better health and less heart disease or diabetes, consumed more alcohol and calcium, did not currently smoke, had a higher family income, had a history of parental fracture and personal fracture at ≥ 55 y of age, and were more active as measured by both METs and minutes walking outside the home. The percentage composition of blacks decreased with increasing magnesium-intake quintiles, with blacks comprising 13.0% of the lowest quintile compared with 4.0% of the highest quintile.

Magnesium intake in this WHI Observational Study cohort study ranged from 0.38 to 9274 mg/d, with the 99th percentile at 958 mg/d. The average daily magnesium intake for the cohort was 335 mg/d, with 85% of this value obtained from the diet and the remainder from supplements.

Magnesium and BMD

A total of 4778 women had BMD data in our sample. The relation of magnesium intake to baseline BMD after multivariate adjustment is shown in **Figure 1**. In women who consumed >422.5 compared with <206.5 mg Mg/d, there was a 3% higher total hip BMD (adjusted least-squares mean: 0.830 compared with 0.855 g/cm², respectively; *P* < 0.001) and a 2% higher whole-body BMD (adjusted least-squares mean: 1.003 compared with

1.021 g/cm², respectively; *P* < 0.001). BMD at 3 or 6 y of follow-up did not differ from baseline when stratified by quintiles of magnesium intake (data not shown).

Magnesium intake, fracture, and falls

During an average of 7.6 y of follow-up, a total of 11,510 participants reported fractures including 844 hip and 2590 forearm and wrist fractures (**Table 2**). Incidences and RRs of hip and total fractures were not significantly different across quintiles of magnesium intake. In contrast, the RR of lower-arm and wrist fractures increased with increasing magnesium intake with a multivariate adjusted HR of 1.15 (95% CI: 1.01, 1.32) in women who consumed 333.8–422.4 mg Mg/d and an HR of 1.23 (95% CI: 1.07, 1.42) in women in the highest quintile of magnesium intake (≥ 422.5 mg/d) (*P*-trend = 0.002). The relation between quintiles of magnesium and fracture risk was not modified by HT use, magnesium supplement or medication use, history of CAD, history of fracture at ≥ 55 y of age, BMI, or physical activity (data not shown). However, there was a significant interaction between age at screening and lower-arm and wrist fractures. Although both younger (50–64 y of age) and older (≥ 65 of age) women had increased risk in higher quintiles, the increase in younger women was considerably greater (quintiles 5 compared with 1: HR of 1.41 (95% CI: 1.16, 1.71) in younger women compared with 1.10 (95% CI: 0.91, 1.32) in older women; *P*-interaction between age and magnesium linear quintiles = 0.03).

Although physical activity did not modify the association of magnesium intake to fracture outcomes, women in the highest 2 quintiles of magnesium intake were more active. Because there is a greater potential for falls with increased activity, we included ≥ 2 falls in the past year as an endpoint in the analysis (**Table 2**). HRs for falls mirrored the pattern seen for lower-arm and wrist fractures, with a significantly increased fall risk in women who consumed >333.8 mg Mg/d (quintile 4 HR: 1.11 (95% CI: 1.06, 1.16); quintile 5 HR: 1.15 (95% CI: 1.10, 1.20); *P*-trend < 0.001).

Magnesium and other bone-active nutrients

We examined calcium and vitamin D intakes for an effect modification and showed no interaction with consumption on the association of magnesium to fracture risk. In addition, because foods that are high in magnesium are often high in potassium, we tested for interaction between these 2 minerals but showed no modification of the effect of magnesium on fracture risk at any site (data not shown).

DISCUSSION

This prospective cohort study of 73,684 postmenopausal women examined magnesium intake and how it relates to BMD and fracture incidence. Higher hip and whole-body BMD were noted with a higher consumption of magnesium at baseline. We showed no detrimental association of low magnesium intake to hip fracture or total fracture risk; lower-arm and wrist fractures and falls increased in women who consumed >333.7 mg Mg/d, which was a value only slightly greater than the current RDA.

Significantly higher BMD of the hip and whole body compared with the referent were noted in women with a higher daily magnesium intake at baseline. This result is in agreement with data from several large studies including the Health, Aging and Body

TABLE 1
Baseline characteristics of the WHI Observational Study participants by quintile of total magnesium intake¹

	<206.5 mg	206.5–270.2 mg	270.3–333.7 mg	333.8–422.4 mg	≥422.5 mg	<i>P</i>
Age [<i>n</i> (Ann %)]						<0.001
50–59 y	4923 (33.9)	4825 (32.7)	4848 (32.6)	4737 (31.6)	4987 (33.5)	
60–69 y	6191 (42.6)	6400 (43.3)	6441 (43.4)	6656 (44.4)	6592 (44.3)	
70–79 y	3426 (23.6)	3544 (24.0)	3560 (24.0)	3607 (24.0)	3294 (22.1)	
Race-ethnicity [<i>n</i> (Ann %)]						<0.001
White	10,877 (74.8)	12,419 (84.1)	12,999 (87.5)	13,464 (89.8)	13,326 (89.6)	
Black	1888 (13.0)	1074 (7.3)	802 (5.4)	668 (4.5)	601 (4.0)	
Hispanic	821 (5.6)	577 (3.9)	425 (2.9)	360 (2.4)	344 (2.3)	
American Indian	82 (0.6)	61 (0.4)	47 (0.3)	34 (0.2)	49 (0.3)	
Asian/Pacific Islander	630 (4.3)	447 (3.0)	410 (2.8)	319 (2.1)	356 (2.4)	
Unknown	242 (1.7)	191 (1.3)	166 (1.1)	155 (1.0)	197 (1.3)	
Parental history of fracture [<i>n</i> (Ann %)]	5353 (36.8)	5772 (39.1)	5890 (39.7)	6186 (41.2)	6184 (41.6)	<0.001
Fracture at ≥55 y of age [<i>n</i> (Ann %)]	1919 (13.2)	2170 (14.7)	2156 (14.5)	2223 (14.8)	2299 (15.5)	<0.001
BMI [<i>n</i> (Ann %)]						<0.001
<25 kg/m ²	5545 (38.1)	6102 (41.3)	6268 (42.2)	6359 (42.4)	6483 (43.6)	
≥25 kg/m ²	8995 (61.9)	8667 (58.7)	8581 (57.8)	8641 (57.6)	8390 (56.4)	
History of MI or angina [<i>n</i> (Ann %)]	1076 (7.4)	1018 (6.9)	888 (6.0)	943 (6.3)	928 (6.2)	<0.001
Treated diabetes [<i>n</i> (Ann %)]	699 (4.8)	599 (4.1)	528 (3.6)	542 (3.6)	486 (3.3)	<0.001
Self-reported health [<i>n</i> (Ann %)]						<0.001
Excellent	2260 (15.5)	2719 (18.4)	2875 (19.4)	2906 (19.4)	3017 (20.3)	
Very good	5537 (38.1)	5975 (40.5)	6294 (42.4)	6482 (43.2)	6385 (42.9)	
Good	4993 (34.3)	4765 (32.3)	4504 (30.3)	4475 (29.8)	4370 (29.4)	
Fair/poor	1750 (12.0)	1310 (8.9)	1176 (7.9)	1137 (7.6)	1101 (7.4)	
HT use [<i>n</i> (Ann %)]						<0.001
Never/past user	9704 (66.7)	9494 (64.3)	9474 (63.8)	9522 (63.5)	9403 (63.2)	
<5 y	1748 (12.0)	1925 (13.0)	1945 (13.1)	1897 (12.6)	1974 (13.3)	
5 to <10 y	1262 (8.7)	1359 (9.2)	1471 (9.9)	1533 (10.2)	1516 (10.2)	
10 to <15 y	776 (5.3)	885 (6.0)	880 (5.9)	967 (6.4)	929 (6.2)	
≥15 y	1050 (7.2)	1106 (7.5)	1079 (7.3)	1081 (7.2)	1051 (7.1)	
Thiazide use [<i>n</i> (Ann %)]						<0.001
Nonuser	13,689 (94.1)	13,983 (94.7)	14,059 (94.7)	14,249 (95.0)	14,185 (95.4)	
<10 y	616 (4.2)	566 (3.8)	532 (3.6)	514 (3.4)	480 (3.2)	
≥10 y	235 (1.6)	220 (1.5)	258 (1.7)	236 (1.6)	208 (1.4)	
Current corticosteroid use [<i>n</i> (Ann %)]	208 (1.4)	207 (1.4)	184 (1.2)	187 (1.2)	181 (1.2)	0.380
Alcohol intake [<i>n</i> (Ann %)]						<0.001
Nondrinker	2088 (14.4)	1649 (11.2)	1556 (10.5)	1406 (9.4)	1350 (9.1)	
Past drinker	3026 (20.8)	2682 (18.2)	2503 (16.9)	2481 (16.5)	2722 (18.3)	
<1 drink/mo	1879 (12.9)	1825 (12.4)	1667 (11.2)	1566 (10.4)	1626 (10.9)	
<1 drink/wk	2922 (20.1)	2920 (19.8)	3034 (20.4)	3023 (20.2)	2999 (20.2)	
1 to <7 drinks/wk	3231 (22.2)	3872 (26.2)	4040 (27.2)	4269 (28.5)	4128 (27.8)	
≥7 drinks/wk	1394 (9.6)	1821 (12.3)	2049 (13.8)	2255 (15.0)	2048 (13.8)	
Smoking status [<i>n</i> (Ann %)]						<0.001
Never	7449 (51.2)	7571 (51.3)	7570 (51.0)	7649 (51.0)	7617 (51.2)	
Past	5758 (39.6)	6211 (42.1)	6477 (43.6)	6631 (44.2)	6719 (45.2)	
Current	1333 (9.2)	987 (6.7)	802 (5.4)	720 (4.8)	537 (3.6)	
Total daily calcium intake [<i>n</i> (Ann %)] ²						<0.001
<600 mg	8233 (56.6)	3331 (22.6)	1168 (7.9)	323 (2.2)	125 (0.8)	
600–1500 mg	5283 (36.3)	9325 (63.1)	10,029 (67.5)	8814 (58.8)	4879 (32.8)	
>1500 mg	1024 (7.0)	2113 (14.3)	3652 (24.6)	5863 (39.1)	9869 (66.4)	
Total daily vitamin D intake [<i>n</i> (Ann %)] ²						<0.001
<200 IU	11,303 (77.7)	7205 (48.8)	3898 (26.3)	1974 (13.2)	1460 (9.8)	
200–500 IU	2516 (17.3)	5253 (35.6)	5804 (39.1)	4778 (31.9)	3435 (23.1)	
>500 IU	721 (5.0)	2311 (15.6)	5147 (34.7)	8248 (55.0)	9978 (67.1)	
Physical activity [<i>n</i> (Ann %)]						<0.001
Inactive	2863 (19.7)	2146 (14.5)	1795 (12.1)	1558 (10.4)	1385 (9.3)	
<5 METs/wk	3460 (23.8)	2956 (20.0)	2759 (18.6)	2573 (17.2)	2191 (14.7)	
5–12 METs/wk	3349 (23.0)	3667 (24.8)	3592 (24.2)	3609 (24.1)	3339 (22.5)	
>12 METs/wk	4792 (33.0)	5918 (40.1)	6602 (44.5)	7155 (47.7)	7860 (52.8)	

(Continued)

TABLE 1 (Continued)

	<206.5 mg	206.5–270.2 mg	270.3–333.7 mg	333.8–422.4 mg	≥422.5 mg	<i>P</i>
Time spent walking [<i>n</i> (Ann %)]						<0.001
0 min/wk	7250 (49.9)	6289 (42.6)	5628 (37.9)	5385 (35.9)	4951 (33.3)	
>0–150 min/wk	5423 (37.3)	6237 (42.2)	6702 (45.1)	6989 (46.6)	6905 (46.4)	
>150 min/wk	1867 (12.8)	2243 (15.2)	2519 (17.0)	2626 (17.5)	3017 (20.3)	
Family income [<i>n</i> (Ann %)]						<0.001
<\$10,000	818 (5.6)	538 (3.6)	421 (2.8)	382 (2.5)	422 (2.8)	
\$10,000–\$19,999	1866 (12.8)	1515 (10.3)	1356 (9.1)	1357 (9.0)	1312 (8.8)	
\$20,000–\$34,999	3316 (22.8)	3234 (21.9)	3128 (21.1)	3155 (21.0)	3045 (20.5)	
\$35,000–\$49,999	2606 (17.9)	2762 (18.7)	2857 (19.2)	2900 (19.3)	2915 (19.6)	
\$50,000–\$74,999	2435 (16.7)	2760 (18.7)	2970 (20.0)	2946 (19.6)	3098 (20.8)	
≥\$75,000	2354 (16.2)	2906 (19.7)	3112 (21.0)	3166 (21.1)	3142 (21.1)	
US region [<i>n</i> (Ann %)]						<0.001
Northeast	3381 (23.3)	3573 (24.2)	3597 (24.2)	3574 (23.8)	3290 (22.1)	
South	4298 (29.6)	3816 (25.8)	3700 (24.9)	3559 (23.7)	3257 (21.9)	
Midwest	2877 (19.8)	3269 (22.1)	3444 (23.2)	3776 (25.2)	3376 (22.7)	
West	3984 (27.4)	4111 (27.8)	4108 (27.7)	4091 (27.3)	4950 (33.3)	

¹ All variables were assessed at the baseline screening visit. Magnesium values include the combined intake from food and supplements (range: 0.38–9274 mg/d; 99th percentile: 958 mg/d). *P* values were based on significant differences between all quintiles. Ann, annual; HT, hormone therapy; MET, metabolic equivalent task; MI, myocardial infarction; WHI, Women's Health Initiative.

² Calcium and vitamin D values include the combined intake from food and supplements.

Composition study, which showed a positive association of total body BMD with magnesium intake in white men and women (32), and cross-sectional data from the Framingham study, which showed higher BMD at the hip in postmenopausal women who consumed greater than two-thirds of the current RDA for magnesium (9). In addition, recent data from Nielsen et al (33) suggest that magnesium intake >237 mg/d is associated with higher total body BMD in postmenopausal women. As with the Framingham study, we showed no longitudinal association between magnesium intake and BMD in WHI women.

Lower magnesium intake was not associated with increased fracture risk at any site in our cohort. This finding was surprising in light of the evidence that magnesium stabilizes amorphous calcium phosphate and slows its transformation to hydroxyapatite (34), and with a greater magnesium content in bone, the hydroxyapatite crystal content decreases and forms smaller but sturdier crystals (35–38), which make bones stronger. The opposite situation of low magnesium and high hydroxyapatite has been more commonly shown in the trabecular bone of osteoporotic women (37).

Rates of lower-arm and wrist fractures in the WHI Observational Study cohort were 15% and 23% higher in women with the greatest magnesium intake (333.8–422.4 and >422.5 mg/d, respectively) than in women with the lowest magnesium intake. This result was most likely attributable to the greater physical activity and risk of falls in this group; however, it possible that regional differences in cortical compared with trabecular bone could also have been a contributing factor. The lower arm and wrist have a greater ratio of cortical to trabecular bone compared with other clinically pertinent sites, including the hip. Previous studies have shown that the magnesium content was normal or increased in cortical bone samples of postmenopausal women with osteoporosis (39–41); thus, increased intake could further increase the magnesium content in the already replete cortical bone-containing regions, which might possibly contribute to the regional susceptibility to a fracture. In addition, cortical bone may be more sensitive than trabecular bone to the diet. This hypothesis

is supported by observational research that suggested less loss of cortical bone, but not trabecular bone, from the tibia in elderly women who consumed a diet higher in several macronutrients and micronutrients, including magnesium (42).

The investigation into the relation of falls to magnesium consumption in WHI participants revealed a 15% increase in risk of ≥2 falls in the past year with magnesium intake >422.5 mg/d. This result may have been related to the increased physical activity in women in the highest quintile; however, it is biologically plausible that excess magnesium intake from supplements may increase fall risk related to hypotension, muscle weakness, and changes in deep-tendon reflexes associated with hypermagnesemia (43–45). Although possible, this seems an unlikely explanation because hypermagnesemia, which usually occurs in the presence of renal insufficiency plus excessive magnesium intake from dietary supplements or medications (46), would not be expected in such a large number of women (*n* = 5016 in quintile 5) in our sample. A more likely explanation is that falls might have been a surrogate marker of women who were more active and, therefore, had a higher potential to fall and fracture a wrist. Indeed, the highest quintile of magnesium intake also had the greatest percentage of women (52%) who were extremely physically active (>12 METs/wk) and the greatest percentage of women (20%) who walked ≥150 min/wk outside the home. Despite these findings, we showed no significant interaction between physical activity and magnesium intake by quintile for any of the 3 fracture variables. More physical activity has been associated with greater risk of wrist fractures that result from falls in other large cohorts of postmenopausal women (47, 48).

In a subgroup analysis, a significant interaction between the highest magnesium intake, lower-arm and wrist fracture, and age at screening was noted such that women <65 y old were more likely to have a wrist fracture if their magnesium intake was >422.5 mg/d. In contrast, results of the National Osteoporosis Risk Assessment trial showed that postmenopausal women <65 y old were less likely to sustain a wrist fracture than were women ≥65 y old (3.9% compared with 5.8%, respectively) (49).

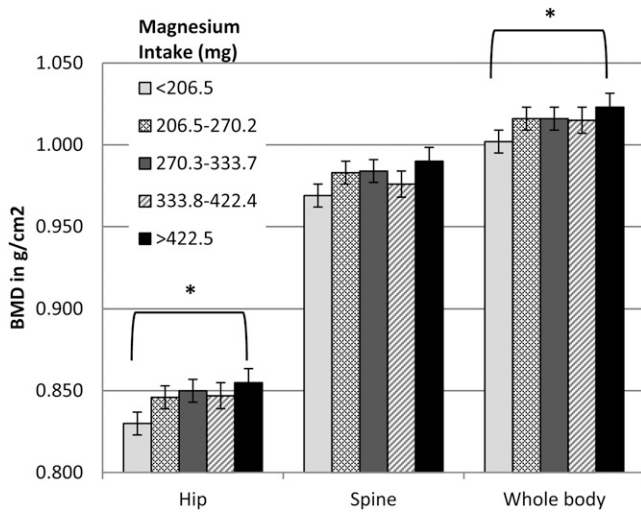


FIGURE 1. Least-squares means (\pm SDs) of BMD at specified sites on the basis of quintiles of magnesium intake. Values were adjusted for covariates (age, race-ethnicity, parental history of fracture, personal fracture at ≥ 55 y of age, BMI, history of coronary heart disease, treated diabetes, self-reported health, hormone therapy use, alcohol intake, total calcium intake, smoking, and physical activity). *Quintile 5 compared with quintile 1, $P < 0.001$ (tests for linear trend across quintiles). BMD, bone mineral density.

Because food sources of magnesium are frequently high in other nutrients that are beneficial to bone such as potassium and calcium, it is difficult to separate effects of individual nutrients. In the Framingham Heart Study, greater potassium plus magnesium

consumption significantly correlated with greater BMD of the radius (9). In this study, potassium, calcium, and vitamin D consumption did not modify the association of magnesium to fracture risk at any site. Women in the highest quintile of magnesium intake also consumed the highest amounts of calcium and vitamin D, which are nutrients known to benefit bone; this result lends support to the idea that increased falls and wrist fractures in this group may have been related to factors other than nutrient intake, such as lower body weight combined with increased physical activity.

One of the primary strengths of this study was the large sample of postmenopausal women in the WHI Observational Study cohort, which made it feasible to examine a biomarker of fracture risk, such as BMD, and actual fracture outcomes. In addition, hip fractures were confirmed by a medical record review, and the validity of self-reported fractures was high. The availability of data on important covariates associated with osteoporosis was also an advantage of this analysis.

This research was limited because of the observational nature of the study, and results should only be generalized to healthy, postmenopausal women. The measurement error associated with a self-report was also a limitation, although the reliability of several self-reported variables, including physical activity, has been shown to be high in the WHI (50). Food intake was obtained from one administration of a baseline FFQ. The FFQ has been shown to correlate highly with food recalls and intake records in this study population, but no biological markers of nutrient intake, including magnesium, were available to confirm self-reported food intake. Dietary magnesium is also highly correlated with other

TABLE 2
HRs for fracture and falls on the basis of total magnesium intake¹

Outcome and magnesium intake	n (Ann %)	Age adjusted		Fully adjusted	
		HR (95% CI)	P	HR (95% CI)	P
Hip fracture			0.162		0.563
<206.5 mg	169 (0.15)	1.00		1.00	
206.5–270.2 mg	198 (0.18)	1.12 (0.91, 1.37)		1.11 (0.90, 1.36)	
270.3–333.7 mg	156 (0.14)	0.88 (0.71, 1.09)		0.90 (0.71, 1.12)	
333.8–422.4 mg	157 (0.14)	0.87 (0.70, 1.09)		0.90 (0.71, 1.14)	
≥ 422.5 mg	164 (0.15)	0.96 (0.78, 1.19)		1.04 (0.81, 1.34)	
Lower-arm and wrist fractures			<0.001		0.002
<206.5 mg	436 (0.40)	1.00		1.00	
206.5–270.2 mg	494 (0.45)	1.10 (0.97, 1.25)		1.06 (0.93, 1.20)	
270.3–333.7 mg	517 (0.46)	1.14 (1.01, 1.30)		1.09 (0.95, 1.24)	
333.8–422.4 mg	555 (0.49)	1.22 (1.07, 1.38)		1.15 (1.01, 1.32)	
≥ 422.5 mg	588 (0.53)	1.32 (1.17, 1.49)		1.23 (1.07, 1.42)	
Total fractures			0.027		>0.999
<206.5 mg	2145 (4.57)	1.00		1.00	
206.5–270.2 mg	2318 (4.67)	1.05 (0.99, 1.12)		1.02 (0.96, 1.08)	
270.3–333.7 mg	2329 (4.81)	1.05 (0.99, 1.11)		1.01 (0.95, 1.07)	
333.8–422.4 mg	2351 (5.14)	1.05 (0.99, 1.11)		1.00 (0.94, 1.06)	
≥ 422.5 mg	2367 (5.37)	1.08 (1.02, 1.14)		1.01 (0.95, 1.08)	
Falls (≥ 2 in past year)			<0.001		<0.001
<206.5 mg	4277 (4.57)	1.00		1.00	
206.5–270.2 mg	4481 (4.69)	1.02 (0.98, 1.07)		1.01 (0.97, 1.06)	
270.3–333.7 mg	4604 (4.81)	1.05 (1.01, 1.10)		1.04 (1.00, 1.09)	
333.8–422.4 mg	4903 (5.14)	1.12 (1.08, 1.17)		1.11 (1.06, 1.16)	
≥ 422.5 mg	5016 (5.37)	1.18 (1.14, 1.23)		1.15 (1.10, 1.20)	

¹Fully adjusted model included the following covariates: age, race-ethnicity, parental history of fracture, fracture at ≥ 55 y of age, BMI, history of coronary heart disease, treated diabetes, self-reported health, hormone therapy use, alcohol intake, total calcium intake, current and past smoking, and physical activity. HRs (95% CIs) were obtained from Cox proportional hazard models. P values are from tests for linear trend. Magnesium values include the combined intake from food and supplements. Ann, annual.

nutrients including potassium and calcium, which may act independently to modify fracture risk. We attempted to address this relation by including calcium intake in our models and testing for an interaction between magnesium, calcium, vitamin D, potassium, and fracture. In addition, this study could not entirely account for previous magnesium intake or stores. Additional research is required to better define adequate compared with excess magnesium intake and its impact on osteoporosis and fracture.

In conclusion, in this large prospective cohort study of postmenopausal women, lower baseline BMD of the total hip and whole body were noted in participants with lower daily magnesium intake. However, lower magnesium intake was not associated with greater risk of hip fracture or total fractures. Magnesium consumption slightly greater than the RDA was correlated with increased falls and increased lower-arm and wrist fractures, which were possibly related to more physical activity in this group of women.

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