JOURNAL OF BONE AND MINERAL RESEARCH
Volume 19, Number 2, 2004
Published online on December 16, 2003; doi: 10.1359/JBMR.0301225

Dietary Silicon Intake Is Positively Associated With Bone Mineral Density in Men and Premenopausal Women of the Framingham Offspring Cohort

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ABSTRACT: The role of dietary silicon in bone health in humans is not known. In a cross-sectional, population-based study (2847 participants), associations between dietary silicon intake and BMD were investigated. Dietary silicon correlated positively and significantly with BMD at all hip sites in men and premenopausal women, but not in postmenopausal women, suggesting that increased silicon intake is associated with increased cortical BMD in these populations.

Introduction: Osteoporosis is a burgeoning health and economic issue. Agents that promote bone formation are widely sought. Animal and cellular data suggest that the orthosilicate anion (i.e., dietary silicon) is involved in bone formation. The intake of silicon (Si, ~30 mg/day) is among the highest for trace elements in humans, but its contribution to bone health is not known.
Materials and Methods: In a cross-sectional, population-based study, we examined the association between silicon intake and bone mineral density (BMD) in 1251 men and 1596 pre- and postmenopausal women in the Framingham Offspring cohort (age, 30–87 years) at four hip sites and lumbar spine, adjusting for all potential confounding factors known to influence BMD and nutrient intake.
Results: Silicon intake correlated positively with adjusted BMD at four hip sites in men and premenopausal women, but not in postmenopausal women. No significant association was observed at the lumbar spine in any group. Categorical analysis by Si intake, or energy-adjusted Si intake, supported these findings, and showed large differences in BMD (up to 10%) between the highest (>40 mg Si/day) and lowest (<14 mg Si/day) quintiles of silicon intake. A significant association at the lumbar spine in men was also observed. Further analyses indicated that some of the effects seen for moderate consumption of alcoholic beverages on BMD might be attributed to Si intake.
Conclusions: These findings suggest that higher dietary silicon intake in men and younger women may have salutary effects on skeletal health, especially cortical bone health, that has not been previously recognized. Confirmation of these results is being sought in a longitudinal study and by assessment of the influence of silicon intake on bone markers in this cohort.
J Bone Miner Res 2004;19:297–307. Published online on December 16, 2003; doi: 10.1359/JBMR.0301225

Key words: silicon, bone mineral density, bone formation, dietary intake, beer

INTRODUCTION

SILICON, AS THE soluble silicate anion [orthosilicic acid; $Si(OH)_4 \Leftrightarrow Si(OH)_3O^-$] has been implicated as important in bone formation in both animal and cellular models.[1–4] In 1972, Carlisle[2] and, Schwarz and Milne[3] showed in independent animal studies that silicon deficiency had profound negative influences on skeletal development. The development of both extracellular matrix (collagen) and bone mineral (hydroxy-apatite) was suboptimal with silicon depletion.[2,3] Although silicate transporters have been identified in lower organisms with high silicon requirements,[5] as have silicate responsive and controlling proteins,[6,7] considerably less is known about this ion in

*Preliminary results from this study were presented at the 23rd Annual Meeting of the American Society for Bone and Mineral Research in Phoenix, Arizona, October 12–16, 2001, and an abstract was published (Tucker KL, Kiel DP, Powell JJ, Qiao N, Hannan MT, Jugdaohsingh R 2001 Dietary silicon and bone mineral density: The Framingham Study. J Bone Miner Res **16:**S1;S510). The final data of this manuscript were presented at the International Bone Mineral Society meeting in Osaka, Japan, June 3–7, 2003, and an abstract was also published (Jugdaohsingh R, Tucker KL, Kiel DP, Qiao N, Powell, JJ 2003 Silicon intake is a major dietary determinant of bone mineral density in men and pre-menopausal women of the Framingham Offspring cohort. Bone **32:**S192).

The authors have no conflict of interest.

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mammalian species, especially in humans. In particular, the complexities of aqueous silicate chemistry and silicon analysis have inhibited detailed mechanistic studies with physiological levels of silicon. Nonetheless, low levels of orthosilicic acid, at typical plasma concentrations after ingestion of silicon-containing foods, stimulate human osteoblasts and osteoblast-like cells to secrete type I collagen and other markers involved in bone cell maturation and bone formation.[4] Soluble silicate may stabilize aqueous hydroxy-radical species,[8] and some have suggested silicate involvement in the radical-dependent prolyl-hydroxylase pathway[9] during type I collagen formation. Others have suggested a structural role in the cross-linking and stabilization of collagen and glycoaminoglycans.[10] Further studies are required at the molecular and mechanistic level, but the finding that orthosilicic acid stimulates human osteoblasts is important and consistent with the few small studies in human subjects[11,12] and the numerous studies in animals.[1–3]

The average daily dietary intake of silicon in the Western world is about 20–50 mg/day, although it is lower in women (24 ± 12 mg/day at the age of 26–39 years) than men (37 ± 23 mg/day at the age of 26–39 years), and decreases with age (~0.1 mg lower for each year after 26–39 years of age).[13,14] Recently, we demonstrated that common silicon-rich foods effectively deliver bioavailable silicon after their ingestion by human volunteers.[13] Phytolithic (plant-based) silicates seem to undergo hydrolysis, forming orthosilicic acid, in the gastrointestinal tract, because soluble orthosilicic acid, but not polysilicate, is well absorbed in human subjects.[15] Major sources of dietary Si in the Western world are cereals/grains and their products (e.g., breakfast cereals, bread, beer), some fruits and vegetables (e.g., bananas, raisins, beans, lentils), and unfiltered drinking water.[13] It seems likely that food preparation in the Western world has reduced our silicon exposure in recent times,[16] especially due to the treatment of drinking water, the processing of cereals, and possibly the hydroponic growth of vegetables.[17] As for all nutrients, however, individual dietary habits mostly dictate our exposure to silicon.

We showed recently that the silicon content of foods is a proxy for silicon absorption in human subjects,[13] so the aims of this study were, first, to determine the relationship between dietary Si intake and bone mineral density (BMD) (adjusting for all potential confounders known to affect BMD and nutrient intake, with and without the inclusion of alcohol intake) and to assess whether the relationship holds across different bone sites, gender, and menopausal status. We also examined the association between sex-specific quintiles of Si intake and BMD to investigate the possibility of nonlinear relationships. Second, we determined whether or not the positive relation between the moderate ingestion of alcoholic beverages and BMD, observed in this cohort, could be explained by Si intake. We hypothesized that there would be a positive association between silicon intake and BMD.

MATERIALS AND METHODS

Study population

Subjects in this study were participants in the Framingham Osteoporosis Study, drawn from the Framingham Offspring cohort. The original population-based Framingham Heart Study was initiated in 1948 to examine the risk factors for heart disease.[18] The Original cohort constituted a two-thirds sampling of the households in Framingham, MA.[18] The Offspring cohort was established in 1971 and consists of the children (and their spouses) of the Original cohort members. Members return every 4 years for a physical examination and to complete a series of questionnaires and tests. In the fifth (1991–1995) and sixth (1995–1999) study visits (or examination cycles), there were 3799 participants (1605 men and 1813 women, 30–87 years of age), of which 1251 men and 1596 women had completed two semiquantitative food frequency questionnaires (FFQ) and had BMD measurements performed between 1996 and 2001. All participants with dietary intake data and BMD measurement were included in this study; otherwise, there were no exclusion criteria (i.e., for bone diseases, other diseases, women with premature menopause or bilateral ovariectomy, or subjects on treatments for bone diseases or other diseases). The study was approved by the Institutional Review Board for Human Research at Boston University (Boston, MA, USA) and the Hebrew Rehabilitation Center for Aged (Boston, MA, USA). Written informed consent was obtained from all participants.

Dietary intake

Dietary silicon intake and major food contributors to Si intake in this population have been previously described by the authors.[13] Usual dietary intake, in the Offspring cohort, was assessed using the Willett semiquantitative 126-item FFQ.[19] This questionnaire has been validated for many nutrients and in several populations.[19] Before the fifth (1991–1995) and sixth (1995–1999) study visits, questionnaires were mailed to the subjects, who were asked to complete them based on their pattern of intake over the previous year and to bring them to their appointments (visits). A completed FFQ was available from both study visits. The average intake from the two questionnaires was used. Completed questionnaires were excluded, as previously reported,[13,20] if calculated energy intakes were below 2.51 MJ/day, above 16.74 MJ/day for women and 17.57 MJ/day for men, or if more than 12 food items were left blank. Processing of the forms to obtain total daily energy intakes and food intake was carried out at Harvard University (Boston, MA, USA).

Silicon intake

Silicon values per 100 g edible portion of each of the 278 food items in the FFQ were obtained from a previous review by Pennington.[14] The Si contents of composite foods were calculated from the individual components of the food. However, where values for reported Si levels of foods varied between laboratories by 3-fold or more, additional analyses were made independently by the authors (King's College London), and with the exception of liquor (0.13 ±

0.04 mg/100 g; range, 0.06–0.21 mg/100 g), beer (2.06 ± 0.70 mg/100 g; range, 0.96–3.94 mg/100 g), and orange juice (0.01 ± 0.01 mg/100 g; range, 0.0004–0.25 mg/100 g), our data correlated highly ($r = 0.82$; $n = 28$) with those of Varo (extensively cited by Pennington[14]). Therefore, as reported previously,[13] we chiefly used the values of Varo with our values for orange juice, beer, and liquor, in the database. These values (mg Si/100 g food) were entered into a database program in the Dietary Assessment and Epidemiology Research Program at Tufts University (Boston, MA, USA) and corrected for the weight of each food item reported for each individual participant. Because the Si content of foods was recorded on a dry weight basis, levels of Si in brown rice, white rice, and pasta were corrected by 0.30, 0.39, and 0.30, respectively, based on United States Department of Agriculture (USDA) published (raw to cooked) conversions.[21] The values (mg Si) for each food item were summed to obtain total Si intake per person per day in each of two study visits (1991–1995 and 1995–1999). The average silicon intake (mg/day) from the two visits was used for each subject.

Intake of alcoholic beverages

Intake (servings per day, per week, or per month) of beer, wine, and liquor were averaged from the two FFQs from the 1991–1995 and 1995–1999 study visits. One serving of beer represented one 356-ml glass, bottle, or can, while one serving of wine (red or white) represented one 4-oz glass (118 ml), and one serving of liquor represented one drink or "shot" (42 ml).

BMD measurements

BMD was measured between 1996 and 2001, during the course of the sixth and seventh examination cycles, using DXA (Lunar DPX-L; Lunar Radiation Corp, Madison, WI, USA). BMD was measured at the left hip (total hip, trochanter, Ward's area, and femoral neck) and at the lumbar spine (L_2–L_4). The precision (CV) was 1.7% at the femoral neck, 2.5% at the trochanter, and 0.9% at the spine.

Confounding factors

Potentially confounding variables, known to influence BMD and nutrient intake that are routinely used in this type of study, measured at the time of bone density measurements (in the sixth examination cycle [1995–1999]), were obtained for each participant, along with overall medical history. Potential confounding factor(s) that may influence Si intake are still not clear, although the usual adjustments were made for energy and potentially colinear nutrients. Age (years), height in inches (converted to meters), and weight in pounds (converted to kilograms) were measured, and body mass index (BMI) was calculated (kg/m^2). BMI (relative weight considering height) and height were included in the statistical models, instead of weight and height, which generally are too highly correlated (colinear) for appropriate inclusion in the same model.[22] Results in this study differed negligibly using either of these combinations. Physical activity was examined using the Physical Activity Scale for the Elderly (PASE) questionnaire.[23] Use of calcium (mg) and/or vitamin D supplements (IU) was obtained from the supplement section of the FFQ. Estrogen use in women was defined as those currently receiving estrogen therapy at the time of BMD measurements, with continuous use for ≥1 year.[24] Information on the use of other osteoporosis medication (e.g., bisphosphonates, selective estrogen receptor modulators, calcitonin) was obtained during the course of the bone density measurements (1996–2001). Other drugs that may affect BMD (corticosteroids, thyroxine) were not included in the models. Total energy intake in calories (converted to Joules), total protein intake (g), dietary calcium intake (mg), dietary vitamin D intake (IU), magnesium (mg) and potassium intake (mg), and intake of alcohol (see above) were averaged from the two FFQs from the 1991–1995 and 1995–1999 study visits. Smoking status (current, past, or nonsmoker) was obtained at 1995–1999 study visit. Finally, to control for potential seasonal effects on BMD measures, a categorical variable for time of BMD measurement was created.[20] July, August, and September were coded as summer; October, November, and December as fall; January, February, and March as winter; and April, May, and June as spring.

Statistical analysis

All analyses were conducted separately for men and pre- and postmenopausal women and were performed with PC SAS for Windows (version 8.1; SAS Institute Inc., Cary, NC, USA). We initially investigated the association between silicon intake and BMD (at the four hip sites and lumbar spine) using Si as a continuous variable in the general linear models. Because the distribution of silicon intake was found to be skewed, the data were transformed by natural logarithm (*ln*). Measures of BMD at the hip sites and lumbar spine were regressed on the *ln* value of the average silicon intake from the two exams. Adjustment was made for potential confounders known to influence BMD and nutrient intake, namely age, height, BMI, physical activity score, smoking status, calcium intake (dietary and supplement use), vitamin D intake (dietary and supplement use), estrogen use (in women), use of other osteoporosis medication, season of BMD measurement, energy intake, protein intake, magnesium and potassium intakes, and with and without the inclusion of total alcohol intake. Because beer is a major source of Si and alcohol intake has been previously associated with BMD in the original Framingham cohort,[25] analyses were repeated with the adjustment for alcohol based on non-beer alcohol. Non-beer alcohol was defined as all alcoholic beverages other than those classed as beer (i.e., wine and liquor).

A number of dietary components do not adhere to linear relationships, such as alcohol (hyperbolic)[25] and many nutrients (threshold),[26] so in addition to treating silicon intake as a continuous variable, and to avoid assumption of linearity between intake and BMD measures, sex-specific quintiles of silicon intake were created, and adjusted BMD means (including adjustment for alcohol based on non-beer alcohol) were compared across these categories. To confirm that these associations were caused by Si and not a factor colinear with Si or because of inadequate adjustment of a confounder, we investigated by Pearson correlations poten-

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION WITH BMD MEASURES*

	Premenopausal women	*Men*	*Postmenopausal women*
n	306	1295	1325
Age (year)	47.0 ± 4.7	59.4 ± 9.6	61.4 ± 8.3
Height (m)	1.64 ± 6.0	1.75 ± 6.69	1.60 ± 6.23
Weight (kg)	72.5 ± 16.7	87.2 ± 15.5	70.4 ± 14.9
BMI (kg/m^2)	26.9 ± 6.0	28.7 ± 4.4	27.4 ± 5.5
PASE	163.9 ± 76.3	155.9 ± 86.8	127.8 ± 68.6
Smoker (%)			
Past smoker	14.4	13.0	14.1
Current smoker	51.3	67.0	53.8
Alcohol use (%)			
Beer	37.3	65.9	23.5
Wine	72.8	58.6	63.0
Liquor	40.6	52.6	38.9
Energy intake (MJ)	7.56 ± 2.24	8.23 ± 2.40	7.25 ± 2.21
Protein (g/day)	79.8 ± 25.8	79.4 ± 24.8	75.0 ± 23.7
Silicon intake (mg/day)	23.8 ± 8.3	27.5 ± 10.7	23.6 ± 8.9
Calcium intake			
Dietary (mg/day)	786.5 ± 318.6	758.4 ± 338.3	735.4 ± 324.9
Supplement use (%)	18.30	4.56	34.87
Vitamin D intake			
Dietary (IU)	207.0 ± 105.0	218.9 ± 122.3	213.7 ± 121.2
Supplement use (%)	0.98	1.16	3.92
Estrogen use (%)	—	—	34.0
Osteoporosis medication (%)†	0.33	0.16	4.44
BMD (g/cm^2)			
Total hip	1.003 ± 0.139	1.049 ± 0.146	0.898 ± 0.145
Femoral neck	0.963 ± 0.137	0.979 ± 0.139	0.854 ± 0.136
Trochanter	0.782 ± 0.132	0.891 ± 0.141	0.705 ± 0.133
Ward's area	0.846 ± 0.157	0.786 ± 0.159	0.703 ± 0.162
Lumbar spine	1.258 ± 0.166	1.329 ± 0.208	1.136 ± 0.202

* Means ± SD.

† Bisphosphonates (FOSAMAX and DIDRONEL), selective estrogen receptor modulator (EVISTA), and calcitonin (CALC-SPR).

tial colinearity between silicon intake and a number of physical and dietary variables, namely age, height, weight, BMI, physical activity score, estrogen use in women, smoking status, total energy intake, protein intake, total alcohol intake, non-beer alcohol intake, and beer intake. The analyses between sex-specific quintiles of silicon intake and adjusted BMD were repeated for energy-adjusted silicon intake, computed using the residual method, as described by Willett.[27]

Finally, associations between BMD and beer intake, and BMD and non-beer alcohol intake, were assessed in the general linear models with all the adjustments above (including intake of other alcoholic beverages), with and without adjustment for silicon intake.

Results are expressed as mean ± SE, unless otherwise stated. Multiple linear regression (equivalently, analysis of covariance) was used to calculate adjusted least-squares means for BMD at each bone site according to sex-specific quintiles of silicon intake. The *p* value for a test for trend in increasing BMD with increasing quintile of silicon intake was also obtained from multivariable linear regression models. Adjusted least-squares means were also compared between quintiles using post hoc *t*-tests. All analyses were conducted separately for pre- and postmenopausal women and men using the GLM procedure in SAS.

RESULTS

Study population

Characteristics of men and pre- and postmenopausal women in the study sample are shown in Table 1. There were 306 premenopausal women, 1295 men, and 1325 postmenopausal women in the study sample. Premenopausal women had the lowest mean age and BMI of the three groups and the highest physical activity score. Postmenopausal women had the lowest mean weight, height, and physical activity score. A higher percentage of men (66%) were beer drinkers (i.e., drank some beer) compared with pre- (37%) and postmenopausal (24%) women, and this was reflected in their mean silicon intakes (see below). For all groups, 39–53% drank some liquor, and 59–73% drank some wine. Energy intake was highest in men and lowest in postmenopausal women. Protein intake was similar in the three groups (Table 1). Silicon intake and major sources of intake in this cohort are shown in Tables 1 and 2, respectively, and are similar to those reported in the same cohort at just one examination (1991–1995).[13] Calcium and vitamin D supplement use was highest in postmenopausal women (35% and 4%, respectively), and this group had the highest estrogen use (34%) as well as other osteo-

Table 2. Top 10 Contributing Foods to Total Silicon Intakes in the Study Population*

	Premenopausal women		*Men*		*Postmenopausal women*	
Rank	*Food source*	*Contribution (%)*	*Food source*	*Contribution (%)*	*Food source*	*Contribution (%)*
1	Bananas	9.53 ± 8.63	Bananas	11.36 ± 10.53	Bananas	12.87 ± 10.37
2	Brown rice	4.85 ± 7.19	Beer	10.27 ± 15.90	Cold cereal	5.23 ± 6.92
3	Muffins/bagels	4.47 ± 3.92	Cold cereal	5.25 ± 7.66	String beans	4.72 ± 4.03
4	White bread	4.33 ± 4.88	White bread	5.06 ± 5.49	White bread	4.61 ± 5.50
5	Cold cereal	4.20 ± 4.45	Beans/lentils	3.93 ± 3.97	Beans/lentils	4.22 ± 4.53
6	String beans	3.95 ± 3.28	Coffee	3.58 ± 3.32	Dark bread	3.94 ± 4.55
7	Beans/lentils	3.95 ± 4.96	Pizza	3.46 ± 3.39	Muffins/bagels	3.92 ± 3.79
8	Pasta	3.75 ± 2.07	Dark bread	3.35 ± 4.35	Potatoes	3.33 ± 2.41
9	Pizza	3.73 ± 2.89	String beans	3.33 ± 2.89	Coffee	3.28 ± 3.36
10	Coffee	3.61 ± 3.60	Muffins/bagels	3.22 ± 3.47	Brown rice	3.12 ± 5.63

* Means ± SD.

porosis medications (4%). BMD, at all sites, was lowest in postmenopausal women.

Linear association between Si intake and BMD: effect of gender and menopause status

Silicon intake was positively associated with BMD at all hip sites for men and for premenopausal women, but not for postmenopausal women (Table 3), after adjusting for all potential confounders except the intake of alcohol. The mean ± SD difference in BMD at the four hip sites per *ln* unit difference in Si intake was 0.085 ± 0.010 g/cm^2 (or 9.6 ± 2.0%) for premenopausal women ($p \leq 0.04$), 0.040 ± 0.003 g/cm^2 (or 4.3 ± 0.4%) for men ($p \leq 0.05$), and −0.010 ± 0.007 g/cm^2 (or −1.3 ± 0.9%) for postmenopausal women ($p \geq 0.23$). There was no significant association between Si intake and BMD of the lumbar spine in any group (Table 3). The β coefficients were largely unchanged after additional adjustments for the intake of beer and/or non-beer alcohol, although significance was sometimes weaker with these additional adjustments (Table 3).

Quintiles of Si intake and BMD

To investigate the possibility of nonlinear relationships and threshold effects, we also examined BMD across sex-specific quintiles of Si intake. The groupings (quintiles) revealed silicon intakes (per day) of 7.1–16.7, 16.7–20.7, 20.7–24.6, 24.6–30.2, and 30.2–63.2 mg for premenopausal women, 7.6–18.8, 18.8–23.9, 23.9–28.5, 28.5–34.4, and 34.4–118.0 mg for men, and 5.9–16.4, 16.4–20.4, 20.4–24.1, 24.1–29.9, and 29.9–83.5 mg for postmenopausal women (Fig. 1). The majority of silicon intakes were within a relatively narrow range (23.6 ± 8.9 mg/day for women and 27.5 ± 10.7 mg/day for men), and along with the corresponding BMDs, were especially similar in the middle three quintiles (Fig. 1). Again, however, even when BMD was adjusted for all potential confounders including the intake of alcohol, significant positive associations were seen between sex-specific quintiles of silicon intake and BMD for premenopausal women and men, but not for postmenopausal women (Fig. 1). We observed a more marked association between Si intake and adjusted BMD for premenopausal women than for men (Fig. 1). However, because of the large differences in numbers ($n = 306$ and 1295 for premenopausal women and men, respectively), this was not always reflected in the significance levels.

Because nutritional effects are most marked and commonly reported between the lowest and highest percentiles of nutrient intake,[26] we investigated differences in BMD between those in the highest versus the lowest quintiles of Si intake. The results indicated marked significant differences in BMD at the hip sites for both premenopausal women (average, 9.9 ± 2.0%; $p \leq 0.02$, except Ward's area, $p = 0.07$) and men (5.1 ± 0.8%; $p \leq 0.03$), with little overlap between the groups (i.e., the highest and lowest quintiles; Fig. 1), but not for postmenopausal women (−0.15 ± 0.57%; $p \geq 0.7$). Similarly, differences in BMD between the highest and lowest quintiles were suggestive at the lumbar spine for premenopausal women (5.1%; $p = 0.16$) and men (4.5%; $p = 0.039$), but not for postmenopausal women (−0.41%; $p = 0.86$).

There was no correlation between silicon intake and any potentially confounding variable except total energy intake, protein intake, total alcohol, and beer, which were positively correlated as shown in Table 4; only energy intake had a correlation in the range of colinearity with silicon intake ($r = 0.67$ and 0.62 for women and men, respectively). As may be expected, energy and nutrient intakes commonly show some degree of colinearity, and energy-adjusted nutrient intakes may be used to correct for this.[20,26,27] Here we used the residual method to remove the variation in Si intake caused by greater energy intake. After adjustment, energy intakes did not significantly differ across sex-specific quintiles of Si intake, but adjusted BMD and energy-adjusted silicon intake remained positively associated for both premenopausal women and men (Fig. 2). Differences between the lowest and highest quintiles of energy-adjusted silicon intake were, however, reduced by about one-third compared with values for energy-unadjusted silicon intakes, whereas the middle three quintiles became more similar in magnitude to the first quintiles for both adjusted BMD and Si intakes (Fig. 1 versus Fig. 2).

Table 3. Linear Regression Analysis of Silicon Intake (Log-Transformed) and Adjusted BMD* at the Four Hip Sites and the Lumbar Spine With and Without Adjustment for Total Alcohol and Non-Beer Alcohol Intake

	BMD (g/cm^2)				
	Total hip	*Femoral neck*	*Trochanter*	*Ward's area*	*Lumbar spine*
Premenopausal women†					
Coefficient (SEM)	0.073 (0.035)	0.082 (0.036)	0.086 (0.032)	0.098 (0.043)	0.050 (0.046)‡
p	0.035	0.023	0.0083	0.022	0.273
Adjusted for total alcohol					
Coefficient (SEM)	0.071 (0.035)	0.075 (0.036)	0.086 (0.033)	0.096 (0.043)	0.046 (0.046)‡
p	0.044	0.039	0.0094	0.027	0.325
Adjusted for non-beer alcohol					
Coefficient (SEM)	0.074 (0.035)	0.082 (0.036)	0.086 (0.032)	0.098 (0.043)	0.050 (0.046)‡
p	0.035	0.022	0.0082	0.022	0.273
Men§					
Coefficient (SEM)	0.039 (0.017)	0.043 (0.016)	0.041 (0.017)	0.036 (0.019)	0.040 (0.020)¶
p	0.021	0.0074	0.013	0.052	0.121
Adjusted for total alcohol					
Coefficient (SEM)	0.032 (0.018)	0.040 (0.017)	0.030 (0.017)	0.038 (0.019)	0.031 (0.027)¶
p	0.065	0.018	0.083	0.053	0.246
Adjusted for non-beer alcohol					
Coefficient (SEM)	0.040 (0.017)	0.043 (0.016)	0.043 (0.017)	0.036 (0.019)	0.041 (0.026)¶
p	0.019	0.0073	0.010	0.055	0.113
Postmenopausal women**					
Coefficient (SEM)	−0.013 (0.016)	−0.0051 (0.016)	−0.0185 (0.015)	−0.0047 (0.020)	−0.013 (0.026)††
p	0.443	0.754	0.231	0.815	0.601
Adjusted for total alcohol					
Coefficient (SEM)	−0.015 (0.016)	−0.0076 (0.016)	−0.021 (0.015)	−0.007 (0.020)	−0.019 (0.026)††
p	0.360	0.642	0.172	0.729	0.463
Adjusted for non-beer alcohol					
Coefficient (SEM)	−0.010 (0.016)	−0.0027 (0.016)	−0.015 (0.015)	−0.002 (0.020)	−0.006 (0.026)††
p	0.547	0.870	0.312	0.918	0.803

* Adjusted for age, height, BMI, physical activity score, smoking status, calcium intake (diet and from supplement use), vitamin D intake (diet and supplement use), estrogen use (in women), use of other osteoporosis medications, season of BMD measurement, energy intake, protein intake, magnesium and potassium intakes, and alcohol intake as indicated.

† $N = 299$; ‡ $N = 300$; § $N = 1220$; ¶ $N = 1221$; ** $N = 1260$; †† $N = 1270$.

Alcohol intake and BMD

Similar regression coefficients between BMD and silicon intake were seen in drinkers and non-drinkers (whether beer, non-beer alcohol, or total alcohol; data not shown), confirming that the above model adequately adjusted for alcohol intakes. However, we also considered the reverse scenario, namely the possibility that silicon intake may affect the association between BMD and alcohol intake.[25,28] We investigated, using the simple linear model, whether adjustment for silicon intake would modulate the β coefficients when BMD was regressed on alcohol intake in men and premenopausal women. This analysis was not aimed at studying the effect of alcohol intake on BMD, which is nonlinear, but to see if adjustment using a global model for silicon would attenuate the β coefficient for BMD and beer (a high contributor to dietary silicon) but not for BMD and non-beer alcohol (a low contributor to dietary silicon). In men, adjustment for silicon intake reduced the positive association by $2.34 \pm 0.45 \times 10^{-4}$ g/cm^2 per serving (mean ± SD of the four hip sites) and negated the significance between beer intake and BMD, but had little effect on non-beer alcohol and BMD (increased by $0.32 \pm 0.06 \times 10^{-4}$ g/cm^2 per serving). Using this model, the association between intake of alcoholic beverages and BMD was not significant in premenopausal women; however, correcting for silicon intake attenuated the magnitude and/or direction of the β coefficients for BMD and beer (by $11.78 \pm 1.58 \times 10^{-4}$ g/cm^2 per serving; mean ± SD of the four hip sites) but had little effect on BMD and non-beer alcohol (increased by $1.15 \pm 0.15 \times 10^{-4}$ g/cm^2 per serving), again suggesting that the effect is either from Si or at least a component strongly colinear with silicon.

DISCUSSION

To our knowledge, this is the first population-based (cross-sectional) study to examine the specific association between dietary silicon intake and BMD in men and women. These findings indicate significant positive associations between silicon intake and BMD at the hip sites for men and premenopausal women, but not for postmenopausal women. No significant correlation was found at the lumbar spine except in men, and only then in one of the models used.

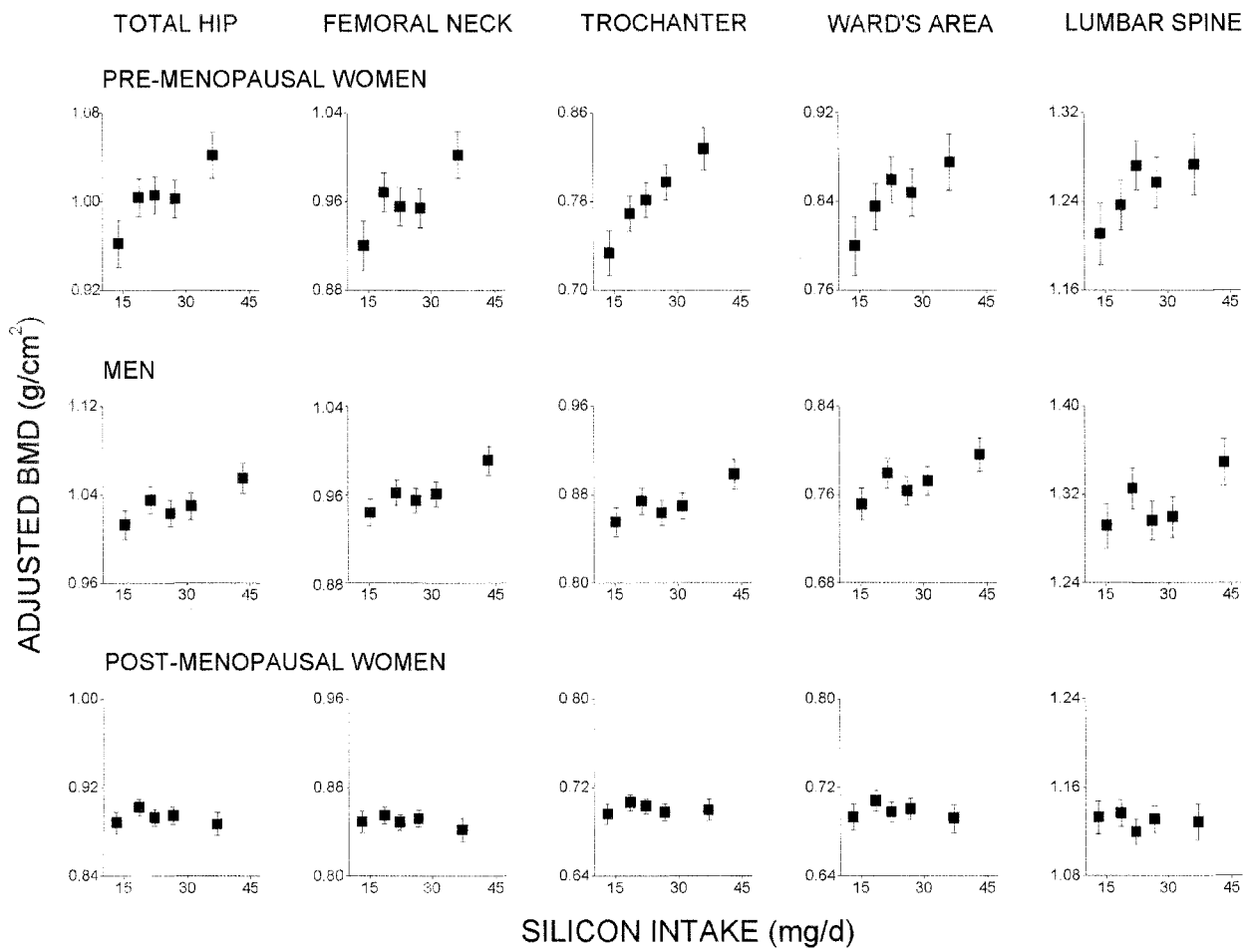

FIG. 1. Associations between silicon intake and mean ± SE adjusted BMD at the four hip sites and lumbar spine for premenopausal women, men, and postmenopausal women. BMD was adjusted for all known potential confounding factors known to influence BMD and nutrient intake, and alcohol, based on non-beer alcohol. Silicon intake is shown as quintiles, and the adjusted BMD is plotted against the mean silicon intake for each quintile. Test for linearity/trend across quintiles of silicon intake was significant at the total hip ($p = 0.04$) and trochanter ($p = 0.004$) for premenopausal women and at the all hip sites except Ward's area for men ($p = 0.04$, 0.01, and 0.03 for total hip, femoral neck, and trochanter, respectively). Difference in BMD between the lowest and highest quintile of silicon intake was also significant at all bone sites except for Ward's area and lumbar spine in premenopausal women ($p = 0.02$, 0.02, and 0.003 for total hip, femoral neck, and trochanter, respectively) and at all bone sites for men ($p = 0.02$, 0.007, 0.02, 0.03, and 0.04 for total hip, femoral neck, trochanter, Ward's area, and lumbar spine, respectively). Axes (x and y) are the same magnitude for ease of comparison between BMD sites and subject groups.

TABLE 4. CORRELATION COEFFICIENTS* BETWEEN SILICON INTAKE AND A NUMBER OF PHYSICAL AND DIETARY VARIABLES

	Age	*Height*	*Weight*	*BMI*	*Energy*	*Protein*	*Total alcohol*	*Beer alcohol*	*Non-beer alcohol*
Premenopausal women									
Coefficient	−0.102	0.023	0.006	−0.008	0.668	0.508	0.208	0.317	0.064
p	0.075	0.693	0.923	0.894	<0.0001	<0.0001	0.0003	<0.0001	0.263
Men									
Coefficient	−0.052	0.085	−0.0009	−0.040	0.619	0.491	0.362	0.460	0.099
p	0.069	0.003	0.975	0.154	<0.0001	<0.0001	<0.0001	<0.0001	0.0004
Postmenopausal women									
Coefficient	−0.0014	0.077	0.017	−0.017	0.753	0.661	0.083	0.227	0.030
p	0.961	0.006	0.545	0.539	<0.0001	<0.0001	0.003	<0.0001	0.281

* Pearson correlation coefficients.

The average difference in BMD between individuals with the lowest and highest quintile of silicon intake was 0.047–0.082 g/cm^2 (or 5.0–8.9%) in the femoral neck for men and premenopausal women. Other nutrients associated with increases in BMD of the femoral neck (e.g., calcium,[26,29,30] magnesium,[20,26] potassium,[20,26] and vitamins C[26] and

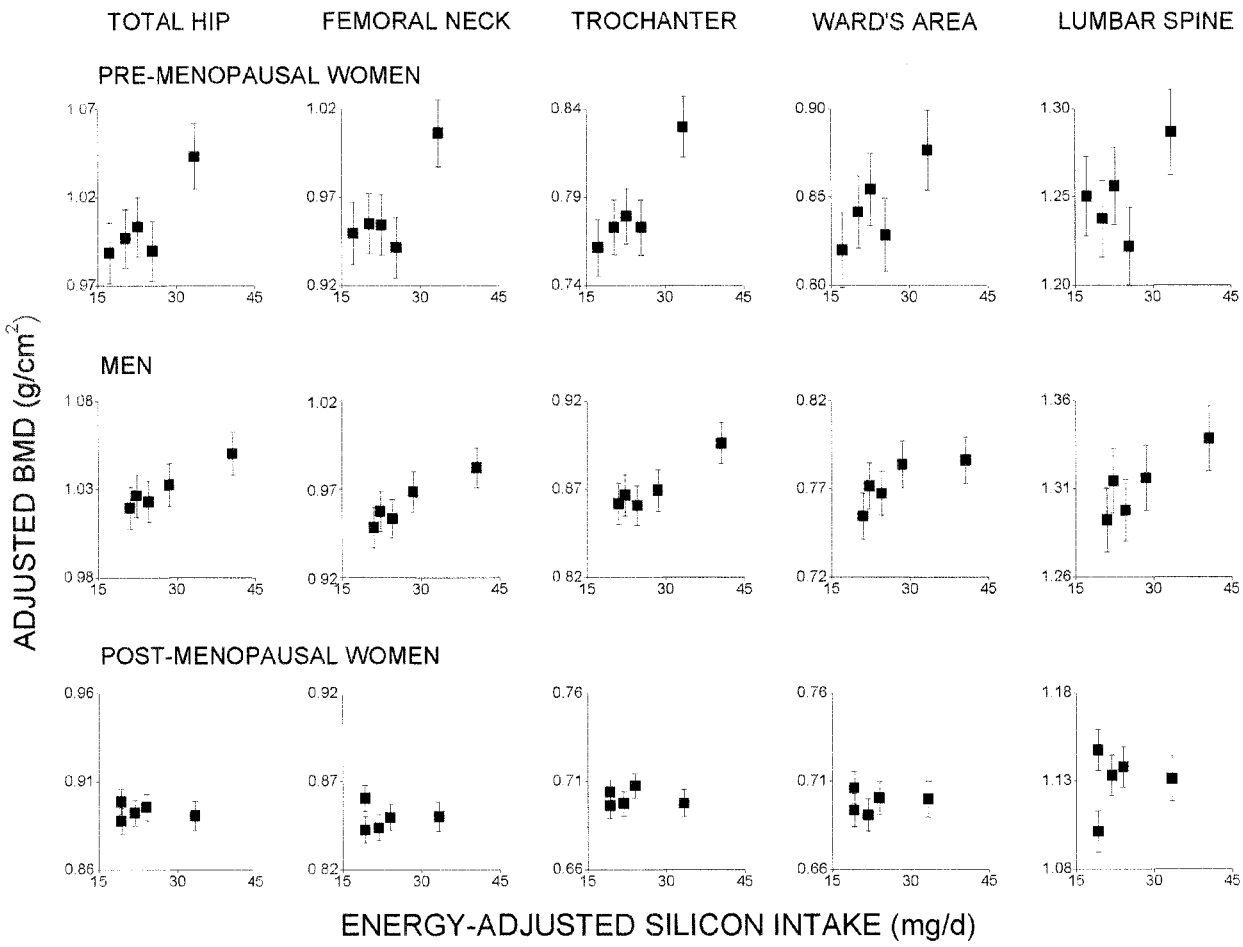

FIG. 2. Associations between energy-adjusted silicon intake and mean ± SE adjusted BMD at the four hip sites and lumbar spine for premenopausal women, men, and postmenopausal women. BMD was adjusted for all known potential confounding factors known to influence BMD and nutrient intake, and non-beer alcohol. Energy-adjusted silicon intake is shown as quintiles, and the adjusted BMD is plotted against the mean energy-adjusted silicon intake for each quintile. Test for linearity/trend across quintiles of energy-adjusted silicon intake was significant at all bone sites except Ward's area and lumbar spine for premenopausal women ($p = 0.04$, 0.03, and 0.004 for total hip, femoral neck, and trochanter, respectively) and at all bone sites except Ward's area for men ($p = 0.02$, 0.006, 0.004, and 0.04 for total hip, femoral neck, trochanter, and lumbar spine, respectively). Difference in BMD between the lowest and highest quintile of silicon intake was also significant at all bone sites except for Ward's area and lumbar spine in premenopausal women ($p = 0.03$, 0.03, and 0.003 for total hip, femoral neck, and trochanter, respectively) and at all bone sites for men ($p = 0.03$, 0.01, 0.01, 0.04, and 0.03 for total hip, femoral neck, trochanter, Ward's area, and lumbar spine, respectively). Axes (x and y) are the same magnitude for ease of comparison between BMD sites and subject groups.

K[31]) generally show maximum differences between the high and low nutrient intake groups of 0.025–0.04 g/cm^2, one-half that observed for silicon. Even controlling for total energy intake (Fig. 2), which correlated with Si intake, the effects of Si were at least comparable with those of other nutrients.

Because this is the first study of the associations between silicon intake and BMD, comparison of our results with others cannot readily be made. However, recent studies in cultured human osteoblasts[4] and in animal models[1–3] support the finding that Si promotes bone formation. Longitudinal analysis and correlation between dietary silicon intake and bone markers, which are to follow in this cohort, will address the consistency of these findings.

The striking difference in silicon effects between postmenopausal women and either men or premenopausal women may have a plausible, biological explanation. From a biological perspective, these and previous results[1–4] point toward the role of orthosilicic acid in bone formation but not in bone resorption. In postmenopausal women, BMD is driven by resorptive processes,[32,33] and silicon would be expected to have no role in ameliorating this effect. However, it is interesting that dietary Si had *no* effect on the BMD of postmenopausal women, suggesting that hormonal factors may overwhelm any nutrient effects on bone. It is possible that the bone-promoting effects of dietary silicon are attenuated postmenopausally. For example, in the postmenopausal state, circulating estradiol levels are markedly reduced,

and expression of estrogen receptors are downregulated in bone.[34,35] In contrast, in older men, there is little change in the expression of estrogen receptors in bone while aromatization of testosterone contributes to tissue exposure to estradiol.[34–36]

Estrogen receptors are potent transcription factors for a number of genes, and recently, certain transport and tissue-specific activities of zinc have been shown to be regulated by estrogen levels and expression of estrogen receptors.[37] Whether the same may be true for Si in bone remains to be determined, but it is of interest to note that the absorption and tissue distribution of silicon is reportedly affected by sex hormone levels.[38] Finally, it should be noted that pre- and postmenopausal dietary habits may differ, making past nutrient exposure difficult to gauge from current intakes rather than suggesting that earlier, premenopausal effects of dietary silicon on BMD are lost over time.

For many nutrients, intake and BMD do not correlate in a simple linear fashion.[26] As seen here for silicon, differences in BMD are often most clearly observed when comparing groups with high and low intakes of a specific nutrient or food group.[20,26] It is possible that silicon deficiency is more apparent in individuals in the lowest quintile of silicon intake, explaining a dramatically lower BMD compared with other quintiles. In contrast, those in the highest quintile of silicon intake could experience a promoting, rather than maintenance, effect of silicon on BMD. Indeed, in ovariectomized rats, a model mimicking the postmenopausal state, very high levels of dietary silicon completely abrogate bone mineral loss and increase bone mineral content (BMC).[1] Thus, whether pharmacologic levels of silicon can overcome the lack of responsiveness to dietary silicon in postmenopausal women needs to be established. Two previous pilot studies using organosilicon compounds suggests that this is possible.[11,12]

It is not known why the association between Si intake and lumbar spine BMD was much weaker compared with the hip sites, because cancellous (or trabecular) bone is often more affected by metabolic factors than cortical bone because of its higher rate of turnover. However, if the affect of silicon is anabolic (i.e., promoting bone formation rather than inhibiting resorption), one clue may be provided by recent work with parathyroid hormone, where, at least in mice, its anabolic action is significantly greater on cortical bone than it is on cancellous bone.[39] In support of this, a previous study in osteoporotic women reported a much larger increase in BMD at the hip compared with the spine after supplementation with a pharmacologic dose of Si, whereas in contrast, the other factors tested (etidronate, fluoride, and magnesium) affected the spine much more greatly than the hip, suggesting that Si may indeed preferentially affect cortical bone.[12] In addition, the lumbar spine is also the site of artifactual calcifications such as degenerative spine changes and vascular calcification, and these could mask and thus weaken the association between Si intake and BMD.[40,41]

This study sought a single a priori hypothesis in a large, well-described population. However, the limitations of this study are recognized. First, the data are cross-sectional; therefore, whereas a relation between Si intake and BMD is indicated, caution must be exercised when drawing conclusions about the influence of Si on bone health.[26] Second, BMD was adjusted for all potential confounders including energy intake, alcohol intake, and BMI, but we cannot rule out the possibility of some imperfect adjustment(s). Mean BMI was above 25 kg/m^2 in all three groups, so a proportion of the subjects were overweight (BMI $\sim$ 25–29.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2), and the influence of body weight on BMD is well established.[42–44] However, the use of energy-adjusted silicon intakes should additionally correct for this, while any confounding effects would have to explain the markedly different results between the three groups. Finally, some unmeasured factor may be responsible for the observed relationship between Si and BMD, although this would have to be highly colinear with Si intake. Overall, however, the positive relationship between dietary silicon and BMD in men and premenopausal women, the reproducibility of these effects across the different hip sites, and the consistency of these findings with other biological models suggest that dietary silicon may be important for bone health in men and premenopausal women. Confirmation of these findings is now required.

Finally, it is noteworthy that, in the Western world, one major potential source of bioavailable and bioactive silicon is from beer ingestion, at least for men (Table 2).[13,14] The positive effect of moderate alcohol consumption on BMD has been well reported and seems to be relatively consistent for men and pre- and postmenopausal women.[28] This may be primarily because of a direct or indirect effect of alcohol on bone resorption.[45,46] However, based on our findings, the additional "silicon effect" adds a further dimension with moderate beer consumption, which is likely to act on bone formation. We therefore also provide the first evidence to support the view that not all the effects of alcoholic beverages on BMD, and perhaps other outcome measures, are attributable to ethanol. The other sources of dietary Si such as whole grains, rice, certain vegetables and fruits, and natural waters would suggest that micronutrients in whole foods and untreated water may contribute importantly to bone health in men and premenopausal women.

ACKNOWLEDGMENTS

The authors thank Janice Maras of Tufts University (Boston, MA, USA) for database development and analysis of silicon intake in the Framingham study, Dr Elizabeth Samelson (HRCA Research and Training Institute, Boston, MA, USA) and Dr Henk Hendriks (TNO Nutrition and Food Research, The Netherlands) for useful discussions, and Prof Sir Richard Thompson (St Thomas' Hospital, UK) for continuous support. Funding for this work was provided by the U.S. Department of Agriculture (contract 53-3K06-5-10), National Institutes of Health (RO1 AR/AG 41398), and the Framingham Heart Study (supported by National Institutes of Health/NHLBI

contract NO1-HC-38038). The sponsors had no involvement in this study (i.e., in the design, collection, analysis, interpretation of the data, writing of the paper, or in the decision to submit the paper for publication). The authors had full access to all the data presented in this manuscript.

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Received in original form April 24, 2003; in revised form August 11, 2003; accepted September 10, 2003.