Association Between Low Bone Density and Stroke in Elderly Women
The Study of Osteoporotic Fractures

Warren S. Browner, MD, MPH; Alice R. Pressman, MS; Michael C. Nevitt, PhD;
Jane A. Cauley, DrPH; Steven R. Cummings, MD;
for the Study of Osteoporotic Fractures Research Group

**Background and Purpose:** To determine whether women with low bone mineral density are at increased risk of stroke, the present study was conducted.

**Methods:** We studied 4024 ambulatory women aged 65 years or older participating in the prospective Study of Osteoporotic Fractures. Bone mineral density was measured at baseline using single photon absorptiometry; strokes were ascertained using a computerized Medicare data base and death certificates. Results: During a mean of 1.98 years of follow-up, 83 women suffered first strokes (five fatal). Osteopenia was associated with an increased stroke risk: Each SD decrease in bone mineral density at the calcaneus (0.09 g/cm²) was associated with a 1.31-fold increase in stroke (95% confidence interval, 1.03-1.65), adjusted for age, follow-up time, and several potential confounders, including diabetes, systolic blood pressure, use of alcohol, cigarettes or postmenopausal estrogens, cognitive ability, grip strength, and functional ability. The observed relation between bone density and stroke was strongest for intracerebral hemorrhages and occlusions.

**Conclusions:** Most likely, low bone density does not cause stroke; some other process probably results in both osteopenia and cerebrovascular disease. *(Stroke 1993;24:940-946)*

**KEY WORDS** • bone diseases, metabolic • osteoporosis • risk factors • women

We previously reported that osteopenia (low bone density) was associated with increased mortality among elderly women.1 This somewhat surprising relation was strongest for the 25 deaths due to stroke: a 74% increase in mortality per SD (0.09 g/cm²) decrease in calcaneus bone density. We speculated that low bone density may be a marker for another factor or factors that are related to fatal strokes.

To confirm these findings and to determine whether bone density is associated with incident strokes, both fatal and nonfatal, we followed more than 4000 ambulatory women aged ≥65 years in the prospective Study of Osteoporotic Fractures who had at least one Medicare claim filed between 1986 and 1989. We compared bone density measured at baseline in women who suffered a stroke during that time with those who did not and adjusted for potential confounding variables.

**Subjects and Methods**

Ambulatory women 65 years of age or older who had not previously had bilateral hip fractures were recruited from September 1986 to October 1988 at four clinical centers: The Kaiser-Permanente Center for Health Research, Portland, Oregon; The University of Minnesota in Minneapolis; the University of Maryland in Baltimore; and the University of Pittsburgh.2 Men and black women were excluded because of their relatively low incidence of osteoporotic fractures. Subjects in Portland and in Minneapolis were recruited primarily from health maintenance organizations. Many of these women did not file Medicare claims during follow-up, and thus women from these two clinics were excluded. Subjects in Baltimore (n=2424) were recruited from holders of driver's licenses and identification cards within Baltimore County, whereas those in the Monongahela Valley, Pennsylvania (n=2401) were recruited from 1985 voter registration lists. A total of 4134 women (2097 in Baltimore and 2037 in Pittsburgh) filed at least one Medicare claim, including inpatient and outpatient services, during the follow-up period from the time of enrollment until December 31, 1989. Women with a history of previous stroke (n=110), in whom 12 subsequent strokes occurred, were excluded from analysis, leaving the cohort of 4024 women who were followed for

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From the Department of Epidemiology and Biostatistics (W.S.B., A.R.P., M.C.N., S.R.C.), the General Internal Medicine Section, Department of Medicine, Veterans Affairs Medical Center (W.S.B.), and the Division of General Internal Medicine, Department of Medicine (S.R.C.), University of California, San Francisco; and the Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa (J.A.C.).

A complete list of the investigators in the Study of Osteoporotic Fractures Research Group appears at the end of this article.

Correspondence to Study of Osteoporotic Fractures, 74 New Montgomery, Suite 600, San Francisco, CA 94105 (Dr Browner).
a mean of 1.98 years. (There were no significant differences in bone density in the women with Medicare claims and those without such claims during the follow-up period.)

Participants completed a questionnaire that was reviewed by an interviewer during the 3-hour baseline examination. The questionnaire asked about use of alcohol and cigarettes, health status compared with other women of similar age (very poor/poor/fair versus good/excellent), previous stroke, diabetes mellitus, hypertension (on diuretic medications or with measured blood pressure >160/90 mm Hg), and current and past use of steroids and postmenopausal estrogens, ability to perform six activities of daily living (with one point for each activity that could not be performed or was performed with difficulty), and physical activity as average number of times per week exercised. Weight, body-mass index, and the waist-to-hip ratio were measured with standard techniques.3 Grip strength was measured in both hands with a hand-held dynamometer; in these analyses, we used whichever side was stronger. Hip abduction strength was measured in the dominant leg using a hand-held isometric dynamometer. A modified version of the Mini-Mental State Examination4 with a maximum score of 26 was administered. Bone mineral density (g/cm²) was measured at three sites—the distal radius, the proximal radius and the calcaneus—using single photon absorptiometry (OsteoAnalyzer, Siemens-Osteon, Wahiawa, Hawaii). Coefficients of variation at these sites were 1.5%, 2.0%, and 1.3%, respectively. Aspirin use was not ascertained at baseline but was measured at the second annual visit, approximately 2 years later.

Many women in the University of Pittsburgh cohort (n=1361) had serum cholesterol levels measured at baseline using a Kodak DT-60 portable chemistry analyzer. Quality control standards were run with each assay; the coefficient of variation was 1.8% for the low standard and 1.1% for the high standard.

We used the Health Care Finance Administration’s Medicare Automated Data Retrieval System (MADRS) to obtain medical records for our study group. We matched our cohort to MADRS data by social security number, sex (the same number can apply to both husband and wife), and date of birth, and searched for hospitalizations with ICD-9-CM codes for stroke (431, 432.9, 433, 434, 436, 437, 437.1, 437.9) as one of the first five diagnoses. We also reviewed death certificates on all women who died during follow-up. Strokes were classified as intracerebral hemorrhage or occlusion (431 or 432.9 or 434), occlusion of precerebral arteries (433), or nonspecific cerebrovascular disease (all other categories).

For women with more than one reported claim for stroke, the first event was used. Fatal strokes were those that resulted in death within 30 days of the incident event. Follow-up began on January 1 of the year of the first Medicare claim or at the time of enrollment into the Study of Osteoporotic Fractures, whichever came last. Follow-up ended on December 31 of the year of the last claim, at the time of a stroke, or at the woman’s death, whichever came first.

Proportional hazards (Cox) models were used to determine the age-adjusted relations between predictors and incident stroke.5 Age-adjusted hazard ratios (RR) with 95% confidence intervals (CI) and two-sided P values are reported; unless otherwise specified, these are reported per SD change in a continuous predictor variable. We examined the effects of potential confounders by adding them to models containing bone mineral density and age and assessing the effect on the coefficients for bone mineral density and mortality. All analyses were performed using SAS software (SAS Institute, Inc, Cary, NC).

Results

Participants in the study were generally healthy women (Table 1). During a mean of 1.98 years of follow-up, 83 women suffered fatal (5) or nonfatal (78) strokes. Of these, 29 women had intracerebral hemorrhage or occlusion, 26 had occlusion of precerebral arteries, and 28 had nonspecific cerebrovascular disease.

Age-adjusted associations are reported in Table 1. Women with osteopenia were at increased risk of stroke: Each 0.09 g/cm² (1 SD) decrease in bone density at the calcaneus was associated with a 30% increase in stroke rate. Among women in the lowest quartile of age-adjusted calcaneus bone density, 26 suffered strokes during follow-up compared with 13 strokes among those in the upper quartile (Figure). This relation between bone density and stroke was similar for measurements made at the proximal radius but was not statistically significant at the distal radius.

Higher systolic blood pressure was associated with an increased stroke rate, as was diabetes mellitus. We found no relation between serum cholesterol level and stroke in the Pittsburgh cohort. There was only one hemorrhagic stroke in the Pittsburgh cohort so we could not look at the relation between serum cholesterol and these events.

Women who currently drank alcohol had a 50% lower rate of stroke. To test the possibility that women who abstain from alcohol do so because of unmeasured health problems that placed them at higher risk of stroke, we compared women who reported alcohol consumption in the past 12 months with those who were lifelong teetotalers. In this analysis, current drinkers remained at a substantially reduced risk (RR=0.48; 95% CI, 0.30–0.79).

Diminished cognitive function, lower grip strength, and reduced functional status were also associated with increased stroke risk. Women with modified Mini-Mental State Examination scores of 23 or less were more than twice as likely to suffer incident strokes as those with higher scores. Reduced grip strength and difficulties in performing activities of daily living were both associated with an increased stroke rate.

The association between low bone density and stroke remained significant in models that included these potential confounders (Table 2). We report models that included cognitive function, grip strength, and functional status separately because these variables measure related attributes. The bone density–stroke association also was not confounded by smoking, use of aspirin or postmenopausal estrogens, weight at age 50 years, current weight, body-mass index, or hip abduction strength. Similar multivariable results were seen when bone density was measured at the proximal radius.
stroke. 70% confidence interval.

*Current users of alcohol, cigarettes, or medications are compared with current nonusers. Use of aspirin was based on second visit data, available in 3760 women. Serum cholesterol levels were available in 1321 women in Pittsburgh clinic.

†Values are mean±SD. Age-adjusted hazard ratios are reported per unit (yes/no) for binary variables and per one unit increase in SD for all continuous variables, except per one unit decrease in SD for bone density measurements.

‡Statistical significance set at P<.10 (two sided) in age-adjusted analysis.

§Hazard ratio reported per activity (of six) that was not performed or was performed with difficulty.

In a post hoc analysis, the relation between bone density and stroke appeared stronger for intracerebral hemorrhages or occlusions than for the other types of strokes (Table 3). This relation was not changed by adjustment for diabetes, alcohol use, systolic blood pressure, functional status, grip strength, and cognitive function.

When we repeated our analysis for incident strokes using the entire cohort of women (not just those with Medicare records) from Baltimore and Pittsburgh who were free of stroke at baseline (n=4646 with the same 83 strokes), we found nearly identical results. For example, the age-adjusted hazard ratio (per SD of bone density at the calcaneus) was 1.31 (95% CI, 1.03-1.65).

Discussion

These results confirm that women with low bone density are at an increased risk of stroke. The magnitude of the increase (a relative risk of about 1.3 per SD) is substantial (a woman with a bone density that is 1 SD below the mean for her age is at a 70% increase in stroke risk compared with a woman whose bone density is 1 SD above the mean) and comparable with that observed for the relation between systolic blood pressure and stroke in the elderly.6

However, unlike the cause-effect relation between blood pressure and stroke, we do not believe that low bone density causes stroke. Besides cause-effect, there are four other explanations for any epidemiologic asso-
association: effect-cause, effect-effect (also known as confounding), chance, and bias. An effect-cause type of association implies that stroke causes low bone density. This could have occurred if there were substantial numbers of women with undetected or unreported strokes at baseline who were at increased risk of subsequent strokes for which they were hospitalized.7 If women with subclinical strokes had reduced their activity levels or were otherwise in frail health, they also may have had lower bone density. We attempted to reduce the possibility of effect-cause (as much as possible given the inherent limitations in measuring these factors) by adjusting for strength (hip abduction, triceps extension, and grip), physical activity, mental status, general

<table>
<thead>
<tr>
<th>Variable (unit)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Model 1</td>
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<tr>
<td>Calcaneus BMD (−0.09 g/cm²)</td>
<td>1.29</td>
<td>1.03-1.62</td>
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<tr>
<td>Systolic BP (+18 mm Hg)</td>
<td>1.20</td>
<td>0.97-1.49</td>
<td>.1</td>
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<td>Current alcohol use</td>
<td>0.54</td>
<td>0.35-0.84</td>
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<td>Diabetes mellitus</td>
<td>3.6</td>
<td>1.11-11</td>
<td>.03</td>
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<tr>
<td>Calcaneus BMD (−0.09 g/cm²)</td>
<td>1.36</td>
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<td>Systolic BP (+18 mm Hg)</td>
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<td>0.99-1.47</td>
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<tr>
<td>Current alcohol use</td>
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<td>0.37-0.90</td>
<td>.02</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>1.11-11</td>
<td>.03</td>
</tr>
<tr>
<td>Mini-mental state examination score ≤23</td>
<td>1.88</td>
<td>1.16-3.04</td>
<td>.01</td>
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<td>Model 3</td>
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<td>1.08-1.70</td>
<td>.009</td>
</tr>
<tr>
<td>Systolic BP (+18 mm Hg)</td>
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<td>0.99-1.48</td>
<td>.06</td>
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<tr>
<td>Current alcohol use</td>
<td>0.57</td>
<td>0.37-0.90</td>
<td>.02</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>1.0-10.6</td>
<td>.05</td>
</tr>
<tr>
<td>Functional disability (per activity)*</td>
<td>1.20</td>
<td>1.05-1.37</td>
<td>.006</td>
</tr>
<tr>
<td>Model 4</td>
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<tr>
<td>Calcaneus BMD (−0.09 g/cm²)</td>
<td>1.31</td>
<td>1.03-1.67</td>
<td>.03</td>
</tr>
<tr>
<td>Systolic BP (+18 mm Hg)</td>
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<td>1.00-1.49</td>
<td>.05</td>
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<tr>
<td>Current alcohol use</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3.4</td>
<td>1.0-10.9</td>
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</tr>
<tr>
<td>Grip strength (−4.3 kg)</td>
<td>1.23</td>
<td>0.99-1.54</td>
<td>.06</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; BP, blood pressure; CI, confidence interval.
*Per activity unable to perform or performed with difficulty.

Table 2. Multivariable Models of Age-Adjusted Association Between Bone Density and Incident Stroke

Table 3. Age-Adjusted Associations* Between Measurements of Bone Density at Various Sites and Type of Incident Stroke†

<table>
<thead>
<tr>
<th>Type of stroke</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Calcaneus bone density</td>
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<tr>
<td>Cerebral hemorrhage/occlusion</td>
<td>1.83</td>
<td>1.21-2.78</td>
<td>.004</td>
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<td>Preocerebral occlusion</td>
<td>1.44</td>
<td>0.95-2.19</td>
<td>.09</td>
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<tr>
<td>Nonspecific cerebrovascular disease</td>
<td>0.88</td>
<td>0.61-1.29</td>
<td>.52</td>
</tr>
<tr>
<td>Proximal radius bone density</td>
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<td></td>
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<tr>
<td>Cerebral hemorrhage/occlusion</td>
<td>1.84</td>
<td>1.25-2.71</td>
<td>.002</td>
</tr>
<tr>
<td>Preocerebral occlusion</td>
<td>1.52</td>
<td>1.02-2.26</td>
<td>.04</td>
</tr>
<tr>
<td>Nonspecific cerebrovascular disease</td>
<td>0.73</td>
<td>0.49-1.07</td>
<td>.11</td>
</tr>
<tr>
<td>Distal radius bone density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage/occlusion</td>
<td>1.35</td>
<td>0.89-2.03</td>
<td>.15</td>
</tr>
<tr>
<td>Preocerebral occlusion</td>
<td>1.36</td>
<td>0.90-2.06</td>
<td>.15</td>
</tr>
<tr>
<td>Nonspecific cerebrovascular disease</td>
<td>0.74</td>
<td>0.51-1.09</td>
<td>.13</td>
</tr>
</tbody>
</table>

CI, confidence interval.
*As the hazard ratio per decrease of SD.
†There were 29 women with cerebral hemorrhage or occlusion (10 in Baltimore), 26 women with preocerebral occlusion (4 in Baltimore), and 28 women with nonspecific cerebrovascular disease (15 in Baltimore). SD of bone density was 0.09 g/cm² at the calcaneus, 0.10 g/cm² at the proximal radius, and 0.08 g/cm² at the distal radius.
health, and functional status at baseline. Adjustment for these variables did not affect the relation between bone density and stroke.

Another possibility is that of effect-effect, namely that both low bone density and stroke are the effects of some other process. Low bone density may be a marker for ill health or other comorbidities, and these conditions may be nonspecifically associated with an increased risk of stroke. There are also several more specific explanations for a link between osteopenia and cerebrovascular disease. Recent work has found that aortic calcification is more common among women with osteoporotic vertebral fractures. If diffuse atherosclerotic disease may cause unfavorable patterns of calcitropic hormones, in particular low levels of vitamin D and its metabolites, high levels of parathormone, or both perhaps as a result of decreased renal function, and thus indirectly have detrimental effects on bone. Effects of calcitropic hormones on vascular reactivity and on the risk of myocardial infarction have been described.  

Both atherosclerosis and osteoporosis may result from estrogen deficiency. Exogenous estrogens reduce perimenopausal bone loss and prevent fractures. Some but not all studies have found that estrogen users have lower rates of fracture. Estrogens also could reduce the risk of thrombosis by altering clotting factors and other vascular mediators. Perhaps endogenous estrogens have similar effects.

Elevated serum levels of homocysteine seen in persons who are heterozygous for cystathionine beta-synthase deficiency have been associated with stroke. Homozygotes (persons with homocystinuria) have premature osteoporosis. We previously compared homocysteine levels in 23 women randomly selected from participants in our study whose bone density was in the highest decile for age with 23 age-matched participants whose bone density was in the lowest decile for age. Although we did not find a relation between homocysteine levels and bone density in these women, that does not eliminate the possibility that hyperhomocysteinemia may be associated with osteopenia and stroke. Importantly, this condition can be reversed with supplemental folic acid.

Several dietary factors may be responsible for the association between bone density and stroke. Low levels of consumption of potassium-rich foods (such as fruits) have been associated with an increased risk of stroke. If such diets also contain more acid residues (ie, have higher protein loads), they also may result in loss of bone calcium as seen in long-standing metabolic acidosis. Finally, dietary ascorbic acid is essential for the synthesis of collagen in bone matrix; decreased intake also has been associated with cardiovascular disease.

The only way to distinguish between effect-cause and effect-effect as explanations for the bone density–stroke association would be to establish a clear temporal sequence by determining whether subclinical strokes preceded changes in bone density. This would require making those measurements and performing a detailed neurologic examination, including imaging of the central nervous system, on all participants at baseline so subclinical events could be detected. Those with normal examinations then would be followed for the occurrence of clinically evident strokes.

The remaining possibilities are that the association between bone density and stroke is due to chance or bias. Chance is an unlikely explanation, given the statistical significance of these results and those we previously reported for fatal strokes. Finally, most forms of bias also seem unlikely: Bone density was measured before the occurrence of stroke, and stroke ascertainment was done without knowledge of a woman’s bone density. We cannot eliminate the possibility that frail women with a limited physiologic reserve (and low bone density) were more likely to be hospitalized if they suffered a stroke and thus be detected by our outcome ascertainment system. This form of detection bias, however, could not explain the association between low bone density and fatal strokes that we previously reported.

The biologic plausibility of a bone density–stroke relation is supported by the recent finding that the stroke-prone spontaneously hypertensive rat develops osteoporosis. In this study, Yamori et al noted that the skulls of these animals seemed abnormally weak; this qualitative impression was supported by the finding that, when compared with control rats, bones from rats who were stroke-prone had lower mineral content and torsion strength. Also, several intriguing studies in cell biology suggest links between the vascular system, blood coagulation, and calcium metabolism. In response to low concentrations of calcium, for example, the parathyroid gland appears to secrete parathyroid hormone and tissue plasminogen activator in parallel. Osteoblasts respond to parathyroid hormone with increased production of plasminogen activator. Perhaps and associates have suggested a role for so-called parathyroid hypertensive factor in the etiology of hypertension in both humans and animals, including the spontaneously hypertensive rat, probably by increasing calcium uptake in smooth muscle cells. Moreover, endothelins, which are extremely potent systemic vasoconstrictors and whose levels are increased in persons with myocardial infarction, are likely to have a role in bone: Endothelin-1 increases bone perfusion pressure and affects bone resorption and collagen production in tissue culture. Perhaps the local effects of plasminogen activators and endothelins on bone and their systemic effects, including hypertension, atherosclerosis, and changes in blood coagulability, are associated. There also may be links mediated through vitamin K-dependent proteins, which are important both in coagulation and bone formation.

We cannot explain why a relation between bone density and stroke was seen when bone density was measured at the calcaneus and at the proximal radius but not at the distal radius. One explanation, of course, is that this represents a chance occurrence; the confidence intervals around the risk estimates do overlap. The observation also is consistent with the heterogeneous nature of bone at different sites. The associations between bone density and fracture risk, for example, vary by site of measurement as well as site of fracture. Given the small numbers of types of strokes, the post hoc observation that bone density was a stronger predictor of strokes ascribed to intracerebral causes might be a chance finding. Conversely, any misclassification of stroke etiology recorded in Medicare records would make it hard to find true associations. Thus, if this
finding is real, the actual relation may be even stronger. Perhaps the factor that links bone mineral density with stroke is more closely related to the integrity of the intracerebral vasculature than to the development of precerbral atherosclerotic plaques.

Our results confirm those of several other studies of risk factors for stroke in elderly women. As expected, diabetes and an elevated systolic blood pressure were both independent predictors of stroke.\textsuperscript{36,37} We also found that women who drank alcohol were at a 50\% lower risk of stroke. Most women in the Study of Osteoporotic Fractures cohort who used alcohol, however, did so in moderation: The average weekly consumption (among drinkers) was less than 1 ounce. These results are consistent with another study that found small amounts of alcohol consumption were associated with a reduced risk of stroke.\textsuperscript{38} Consistent with other findings,\textsuperscript{6,35} we found no evidence that bone mineral density with other findings,6,35 we found no

References


Association between low bone density and stroke in elderly women. The study of osteoporotic fractures.

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