The Risk of Fracture Following Hospitalization in Older Women and Men

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Background: Hospitalization may cause bone loss and decrease physical function; however, the risk of fracture following hospitalization is not known.

Methods: A prospective study of a cohort of 3075 white and black women and men, aged 70 to 79 years, recruited from 2 communities from 1997 to 1998. Incident hospitalizations and fractures were validated by medical records by investigators blinded to patient groupings. Analyses of the association between hospitalization, length of stay, number of admissions, and risk of fracture were adjusted for age, race, sex, and other potential confounding factors.

Results: During follow-up with a mean duration of 6.6 years, 2030 (66%) of the 3075 participants were admitted to a hospital and 809 (26%) were admitted 3 or more times; 285 experienced a fracture, including 74 hip fractures. After adjusting for age, race, and sex, those who had any hospitalization had a 2-fold increased risk of fracture (hazard ratio [HR], 2.01; 95% confidence interval [CI], 1.57-2.57), including an increased risk of hip fracture (HR, 2.15; 95% CI, 1.32-3.50). Those who were hospitalized twice during the follow-up period had a 2.42-fold increased risk of hip fracture (95% CI, 1.16-5.05), and 3 or more hospital stays indicated a 3.66-fold increased relative hazard for hip fracture (95% CI, 1.78-7.53).

Conclusions: Hospitalizations, particularly multiple admissions, are very common in elderly individuals and are strongly associated with an increased risk of hip and other types of fracture. Hospitalizations present opportunities to take measures to reduce the risk of fractures.

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FRACTURES CAUSE SUBSTANTIAL disability and mortality in elderly patients, and these consequences may be greater among those who already have medical problems.1-3 A variety of risk factors for hip and other types of fractures have been used to identify people who have a high risk of fracture that could be reduced by several types of interventions.4-6

Many older adults in the United States are admitted to hospitals; in 2003, men and women 65 years or older had more than 13 million hospitalizations with a mean length of stay (LOS) of 5.7 days.7 Although many hospitalizations involve relatively healthy adults who have short hospital stays for elective procedures, longer hospital stays or repeated stays may indicate poor health, medical conditions, or frailty that may be markers for increased risk of fracture.

Hospitalization itself might also contribute to an increased risk of fracture. Older adults who are hospitalized often lose physical function with loss of independence in activities of daily living (ADLs)8 and declines in functional status9,10 that are risk factors for hip fracture.4,3 Immobility has been shown to acutely increase bone turnover and decrease bone mineral density (BMD) in bed-bound adults, including patients in intensive care units (ICUs).11-17 Patients who experience strokes18-20 or spinal cord injury also have rapid bone loss and a high risk of hip fracture.21-23 and hospitalization has been associated with bone loss at the spine and hip in women.25 One study suggested an increased fracture risk after an inpatient stay for mental illness, but the analysis did not adjust for potential confounders.27,28 To our knowledge, there have been no studies of the risk of fracture after a medical or surgical hospitalization.

We hypothesized that older adults who had long hospital stays and multiple hospitalizations would have an increased risk of hip and other fractures after discharge. We studied the postdischarge risk of fracture in the Health Aging and Body Composition (Health ABC) Study,29 a prospective study of a large cohort of healthy elderly men and women.

METHODS

STUDY PARTICIPANTS

From April 1997 to June 1998, 3075 white and black adults, aged 70 to 79 years, were recruited from Pittsburgh, Pennsylvania, and...
Memphis, Tennessee. Men and women were eligible if they had no reported difficulty walking a quarter of a mile, climbing 10 steps, or performing ADLs; no active treatment for cancer within the past 3 years; and no plans to move from the study area for at least 3 years. All participants provided informed consent, and the institutional review boards at each site approved the study. Details of the study’s methods have been published.29

ASCERTAINMENT AND CONFIRMATION OF HOSPITALIZATIONS AND FRACTURES

Incident clinical fractures and hospitalizations were assessed by self-report at annual clinic visits and at intervening 6-month interviews. Participant report of fracture was verified by radiology reports or review of the radiograph. Based on medical record review, 37 fractures were classified as having been caused by excessive trauma (mainly motor vehicle crash), and these were excluded from the analysis. We also excluded pathologic fractures (n=15), stress fractures (n=8), and fractures for which it was uncertain whether the fracture was pathologic or the trauma severe (n=24). The decision to exclude these fractures from the analysis was made a priori. For the hospitalized group, we included only fractures that occurred after a hospital stay. Participant report of the index hospitalization was verified by physician review of discharge summaries, and discharge diagnoses and LOS were recorded. Hospital admissions for fracture were excluded.

COVARIATES

Age, sex, race, a health history (including prior fractures), and a medication inventory were assessed by an interviewer-administered questionnaire at the baseline visit. Smoking, alcohol use, physical activity, income, family history, cognitive assessment, and self-reported health status also were evaluated at the baseline interview. Corticosteroid, statin, benzodiazepine, thiazide diuretic, antidepressant, estrogen, osteoporosis medications (bisphosphonates, calcitriol, raloxifene hydrochloride, and fluoride), and calcium and vitamin D supplement use was coded using the Iowa Drug Information System ingredient codes.30 Medication use was also ascertained at the annual follow-up study visits.

Height was measured using a stadiometer (Harpenden, Pembrokeshire, Wales), and weight was measured with a calibrated balance beam scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Bone mineral density of the proximal femur was assessed by dual-energy x-ray absorptiometry (DEXA) (Hologic QDR 4500A; Hologic Inc, Bedford, Massachusetts). The 6-m pace was performed by timing participants walking at their usual pace along a 6-m walking course. The subjects performed the walk twice, and the 2 times (in seconds) were averaged and reported in meters per second walked. Grip strength was measured using a hydraulic, isometric dynamometer (Jamar Hydraulic Hand Dynamometer; Sammons Preston, Bolingbrook, Illinois). While seated, the subject performed the test twice in both hands; the strength in kilograms was averaged for each hand, and the value that was higher (ie, the strength of the dominant hand) was used for the analysis.

STATISTICAL ANALYSIS

We first compared subjects with a hospital admission vs those without during participation in the study using the t test, Wilcoxon rank sum test, and \( \chi^2 \) test as appropriate. We then used Cox proportional hazards models to assess the associations of hospitalization and LOS with the risk of subsequent fracture. We considered time to first clinical fracture as well as time to first hip fracture; participants who did not experience the end point for each analysis were censored as of their last contact date or at the time of their death. We included multiple fractures in the analysis using the Anderson-Gill extension of the Cox model, in which participants experiencing a fracture and remaining in follow-up afterward are included in subsequent risk sets after their fracture occurs rather than being dropped from the study, as in the basic Cox model. Robust standard errors are used to account for the potential clustering of events among higher-risk participants. Multiple hospitalizations are included as time-dependent covariates in this analysis, with the number of hospital stays defined in terms of the timing of each fracture event.

In addition to modeling the effect of any prior hospitalization after study entry as a time-dependent covariate, we examined associations with a history of 1, 2, or 3 or more hospitalizations, also using time-dependent indicator variables; standard orthogonal contrasts were used to assess the linear trend in estimated fracture rates across the 4 levels of this ordinal predictor. We also considered including the total days of hospitalization in the model, but the 2 covariates (number of hospital stays and total hospital days) were very highly correlated \( (r=0.8) \). The magnitude of association was similar using either covariate. We chose to study the total number of hospitalizations because we believed it captured the total effects of hospitalization and is more practical for a physician to calculate.

To assess the effect of LOS, we stratified estimates for the most recent hospitalization according to whether that stay was at least 3 days; in exploratory analysis we used an LOS cut point of 3 days, following another study that examined the impact of hospitalization on elderly patients.31 We also chose this cut point because short hospital stays (1-2 days) are often for elective surgical procedures and for milder and more transient problems (such as “rule out myocardial infarction”). Furthermore, we hypothesized that longer stays (≥3 days) were more likely to cause impaired function and bone loss. We allowed the effect of LOS to differ for the first, second, or third or greater hospitalization. These analyses were first performed adjusting first for age, race, and sex only to determine whether hospitalization strongly predicted future fractures.

We adjusted for potential confounding factors that differed between the 2 groups at \( P \leq 0.20 \). Medication use was ascertained at most annual visits, and time-dependent covariates were calculated to indicate whether a specific medication was used at any point prior to a fracture. We also considered medication use at baseline in the model, and there was no effect on the magnitude of the association when baseline use was included instead.

In addition, we added potential risk factors for hip and nonvertebral fracture (BMD, past history of fracture, BMI, use of osteoporosis medications, and health status) to the fully adjusted model, regardless of whether these factors differed between the hospitalized and nonhospitalized groups. In a final step, we considered whether decreased neuromuscular function might confound the association between hospitalization and risk of fracture by adding grip strength and 6-m pace to the fully adjusted models.

Finally, to characterize absolute fracture risks, we estimated fracture rates stratified by race, sex, and hospitalization history using person-time methods and constructed Kaplan-Meier estimates of the cumulative incidence of clinical and hip fractures as a function of days since discharge from the most recent hospitalization.

A 2-sided \( P \) value of \( P < 0.05 \) was considered statistically significant. All analyses were performed using SAS statistical software (version 9.1.2; SAS Institute, Cary, North Carolina).
A total of 2030 participants had 5680 hospitalizations during 6.6 years of follow-up. The median LOS was 4 days (interquartile range [IQR], 2-7 days). Among hospitalized subjects, 50% were women and 58% were white. Participants who were hospitalized were slightly older, more likely to be male, more likely to smoke, and more likely to have diabetes mellitus and cardiovascular disease. There was no significant difference in femoral neck bone density between the 2 groups (see Table 1 for P values).

Follow-up for fractures was 97% complete, and we validated that 285 subjects (9.3%) had 362 postdischarge fractures, including 74 participants who experienced 80 hip fractures. The most common fracture sites were the distal radius and ulna (15%), the femoral neck (14%), and the vertebrae (19%). A median time of 323 days (IQR, 104-659 days) elapsed between hospital discharge and occurrence of a fracture.

Hospital stays were associated with a 2-fold increased risk of fractures (hazard ratio [HR], 2.01; 95% confidence interval [CI], 1.57-2.57) after adjusting for age, race, and sex (Table 2). The adjusted risk of fracture increased with the number of times a patient was hospitalized (Figure 1). The HR for any fracture after 1 hospitalization was 1.45 (95% CI, 1.09-1.93), after 2 hospitalizations it was 2.02 (95% CI, 1.38-2.96), and after 3 or more hospitalizations it was 3.65 (95% CI, 2.51-5.29), adjusting for age, race, and sex. A similar pattern was seen with hip fractures (Table 2).

There was a modest attenuation in the risk when the model was adjusted for all potential confounding factors that differed between the 2 groups at P ≤ .20 (Table 2). The HR for fracture was 1.38 (95% CI, 1.02-1.86) with 1 hospital stay, 1.92 (95% CI, 1.30-2.85) with 2 hospitalizations, and 3.65 (95% CI, 2.51-5.29) with 3 or more hospitalizations.

### Table 1. Baseline Characteristics of Cohort by Hospitalization Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hospitalized (n=2030)</th>
<th>Not Hospitalized (n=1045)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>73.8 (2.9)</td>
<td>73.4 (2.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>49.5</td>
<td>58.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White race</td>
<td>58.2</td>
<td>60.1</td>
<td>.16</td>
</tr>
<tr>
<td>Study site, % in Pittsburgh, PA</td>
<td>52.4</td>
<td>44.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Never</td>
<td>40.2</td>
<td>51.1</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>47.8</td>
<td>41.8</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>12.0</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>3.9</td>
<td>3.3</td>
<td>.45</td>
</tr>
<tr>
<td>Prior fracture after age 45 y</td>
<td>22.9</td>
<td>20.4</td>
<td>.12</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.0</td>
<td>4.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17.2</td>
<td>11.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>30.0</td>
<td>14.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>18.2</td>
<td>15.4</td>
<td>.05</td>
</tr>
<tr>
<td>COPD</td>
<td>12.4</td>
<td>6.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression</td>
<td>10.0</td>
<td>8.7</td>
<td>.23</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.4 (4.8)</td>
<td>27.2 (5.0)</td>
<td>.25</td>
</tr>
<tr>
<td>BMD at hip, mean (SD)</td>
<td>0.89 (0.17)</td>
<td>0.88 (0.17)</td>
<td>.61</td>
</tr>
<tr>
<td>T score for hip, mean (SD)</td>
<td>−1.04 (0.02)</td>
<td>−1.03 (0.03)</td>
<td>.25</td>
</tr>
<tr>
<td>Yearly income, &lt;$25 000</td>
<td>52.6</td>
<td>51.7</td>
<td>.66</td>
</tr>
<tr>
<td>Health status, poor or fair</td>
<td>18.4</td>
<td>11.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity, mean (range), kcal/kg/vk</td>
<td>61.7 (36.1-101.1)</td>
<td>70.2 (41.9-114.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grip strength, mean (SD), kg</td>
<td>31.0 (10.5)</td>
<td>29 (10.5)</td>
<td>.36</td>
</tr>
<tr>
<td>6-m pace, mean (SD), m/s</td>
<td>1.15 (0.24)</td>
<td>1.19 (0.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol drinks/wk, &gt; 7</td>
<td>7.7</td>
<td>6.8</td>
<td>.36</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2.6</td>
<td>1.6</td>
<td>.10</td>
</tr>
<tr>
<td>Statin</td>
<td>13.5</td>
<td>11.8</td>
<td>.19</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>18.7</td>
<td>16.9</td>
<td>.21</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>5.6</td>
<td>5.4</td>
<td>.61</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>7.1</td>
<td>5.0</td>
<td>.02</td>
</tr>
<tr>
<td>Estrogen (women)</td>
<td>21.2</td>
<td>24.2</td>
<td>.17</td>
</tr>
<tr>
<td>Osteoporosis medicationc</td>
<td>3.3</td>
<td>5.1</td>
<td>.02</td>
</tr>
<tr>
<td>Calcium</td>
<td>16.2</td>
<td>21.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>7.2</td>
<td>11.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease.

a Data are given as percentages except where noted.

b Computed by χ² when comparing percentages, t test when comparing means, and Wilcoxon rank sum tests when comparing medians.

c Includes bisphosphonates, calcitonin, raloxifene hydrochloride, and fluoride.
tal stays, and 3.17 (95% CI, 2.28-4.62) with 3 or more hospital stays. A similar pattern was also seen with hip fractures in the fully adjusted model (Table 2).

Adding measures of neuromuscular function—grip strength and 6-m pace—into the models also modestly attenuated the association between hospitalization and risk of fracture (HR, 1.78; 95% CI, 1.41-2.29). When we further adjusted for potential risk factors for hip and non-vertebral fractures, there was no substantial effect on the magnitude of the association. Because of the known high risk of fracture after stroke, we also excluded hospitalizations due to stroke, and this also did not change the magnitude of the associations (data not shown).

We considered the possibility that a longer hospital LOS might increase fracture risk. Compared with subjects who had no hospital stays, the relative hazard of any fracture was 2.60 (95% CI, 1.54-4.41) for 3 or more days of hospitalization and 1.68 (95% CI, 0.93-3.05) for shorter stays. However, when we then added the number of hospital stays to the model, the LOS of the most recent hospitalization was no longer independently predictive of fracture risk. In addition, we found no notable interaction between LOS and the number of previous hospitalizations in models that were also adjusted for age, race, and sex and all other covariates.

We estimated that white women aged 70 to 79 years with no hospitalization in the prior 6 years would have an absolute fracture rate of 2.5% (95% CI, 2.0%-3.0%) per year, and this risk increased to 4.0% (95% CI, 2.8%-5.2%) with 1 hospitalization, 4.6% (95% CI, 2.4%-6.8%) after 2 and 7.2% (95% CI, 4.9%-9.6%) after 3 hospitalizations. The absolute rates of fracture were lower for men and black women; however, there were too few fractures in these groups to allow precise estimates.

Figure 1. Fracture risk increases with number of hospital stays. Relative hazards with 95% confidence intervals (bars) for (A) any clinical fracture and (B) hip fracture with increasing numbers of hospitalizations during a mean follow-up of 6.6 years, adjusted for age, race, and sex.

In this prospective study of a community-based cohort of relatively high functioning older adults, we found that hospitalization was associated with an increased subsequent risk of hip and other fractures. The risk of fracture was especially increased among patients who were hospitalized more than once during the mean 6.6 years of the study. Hospitalization is a very common risk factor for fracture. During the study period, about two-
thirds of this relatively healthy cohort of elderly men and women had at least 1 hospital admission, and 26% were admitted 3 or more times.

To our knowledge, this is the first study to describe an association between non–stroke-related hospitalization and subsequent risk of fracture. Previous studies have reported an increased risk of fracture after stroke, and it has been shown that patients with stroke or spinal cord injury have increased bone turnover or bone loss.

On the one hand, hospitalization may be a marker for decreased neuromuscular function that would increase the risk of fracture. It may also be a marker for lower bone mass, although we found no notable difference in the mean hip bone density of those who had subsequent hospitalizations vs those who did not. On the other hand, prolonged or frequent hospitalizations, and the conditions that lead to the hospital stay could also cause loss of neuromuscular function or bone loss that would increase fracture risk. Using combined data from the placebo group of clinical trials of risedronate, Heaney et al found about 0.5% to 2% more bone loss in the hip and spine after hospitalization for diverse causes than observed in participants over a similar period of time who were matched for age, weight, height, and prior fracture.

These findings have important clinical implications. The number of hospitalizations in older men and women is increasing each year. Interventions that effectively decrease the risk of fracture in this group could have a large impact on rates of fracture, quality of life, and health care expenditures. Whether hospitalization increases the risk for fractures or is a marker for frailty requires further research; however, this study identifies an important group at high risk for fractures and demonstrates an opportunity for interventions to decrease this risk.

Physicians should recognize that elderly patients, especially white women who have had 2 or more hospitalizations, have a substantially increased risk of fracture. The hospital stay may be an opportunity to begin evaluation of potential causes of increased risk of fracture and appropriate treatments to reduce that risk. Because the risk of fracture is greatest soon after hospital discharge, assessment and interventions to reduce risk should be started during the hospital stay or shortly after discharge. The evaluation might include measurement of BMD, assessment of risk of falls, and initiation of treatments to reduce bone loss and the risk of falls. Recognition that frequent hospital stays indicate an increased risk of fracture should prompt the development of guidelines for assessing and reducing risk of fracture in these patients.

Vitamin D deficiency is common in hospitalized patients; 1 study found a prevalence of 57% among patients in a general medical inpatient ward. Treatment of vitamin D deficiency may decrease bone loss, increase muscle strength, and improve coordination, which in some studies has been associated with a reduction in falls. Clinical trials and meta-analyses indicate that at least 800 IU of vitamin D supplementation reduces the risk of falls and fractures in elderly patients. Therefore, adequate supplementation with vitamin D should be part of hospital care and discharge treatment for older adults who have a vitamin D deficiency. The value of calcium supplementation is less certain, but it is reasonable to assure adequate intake of calcium along with vitamin D supplementation.

Physical therapy may minimize or restore the loss of neuromuscular function that occurs in the hospital, specifically, these interventions may include structured walking programs and exercise repetitions for flexibility, strength, and balance. Visual impairment is common in elderly patients, and screening for and treatment of impaired visual function can decrease the risk of falls and fractures.

A randomized trial found that risedronate reduced the risk of hip fracture in patients with stroke. Bisphosphonates may also protect against hospital-related bone loss. Guidelines recommend pharmacologic treatment for postmenopausal women who have low bone density, such as a femoral neck T score below −2.0 and at least 1 strong risk factor for fracture. Multiple hospitalizations might be considered a strong risk factor for fracture, similar to a history of fracture, when making decisions about pharmacologic treatment to prevent fractures.

This study has several strengths. The Health ABC Study cohort was drawn from population-based listings and includes men, women, black persons, and white persons. Data about hospitalization was collected prospectively, and the duration and discharge diagnoses were validated by expert review of medical records. Follow-up rates were very high, and fractures were systematically ascertained and validated by central review of radiographs. The study also has limitations. Participants were 70 to 79 years old and able to walk a quarter of a mile and climb steps without difficulty at entry into the study. Our findings might not be directly applicable to people of different ages and poorer physical function. There were too few fractures in men and black participants to reliably estimate their absolute risks of fracture after hospitalizations.

We conclude that among older patients, hospitalization, especially multiple admissions, indicates a substantially increased risk of hip and other fractures. This ob-
sorntional study cannot show that hospitalization caused the subsequent fractures; nevertheless, it is a strong marker of increased risk. Hospitalization is an unrecognized opportunity to assess and reduce the risk of fractures in a very large number of elderly women and men.

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Author Contributions: All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gardner and Cummings.
Acquisition of data: Cummings. Analysis and interpretation of data: Gardner, Harris, Vittinghoff, and Cummings. Drafting of the manuscript: Gardner, Harris, Vittinghoff, and Cummings. Critical revision of the manuscript for important intellectual content: Gardner, Vittinghoff, and Cummings. Statistical analysis: Harris and Vittinghoff. Obtained funding: Cummings. Administrative, technical, and material support: Cummings. Study supervision: Cummings.

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Previous Presentation: This study was an oral presentation at the Society of General Internal Medicine 30th Annual Meeting; April 27, 2007; Toronto, Ontario, Canada.

REFERENCES


