Increased Falling as a Risk Factor for Fracture among Older Women

The Study of Osteoporotic Fractures

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More frequent falling is associated with a higher risk of fracture among older women, but it is not known whether an increased rate of falling, independent of the average rate, also increases fracture risk. The authors examined the relation between an increase in the rate of falls during the first 4 years of follow-up and the subsequent fracture rate, reported for a median of 6.3 years (1986–1998), in 9,106 US women aged 65 years or more. Women in the upper quartile of increasing falls (>0.44 falls/year/year) had greater risks of subsequent hip fracture (rate ratio = 1.42, 95% confidence interval: 0.99, 2.04) and fracture of the proximal humerus (rate ratio = 1.79, 95% confidence interval: 1.08, 2.95) than women without an increase in falls, after adjustment for age, average rate of falls over 4 years, and known risk factors for fracture. Risks of distal forearm, ankle, or foot fracture were not elevated. The associations between fracture risk and increasing falls were not accounted for by baseline physical or cognitive function. An increase in the rate of falls, independent of the average rate, may be associated with a higher risk of frailty (hip and proximal humerus) fractures but not fractures at other sites.

accidental falls; aged; fractures; prospective studies; women

Abbreviations: CI, confidence interval; OR, odds ratio; RR, rate ratio; SOF, Study of Osteoporotic Fractures.

Osteoporotic fractures represent an important health and economic burden, with estimated annual costs in the United States of almost $15 billion (1). In persons aged 65 years or more, falls are a factor in over 80 percent of all nonspine fractures and over 90 percent of fractures of the hip, distal forearm, and proximal humerus (2). A history of falls is associated with an increased risk of fractures of the hip (3–5), proximal humerus (6, 7), distal forearm (8), and ankle (9), although an association has not been found for foot fractures (9). In addition to the number of falls, fracture risk is influenced by the direction of the fall, the protective responses of the faller, and bone strength (10). An increase in the rate of falling may reflect greater frailty and increased risk of fracture when a fall occurs. In this study, we considered the relation between an increase in the rate of falls over a period of several years and the subsequent rate of fractures of the hip, proximal humerus, distal forearm, ankle, and foot, using data from the Study of Osteoporotic Fractures (SOF), a prospective study of older women.

MATERIALS AND METHODS

The SOF, a prospective study of factors associated with osteoporosis and fractures, has been described in detail previously (3, 11). Briefly, 9,704 community-dwelling, mostly White women aged ≥65 years were recruited for the study in four areas: Portland, Oregon; Minneapolis, Minnesota; Baltimore, Maryland; and the Monongahela Valley, near Pittsburgh, Pennsylvania. Black women were excluded because of their low rate of hip fracture (12). Women who could not walk independently and those who had undergone bilateral hip replacement were also excluded. Baseline clinic visits took place during 1986–1988. All of the participants provided informed consent, and the institutional review
boards of the participating institutions approved the study protocol.

**Measurement of falls and fractures**

Following the baseline visit, the participants’ falls were monitored every 4 months. A letter with a return postcard was mailed to each participant asking whether she had fallen in the past 4 months and, if so, how many times. A fall was not defined in the letter but was described to participants during the baseline visit and semiannual interviews as “landing on the floor or ground, or falling and hitting an object like a table or stair.” For the results reported here, information on falls from the first 12 postcards, or approximately 4 years of follow-up, was used to determine the rate of falling for each participant. Two hundred and nineteen participants who returned fewer than six postcards were excluded. The remaining 9,485 women returned an average of 11.8 postcards (standard deviation, 0.8), for an average follow-up time of approximately 3.9 years (standard deviation, 0.3).

Study participants were asked to notify the local clinical center as soon as possible after any fracture. In addition, every 4 months, participants were asked about the occurrence of a fracture in the letter requesting information on falls. If a fracture was reported, the participant was contacted by telephone for additional information, including the immediate cause of the fracture. Medical records were requested for confirmation of the participant’s report of a fracture. Only fractures confirmed by a radiologist’s report were included (13).

The results reported here included fractures that occurred after the 12th postcard report (approximately 4 years after the baseline visit), up to October 1998, for a median follow-up time (counting from the 12th postcard) of 6.3 years. Of the baseline cohort of 9,704 women, 522 were deceased and 76 were lost to follow-up, leaving 9,106 participants available for analysis of fracture risk. All of these women had returned at least six of the 12 postcards; 99.8 percent had returned all 12. Fractures due to pathologic conditions, such as a neoplasm, and those caused by severe trauma, such as a motor vehicle accident, were excluded. Only the first fracture occurring after the 12th postcard at each specific site considered was included in these analyses. The specific fracture sites of interest were the hip, the proximal humerus, the distal forearm, the ankle, and the foot. In addition, all nonspine fractures were analyzed as a group.

**Measurement of covariates**

Measurement of covariates has been described previously (3, 14–16). At the baseline clinic visit, a self-administered questionnaire and in-clinic interview included assessment of physical activity, alcohol consumption in the past year, current cigarette smoking, medical history, personal and family history of fracture, use of medications, performance of instrumental activities of daily living, and cognitive function.

The following measurements were obtained during the baseline clinic visit: height, weight, waist and hip circumferences, grip strength, triceps extensor strength, tandem stand, gait speed, chair stand, corrected visual acuity, near and far depth perception, and contrast sensitivity. Bone mineral density was measured at the distal radius, the proximal radius, and the calcaneus (11).

**Statistical analysis**

Age-specific incidence rates and 95 percent confidence intervals for number of falls per year were calculated using age at the time of the fall. The numerator was the number of falls occurring during the 4-year study period, and the denominator was person-years of follow-up during the same 4 years, based on the number of postcards returned (17). Change in the rate of falling over the first 4 years was estimated for each participant using a within-person linear regression method. The rate of falls (determined using each returned postcard) was regressed on time, and the resulting slope is reported as the change in the rate of falls per year (falls/year/year).

The Cox proportional hazards model (18) in SAS (19) was used to assess the association between rate of falls in the first 4 years and time to first subsequent fracture. Since the rate of falls and the rate of fracture increased with age, data in all of the models were adjusted for age at baseline. In these models, the participant’s rate of change in the fall rate (slope described above) was used as a main independent variable, with the participant’s average rate of falls entered as a covariate. Both the change in the rate of falls and the average rate of falls were entered into the model as categorical variables. The reference group for the average rate of falls was participants who reported no falls in the first 4 years. For change in the rate of falls, the reference group was women who had a stable or decreasing rate of falls in the first 4 years, including those who reported no falls.

In the reported analyses, except where specifically noted, we included fractures due to a fall from any height and fractures due to other minimal or moderate trauma. When the analyses were restricted to fractures due to a fall, the associations with number of falls and change in the rate of falls were not altered substantially, and the results are not shown.

To assess the relations between an increasing rate of falls and variables known to be associated with fracture risk, such as impaired functional ability, we used logistic regression models. The outcome was being in the top quartile of persons with an increasing rate of falls. All models were adjusted for age at baseline.

Using variables that are known to be associated with fracture risk, we then constructed separate multivariate Cox proportional hazards models for fractures of the hip, proximal humerus, distal forearm, ankle, and foot using backward regression. Covariates were selected for initial entry into the models on the basis of factors (excluding falls) associated with fractures of the hip (3), proximal humerus (20), distal forearm (20), ankle (9), and foot (9) in previous reports on the SOF cohort—including body size, medication use, lifestyle factors, physical function, cognitive function, vision, and comorbid conditions. Variables for the average rate of falls and the change in the rate of falls for the first 4 years were added to the variables selected as a result of back-
ward regression ($p < 0.05$) to obtain the multivariate models discussed here.

RESULTS

The average age at baseline of the 9,485 women included in the analyses was 71.6 years (standard deviation, 5.3; range, 65–99 years). The age-specific rate of falling was higher at older ages, ranging from 43 falls per 100 person-years for women aged 65–69 years to 87 falls per 100 person-years among women aged 85 years or more. Forty percent of the participants reported no falls in the 4-year period. Approximately 5 percent of the participants fell at an average rate of more than 1.75 falls per year.

During follow-up, the rate of falls increased for approximately 30 percent of the participants and decreased for another 30 percent. The average change in the rate of falls increased with age, ranging from an annual increase of 1.2 falls per 100 years per year for women aged 65–69 years to 17.4 falls per 100 years per year for women aged 85 years or more.

During follow-up after the 12th postcard, 1,541 women reported at least one confirmed nonspine fracture, excluding fractures due to severe trauma or pathology. The 1,933 confirmed fractures included fractures of the hip ($n = 388$), distal forearm ($n = 326$), proximal humerus ($n = 212$), ankle ($n = 148$), foot ($n = 144$), and other sites.

Compared with the 3,634 women who had no falls in the first 4 years, women who reported an average rate of more than 1.75 falls per year in the first 4 years of follow-up (“frequent fallers”) had nearly double the rate of subsequent hip fracture (rate ratio [RR] = 1.85) and distal forearm fracture (RR = 1.87) (table 1). Frequent fallers had a somewhat increased rate of foot fracture (RR = 1.50) but only a slightly increased rate of ankle (RR = 1.24) and proximal humerus (RR = 1.17) fracture in comparison with women who never fell. Frequent fallers also had an increased rate of all nonspine fractures (RR = 1.88).

Women with a decreasing rate of falls ($n = 2,629$) had rates of subsequent fracture for the five specific fracture sites and for all nonspine fractures that were similar to those of women who experienced no change in the rate of falls. Therefore, women with decreasing and stable rates of falls were combined into one reference group ($n = 6,379$) in further analyses of an increase in falls and risk of fracture. This included the 3,634 participants who reported no falls during the 4 years of follow-up, 116 women who fell at least once but had no change in the rate of falls, and the 2,629 women with a decreasing rate of falls.

In age-adjusted models, women in the top quartile of rate of increase in falls during the first 4 years of follow-up were at greater risk of subsequent hip fracture (RR = 1.83, 95 percent confidence interval [CI]: 1.35, 2.48), proximal humerus fracture (RR = 1.58, 95 percent CI: 1.02, 2.44), and all nonspine fractures (RR = 1.49, 95 percent CI: 1.26, 1.76) than women who had no change or a decline in the rate of falls. In models adjusted for the average rate of falls in the first 4 years (table 2), being in the top quartile of increasing falls continued to be associated with hip (RR = 1.57) and proximal humerus (RR = 1.65) fracture. An increasing rate of falls was not associated with a higher rate of distal forearm, ankle, or foot fracture, with or without controlling for the average rate of falls. These results were similar in analyses that excluded the 3,634 women who did not report any falls (results not shown).

To determine whether an increasing rate of falls was associated with a higher fracture risk because of its association with a higher rate of falls during fracture follow-up, we considered models adjusting for the average rate of falls in years 5–8 in addition to the average rate of falls in years 1–4. Being in the top quartile of an increasing rate of falls remained associated with a higher rate of hip and proximal humerus fractures in these models (results not shown).

To determine whether an increase in the rate of falls was associated with higher fracture rates because of an association with other known risk factors for fractures, such as poor physical function, we used the risk factors for fracture identified in previous studies of this cohort (3, 9, 20). We first assessed whether these risk factors for fracture were also associated with being in the top quartile of increasing falls. For the variables considered, the associations were relatively weak (for a one-standard-deviation change, odds ratio [OR] < 2.0). For example, women with weaker grip strength (for a reduction of 4.3 kg, OR = 1.13, 95 percent CI: 1.04, 1.23), slower walking speed (for a reduction of 0.22 seconds, OR = 1.14, 95 percent CI: 1.05, 1.24), or poorer visual acuity were associated with a higher rate of hip and proximal humerus fractures in these models (results not shown).
Ankle, or forearm fractures, is consistent with our hypothesis that an increased rate of falls is indicative of greater frailty. Hip and proximal humerus fractures are considered “frailty” fractures, distinguished by their strong association with declines in physical function. Different risk factor profiles among older women for sustaining a hip fracture versus a distal forearm fracture (21, 22) or for sustaining a proximal humerus fracture versus a distal forearm fracture (20) have been previously reported.

The increases in falling associated with higher fracture risk were relatively modest. Among women in the top quartile of an increasing rate of falls (n = 672), the average increase was 1.04 falls per year per year (range, 0.45–23.7 falls/year/year). At this average rate of increase, a participant who fell once during the first year of the study would have had four falls in the fourth year of the study.

Using prospective data on 4 years of fall history, we also confirmed previous reports, based on retrospective reports of falls, of a positive association between a history of falls and the risk of fractures of the hip (3–5) and distal forearm (6, 8, 20) and a lack of association for foot fractures (9). A previous report from the SOF using a baseline report of falls in the previous year also found no increased risk of proximal humerus fracture among women who had fallen (20). However, other investigators have reported that a history of falling is associated with risk of proximal humerus fracture (6, 7). We found little association between falls and subsequent ankle fracture, in contrast to a previous report of a positive association in the SOF cohort, using a baseline report of falls in the previous year (9).

An increase in the rate of falls appears to provide additional information regarding subsequent risk of fracture as compared with the absolute number of falls. An increasing rate of falls in one time period may simply be a better predictor of the subsequent rate of falls. However, it may also predict factors that contribute to the risk of fracture given a fall, including reduced protective responses, the direction of a fall, and lower bone mineral density. In our analyses, adjusting for the average rate of falls before (years

### Table 2. Rate ratios* for the association between increasing rate of falls in the first 4 years of follow-up and subsequent fractures among women aged 65 years or more, by fracture site, with adjustment for age at baseline and rate of falls in the first 4 years, Study of Osteoporotic Fractures, 1986–1998

<table>
<thead>
<tr>
<th>Change in rate of falls in the first 4 years (no. of falls/year/year)</th>
<th>No. of participants</th>
<th>Site of fracture</th>
<th>Rate ratios†</th>
<th>95% CI†</th>
<th>Rate ratios†</th>
<th>95% CI†</th>
<th>Rate ratios†</th>
<th>95% CI†</th>
<th>Rate ratios†</th>
<th>95% CI†</th>
<th>Rate ratios†</th>
<th>95% CI†</th>
<th>Rate ratios†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change or decrease</td>
<td>6,379</td>
<td>Hip</td>
<td>1.00‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Quartile of increasing fall rate</td>
<td></td>
<td>Proximal humerus</td>
<td>1.00‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.001–0.13</td>
<td>681</td>
<td>Distal forearm</td>
<td>0.85</td>
<td>0.55, 1.31</td>
<td>0.84</td>
<td>0.45, 1.57</td>
<td>0.89</td>
<td>0.73, 1.09</td>
<td>0.89</td>
<td>0.73, 1.09</td>
<td>0.89</td>
<td>0.73, 1.09</td>
<td>0.89</td>
<td>0.73, 1.09</td>
</tr>
<tr>
<td>0.14–0.27</td>
<td>634</td>
<td>Ankle</td>
<td>0.85</td>
<td>0.47, 1.54</td>
<td>0.66</td>
<td>0.40, 1.09</td>
<td>0.70</td>
<td>0.33, 1.48</td>
<td>0.84</td>
<td>0.44, 1.61</td>
<td>0.83</td>
<td>0.67, 1.03</td>
<td>0.83</td>
<td>0.67, 1.03</td>
</tr>
<tr>
<td>0.28–0.44</td>
<td>740</td>
<td>Foot</td>
<td>0.92</td>
<td>0.53, 1.59</td>
<td>0.67</td>
<td>0.42, 1.07</td>
<td>0.89</td>
<td>0.48, 1.67</td>
<td>0.87</td>
<td>0.47, 1.59</td>
<td>1.02</td>
<td>0.85, 1.23</td>
<td>1.02</td>
<td>0.85, 1.23</td>
</tr>
<tr>
<td>&gt;0.44</td>
<td>672</td>
<td>All nonspine fractures</td>
<td>0.98</td>
<td>0.64, 1.51</td>
<td>0.53</td>
<td>0.23, 1.20</td>
<td>0.64</td>
<td>0.30, 1.39</td>
<td>1.15</td>
<td>0.95, 1.40</td>
<td>1.15</td>
<td>0.95, 1.40</td>
<td>1.15</td>
<td>0.95, 1.40</td>
</tr>
</tbody>
</table>

* Rate ratios were calculated by means of the Cox proportional hazards model. Data in all models were adjusted for age at baseline and rate of falling during the first 4 years of follow-up.
† RR, rate ratio; CI, confidence interval.
‡ Reference category.

(for a reduction of 7.3 letters read, OR = 1.10, 95 percent CI: 1.02, 1.19) were just slightly more likely to be in the top quartile of increasing falls. The largest association was with use of seizure medications at baseline (OR = 1.87, 95 percent CI: 1.03, 3.37).

We next assessed whether these previously identified risk factors for fracture might alter the association between an increase in the rate of falls and risk of fracture. The results for hip and proximal humerus fracture are presented in table 3. For hip fracture, the association between being in the top quartile of an increasing rate of falls and subsequent fracture (RR = 1.42, 95 percent CI: 0.99, 2.04) in the resulting multivariate model was attenuated by approximately 10 percent in comparison with models adjusted only for age and number of falls (RR = 1.57, 95 percent CI: 1.10, 2.23). For proximal humerus fracture, there was a slightly greater association between the upper quartile of increase in falls and the risk of proximal humerus fracture (RR = 1.79, 95 percent CI: 1.08, 2.95) in the multivariate model than in the model adjusted only for age and number of falls (RR = 1.65, 95 percent CI: 1.00, 2.72). For the other specific fracture sites considered (distal forearm, ankle, and foot), there was no association in the multivariate models between being in the upper quartile of increase in the rate of falls and the risk of fracture, as found in the models adjusted only for age and number of falls.

### DISCUSSION

In this study, we found that an increasing rate of falling was associated with a higher rate of subsequent hip and proximal humerus fracture, controlling for the average rate of falling, but increasing falls were not associated with distal forearm, ankle, or foot fractures or all nonspine fractures. To our knowledge, information on change in the rate of falls and the subsequent fracture rate has not been reported before.

Our finding of an association between an increased rate of falls and hip and proximal humerus fractures, but not foot, ankle, or forearm fractures, is consistent with our hypothesis that an increased rate of falls is indicative of greater frailty. Hip and proximal humerus fractures are considered “frailty” fractures, distinguished by their strong association with declines in physical function. Different risk factor profiles among older women for sustaining a hip fracture versus a distal forearm fracture (21, 22) or for sustaining a proximal humerus fracture versus a distal forearm fracture (20) have been previously reported.

The increases in falling associated with higher fracture risk were relatively modest. Among women in the top quartile of an increasing rate of falls (n = 672), the average increase was 1.04 falls per year per year (range, 0.45–23.7 falls/year/year). At this average rate of increase, a participant who fell once during the first year of the study would have had four falls in the fourth year of the study.

Using prospective data on 4 years of fall history, we also confirmed previous reports, based on retrospective reports of falls, of a positive association between a history of falls and the risk of fractures of the hip (3–5) and distal forearm (6, 8, 20) and a lack of association for foot fractures (9). A previous report from the SOF using a baseline report of falls in the previous year also found no increased risk of proximal humerus fracture among women who had fallen (20). However, other investigators have reported that a history of falling is associated with risk of proximal humerus fracture (6, 7). We found little association between falls and subsequent ankle fracture, in contrast to a previous report of a positive association in the SOF cohort, using a baseline report of falls in the previous year (9).
1–4) and during (years 5–8) the fracture follow-up period did not account for the association between an increasing rate of falls and the risk of hip and proximal humerus fractures. This suggests that an increase in the rate of falls is associated with an increased risk of sustaining a fracture when a fall occurs.

We had originally hypothesized that an increase in the rate of falls might be a marker for poor function and that any association between increasing falls and the risk of subsequent fracture would be largely accounted for by associated poor function or performance. We did find that an increasing rate of falls was weakly associated with several measures of poor physical function. However, in the multivariate models constructed for hip and proximal humerus fracture, we found that the association between increasing falls and the risk of fracture was not substantially attenuated in comparison with models adjusted only for age and the average rate of falls. This suggests that there is an aspect of poor function that was not adequately captured in the available measures. The battery of tests performed at the clinic visits included measures of the major risk factors generally associated with falls (2). However, the tests used may not be able to distinguish smaller decrements or specific aspects of performance that are nevertheless important in determining the outcome of a fall. In addition, level of function at baseline may not adequately predict changes in function over time, and these changes may be more influential in determining risk of fracture in a fall.

We have reported findings for all nonspine fractures, but we believe that these results should be interpreted with caution. In the analyses of specific fracture sites, associations between the average rate of falls and risk of fracture differed across sites, and so did associations between increasing falls and risk of fracture. Therefore, it can be misleading to combine them.

This study included extensive prospective data on both falls and fractures in older women. However, it also had certain limitations. Falls were ascertained every 4 months. It is likely that some falls were forgotten and not reported and also possible that some falls were reported more than once (23). However, the age-specific incidence rates of falls in this study are consistent with results from studies that collected fall reports on a monthly basis (24, 25). The study population was almost entirely White, and the study was conducted among community-dwelling women. The results may not apply to non-White women or to older women residing in institutions.

In summary, in our study, a more rapid increase in the rate of falls appeared to be associated with hip and proximal

| TABLE 3. Multivariate adjusted rate ratios* for the associations between change in the rate of falls during the first 4 years of follow-up and subsequent hip and proximal humerus fractures among women aged 65 years or more, Study of Osteoporotic Fractures, 1986–1998 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Measurement                      | Site of fracture | Hip†            | Proximal humerus‡ |
| No change or decrease            | RR§             | 95% CI§         | RR              | 95% CI          |
| Quartile of increasing rate of falls |                 |                 |                 |
| 0.001–0.13                       | 1.00¶           | 1.00¶           |                 |
| 0.14–0.27                        | 1.04            | 0.69, 1.55      | 0.89            | 0.50, 1.60      |
| 0.28–0.44                        | 0.97            | 0.64, 1.47      | 0.87            | 0.48, 1.60      |
| >0.44                            | 1.33            | 0.93, 1.91      | 0.97            | 0.56, 1.69      |
| Rate of falls in the first 4 years (no. of falls/year) |                 |                 |                 |
| 0                                | 1.00¶           | 1.00¶           |                 |
| 0.01–0.75                        | 1.16            | 0.88, 1.52      | 1.00            | 0.70, 1.41      |
| 0.76–1.75                        | 1.25            | 0.88, 1.79      | 0.83            | 0.49, 1.39      |
| >1.75                            | 1.38            | 0.86, 2.21      | 0.75            | 0.36, 1.56      |

* Rate ratios were calculated by means of the Cox proportional hazards model, using backward regression first and then adding variables for falls.
† Adjusted for the other variables in the table and for age, current use of thyroid hormone pills, current smoking, alcohol consumption in the past year, fracture after age 50 years, history of maternal hip fracture, being on one’s feet for less than 4 hours per day, gait speed, using arms for chair standing, contrast sensitivity, height at age 25 years, weight, and calcaneal bone mineral density (n = 8,864; 242 women had missing values for one or more variables).
‡ Adjusted for the other variables in the table and for height loss since age 25 years, gait speed, waist:hip ratio, and distal radius bone mineral density (n = 8,990; 116 women had missing values for one or more variables).
§ RR, rate ratio; CI, confidence interval.
¶ Reference category.
humerus fractures, taking into account the average rate of falls, but not with distal forearm, ankle, or foot fractures. The increasing rate of falls may be a marker for aspects of frailty that contribute to the risk of sustaining a hip or proximal humerus fracture in a fall. The associations between risk of hip and proximal humerus fracture and an increasing rate of falls were not fully accounted for by the baseline measurements of physical and cognitive function.

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REFERENCES