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*Original Article*

# Family History of Appendicular Fracture and Risk of Osteoporosis: A Population-Based Study

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**Abstract.** Family and twin studies demonstrate a strong genetic component to osteoporosis, suggesting that a positive family history for this disease may be an important clinical risk factor. We have therefore explored the extent to which a history of wrist fracture in a female first-degree relative was associated with an increased risk of prevalent fracture at both appendicular and vertebral sites in a cross-sectional study design. One thousand and three Caucasian women (age range 45–64 years) were studied from a UK population cohort. Bone mineral density (BMD) was measured at the lumbar spine and femoral neck using dual-energy X-ray absorptiometry. Appendicular fractures (wrist and hip) were recorded by questionnaire and validated from radiographs and hospital records. Vertebral fractures were assessed using radiologic survey of the thoracolumbar spine and semi-automated morphometric analysis. A positive family history of osteoporotic fracture (hip and/or wrist) in either a mother and/or sister was reported in 138 of the 1003 women. When compared with those with a negative family history of fracture, BMD was significantly reduced in those with a positive history at both the spine ($p = 0.02$) and the hip ($p = 0.02$). In total, there were 63 validated fragility fractures found in the 1003 women (16 wrist, 6 hip and 41 vertebral). Family history of osteoporotic fracture was associated with an increased total risk for osteoporotic fracture, with an odds ratio (95% confidence interval) of 2.02 (1.02, 3.78). Site-specific analysis showed that a positive family history of wrist fracture was associated with a considerably elevated risk of wrist fracture, with an odds ratio of 4.24 (1.44, 12.67). These increases in risk remained after adjustment for BMD, suggesting that other genetic factors account for the familial risk of osteoporosis and fracture.

**Keywords:** Colles' fracture; Familial; Fracture; Genetic; Osteoporosis; Wrist

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## Introduction

Osteoporosis is an increasing health care problem, with a Caucasian woman having a 30% lifetime risk for sustaining an osteoporotic-related fracture. Family and twin studies have demonstrated that osteoporosis is under strong genetic control, with female first-degree relatives of women with osteoporosis having reduced bone mineral density (BMD) at both the spine and hip when compared with healthy controls [1–5]. Maternal history of fracture at the hip and wrist has recently been shown to be a positive risk factor for fracture in elderly women [6,7], although the relationship between family history and fracture occurring at earlier ages and at other important sites such as the spine remains unclear. The principal aim of this study was therefore to investigate whether a history of fracture in female first-degree relatives (i.e., mother and/or sisters) was associated with both low BMD and prevalent fracture risk in women aged 45–64 years from a UK general-practice-based population, where validated information was available on both peripheral and vertebral fractures.

## Subjects and Methods

### *Subjects*

The study design was a cross-sectional case–control study. Women in the age range 45–64 years were selected from a large single general practice in Chingford, North-East London (total of 11 000 registered patients) to participate in a longitudinal epidemiologic study of rheumatic diseases [8,9]. A total of 1353 women were found to be in the age range specified, and of these 78% (1003) agreed to participate [8]. The area is predominantly middle class, 98% are white and the population is similar to UK normals in terms of height, weight, smoking status, hysterectomy rates and use of hormone replacement therapy (HRT). The study was approved by the local ethics committee and all women gave informed consent to participate.

### *Questionnaires*

At their initial visit all women completed a nurse-administered questionnaire detailing risk factors for osteoporosis. Self-reported personal history of fracture was taken for the 10-year period preceding the study's onset (1978–88), with osteoporotic fractures defined as fractures at the wrist and hip that had occurred after minimal trauma and at age over 35 years. The circumstances under which the fracture had occurred were detailed in a postal trauma questionnaire that had been previously validated [9]. Major traumatic fractures were classified as those occurring following a road traffic accident, a fall from the height of a chair or greater, or a fall down a flight of stairs. Reported family history of osteoporotic fractures occurring at either hip or wrist in a female first-degree relative aged more than 35 years and after minimal trauma was also recorded by the study nurse at the subject's initial visit. These fractures occurring in relatives were not able to be validated.

### *Fracture Validation*

To validate fractures, the general practitioner's notes were examined for all women reporting a fracture and for 50 randomly selected subjects who had not reported fracture, as previously described [9]. A fracture was confirmed if the notes contained a radiology report or a direct reference to it in a letter from the casualty or orthopedic departments. The percentage of total reported fractures that were validated by this process has been reported as 100% at the hip and 67% at the wrist [9]. Spine fractures, which are mostly asymptomatic, were defined morphometrically by radiologic survey of the thoracic (T4–12) and lumbar (L1–4) vertebrae using standardized procedures. Morphometric analysis was performed using a semi-automated digitizer and a validated algorithm that utilized standard deviation (SD) cutoffs of anterior and posterior height [10]. A fracture was defined as at least two 2 SD deformities or one 3 SD deformity, with these criteria being shown to be equivalent to more stringent cutoffs used by other groups [11,12]. As the majority of vertebral fractures are asymptomatic, it was not possible to perform a trauma questionnaire accurately. All vertebral fractures were therefore assumed to be nontraumatic.

### *Bone Densitometry Measurement*

BMD was measured at the lumbar spine (L1–4) and femoral neck using dual-energy X-ray absorptiometry with a Hologic QDR-1000 (Hologic, Waltham, MA). Reproducibility (CV%), assessed by duplicate measures in healthy volunteers, was 0.8% at the spine and 1.4% at the hip. Subjects were classified as having definite osteoporosis at either the spine or hip using the criteria defined by the World Health Organization (i.e., BMD more than 2.5 SD below the mean peak young adulthood value for that site) [13].

### *Statistical Analysis*

Differences in demographic variables between subjects with a positive family history for fracture and those with a negative history were compared by an unpaired *t*-test for normally distributed variables and by a Mann–Whitney *U*-test for nonparametric variables. Categorical variables were analyzed using a $\chi^2$ test. Multivariate analysis was performed using logistic regression to estimate the odds ratio and 95% test-based confidence intervals for sustaining a fracture by family history fracture status with adjustment for potential confounders. The sensitivity, specificity, and positive and negative predictive values for family history of fracture as tools in the assessment of osteoporosis and fracture risk were assessed. The positive and negative likelihood ratios for a positive family history were also calculated. All analysis was performed using the PC software statistical program STATA.

## Results

Cross-sectional data were available on 1003 women, mean age (SD) 54.2 (6.0) years. A history of hip fracture in female first-degree relative was reported in 44 subjects (39 maternal and 5 sibling fractures). At the wrist 107 fractures were reported (83 maternal and 24 sibling), with 6 subjects having a history of fracture at this site in both their mother and a sister. In total, a positive family history of osteoporotic fracture at hip and/or wrist in either a mother and/or sister was reported in 138 of the 1003 women.

There were no significant differences between the family fracture history groups with regard to the potential confounders of age, body mass index (BMI), menopause age and duration, smoking status and HRT

**Table 1.** Characteristics of 1003 women according to the presence or absence of a family history for osteoporotic fracture (hip and/or wrist) in a female first-degree relative

| Variable | Positive family history ($n$ = 138) | Negative family history ($n$ = 865) | $p$-value |
|---|---|---|---|
| Age (years) | 54.2 (6.2) | 54.2 (6.0) | 0.99 |
| No. of postmenopausal subjects (%) | 102 (74%) | 622 (72%) | 0.64 |
| Time since menopause (years) | 8.0 (5.4) | 8.6 (6.0) | 0.29 |
| BMI (kg/m$^2$) | 25.4 (4.5) | 25.6 (4.3) | 0.54 |
| No. ever use of HRT (%) | 31 (22%) | 207 (24%) | 0.70 |
| No. ever smoking (%) | 61 (44%) | 402 (46%) | 0.63 |
| Lumbar spine BMD (g/cm$^2$) | 0.94 (0.16) | 0.98 (0.16) | 0.02 |
| Femoral neck BMD (g/cm$^2$) | 0.74 (0.12) | 0.77 (0.12) | 0.02 |
| No. of subjects with osteoporotic fractures (%) | 14 (10%) | 46 (5%) | 0.03 |

Values are the mean $\pm$ SD unless indicated.
BMI, body mass index.

use (Table 1). When compared with those with a negative family history of fracture, BMD was significantly reduced in those with a positive history both at the spine [mean difference (95% CI) of 0.04 g/cm$^2$ (0.00, 0.08), $p = 0.02$] and at the hip [mean difference 0.03 g/cm$^2$ (0.00, 0.05), $p = 0.02$]. Within the total cohort of 1003 women the prevalence of established osteoporosis was 9.9% at the lumbar spine and 2.5% at the femoral neck. The risk of a subject having spinal osteoporosis was increased in those with a positive family fracture history when compared with those with a negative history, with an odds ratio (95% CI) of 1.82 (1.08, 3.05), $p = 0.02$. A similar trend was also seen at the hip, although this was nonsignificant, with an odds ratio of 1.72 (0.63, 4.71), $p = 0.29$.

After validation, there were 23 reported fractures at the wrist and 6 at the hip. After exclusion of fractures due to major trauma, 16 wrist fractures were assumed to be fragility fractures related to osteoporosis. All 6 hip fractures occurred after minimal trauma. From the radiologic survey of the thoracolumbar spine, 41 prevalent vertebral deformities consistent with fracture were identified. In total, therefore, 60 subjects were found to have validated evidence of prevalent osteoporotic fractures at either the spine, hip or wrist, with 1 woman having fractures at both hip and spine whilst a further 2 women had fractures at both the spine and wrist.

Family history of osteoporotic fracture was associated with an increased fracture risk, with an odds ratio of 2.02 (1.02, 3.78). This increase in risk was virtually unchanged after adjustment for BMD and other potential confounding variables (Table 2). The increase in risk associated with the positive family history appeared related to appendicular fractures rather than vertebral deformity/fracture, and site-specific analysis showed that a positive family history of wrist fracture was associated with a 4-fold increased risk of wrist fracture (Table 3). Again, this increase in risk remained significant after adjustment for BMD. There was, however, no significant relationship between a positive family history of wrist fracture and prevalent fracture status at either the spine or hip. There was also no apparent relationship between

**Table 2.** Fracture risk associated with a positive family history for osteoporotic fracture at wrist and/or hip

| Fracture site in study subjects | Odds ratio | |
|---|---|---|
| | Crude | Adjusted[a] |
| Any fracture ($n$ = 60 subjects) | 2.02 (1.02, 3.78) | 2.00 (1.04, 3.83) |
| Spine ($n$ = 41 subjects) | 1.20 (0.52, 2.74) | 1.11[b] (0.48, 2.59) |
| Appendicular ($n$ = 22 subjects) | 3.04 (1.21, 7.59) | 2.70 (1.05, 6.92) |
| Wrist ($n$ = 16 subjects) | 2.91 (0.99, 8.50) | 2.54 (0.85, 7.65) |
| Hip ($n$ = 6 subjects) | 3.17 (0.57, 17.45) | 2.72 (0.48, 15.26) |

Values are the odds ratio (95% CI).
[a] Adjusted for age, hip BMD, BMI.
[b] Adjusted for age, spine BMD, BMI.

**Table 3.** Fracture risk associated with a positive family history for osteoporotic fracture at wrist

| | Prevalent vertebral fracture: odds ratio | | Prevalent wrist fracture: odds ratio | | Prevalent hip fracture: odds ratio | |
|---|---|---|---|---|---|---|
| Family fracture history | Crude | Adjusted[b] | Crude | Adjusted[a] | Crude | Adjusted[a] |
| Wrist | 1.79 (0.77, 4.13) | 1.87 (0.79, 4.41) | 4.24 (1.44, 12.67) | 4.74 (1.55, 14.51) | 1.79 (0.21, 15.51) | 1.81 (0.21, 15.95) |

Values are the odds ratio (95% CI).
[a] Adjusted for age, hip BMD, BMI.
[b] Adjusted for age, spine BMD, BMI.

**Table 4.** Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios for family fracture history for risk of osteoporosis and osteoporotic fracture

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | +ve likelihood ratio | −ve likelihood ratio |
|---|---|---|---|---|---|---|
| Spinal osteoporosis | 15.2 | 91.0 | 21.2 | 87.1 | 1.7 | 0.93 |
| Hip osteoporosis | 20.3 | 84.2 | 17.0 | 86.9 | 1.3 | 0.95 |
| Any osteoporotic fracture | 10.1 | 94.7 | 23.3 | 86.8 | 1.9 | 0.95 |
| Spine fracture | 16.3 | 86.3 | 54.3 | 50.8 | 1.2 | 0.97 |
| Hip fracture | 33.3 | 86.4 | 14.6 | 99.5 | 2.4 | 0.77 |
| Wrist fracture | 31.3 | 86.5 | 3.6 | 55.3 | 2.3 | 0.79 |

a positive family history of hip fracture and risk of prevalent fracture at spine, hip or wrist. Specifically, the risk of prevalent hip fracture in those with a positive family history of hip fracture was not significantly increased [crude OR = 3.83 (0.44, 33.49)]. The wide confidence intervals of this estimate reflect the fact that the number of hip fractures in subjects and their first-degree relatives was small and the model is potentially unstable. The results relating family history of fracture to risk of fracture were also essentially unaltered if all reported osteoporotic fractures were included rather than only those that had been validated (data not shown).

The sensitivities, specificities, and positive predictive and negative predictive values of family fracture history for assessment of spinal and hip osteoporosis, and for any osteoporotic fracture at the wrist, hip and spine, are shown in Table 4. Site-specific analysis at the wrist showed that for a positive family history of wrist fracture the sensitivity to predict prevalent wrist fracture was 5%, the specificity 98.8%, the positive predictive value 31.3% and the negative predictive value 90.3%. The corresponding positive likelihood ratio for a positive family history of wrist fracture and risk of prevalent wrist fracture was 4.17, with the negative likelihood ratio being 0.96.

## Discussion

In this cohort of women, history of fracture in a female first-degree relative was associated with a 2-fold increased risk of osteoporotic fracture. This increase in risk appeared site-specific, as a 4-fold increased risk of wrist fracture was observed in subjects with a mother and/or sister who had previously sustained fractures at this site. These data support a strong genetic component to factors associated with osteoporotic fracture, particularly at the wrist. Epidemiologic data show forearm fracture incidence rates in women increase linearly from age 40 to 65 years and then plateau [14]. Wrist fracture is therefore one of the earliest signs of skeletal failure secondary to osteoporosis, and fracture at this site has been shown to be associated with the more serious increased risk of vertebral and hip fracture in later life [15]. Our findings therefore suggest that a positive family history of wrist fracture may identify women at increased risk of skeletal fragility in later life.

In this study we have been able to uniquely address the issue of site specificity for family history and fracture as we have validated data on both appendicular and vertebral fractures. Family history was obtained only for appendicular fractures (hip and/or wrist) as most vertebral fractures are asymptomatic, and to identify these accurately in female first-degree relatives would have required radiologic screening. Our data suggest that family history is site-specific, as a positive family history for appendicular fracture was associated with wrist and/or hip fractures but not with spinal fractures. The finding that the increase in fracture risk associated with a positive family history was unaltered after adjustment for BMD suggests that common, within-family factors (both genetic and environmental) other than BMD may be contributing to this familial clustering of fracture risk. Bone structure and architecture have been shown to be under genetic control independent of BMD [1], and have also been demonstrated to be independent predictors of hip fracture in elderly populations [16,17]. The finding that the increase in risk was independent of BMD may also indicate a possible familial component to the risk of falling, with the genetic effect being mediated through factors such as muscle strength and proprioception [18]. The finding that that a positive family history for wrist fracture was associated with a 4-fold increased risk of wrist fracture although no increase fracture risk was observed at the hip would support the concept of a site-specific predisposition to fracture associated with family history rather than it being related to the risk of falling.

To date, evidence for site specificity in fracture risk has been observed in the Study of Osteoporotic Fractures, where the risk of incident hip fracture was increased 2-fold in those with a positive maternal history of hip fracture, although other types of maternal fracture associated with falling did not increase the risk of hip fracture [6]. In addition, further work from this group has recently shown that parental (both mother and father) history of wrist fracture was associated with an increased risk of incident wrist fracture, whereas a family history of hip fracture was not associated with any increased risk [7]. These increases were also independent of a subject's BMD at both the radius and hip, for wrist and hip fracture respectively [6,7]. History of wrist fracture in a sister or brother was also not associated with any increase in incident wrist fracture risk. Torgerson et al. [19] have also shown in a 2-year study of 1857

perimenopausal women (age range 47–51 years) that the risk of any self-reported appendicular fracture was increased 3-fold in those with a history of hip fracture in a maternal grandmother. This increase in risk also appeared independent of a subject's BMD. Due to the younger age of this cohort no hip fractures were observed during the study period. Site specificity in fracture risk may also explain the results obtained from the European Vertebral Osteoporosis Study (EVOS) [20]. In this study, a parental history of hip fracture was not associated with an increased risk of prevalent vertebral deformity in women, although a modest association was observed between maternal history of hip fracture and vertebral deformity in men. Other work from this study has suggested that these deformities in men are more likely to be traumatic in etiology, and the importance of family history in this instance is therefore unclear [21,22]. Two further studies have examined the relationship between family history of osteoporosis and wrist fracture. In a population study of 877 women (mean age 74 $\pm$ 7 years), Soroko et al. [23] have demonstrated that paternal, but not maternal, history of osteoporosis and/or fracture was associated with personal history of any fracture (spine, hip, wrist, forearm and pelvis) after the age of 50 years. In this study, family history included any fracture sustained after the age of 50 years with no assessment of the circumstances regarding trauma. In addition, there was no record of fracture validation in either the cases or relatives. In a population-based case–control study of 302 women (mean age 63 $\pm$ 10 years), Mallmin et al. [24] have demonstrated a 48% increased risk for wrist fracture in women reporting a positive parental history of fracture at either the hip and/or wrist, with this increase in risk again appearing to be predominantly due to paternal history. Fractures were again not validated in the relatives and results were not subdivided to show the direct relationship between a family history of wrist fracture and wrist fracture in the cases.

Our study being retrospective in design makes it subject to several potential limitations. Prevalent appendicular fractures were determined by reported history and subsequently validated from patients' medical records. The main reason that fractures could not be validated was that subjects had either died or moved away from the area and we were therefore not able to access their medical records. The proportion of reported fractures that were not subsequently validated did not differ between the family history groups. In addition, our results were essentially unaltered if all reported fractures rather than verified fractures were analyzed. Our results are also similar to those that have recently been reported with incident wrist fractures in a more elderly population [7]. We were not able to define clinically apparent vertebral fractures and it was also not possible accurately to assess trauma details in these instances. We therefore cannot exclude the possibility that we have included vertebral deformities and traumatic, nonosteoporotic-related vertebral fractures in our analysis. Our definition for vertebral fracture was, however, stringent and has been shown to be associated with low BMD and reduced height [25]. At present there is no agreed gold standard for the definition of vertebral fractures, although the prevalence of vertebral deformities consistent with fracture in our population was 4% and was similar to that observed in women of a similar mean age in the EVOS study [22].

As with all the quoted family-based studies above, our estimates of family history were based on recall only and we were unable to validate these fractures directly in relatives. Reporting of osteoporotic fracture in family members may also have been biased by the subjects' awareness of their own fracture status, with fracture cases having better recall. This is particularly valid given that prevalent rather than incident fractures were assessed. If the rate of misclassification in reporting family information were the same between cases and controls (i.e., nondifferential) the estimated odds ratio would be underestimated. When, however, there is differential recall between cases and controls then the estimated odds ratio will differ. If cases over-reported positive family history then the estimated odds ratio would be falsely elevated, whereas if they under-reported positive family history compared with controls then the estimated odds ratio would be lower than its true value. In the absence of definite information about the true fracture status of relatives we cannot exclude the possibility of differential recall. At the time of assessment most of the subjects were, however, unaware of their osteoporosis status and we found no significant differences in the use of either HRT or calcium and vitamin D supplements between the family history groups. Unfortunately we did not record information on either fathers or brothers, and were therefore not able to confirm reports that paternal history may be an important, although less frequent, risk factor [7,23,24]. We have also assumed that any increase in fracture risk would be similar for mothers' and sisters' fracture history, as a subject shares on average 50% of her genes with parents and siblings. Our data present pooled results and we cannot confirm that a maternal history of fracture appears more important than a sibling history for risk of wrist fracture [7]. Another concern with case–control studies is the possibility of selection bias. This was minimized by using data from all 1003 subjects from a normal population cohort with a good response rate of 78% [8]. A nonresponse survey has also shown the responders to be similar to nonresponders for a range of key variables.

Our finding that a positive family history of wrist fracture is associated with a 4-fold increased risk of fracture at this site is of major importance, and compares favorably with other studies that have examined the risk of fracture associated with previous fracture in an individual [6]. Such a family history may allow identification of women at increased risk of fracture earlier in life, prior to the onset of significant disease. This would allow targeting of preventive treatments prior to the onset of bone loss to maintain BMD and thereby reduce the possibility of fracture. Family history

alone is, however, probably too insensitive to be used as a sole indicator for measurement of BMD, although it appears to have high specificity and a good negative predictive power. These findings regarding the sensitivity and specificity of family fracture history are similar to those observed by Soroko et al. [23]. The demonstration that the increase in fracture risk associated with a positive family history is still apparent after adjustment for BMD also suggests that family history of fracture should be viewed in its own right as an important tool for determining future fracture risk rather than as a direct indicator of or surrogate for BMD measurement. The importance of taking a full and specific clinical history for family fracture history should be emphasized in the diagnosis and management of osteoporotic patients.

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