Risk of Wrist Fracture in Women Is Heritable and Is Influenced by Genes That Are Largely Independent of Those Influencing BMD

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ABSTRACT: Using a classical twin design study, we estimated the genetic contribution to liability of wrist fracture in women to be statistically and clinically significant. BMD is highly heritable, but statistical models showed very little overlap of shared genes between the two traits.

Introduction: Studies have observed contradictory evidence for genetic effects influencing the outcome of osteoporotic fracture, in part because of the methodological problems involved in analyzing age-related “censored” outcomes. Although a shared genetic etiology is often assumed between fracture and low BMD, this has not been shown to be the case.

Materials and Methods: In a study of 6570 white healthy female volunteer twins between 18 and 80 years of age, we identified and validated 220 nontraumatic wrist fracture cases. From this we estimated the population prevalence, case-wise twin concordance, heritability in liability to wrist fracture (WF), and the genetic contribution to WFs controlling for age by analyzing the survival outcome using generalized linear mixed models implemented in Winbugs software. We included forearm BMD as a co-variate in some of the models to test whether there is a shared genetic etiology between WFs and BMD.

Results: The prevalence of WFs in women was estimated to be 3.3% with a case-wise concordance in monozygotic twins of 0.28 and 0.11 in dizygotic twins. The additive polygenic heritability in liability was ∼54%, and a significant genetic etiology was confirmed by analyzing WFs as a survival outcome. The magnitude of the genetic influence on risk of WFs reduced very little when BMD was included as a co-variate in the survival analysis model.

Conclusions: There is an important genetic contribution to the risk of WFs, but for the most part, these genes are unlikely to play a direct etiological role in the development of low BMD. If these results are confirmed for other sites, fracture and low BMD will have their own specific genetic risk factors that are unlikely to be shared between the two traits. This has important clinical and research implications.

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Key words: osteoporosis, fracture, genetic correlation, aging, censored data

INTRODUCTION

Wrist fractures (WFS) are the most common fractures among perimenopausal women and are phenotypically associated with low BMD.1–3 Data from several twin and family studies have shown that up to 80% of bone mass variability at the clinical sites is explained by genetic factors.4–6 Including the distal radius.5 Strong site-specific familial clustering has been shown for osteoporotic fractures (OFs).6,7 although these studies did not discriminate between clustering caused by genetic and common environmental influences. To date, studies of WFs have only found moderate or contradictory evidence for genetic effects influencing this trait. A Finnish national twin cohort study observed clear familial effects for non-site-specific OFs in elderly women, but failed to unambiguously attribute these to genes or shared environment.8 Similarly, a study of 50 families, selected through probands with a BMD Z score ≤−1.28, failed to show a genetic component in risk of WF,9 contrasting with an earlier study by the same group of 293 WF females and their families, which did suggest a genetic influence.10 There are a number of methodological problems in studying WFs, such as inconsistent phenotypic definition, variable ascertainment schemes between studies, and the age-related character of fracture, all of which can contribute to the uncertainty.

Here a classical twin study has been conducted, in which identical and nonidentical twins were compared for risk of WFs using cross-sectional recall data. Risk of OFs is strongly age dependent,11 and hence, age of fracture was analyzed using methods to correctly handle unaffected individuals at interview who may nevertheless subsequently fracture in later years.12,13 Two genetic hypotheses were investigated. First, the data were examined for evidence

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that genetic factors contribute to the etiology of WFs. Second, contingent on evidence for heritability of WF, we tested for evidence of shared genetic risk factors between WF and variation in BMD. The presence or absence of a significant genetic correlation between the two heritable traits would imply shared or specific genetic risk factors, respectively. The latter research question is of direct relevance to the task of finding genes related to osteoporosis, because investigators often use BMD as a proxy risk factor for OFs and assume (without evidence) that the two traits share the same genetic risk factors.\(^{(3,9,14,15)}\)

**MATERIALS AND METHODS**

**Study sample**

Study subjects comprised a total of 6570 white women with fracture status data (3165 complete female-female twin pairs) available from the St. Thomas’ UK Adult Twin Registry, between 18 and 80 years of age at first interview. Information on WF status and associated risk factors were obtained by nurse-administered questionnaire for twins who visited the hospital for a clinical study (\(n = 5380\) women) and/or by postal questionnaire (\(n = 5020\)), with 3830 women questioned twice. Osteoporotic WF was defined as a fracture obtained as the consequence of minimal trauma, including falls no higher than the height of a chair. Fractures caused by high-energy trauma, such as a vehicular accident, were excluded. For twins with a clinical visit, left forearm BMD was also measured using DXA on a Hologic QDR-2000 (Hologic, Waltham, MA, USA). Ethics approval was obtained from the hospital ethics committee, and written consent was obtained from all subjects.

Of the 5380 women asked at clinical visit whether they had ever suffered from a WF, 281 individuals (5.2%) initially responded affirmatively. Replies on WF status were obtained from 5020 of 7800 women who were sent postal questionnaires (a postal survey response rate of 64%), and of these, 275 women (5.5%) initially reported having suffered at least one WF. When the clinical visit and questionnaire data for WFs were combined, the total response was 6570/7800 (84%).

To investigate reliability, self-reported fracture status was analyzed where data were obtained from 3830 women on two occasions, once by postal questionnaire and once as part of a clinical visit. Of these, 137 responded affirmatively on both occasions, and 185 gave contradictory replies. Given the scope for misclassification, general practitioners (GPs) were contacted to validate the fractures for a total of 313 potential or ambivalent cases, where contradictory responses were obtained or we were unable to confirm the nontraumatic character of the WF from the data or by reference to radiological reports. In 158 cases, GPs confirmed that their patient had suffered a wrist fracture. When GPs had no records of patient fracture or no written response was obtained from a GP, the twin was contacted again by a physician (LA) to ascertain more carefully the medical history of the injury to the wrist. Of the 155 respondents contacted in this way, 63 were deemed to have suffered a nontraumatic wrist fracture. Only validated WFs were used for final analysis in this study.

In addition to the subject’s fracture data, twins were asked at the clinical visit to recall if their mother had ever suffered from a nontraumatic WF. This was self-reported and was not checked for validity by reference to medical records.

**Statistical methods**

The population prevalence for validated WF and twin case-wise concordances were estimated.\(^{(16)}\) The case-wise concordance for WFs is the probability that a twin is affected given her co-twin has fractured. The probability has the same interpretation as the epidemiological measure of \(\lambda_s\)\(^{(17)}\) and can be used to assess the degree of familial risk by comparison with population prevalence. Under the assumption of random ascertainment, case-wise concordance can be calculated by the equation \(2C/(2C + D)\), where \(C\) and \(D\) are the number of concordant and discordant twin pairs, respectively.\(^{(18)}\)

The heritability of fracture liability can be estimated by assuming an underlying continuous normal distribution in risk of WFs. A single threshold in liability is used to define two categories: affected and unaffected.\(^{(19,20)}\) Heritability is defined as the proportion of total variation in liability that can be attributed to genetic factors.\(^{(19)}\) The heritability in liability to WFs was estimated using an extension to DeFries-Fulker regression, with model fitting to twin data being used to decompose the liability variance into estimated genetic and environmental components.\(^{(21)}\) The genetic variance consists of an additive component (\(A\)) and a dominance component (\(D\)), the latter representing the intralocus interaction of alleles. Epistasis and gene–environment interactions were not modeled. Environmental variation between twins was further partitioned in the model into components common to both members of a twin (the shared or common environment, \(C\)) and random environmental effects (\(E\)). When standardized, the variance components equal one.

It should be noted, however, that case-wise concordance and heritability estimates for censored data are likely to be biased. Observed fracture status is a right-censored outcome, because risk of fracture is strongly related to age. Women classified as unaffected at interview, particularly if young, may subsequently fracture in later life. The analysis of retrospective recall data using survival analysis methods is also strictly not valid, because the individuals do not form a true cohort, but such techniques do nevertheless provide valid significance tests.\(^{(22)}\) Hence the primary analyses conducted for this study were survival analyses. Case-wise concordance and heritability estimates are presented for illustrative purposes, but can only be considered to be qualitatively valid if confirmed by survival analysis techniques.

**Generalized linear mixed models for survival data**

Generalized linear mixed models (GLMMs) provide a general and flexible framework that can be applied to a wide variety of problems and data structures, including survival outcome and family data. Liability models\(^{(23)}\) and GLMM survival models both assume underlying continu-
WF IS HERITABLE WITH LITTLE GENETIC OVERLAP WITH BMD

TABLE 1. MEAN, SD (BETWEEN TWIN PAIRS), AND SAMPLE SIZE FOR TWIN AGE, FOREARM BMD, WRIST FRACTURE PREVALENCE, WEIGHT, AND HEIGHT

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>WF prevalence</th>
<th>Forearm BMD</th>
<th>Weight</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>n</td>
<td>Prev</td>
<td>SD</td>
</tr>
<tr>
<td>MZ</td>
<td>50.1</td>
<td>14.3</td>
<td>2445</td>
<td>0.042</td>
<td>0.156</td>
</tr>
<tr>
<td>DZ</td>
<td>47.0</td>
<td>12.6</td>
<td>3553</td>
<td>0.032</td>
<td>0.131</td>
</tr>
<tr>
<td>All</td>
<td>47.8</td>
<td>13.2</td>
<td>6570</td>
<td>0.033</td>
<td>0.134</td>
</tr>
</tbody>
</table>

Survival analysis of wrist fracture

Fracture status was analyzed as the outcome, with “survival time” being the observed period of recalled exposure from the age of 16 years until age at fracture or age at interview. If an individual had a WF, and the fracture age was recorded, the survival time was equal to the fracture age, and the outcome variable was equal to one. If the individual had no WF, the survival time was set to equal the current age, and the outcome variable was equal to zero. Co-variates for affected and unaffected individuals included in the model were height, body mass index (BMI; kg/m²), and smoking status (ever smoked, Y/N). Further details of the piecewise exponential GLMM used to analyze the twin data are provided in Appendix 1.

Survival analysis of wrist fracture and forearm BMD

In addition to examining the genetic and environmental etiology of WFs, we also fitted GLMMs to determine whether the same or different genes influence the risk of WFs and forearm BMD. If risk of fracture and forearm BMD are genetically correlated, the size of the additive genetic variance component, $\sigma^2_A$, would be expected to be smaller in the model that includes BMD compared with the model without BMD. In the first model, we included BMD as a fixed effect co-variate and freely estimated the variance component $\sigma^2_A$ attributable to additive polygenic effects, $\sigma^2_A[\text{Estimated}]$ ($\sigma^2_A[\text{II}]$), using an unconstrained model. In the second, we retained BMD as a fixed effect co-variate in the model, but this time $\sigma^2_A$ was constrained to be a constant, $\sigma^2_A[\text{Original}]$ ($\sigma^2_A[\text{CO}]$), derived from the estimate of $\sigma^2_A$ under the original model of WF without BMD. Hypothesis testing was then conducted using likelihood profile comparisons (Appendix 2).

TABLE 2. FINAL VALIDATED WRIST FRACTURE COMPARED WITH PRELIMINARY SELF-REPORT SCREEN FOR WF (POSTAL QUESTIONNAIRE AND CLINICAL VISIT)

<table>
<thead>
<tr>
<th></th>
<th>WF (validated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>WF (preliminary screen)</td>
<td>6145</td>
</tr>
<tr>
<td>Yes</td>
<td>205</td>
</tr>
<tr>
<td>Total</td>
<td>6350</td>
</tr>
</tbody>
</table>

The sensitivity (156/220) of self-report data was 71% and the specificity (6145/6350) was 97%. Note, however, the positive predictive value (156/361) based on preliminary self-report was only 43%.

RESULTS

From a large register of 7800 twins, we identified 220/6570 women with a validated or carefully ascertained wrist fracture, comprising 180 discordant and 20 concordant pairs (14 monozygotic [MZ] and 6 dizygotic [DZ]). Table 1 presents a description of all twins identified in the St. Thomas’ UK Adult Twin Registry with fracture data. For these data, MZ twins were on average slightly older than DZ twins, with a correspondingly lower mean BMD and higher prevalence of WFs. In addition, even when stratified by age, the adult weight of MZ twins was on average slightly lighter than DZ twins. These differences were accounted for in the analyses by stratifying by age at fracture (or interview) and including the variables BMI, height, and smoking status as co-variates.

Data reliability

The sensitivity and specificity of preliminary self-reported data in predicting the final diagnosis of nontraumatic WF were 71% and 97%, respectively (Table 2). Where self-reported fracture data were collected twice for an individual, at clinic and by postal questionnaire, preliminary screen WF was defined as self-reported fracture on one or more occasions. Both clinical and postal questionnaire data predicted final outcome status with a similar degree of accuracy (data not shown).

Prevalence, case-wise concordance, and liability heritability

The mean age ± SD at interview for those who had fractured was 58.7 ± 10.8 years compared with 48.1 ± 12.9 years for those who were unaffected, with a mean recalled frac-
ture age of 46.5 ± 14.9 years. The estimated prevalence of WFs was 3.3% for the sample total.

The case-wise concordance in MZ twins of 0.28 was significantly >0.11 in DZ twins (χ² = 6.1, p = 0.01), suggesting a genetic contribution to risk of WFs. The best-fitting parsimonious model included parameters for additive polygenic variance (A) and unique environmental variance specific to the individual (E), with an estimated heritability in liability of 54% (CI, 0.38–0.69). The variance estimated caused by dominant genetic effects and shared sibling environment could both be dropped without significant deterioration in model fit (χ² = 0.05, p = 0.83).

**Family history**

In contrast to the relatively low prevalence in WFs for sisters 18–80 years of age (3.3%), 12% of all twin pairs reported that their mother had suffered from a nontraumatic WF during her lifetime. The reported prevalence of WFs among mothers increased from 0.01 ± 0.31 among twin pairs with no WFs (n = 1330) to 0.21 ± 0.41 for twin pairs (n = 145) with at least one sister affected (odds ratio [OR], 2.2; CI, 1.4–3.3; p = 0.0002).

There was no difference in reported maternal fracture prevalence for unaffected MZ and DZ twins, but there were differences by zygosity for discordant and concordant affected twin pairs for WFs. Discordant MZ twin pairs reported a maternal fracture prevalence of 13% (n = 6/47) compared with 26% (n = 21/82) for discordant DZ pairs (OR, 2.4; CI, 1.03–5.4; p = 0.045, one-tailed test). Concordant affected MZ twin pairs reported a higher maternal fracture prevalence of 33% (n = 4/12) compared with 0% (n = 0/6) for concordant affected DZ twin pairs, but here, concordant numbers were too small for reliable inference.

**GLMM survival analysis of WFs**

The number of fractures and observations within each time interval used for the piece-wise exponential model are shown in Table 3. There were 163 fractures in total, with valid observations for most co-variates (146/163 cases had valid BMI, smoking, and BMD measures). The minimum fracture time was 16 years, and the maximum was 73 years. The minimum censoring age was 18 years, and the maximum was 80 years.

A number of models were fitted to the WF data. The co-variates height and BMI were centered about their mean before inclusion in the model. None of the co-variates seemed to be associated with fracture risk for these data (Table 4). However, co-variates were retained in all models because they are established risk factors associated with WFs. The risk of WFs increased with age, and this is reflected in the models by the baseline hazard increasing monotonically with time (baseline hazard estimates not presented in Table 4). The estimate for the additive polygenic variance component, σ²_A, was positive at 5.43 (95% credible interval, 3.1–8.2; p = 0.00002). This provides strong evidence that genes influence the risk of WFs. By way of illustration, a woman at the 90th quantile on this scale of additive polygenic risk would have an 8-fold increase in risk of fracture compared with that of a woman at the median level of additive polygenic risk. When potential shared environmental risk factors were excluded from the model by fixing σ²_C to be zero, the estimate of σ²_A was reduced to 2.57 but still remained significantly greater than zero (95% credible interval, 1.4–4.0; p = 0.00006). Under this model, a woman at the 90th quantile of additive polygenic risk would have an 8-fold increase in risk of fracture compared with that of a woman at the median level of additive polygenic risk. However, regardless of whether shared environmental factors were included in the model, there was strong evidence for a genetic etiology to WFs.

**GLMM survival analysis of WFs with forearm BMD**

Variance components models were fitted to the same data and co-variates as described in Table 3, but forearm BMD was also included as a co-variate. Results from the full unconstrained model are presented in Table 4.

A strong negative relationship was observed between time to fracture and forearm BMD, as expected. This confirms the known phenotypic association between fracture and BMD, but does not necessarily imply a genetic asso-

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**Table 3. Number of Fractures and Valid Observations by the Time Exposed to Risk of WF**

<table>
<thead>
<tr>
<th>Observed time interval in years until WF or interview</th>
<th>Number of WF</th>
<th>Total number of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–30</td>
<td>31</td>
<td>4132</td>
</tr>
<tr>
<td>30–40</td>
<td>20</td>
<td>3721</td>
</tr>
<tr>
<td>40–50</td>
<td>25</td>
<td>3073</td>
</tr>
<tr>
<td>50–60</td>
<td>52</td>
<td>2073</td>
</tr>
<tr>
<td>60–73</td>
<td>35</td>
<td>844</td>
</tr>
</tbody>
</table>

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**Table 4. Model Parameter Estimates for (A) WF Only and (B) WF Including BMD as a Covariate**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% credible interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>σ²_A</td>
<td>5.43</td>
<td>3.66–8.19</td>
</tr>
<tr>
<td></td>
<td>σ²_C</td>
<td>–2.06</td>
<td>–3.66–0.05</td>
</tr>
<tr>
<td>B</td>
<td>σ²_BMD</td>
<td>–7.14</td>
<td>–10.6–3.74</td>
</tr>
<tr>
<td></td>
<td>σ²_A</td>
<td>4.78</td>
<td>2.44–7.47</td>
</tr>
<tr>
<td></td>
<td>σ²_C</td>
<td>–1.81</td>
<td>–3.38–0.24</td>
</tr>
</tbody>
</table>

Estimates and SE (on a natural logarithmic scale) for the influence of additive polygenic effects (σ²_A), shared sibling environment (σ²_C), and known risk covariates. (p values were calculated by comparing a Wald test statistic for each parameter with an asymptotic χ² distribution. The models used a burn-in period of 10,000 cycles and the analysis 40,000, using two parallel chains.)
WF IS HERITABLE WITH LITTLE GENETIC OVERLAP WITH BMD

Table 5. Test for Genetic Correlation Between WF and Forearm BMD. Estimates and Model Fit Comparison for (1) Additive Polygenic Effects Freely Estimated ($\sigma_A^{2\text{E}}$) and (2) $\sigma_A^2$ Constrained to be Equal to $\sigma_A^{2\text{O}}$ Obtained From (3) the Original Model With BMD Not Included as a Covariate

<table>
<thead>
<tr>
<th>Model</th>
<th>Constraint</th>
<th>Parameter estimates/constrained value</th>
<th>Test statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\sigma^2_A$</td>
<td>95% CI</td>
</tr>
<tr>
<td>1) WF + BMD</td>
<td>None</td>
<td>4.78</td>
<td>2.4–7.5</td>
</tr>
<tr>
<td>2) WF + BMD</td>
<td>$\sigma_A^2 = \sigma_A^{2\text{O}}$</td>
<td>5.43</td>
<td>—</td>
</tr>
<tr>
<td>3) WF</td>
<td>None</td>
<td>5.43</td>
<td>3.1–8.2</td>
</tr>
</tbody>
</table>

Parameter estimates for the full model are presented in Table 3B. (LL = log-likelihood, $-2\text{LL} = \text{minus twice the log-likelihood difference}$).

ciation. The phenotypic association was equivalent to an OR for WFs of 2.4 for every SD decrease in forearm BMD (95% CI, 2.0–2.8). To assess whether a genetic correlation exists, two models were contrasted, each with forearm BMD included as a co-variate. The first model freely estimated the value of the additive polygenic variance ($\sigma^2_A$), whereas in the second model, $\sigma_A^2$ was constrained to be equal to the value of $\sigma_A^{2\text{O}}$ estimated under the original model excluding BMD (i.e., the estimate of $\sigma^2_A$ presented in Table 4). The results for these two models are presented in Table 5.

The estimate of $\sigma_A^{2\text{O}}$ in the original survival model for WF without BMD was 5.43 (95% CI, 3.1–8.2), whereas the estimate of $\sigma_A^{2\text{E}}$ with BMD included was 4.78 (95% CI, 2.4–7.5). Although the estimated decline in additive polygenic variance from 5.43 to 4.78 (−88% of $\sigma_A^{2\text{O}}$ is small, the result is highly statistically significant (−2LL = 26.8, $p = 2.5 \times 10^{-13}$) and consistent with an approximate overlap of 12% in genetic determinants for WFs and forearm BMD (Table 5).

Similar results were seen when the effects of shared common environment were excluded, with parameter estimates of $\sigma_A^{2\text{O}} = 2.563$, and $\sigma_A^{2\text{E}} = 2.355$ (−92% of $\sigma_A^{2\text{O}}$) consistent with an −8% overlap in genetic determinants. From this it can be concluded that there seems to exist a small, but detectable, genetic correlation of −10% between WFs and forearm BMD.

**DISCUSSION**

In a large total sample of over 3000 UK adult female twin pairs, we screened and identified 220 women with validated nontraumatic WFs. The prevalence of WF was 3.3%, comparable with estimates obtained in other populations of similar age range.\(^{(10)}\)

Elevated case-wise concordance for twins compared with the population prevalence and increased prevalence of reported maternal wrist fracture for twin pairs suffering from WFs suggested clear familial clustering. The case-wise concordance for WF in MZ twins (0.27) significantly exceeded the case-wise concordance rate in DZ twins (0.11), implying a genetic basis to the familial clustering. Although these estimates may be potentially inaccurate because of censoring, they are consistent with the observed GLMM results and are readily comparable with the population prevalence as a measure of familial risk. Using the twin model and ignoring the censored character of age-related WFs, we estimated a heritability of 54% in liability to WF for women.

The reported family history for the twins also provided support for a genetic etiology to WFs. The prevalence of reported WFs for mothers of twin pairs with no WFs was significantly smaller (11%) than twin pairs with at least one sister affected (21%), with an OR of 2.2 (95% CI, 1.4–3.3; $p = 0.0002$).

Discordant affected MZ twin pairs reported a significantly lower prevalence for maternal WF (13%, 6/47) compared with discordant DZ pairs (26%, 21/82), which is consistent with environmental risk factors playing a greater role in these cases. In contrast, although concordant numbers were too small for reliable inference, concordant affected MZ twin pairs (4/12) reported a greater family history of WF compared with concordant affected DZ twins (0/6), which is also consistent with classical twin model predictions.

Analyzing the fracture data as censored survival outcomes using GLMM, we confirmed strong evidence for a substantial genetic etiology to WF. For all models considered, the additive polygenic effect was the most important. We further tested whether the association between WF and BMD is mediated by genetic or environmental factors. We observed a small genetic correlation of about 10% between WF and forearm BMD (Table 5).

The Finnish twin study\(^{(6)}\) found genetic factors to be related to likelihood of osteoporotic fracture in men, but the evidence was ambivalent for women. Osteoporotic fracture cases for the study were selected from the national hospital discharge register rather than the population. and as a result (apart from hip fracture), insufficient cases were obtained for site-specific analysis. No concordant MZ or DZ pairs were obtained for wrist fracture, for example, precluding direct comparison with our study, because of potential OF heterogeneity at different bone sites.\(^{(30,31)}\) In addition, WF ascertainment in our sample will have captured a broader fracture type than the stricter criteria of hospital admissions,\(^{(8)}\) although this is unlikely to reflect a different etiology.
Deng et al.\(^{(10)}\) reported a heritability in liability of 25\% for WFs using a familial postal questionnaire from 2471 “probands” women (67\% response rate), of whom 293 (11.9\%) were identified to have had a WF. The prevalence of WFs among sisters of the probands was 4.4\%, only slightly larger than the population prevalence estimate of 3.3\% for these data. A second study\(^{(39)}\) failed to show heritability in liability to WFs, which the authors attributed to small WF sample size. Significant heritability in liability to hip fracture was found (53\% of the residual phenotypic variance in susceptibility attributable to genetic factors). However, an insignificant proportion (<1\%) of total additive genetic variance seemed to be shared between hip BMD and hip OFs. Although for a different site, this result qualitatively agrees with our findings for WFs. We conclude that if site-specific genetic correlations for OFs and BMD exist, they are likely to be small.

This conclusion might seem to be counterintuitive or even contradicted by recent genetic studies, such as Styrkarsdottir et al.,\(^{(15)}\) who used a combined fracture/BMD phenotype. However, a low genetic correlation between BMD and OFs does not exclude the possibility of candidate genes that are shared by both phenotypes (i.e., pleiotropic), but does imply that most candidate genes are likely to be specific to each phenotype and not shared. For example, in a genome-wide linkage and follow-up association study of 207 extended Icelandic osteoporotic families, strong linkage was observed at 20p12 using four phenotypic definitions that combined low BMD thresholds (10th and 16th percentiles) at the hip and spine with fracture cases or patients being treated for osteoporosis using bisphosphonates. The numbers of affected cases were made up equally by individuals with low BMD scores, or alternatively, osteoporotic fracture or patients on treatment. When patients being prescribed bisphosphonates were excluded from the sample, a low BMD threshold (with no osteoporotic fracture) defined 70–80\% of affected cases.

As a result, despite the authors’ claim, the combined phenotype used in the Icelandic study does not unambiguously show that the reported linkage region is pleiotropic or coincident for both phenotypes. A re-examination of the same data using multivariate linkage methods\(^{(32)}\) would be required to either confirm the suspected pleiotropic (or coincident) effect, or in contrast, might reveal a strong specific effect for only one of the phenotypes—most likely to be BMD in this case because the majority of the information for this study was derived using low BMD threshold criteria and not fracture.

Possible limitations of this study include the validation of self-reported fracture status, ascertainment bias, the use of retrospective data, and the representativeness of twins compared with the general population. Although previous studies have reported satisfactory accuracy for self-reported WFs,\(^{(33,34)}\) we found the sensitivity of self-report compared with validated status to be relatively low at 71\% (Table 1). The positive predictive value of 43\% was very poor, largely because of the recorded cause of WFs sometimes being ambiguous, inaccurate, or missing, which in turn, resulted in the preliminary overestimation of nontraumatic WF cases.

Several validation methods were used to ascertain WF status accurately: a rheumatological clinician (LA) consulted radiological reports, GPs were recontacted, and twins were further questioned. We only used validated data for the final analyses.

Ascertainment bias is important because we have no direct means of assessing whether the St. Thomas’ Hospital UK Adult Twin register of volunteers contains representative numbers of twin pairs unaffected and affected with WFs. However, the prevalence of WFs for this data is similar to other studies with similarly aged women.\(^{(19)}\) In addition, when we analyzed the data using Cox survival regression (in which the outcome was the survival time and fracture status of twin 2 conditional on twin 1 having suffered a WF), we observed the same evidence for a genetic etiology to WFs compared with GLMMs that used all the data. Such a conditional test is robust to ascertainment bias.

Survival analysis is designed for prospective data, and because we used retrospective recall at clinical and survey interview, this may be considered methodologically to be strictly invalid, because the data do not form a true cohort. Nevertheless, although recall data potentially may lead to biased relative risk estimates, the correct analysis of survival outcomes, such as with GLMM, gives rise to valid significance tests.\(^{(22)}\)

Finally, the representativeness of volunteer twins compared with the general twin population and whether twins are representative of singletons is phenotype specific and needs to be tested. For the St. Thomas’ Hospital Adult Twin UK register, we have shown that, for BMD and lifestyle variables such as prevalence of smoking, our data are indistinguishable from population-based data.\(^{(37)}\) We also have no reason to believe that the etiology of fracture in twins differs from singletons.

In conclusion, this study is the first to provide unambiguous evidence for the genetic etiology of WFs and a low genetic correlation between WFs and BMD at the forearm. Although low BMD is undoubtedly one of the main risk factors for WFs, it is unlikely that these phenotypically associated traits share many common genetic risk factors. Because the shared overlap in genetic determinants between WFs and forearm BMD seem to be small, future genetic research should focus on fracture specific genes in addition to potential pleiotropic effects. If these data are extrapolated or confirmed at other sites, the widely held view in genetic research that genes found to be associated with BMD also need to be validated for fracture is likely to be flawed.

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APPENDIX 1. GLMM SURVIVAL ANALYSIS OF WRIST FRACTURE

A piecewise exponential model was used, which requires division of the total time scale into distinct intervals for each individual. For this model, five time intervals were used: [0,30], [30,40], [40,50], [50,60], and [60,73]. The breakpoints were chosen so that each interval was short enough for the assumption of constant within-interval hazards to be reasonable, but still included sufficient fractures within each interval to allow estimation. For each interval, the hazard function was assumed to be constant, but the overall hazard function was a step function. Each individual then had an interval exposure time and an interval variable, indicating whether the individual fractured or was “censored” during an interval.

The basic generalized linear model (GLM), consisting of line predictor and an error term, was extended to a variance components model (or GLMM) by the inclusion of fixed and random effects. The actual model fitted was:

\[
\log(\mu_{ik}) = \beta_{0} + \log(t_{ik}) + \beta X_{i} + M_i \quad \text{(for MZ twins)}
\]
\[
\log(\mu_{ik}) = \beta_{0} + \log(t_{ik}) + \beta X_{i} + D_i + B_{ik} \quad \text{(for DZ twins)}
\]
\[
d_{ik} - \text{Poisson}(\mu_{ik})
\]
where \(j = 1, 2\) for each individual in twin pair \(i\), \(t\) = time interval, \(d_{ik}\) = censoring indicator variable coded 0, 1, and \(M_i\) are random effects with zero mean-centered normal distributions and variances estimated under the assumption that additive polygenic effects (\(\sigma^{2}_A\)) and common environmental effects (\(\sigma^{2}_C\)):

\[
M_i = N(0, \sigma^{2}_A + \sigma^{2}_E)^{1/2}
\]
\[
D_i = N(0, 1/2\sigma^{2}_A + \sigma^{2}_E)^{1/2}
\]
\[
B_{ik} = N(0, 1/2\sigma^{2}_E)^{1/2}
\]

1Each fixed effect parameter (\(\beta_{0}\) + \(\beta\)) was assigned a vague normal \(N(0, 1000)\) prior distribution. The precision (inverse of the variance) of each random effects distribution was assigned a Pareto (1,0.01) prior, equivalent to a uniform (0,100) prior for each of the variance components.

2\(\sigma^{2}_A\) is kept constant throughout each cycle of ~50,000 iterations, rather than being updated at each iteration as with the other variance components. Convergence was achieved when the estimate of \(\sigma^{2}_A\) was within 10% of the fixed value of \(\sigma^{2}_A\).

The cycling technique proposed by Burton et al.\(^{(24)}\) was used to ensure an unbiased estimate of \(\sigma^{2}_A\) by allowing negative values of \(\sigma^{2}_A\) to be sampled, whereas the variance \(1/2\sigma^{2}_E\) of the unshared random effect in DZ twins, \(B_{ik}\), was constrained to be constant in each cycle. The above model is equivalent to Model \(S^{(3)}\) when that model is applied to families consisting of MZ and DZ twins. Because the Poisson distribution is fully specified through \(\mu\), a random error variance component (\(\sigma^{2}_x\)) was unnecessary, and therefore, was not included in the models.

In almost all models, the Markov chain seemed to converge very quickly, typically within 1000–5000 iterations. The two parallel chains used to check parameter estimates also converged to the same location quickly. The variance components \(\sigma^{2}_A\) and \(\sigma^{2}_x\) were highly negatively correlated (typically, \(p = -0.8\)), which was expected and has been commented on before.\(^{(38)}\)

APPENDIX 2. GLMM SURVIVAL ANALYSIS OF WRIST FRACTURE AND FOREARM BMD

As this was not a standard nested model problem, the hypothesis test of whether the two models fitted the data equally well was performed using profile likelihood techniques.\(^{(36)}\) The likelihoods from the unconstrained and constrained models were estimated, and the ratio of the likelihoods was calculated. In a standard nested model problem, the value of minus twice the log-likelihood difference (~2LL) equals \(1.92\),\(^{3}\) or equivalently, a likelihood ratio of \(\chi^2 = 6.82\), has a corresponding \(p\) value of 0.05. As a guideline, a likelihood ratio >10 (or ~2LL > 2.3) provides moderate evidence for a change in \(\sigma^{2}_A\), whereas a likelihood ratio in excess of 100 (~2LL > 4.6) provides strong evidence.\(^{(36)}\)

For all three models presented in Table 5, the variance component attributable to the shared common environment, \(\sigma^{2}_C\), was estimated to be significantly less than zero (approximately -2.0). Whereas it is not possible to observe a negative variance, it is possible, as here, to estimate a negative variance component.\(^{(37)}\) However, whether the result has a meaningful interpretation for twin data are unclear. It is possible to speculate, for example, that the shared negative environmental effect may reflect the modification of an individual’s behavior to reduce the risk of WF on the knowledge that her twin sister has suffered a fracture.

\(^{3}\)The value 1.92 is used because this value is equal to \(1/2 \times 3.84\). The value 3.84 is the 95th quantile of a \(\chi^2\) distribution, and it is halved because the value under the null hypothesis lies on the boundary of the parameter space.\(^{(36)}\)