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Family history of fracture and fracture risk: a meta-analysis to update the FRAX® risk assessment tool

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Conflict of interest

JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases; he is a director of Osteoporosis Research Ltd., which maintains FRAX.

EV McCloskey, WD Leslie, M. Lorentzon, NC Harvey, M. Schini, E. Liu, L. Vandenput, and H. Johansson are members of the FRAX team. JA Kanis, NC Harvey, and EV McCloskey are members of the advisory body of the National Osteoporosis Guideline Group. He is a director of Osteoporosis Research Ltd., which maintains FRAX.

KE Akesson has no financial interest related to FRAX and chaired the National SALAR Group for Person-Centered Care Pathway Osteoporosis.

FA Anderson led the team that developed GLOW while being the director of the Center for Outcomes Research at the University of Massachusetts Medical School; he has no financial interest in FRAX.

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CL Bager is employed at Nordic Bioscience and owns stock in Nordic Bioscience. She declares no competing interests in relation to this work.

HA Bischoff-Ferrari has no financial interest in FRAX. For the DO-HEALTH trial cohort, Prof. Bischoff-Ferrari reports independent and investigator-initiated grants from the European Commission Framework 7 Research Program, from the University of Zurich, from NESTEC, from Pfizer Consumer Healthcare, from Streuli Pharma, plus non-financial support from DNP. For the study cohort extension, she reports independent and investigator-initiated grants from Pfizer and Vifor. Further, Prof. Bischoff-Ferrari reports non-financial support from Roche Diagnostics and personal fees from Wild, Sandoz, Pfizer, Vifor, Mylan, Roche, and Meda Pharma, outside the submitted work with regard to speaker fees and travel fees.

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C. Christiansen owns stock in Nordic Bioscience. He declares no competing interests in relation to this work.

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Abstract

Summary/Mini abstract

In the largest meta-analysis of international cohorts to date, a family history of fracture is confirmed as a significant BMD-independent predictor of future fracture risk. Parental and sibling histories of fracture carry the same significance for future fracture, including the impact of family hip fracture on future hip fracture risk.

Purpose

We have undertaken a meta-analysis of international prospective cohorts to quantify the relationship between a family history of fracture and future fracture incidence.

Methods

The analysis dataset comprised 350542 men and women from 42 cohorts in 29 countries followed for 2.8 million person-years. We investigated the relationship between family history of hip fracture or any fracture and the risk of any clinical fracture, any osteoporotic fracture, major osteoporotic fracture (MOF) and hip fracture alone using an extended Poisson model in each cohort. Models were adjusted for current age, sex, BMD, and follow up time.

Results

As no difference in influence of family history of fracture was seen between genders, results are presented for men and women combined. A parental history of hip fracture was associated with higher risk of incident fracture across all fracture outcome categories with a stronger relationship with future hip fracture (hazard ratios [HR, 95%CI] for hip and MOF 1.37, 1,23-1.52 and 1.19, 1.12-1.27 respectively). Associations were slightly reduced but remained significant when additionally adjusted for BMD, and didn't vary by baseline offspring age, follow-up time or parent affected. In a more limited analysis, parental history of any fracture or a sibling history of hip or any fracture showed similar associations to those observed with parental history of hip fracture.

Conclusions

A family history of fracture is confirmed as a significant BMD-independent predictor of future fracture risk. While parental hip fracture appears the strongest factor for future hip fracture, a family history of other fractures might be appropriate for inclusion in future iterations of the FRAX tool.

Keywords: Family history; Parental history; FRAX; Hip fracture; Osteoporotic fracture; Meta-analysis

Introduction

The role of a family history of fracture in informing an individual's risk of future fracture is well established from multiple cross-sectional and prospective studies[1-10]. Most studies have been based on a self-reported history of parental fracture but at least one study has shown good concordance with self-reported and documented parental hip fracture[11]. Estimates suggest that the heritability of fracture risk is of the order of 30%, but the mechanisms conveying this hereditary component remain unclear. In a recent GWAS meta-analysis for fracture, 15 genetic determinants were identified all of which also influenced bone mineral density (BMD)[12] with the latter showing heritability of 50-80%[12, 13]. Nonetheless, other heritable or shared environmental factors are important as family history remains a predictor following adjustment for BMD. Other heritable factors might include bone size, shape, architecture, matrix properties, bone turnover and height [14]. Indeed, the heritability of height is comparable to, or greater than, that of BMD[15].

Irrespective of the mechanism, the fact that the risk of fractures is greater in individuals with a family history of fractures than in those with the same level of BMD but no family history was confirmed in a meta-analysis of international cohorts in the development of the FRAX® fracture risk assessment tool [16]. The meta-analysis comprised data from 34,928 men and women drawn from seven prospective population studies followed for a total of 134,000 person-years. The magnitude of the association was greatest for a parental history of hip fracture, and appeared of similar magnitude in women and men, though the number of outcome fractures in men was relatively limited [16]. The analysis resulted in a parental history of hip fracture being included as an input variable within FRAX when launched in 2008. Since then, many more prospectively studied cohorts have become available that have the potential to improve the accuracy of FRAX [17]. Using an expanded FRAX cohort collection, the aim of the present study was to quantify the risk for future fracture associated with a family history of fracture, particularly parental hip fracture, in an international setting, and to explore the dependence of this risk on age, sex, time since baseline assessment and BMD.

Methods

The analysis dataset comprised up to 42 cohorts from 29 countries with data on women provided within 36 cohorts and on men within 20 cohorts. Details of the cohorts studied have been given previously[17] and are summarized in Table 1. The review identifying these cohorts was registered with the International prospective register of systematic reviews, PROSPERO (CRD42021227266), and followed the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Baseline family history of fracture

A parental history of hip fracture was captured by questionnaire. Of the 42 cohorts, 36 (85.7%) had captured a history of hip fracture in both parents, while the remaining studies had only recorded a maternal history of hip fracture (Table 1). A smaller number of studies had recorded data on parental history of any fracture and an even smaller number had reported a history of hip or any fracture in siblings (details provided below).

Outcome fractures

Incident fractures were classified as all clinical fractures ('any fracture') with further sub-categories used including fractures considered to be associated with osteoporosis ('osteoporotic fractures' – excluded fractures of the skull, face, hands, feet, ankle and patella in both genders as well as tibial and fibular fractures in men)[18]. Hip fracture and major osteoporotic fracture (MOF – distal forearm, proximal humerus, hip and vertebral) were also analysed. No distinction was made according to trauma since both high- and low-trauma fractures show similar relationships with low BMD and future fracture risk [19-22].

Statistical methods

The primary analysis focused on the relationship between parental hip fracture history and fracture risk. The risk of fracture was estimated by an extended Poisson model applied separately to each cohort (and also separately by sex for those cohorts with both men and women) [23, 24]. In this approach, each observation period was divided into short consecutive intervals and evaluated to generate a complete continuous hazard model as opposed to the commonly used Cox proportional hazards model. Complete continuous hazard functions can incorporate virtually any covariate or interaction, including time, and can be applied to an arbitrary population to compute the expected outcome in that population. Because of an embargo on data transfer, Cox regression was used on the Manitoba cohort. Covariates included current time since start of follow up, current age, parental history of hip fracture, and BMD at the femoral neck. Femoral neck BMD was adjusted for manufacturer and T-scores were calculated from the NHANES III White female reference values [17, 25, 26]. Differences in risk with and without BMD were additionally explored in those cohorts that contributed information on family history and BMD. Further models included the interaction term 'parental hip fracture · sex', or 'parental hip fracture · current time since

baseline' to determine whether the strength of the association of parental hip fracture and fracture risk differed with sex or time. An additional model included the interaction term 'parental hip fracture · current age' to determine whether the strength of the association of parental hip fracture and fracture risk changed with age. The hazard ratio (HR) for parental hip fracture was determined for each cohort from the Poisson model, without a time interaction; inverse-variance weighted β-coefficients were used to merge the cohort-specific, gender-specific results and determine the weighted means and standard deviations. The HR of those with a prior parental hip fracture history versus those without such a history was equal to $e^{\text{weighted mean of } \beta}$. Heterogeneity between cohorts was tested on the major co-variate (a parental history of hip fracture) by the I^2 statistic [27]. There was moderate heterogeneity in risk between cohorts (index of heterogeneity I^2 = 0-50% depending on fracture outcome), and a random effects model was used in the meta-analysis. Secondary analyses, using the same analytic approach, were undertaken to examine the relationship between fracture risk and parental history of any fracture as well as sibling history of hip or any fracture.

The component of the risk ratio explained by BMD was computed from a meta-analysis of BMD and fracture risk in men and women combined using a method and assumptions that have been previously published [28-30].

Sensitivity analyses

As noted above, the effect of sex on the hazard ratio for fracture was examined in those cohorts that contributed both men and women. We additionally excluded BMD from the model, and in a separate model included height as another potentially inherited trait. Assessment of the effects of race and ethnicity was confined to those cohorts recording more than one self-reported race or ethnic group (Asian, Black, Hispanic, White), comprising WHI, SOF, MrOS USA and Manitoba. Results were also computed according to study quality as previously defined[17]. In brief, each cohort was assessed for quality based on a 0/1 score for four criteria: population-based cohort? yes scores 1, other scores 0; fracture ascertainment? self-report scores 0, others score 1; Duration of follow-up? >2 years scores 1, else scores 0; average loss to follow-up/year? Less than 10% scores 1, others score 0. With a possible range of scores from 0-4, poor quality was classified as a score of 0-1, intermediate quality as 2-3 and high quality as 4.

Results

The mean age of the total analysis population was 66.9 years (range 20-111 years), comprising 312,366 women and 38,176 men in 42 cohorts (Table 1). The total follow-up was 2.78 million person-years. Overall, a parental history of hip fracture was present in 11.7% of the individuals, with a similar overall prevalence in men and women (9.6% and 12.0% respectively). Baseline BMD measurements were available in 164,579 individuals (46.9% of the whole study population).

During follow up, 44,762 individuals (4,802 men and 39,960 women) were identified as having a subsequent fracture of any kind, with 36,535 classified as incident osteoporotic fractures and 8,977 characterized as hip fractures (Table 1).

Parental history of hip fracture

Risk of fracture associated with parental history of hip fracture in women and men including adjustment for BMD

The prevalence of parental history of hip fracture rose with age from the age of 40 years in both men and women and peaked in the 60-69 years age group (Supplementary Data, Table A). The HR for future fractures were very similar in men and women (Supplementary Data, Table B), and when tested in those cohorts that contributed both genders to the analysis, there was no statistical difference in the HR between men and women for all fracture outcomes (Supplementary Data, Table C). Thus, further analyses were performed in men and women combined; for additional information some of the analyses in each sex are provided in the supplementary data.

In men and women combined, a parental history of hip fracture was associated with an increased risk of subsequent fracture regardless of the outcome fracture category (Table 2). The HRs ranged from 1.15 for any fracture to 1.37 for hip fracture and were similar whether analysed in all the cohorts or when confined to those cohorts with measurements of BMD available (Table 2). Adjustment for BMD in the latter cohorts reduced the HRs slightly, but a parental history of hip fracture remained a significant predictor of fracture risk across all fracture outcomes. In the case of hip fracture, if it is assumed that the risk of any fracture increases 2.07-fold for each standard deviation (SD) decrease in hip BMD, then the difference in risk between those individuals with and without a parental history of hip fracture is equivalent to an expected difference in BMD of 0.35SD. However, the difference in BMD was only approximately 0.12SD demonstrating that lower BMD accounted for only a minority (35.0%) of the difference in risk of hip fracture.

In those cohorts where it was possible to identify whether the parental history of hip fracture was in the mother (21 cohorts comprising 203,705 individuals) and/or the father (16 cohorts comprising

18,281 individuals), the prevalence of paternal hip fracture was substantially lower than that of maternal hip fracture (2.7% vs. 10.7%, respectively, p<0.001). Nonetheless, the risk of future fracture related to a parental history of hip fracture was similar if the fracture had occurred in the mother or father (Table 3).

Despite the moderate heterogeneity observed across the studies, the increase in fracture risk among those who reported a parental history of hip fracture was reasonably consistent as shown in the Forest plots in Figure 1 for hip and MOF fracture outcomes in women and men combined.

Interaction with age and time since baseline

A parental history of hip fracture was a significant risk factor for fracture at all ages, with no significant interaction with age for any of the fracture outcomes in women, men or both genders combined. The relationship between the HR for MOF and age is shown in Figure 2A for women and men combined. The HR at age 40 years was 1.21 and that at 90 years was 1.08, with a p-value for the interaction of 0.53. Likewise, the fracture risk associated with a parental history of hip fracture showed no interaction with time since baseline (Figure 2B).

Sensitivity analyses including height and race/ethnicity

18 cohorts contributed data on baseline height and a parental history of hip fracture. Adjustment for height had no significant impact on the relationship between parental hip fracture and subsequent fracture risk (Supplementary Data Table D).

The ability to examine the relationship between ethnicity and parental history of hip fracture was confined to 4 cohorts (WHI, SOF, MrOS USA and Manitoba). The HRs for hip and MOF outcomes, adjusted for age and time since baseline, suggest that the relationship between parental history and fracture risk is largely independent of ethnicity (Table 4)

Risk of death

A parental history of hip fracture was associated with a significant decrease in the risk of death in men and women combined (HR 0.90, 0.83-0.96, p=0.0032 (Table 5) with very similar effect sizes in both genders. Hazard ratios remained unchanged when adjusted for femoral neck BMD.

Risk of fracture associated with a parental history of any fracture and sibling history of fracture

A total of 12 cohorts contained baseline data on a history of any fracture in the mother or the father or both. In a total of 131,270 men and women, 32.0% reported such a history. The risk (HR) conferred by a parental history of any fracture on future fracture risk was similar to that observed for a parental history of hip fracture across the range of fracture outcomes, other than hip fracture (HRs for any fracture, MOF and osteoporotic fracture were 1.23, 1.22, 1.27, and 1.25 respectively; all $p>0.28$ compared to any fracture). In contrast, the HR for the hip fracture outcome was somewhat lower for parental history of any fracture than that for a parental history of hip fracture (1.22 vs. 1.38, respectively, when adjusted for age and time since baseline) (Figure 3).

A sibling history of hip fracture was only recorded in 6 cohorts comprising 25,887 individuals, and a sibling history of any fracture in 4 cohorts with a total of 16624 men and women. The overall prevalence of sibling hip fracture was 3.5% and that of any fracture was 24.2%. Both were also associated with an increase in future fracture risk, similar to that of a history of comparable fracture in a parent (Figure 3).

Quality scores

While the HRs were slightly higher in moderate quality studies than in those judged to be high quality, there was no statistically significant difference in fracture outcome HRs when cohorts of high quality were compared with those of moderate quality and a single low quality study (Supplementary Data Table E).

Discussion

The present study, undertaken using primary data from a large number of international population-based cohorts, confirms that a family history of fracture confers an increase in fracture risk as shown in a previous meta-analysis[16]. Since that publication, several other individual cohort studies have confirmed the association[6, 9, 10]. As seen in the previous meta-analysis, a parental history of hip fracture is a stronger predictor of future hip fracture risk than parental fractures at other sites but also predicts other fracture outcomes[16]. Notably, this predictive performance is now observed to be similar in the presence of a sibling history of hip fracture. In addition, both a parental and sibling history of any fracture show similar relationships with future fracture risk though the performance for hip fracture risk is somewhat weaker than that for a parental or sibling history of hip fracture. Additionally,

the associations are similar in men and women and the parental history is of equivalent performance regardless of whether the history of fracture is maternal or paternal. Importantly, the associations are independent of age, duration of follow-up and, as demonstrated previously, are largely independent of BMD. Some of these results differ from those derived in the previous smaller meta-analysis and these are discussed in more detail below.

A major difference in the present analysis from our previous meta-analysis [16] is the observation that a family history of fracture (hip or any) has very similar effects on fracture risk in men and women. In the earlier analysis, probably due to a relatively small sample size of men, a paternal history of any fracture was a significant risk factor for hip fracture in women (RR = 2.04), but not in men (RR = 0.99). The earlier analysis also showed that a maternal history of fracture was also apparently a stronger risk factor for hip fracture amongst men (RR = 2.18) than amongst women (RR = 1.29). The current analysis clearly shows that the impact of parental history of fracture is the same in men and women and is the same regardless of whether the fracture had occurred in the mother or father. Given that the relationships reflect a genetic component of risk, predominantly related to small effects of multiple autosomal genes, one might expect a similar impact from maternal or paternal fracture as the offspring inherits approximately half of their genome from each. In addition, siblings on average share half of their genes with each other[31], so that a similar genetic relationship in siblings and parents is not unexpected.

The hazard ratios reported here for family history of hip fracture on the outcomes of hip and osteoporotic fractures are somewhat lower than those from the previous meta-analysis. For example, parental history of hip fracture previously had a hazard ratio of 1.75 (95%CI 1.17–2.63) for offspring hip fracture[16], compared to 1.37 (1.23-1.52) in the present analysis. The respective ratios for the outcome of osteoporotic fracture are 1.38 (1.16–1.65) and 1.16 (1.10-1.23). The increased sample size has improved the certainty of the estimates with substantially narrower confidence limits, but it should be noted that the new point estimates for the hazard ratios still lie within the confidence limits from the earlier analysis. Furthermore, the hazard ratio reported here for subsequent MOF associated with parental hip fracture (1.19, 1.12-1.27) is similar to that observed in two analyses from a single cohort using electronic record linkage to examine the relationship between parental hip fracture risk and subsequent MOF fracture risk (HRs 1.26 and 1.30, respectively)[9, 10].

It is worth noting the additional new information about the interaction, or more correctly the lack of interaction, between age and a family history of fracture for subsequent fracture risk. One could speculate that an age interaction might be expected; for example, fewer parental hip fractures are likely to be observed for younger offspring as their parents may also not be that old and have not yet sustained

a fracture. However, in those younger offspring with a parental history of hip fracture, the latter may also have occurred at a relatively young age and relate more to heritable factors. In the earlier meta-analysis, the HR for osteoporotic and/or hip fractures showed a decrease with age, an effect that was observed for both a parental history of any fracture and was particularly marked for parental hip fracture[16]. For example, for the latter risk factor and an outcome of hip fracture, the HR decreased from 2.34 at the age of 40 years to 1.33 at the age of 85 years. However, the confidence intervals were wide and the p-values for age interaction did not reach statistical significance[16]. In this updated analysis, the decrease in HR with age is much more subtle and, in the presence of a much greater sample size, shows no interaction with age. Again, this analysis does not contain information about the age of parents at the time of hip fracture; recent analysis from a single large cohort suggests that the increase in risk is significantly lower at older age of hip fracture in the parents [10]. Both the earlier and present meta-analyses also confirm no interaction between a family history of hip fracture and time of follow-up.

As FRAX probabilities are derived using age-specific incidences of fracture and mortality, this analysis also examined the relationship between a family history of fracture and mortality. Perhaps surprisingly, it shows that a parental history of hip fracture is associated with an approximate 10% lower mortality risk, an effect that persists following adjustment for age, time since baseline and BMD. In the absence of information about the age of death in the parents, it could be speculated that the occurrence of hip fracture provides a surrogate measure of longevity in the parent (those living into older age being at increased risk of hip fracture). While lifespan has a relatively low heritability (25% or less), longevity (survival to extreme ages e.g. top 10% of long-term survivors) clusters strongly within families[32].

The study has a number of strengths and limitations. The family history is based on self-reported data and may be open to recall bias. However, studies have reported that the validity of self-reported fractures, particularly non-vertebral fractures, is generally good[33, 34], and a single well-conducted study has also confirmed good agreement between offspring reports and diagnosis of parental hip fracture using hospitalization data in Manitoba (kappa = 0.68, sensitivity 70%, specificity 96%)[11]. As a further strength, the estimates of risk are derived in an international setting largely from population-based cohorts, and the calculations, based on primary data, decrease the risk of publication bias. Additionally, non-response biases, for example from frail individuals, which might result in an underestimate of the probability associated with a family history of fracture, are unlikely to affect risk ratios. The construct of the question(s) to capture family history differed somewhat between cohorts, especially on the breadth of family history particularly of sibling history. Nonetheless, there is good evidence for a degree of homogeneity across the cohorts and family histories that are consistent with

genetic and/or shared environmental effects. The study suggests that family history is also an important risk factor across ethnicities, though this conclusion is somewhat limited by the relatively small non-white populations included. Importantly, the use of a family history as a risk factor to identify patients also appears to identify a risk that is amenable to treatment with bone-active medications. For example, there was no difference in treatment efficacy according to family history of fracture or osteoporosis in studies of raloxifene or strontium ranelate[35, 36]. More recently, in the SCOOP study of screening for high hip fracture risk in the UK, family history of fracture was a major driver of identifying a high-risk subgroup for subsequent treatment[37]. Treatment was associated with a 28% overall reduction in hip fracture incidence in the screening arm, with an approximate 45% reduction in hip fracture risk in those at highest risk and receiving treatment, of whom 39% had a history of parental hip fracture[37, 38].

The mechanism for the BMD-independent increase in risk, including skeletal factors such as bone size, shape and microarchitecture[39], remains elusive and could not be addressed in our analysis. As previously, we have determined that height, a relatively highly genetic component, did not affect the relationship between family history and fracture outcome[16] despite a strong genetic component to height [40]. That family history is independent of other risk factors used in FRAX, in addition to age, sex and BMD, will also need to be examined in further analyses before a final update of the FRAX tool.

In summary, this updated and much enlarged meta-analysis has quantified the magnitude of the risk for future fractures conferred by a family history of hip or any fracture. A family history of hip fracture remains the strongest family-based predictor of future hip fracture, and this is true if the hip fracture occurs in either parent or a sibling. Nonetheless, a family history of any fracture is also a significant contributor to future fracture risk and the effect is similar in men and women. As shown previously, and irrespective of the mechanism, these data indicate that the risk of hip or all osteoporotic fractures is greater in men and women with a family history of fractures than in individuals with the same level of BMD but with no family history. The consistency of the association between family history and fracture risk in an international setting provides the rationale for the continuing use of family history of fracture in the next iteration of FRAX.

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Declarations

Ethical approval and consent to participate. All individual cohorts with candidate risk factors available have been approved by their local ethics committees, and informed consent has been obtained from all study participants. General ethics approval for the use of all cohorts is also given by the University of Sheffield. This study does not contain any original studies with human participants or animals performed by any of the authors. Participant data are stored in coded, de-identified form. Only summary statistics and aggregate data are published, not allowing for the identification of individual study participants.