Prior fracture as a risk factor for future fracture in an Australian cohort

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Abstract

Purpose: To determine the impact of prior fracture on the risk of subsequent fracture across the adult age range in Australian males and females.

Methods: All-cause fractures were grouped into age categories for males and females enrolled in the Geelong Osteoporosis Study (Australia) using retrospective self-report data and prospective radiology-confirmed data. For all age categories, the relative risk (RR and 95%CI) of subsequent fracture in a later age category was compared between those with prior fracture and those without.

Results: For both sexes, childhood fracture increased the risk of subsequent fracture in adolescence (males: RR 21.7; 95%CI 16.0, 27.4; females: RR 8.1; 3.5, 12.8). Males with adolescent fracture had increased risk of subsequent fracture in early adulthood (RR 11.5; 5.7, 17.3) and mid-adulthood (RR 13.0; 6.3, 19.7). Additionally, males with young adulthood or mid-adulthood fracture had increased risk of subsequent fracture in the following age group (RR 11.2; 4.4, 17.9 and RR 6.2; 0.8, 11.7, respectively). Mid-adult fractures increased the risk of subsequent fracture in older adulthood (RR 6.2; 0.8, 11.7). Females with childhood or adolescent fracture had an increased risk of fracture in young adulthood (RR 4.3; 0.7, 7.9 and RR 10.5; 4.4, 16.6) and prior fracture in older adult life increased the risk of subsequent fracture in old age (RR 14.9; 6.4, 23.3).

Conclusions: Fracture prevention strategies may be more effective if attention is directed towards individuals with prior fracture at any age as they have a higher likelihood of sustaining a subsequent fracture later in life.

Keywords: prior fracture, fracture risk, epidemiology, relative risk

Mini abstract:

This study investigated the influence of prior fracture on the risk of subsequent fracture.

There was a higher risk of subsequent fracture in both young and older adult age groups when Australian males or females had already sustained a prior fracture. Fracture prevention is important throughout life for both sexes.

Introduction

Many studies investigating prior fracture as a risk factor for subsequent fracture only consider prior fragility fracture or prior fracture after age 45-50 years and usually only in postmenopausal females [1-19]. Several studies have shown that fractures occurring early in a person's life can have an impact on the risk of subsequent fracture [20-22]. Childhood fractures are common; approximately 27-40% of girls and 42-51% of boys sustain at least one fracture during growth [23]. Additionally, children who sustain a fracture have a 2-3 times higher probability of sustaining a subsequent fracture compared to those who have never sustained a fracture [24, 25]. In this study, we investigated the impact of prior fracture at any age on the risk for subsequent fracture at any older age in order to determine the importance of prior fractures during the life-course.

Methods

Participants

This study uses data from the Geelong Osteoporosis Study (GOS); a population-based study set in the Barwon Statistical Division (BSD), south-eastern Australia. This region has a large, stable population (n~250,000) with a range of social, cultural and geographical settings and is representative of the Australian population, making it ideal for epidemiological studies.

Further details of the study are provided elsewhere [26]. This study included 1538 males and 1731 females enrolled in GOS with an age range of 21 to 110 years. Baseline recruitment for males was from 2001 to 2006, (1540 recruited, 67% response). Females underwent baseline assessments from 1993 to 1997 (1494 recruited, 77% response) and a further subset of females aged 20-29 years was recruited from 2006 to 2008 (246 recruited, 82% response).

The cohort has been re-assessed every few years. In this analysis, age corresponded to the date of last follow-up, from X-ray reports for fracture, death or emigration from the study region. Two males and nine females were excluded from this analysis because of incomplete data. Written, informed consent was obtained from all participants and this study was approved by the Barwon Health Human Research and Ethics Committee.

Fracture ascertainment

Pre-baseline fractures

Fractures that occurred pre-baseline for both sexes were obtained by self-reported fracture history [27]. Information regarding skeletal site, age at the time of fracture and circumstances of fracture were collected by questionnaire. All fractures regardless of trauma level or skeletal site were included in this study. We made an *a priori* decision to include all fractures because prior fractures at all skeletal sites (except the clavicle) have been shown to be associated with an increased risk of subsequent fracture [8].

Post-baseline fractures

Post-baseline fractures were identified using a computerised keyword search of all radiological reports from the medical imaging centres serving the BSD region. This method of fracture ascertainment has been previously validated [34]. Cause of fracture was determined by questionnaire or from medical histories. Participants were identified by name and date of birth to avoid multiple ascertainment of the same fracture event.

Statistical analyses

Age categories were created based on the development of the skeleton at different stages of life. For males, the youngest age category was 0-14 years and for females it was 0-12 years because of the differences in peak height velocity and childhood fracture rates between the sexes [23, 28]. The next age category included adolescents; 15-19 years for males and 13-19 years for females. All other age categories were the same for both sexes; 20-25 years, 26-50 years, 51-70 years and 71+ years. The age category 20-25 years was chosen because it reflects peak bone mass and transition from adolescence to adulthood [29], whereas the other age categories were chosen to separate menopausal women from pre-menopausal women [30]. Each participant was included in all age categories up to and including their current age. For example, a 35 year old male would be included in the 0-14, 15-19, 20-25 and 26-50 year age categories.

Males and females were analysed separately because of sex-related differences in the patterns of incident fractures [31]. For each age category separately, participants were divided into those who had sustained at least one fracture in that age group and those who had not. Then, for each older age category, the proportion of those who sustained a fracture was recorded. The denominator used to calculate these proportions represented the number of individuals at risk for fracture and this was recalculated for each age category.

Since dividing ages into six categories reduced the power of our analyses, we also conducted an analysis using only three categories; <20 years, 20-50 years and >50 years in both males and females separately.

A comparison was then conducted to determine the relative risk (RR) of sustaining a subsequent fracture later in life after sustaining a fracture in an earlier age group. Statistical

analyses were performed using Minitab (version 16) and a p value of <0.05 was considered significant.

Results

Of the total cohort, 934 males and 870 females sustained at least one fracture, which corresponded to 55.2% of all GOS participants. There were 1861 fractures among 934 males and 1573 fractures among 870 females.

Fractures among males

Table 1 shows the proportion of males who sustained at least one fracture in each specific age category, stratified into those with and without a fracture sustained earlier in life. Table 2 shows the RR for fracture given the presence of a prior fracture. The presence of a fracture sustained between ages 0 and 14 years increased the risk for subsequent fracture between the ages of 15 and 19 years (RR 21.7, 95%CI: 16.0, 27.4). Males who sustained a fracture between 15 and 19 years of age were at increased risk for sustaining subsequent fractures in the following two age categories (20-25 and 26-50 years) than those who did not sustain a fracture during this age (RR 11.5, 95%CI: 5.7, 17.3 and RR 13.0, 95%CI: 6.3, 19.7, respectively). A fracture between ages 20 and 25 years increased the risk for subsequent fracture between the ages of 26 and 50 years (RR 11.2, 95%CI :4.4, 17.9) and a fracture in the 26-50 year age category increased the risk for subsequent fracture in the 51-70 year age group (RR 6.2, 95%CI: 0.8, 11.7). No other associations were observed between combinations of other age categories for males.

Fractures among females

Table 3 shows the proportion of females who sustained at least one fracture in each specific age category, stratified into those with and without a fracture sustained earlier in life. Table 4 shows the RR for fracture given the presence of a prior fracture. The presence of a fracture between ages 0 and 12 years increased the risk for subsequent fracture between the ages of 13 and 19 years as well as 20 to 25 years (RR 8.1, 95%CI: 3.5, 12.8 and RR 4.3, 95%CI: 0.7, 7.9, respectively). Females who sustained a fracture between the ages of 13 and 19 were also at increased risk for sustaining subsequent fracture between the ages of 20 and 25 years than those who had not sustained a fracture in this age category (RR 10.5, 95%CI: 4.4, 16.6). Finally, females that sustained a fracture between the ages of 51 and 70 were at increased risk of sustaining a subsequent fracture in the oldest age category (71+ years) than those who had not sustained a fracture in this age category (RR 14.9, 95%CI: 6.4, 23.3).

Fractures among men and women for age groups <20, 20-50 and >50 years

Table 5 shows the relative risks, for both sexes, of sustaining a subsequent fracture after a prior fracture in a younger age group, but divided into only 3 analysis groups (<20, 20-50 and >50 years). The grouped analyses for both sexes showed an increased risk of sustaining a fracture in the 20-50 year age group if they had sustained a prior fracture in the <20 year age group. In addition, the analyses for females showed a decreased risk of sustaining a fracture in the >50 year age group if they had sustained a fracture in the 0-19 year age group.

Discussion

Data from our prospective cohort study provide risk predictions of subsequent fractures after prior fracture throughout the life-course for males and females. There are several findings to report. First, males who sustained fractures during childhood (0-14 years), adolescence (15-

19 years), young adulthood (20-25 years) or mid-life (26-50 years) were at increased risk of sustaining a fracture during the following age category than those who had not sustained a prior fracture. Interestingly, males who sustained a fracture during adolescence and young adulthood had a higher risk of sustaining a fracture in the age category 26-50 years. For females, sustaining a fracture in childhood (0-12 years), adolescence (13-19 years) or older adulthood (51-70 years) increased the risk of sustaining a subsequent fracture in the following age category. Males with a prior fracture in adolescence (15-19 years) also had an increased risk of fracture in the mid-life age category (26-50 years). Females with a fracture in childhood (0-12 years) had an increased risk of fracture in the young adulthood age category (20-25 years). No other associations were observed between combinations of other age categories for males.

There are few studies investigating the impact of childhood fractures on subsequent fracture later in childhood or adolescence. One study by Goulding et al [32] investigated the effect of childhood fracture in males and females on subsequent childhood or adolescent fracture up to the age of 18 years. Of 601 children and adolescents, 310 participants (51.6%) reported no fractures and 291 (48.4%) reported sustaining at least one fracture. Children and adolescents who had sustained at least one prior fracture had a higher risk of sustaining subsequent fracture. This result is concordant with our study. To our knowledge, few studies have examined the effect of childhood fracture on subsequent fracture risk in adulthood. One of these studies [33] reported that childhood fractures (8-18 years) do not impact future fracture risk after the age of 50 years, concordant with our results for females but not for males. Another study [22] reported that fractures occurring before 20 years were not associated with a higher risk of fracture after age 50, which is in agreement with our results for males, but not for females.

Kanis et al [9] have conducted a meta-analysis of previously published studies on the evidence of prior fracture as a risk factor for subsequent fracture. The final analysis included 15,259 men and 44,902 women from 11 different cohorts, covering a range of geographical regions and age categories. The authors concluded that a history of prior fracture resulted in an increased risk of subsequent fracture, independent of bone mineral density. More studies focused on the impact of early adulthood fractures on the risk of subsequent fracture later in life have also been conducted. Honkanen et al [20] used data from a cohort of 12,162 postmenopausal females from Finland to report that females who sustained a fracture between 20 and 34 years of age had a 90% higher risk of sustaining a fracture between the ages of 35 and 57 years. Wu et al [22] showed in a sample of 1284 postmenopausal females from New Zealand, that fractures occurring between the ages of 20 and 50 years increased the risk of subsequent fracture after age 50 years. Hosmer et al [21] investigated the impact of premenopausal fractures on subsequent fracture in a sample of 9086 postmenopausal females aged 65 years or older from the United States of America. The age at menopause was determined for each female to ensure the separation between pre- and post-menopausal fracture. The main finding from this study was that females with premenopausal fracture (from age 25 years to menopause) were approximately 35% more likely to have a fracture during the 12-year study period than those without premenopausal fracture.

In our data, we did not observe an increased risk of postmenopausal fractures after prior premenopausal fracture in women. However, we did observe an increased risk of subsequent fracture in the 71+ year age category in females for those who sustained a prior fracture in the 51-70 year age category. The reason for this difference could be differing study designs and

cohort demographics. The aforementioned studies included mainly postmenopausal females whereas our study included females of all ages. In our cohort, female fracture rates were low until 50+ years of age. This may have impacted on the power of our study to detect age-related differences in fracture risk. Additionally, none of these previous studies examined the effect of prior fractures on probability of sustaining a subsequent fracture in males.

To address the problem of power to detect differences, we also performed an analysis involving only three age categories. The results of this analysis were similar to what was observed with the larger number of age categories; childhood and adolescent fractures resulted in an increased risk of fractures in the 20-50 year age group for both sexes. However, we found that females who sustained a fracture before age 20 had a decreased risk to fracture in the 51+ year age group. This could be due to recall bias of older women in remembering childhood and adolescent fractures, but the reason for this result this is unclear.

The major strength of this study is that participants were randomly selected from the general population using the Commonwealth electoral roll as the sampling frame. In Australia, voting is compulsory and therefore the electoral rolls provide a comprehensive list of all adult Australians. At baseline, participation was high as was subsequent retention. However, the study cohort lacks the ethnic diversity of today's population as the majority of our cohort is Caucasian (99%) and this might limit the generalizability of the study findings. Finally, although self-reported fractures have previously been shown to be reliable [8, 27, 34], we cannot ensure the accuracy of self-reported fractures that occurred prior to baseline. We found that in males, 19.9% of adolescents (15 to 19 years) recalled sustaining a fracture in childhood (0-14 years) but only 11.3% of those aged over 70 years recalled sustaining a

childhood fracture. Data for females was similar. This could indicate an increase in reckless behaviour in children but also difficulties in recollection, or a combination of both.

Conclusions

Males who sustained a fracture before 51 years of age had a higher risk of sustaining subsequent fractures during the following age category than those who did not sustain a prior fracture. Additionally, males who sustained a fracture during adolescence had a higher risk of fracturing in the age category 26-50 years. Females who sustained a fracture in childhood (0-12 years), adolescence (13-19 years) or older adulthood (51-70 years) had a higher risk of sustaining a subsequent fracture in the following age category than those who had not sustained a prior fracture. Preventative measures aimed at any subsequent fracture should be focused on males who sustained a prior fracture early in life. In females, preventative strategies should aim to target all ages across the lifespan.

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Table 1: Number of males (number with fracture/total number in age group; proportion, %) who sustained a fracture in specific age categories, divided into those that did and did not fracture earlier in life^a. Bold indicates significant difference between the fracture and non-fracture groups based on relative risk calculations ($p < 0.05$).

Prior fracture age		Fracture age categories (years)				
category (years) ^b		15-19	20-25	26-50	51-70	71+
0-14						
Prior	110/307	50/307	79/293	28/153	13/64 (20.3)	
fracture	(35.8)	(16.3)	(27.0)	(18.3)		
No	174/1232	173/1232	275/1188	102/857	110/503	
fracture	(14.1)	(14.0)	(23.1)	(11.9)	(21.9)	
15-19						
Prior	-	56/231	77/220	19/125	8/46 (17.4)	
fracture		(24.2)	(35.0)	(15.2)		
No	-	167/1308	277/1260	111/884	115/520	
fracture		(12.8)	(22.0)	(12.6)	(22.1)	
20-25						
Prior	-	-	71/212	15/113	11/58 (19.0)	
fracture			(33.5)	(13.3)		
No	-	-	283/1268	161/896	112/508	
fracture			(22.3)	(18.0)	(22.0)	
26-50						
Prior	-	-	-	40/226	27/110	
fracture				(17.7)	(24.5)	

No	-	-	-	90/783	96/456
fracture				(11.5)	(21.1)
51-70					
Prior	-	-	-	-	18/66 (27.3)
fracture					
No	-	-	-	-	105/500
fracture					(21.0)

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^aFor example, for individuals with fractures in the 0-14 year age group (left column), 35.8% of them sustained a subsequent fracture in the 15-19 year age group. Only 14.1% of the individuals with no fracture in the 0-14 year age group sustained a subsequent fracture in the 15-19 year age group.

^bAge category where fracture was sustained (years).

Table 2: Relative risk (risk, 95% CI) for males in each age category to sustain a fracture after a prior fracture in a younger age group. Bold indicates significant difference between the fracture and non-fracture groups ($p < 0.05$).

Prior fracture age category (years) ^a	Fracture age categories (years)				
	15-19	20-25	26-50	51-70	71+
0-14	1.22 (1.16-1.27)	1.02 (0.98, 1.07)	1.04 (0.98, 1.09)	1.06 (1.00, 1.13)	0.98 (0.99, 1.09)
15-19	-	1.12 (1.06, 1.17)	1.13 (1.06, 1.20)	1.03 (0.96, 1.09)	0.95 (0.98, 1.07)
20-25	-	-	1.11 (1.04,1.18)	0.95 (0.89, 1.21)	0.97 (0.99,1.08)
26-50	-	-	-	1.06 (1.01, 1.12)	1.04 (0.95,1.12)
51-70	-	-	-	-	1.06 (0.95,1.18)

^aInitial age category where fracture was sustained (years).

Table 3: Number of females (number with fracture/total number in age group; proportion, %) who sustained a fracture in specific age categories, divided into those that did and did not fracture earlier in life^a. Bold indicates significant difference between the fracture and non-fracture groups based on relative risk calculations ($p < 0.05$).

Prior age category ^b		Subsequent age categories (years)				
		13-19	20-25	26-50	51-70	71+
0-12						
Prior fracture		34/236 (14.4)	19/236 (8.1)	30/203 (14.8)	19/103 (18.4)	19/43 (44.2)
No fracture		94/1495 (6.3)	56/1495 (3.7)	178/1414 (12.6)	223/1018 (21.9)	253/657 (38.5)
13-19						
Prior fracture		-	18/128 (14.1)	20/117 (17.1)	6/48 (12.5)	6/20 (30.0)
No fracture		-	57/1603 (3.6)	188/1500 (12.5)	236/1073 (22.0)	266/680 (39.1)
20-25						
Prior fracture		-	-	12/61 (19.7)	9/24 (37.5)	3/9 (33.3)
No fracture		-	-	196/1556 (12.6)	233/1097 (21.2)	269/691 (38.9)
26-50						
Prior fracture		-	-	-	29/137 (21.2)	28/65 (43.1)

No	-	-	-	213/984	244/635
fracture				(21.6)	(38.4)
51-70					
Prior	-	-	-	-	88/176
fracture					(50.0)
No	-	-	-	-	184/524
fracture					(35.1)

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^aFor example, for individuals with fractures in the 0-12 year age group (left column), 14.4% of them sustained a subsequent fracture in the 13-19 year age group. Only 6.3% of the individuals with no fracture in the 0-12 year age group sustained a subsequent fracture in the 13-19 year age group.

^bInitial age category where fracture was sustained (years).

Table 4: Relative risk (risk, 95% CI) for females in each age category to sustain a subsequent fracture after a prior fracture in a younger age group. Bold indicates significant difference between the fracture and non-fracture groups ($p < 0.05$).

Prior fracture age category (years) ^a	Fracture age categories (years)				
	15-19	20-25	26-50	51-70	71+
0-12	1.08 (1.04, 1.13)	1.04 (1.01, 1.08)	1.02 (0.97, 1.07)	0.97 (0.89, 1.05)	1.06 (0.90, 1.21)
13-19	-	1.11 (1.04, 1.17)	1.05 (0.98, 1.12)	0.91 (0.81, 1.00)	0.91 (0.71, 1.11)
20-25	-	-	1.07 (0.97, 1.17)	1.16 (0.97, 1.36)	0.94 (0.96, 1.25)
26-50	-	-	-	1.00 (0.92, 1.07)	1.05 (0.92, 1.17)
51-70	-	-	-	-	1.15 (1.06, 1.23)

^aInitial age category where fracture was sustained (years).

Table 5: Relative risk (risk, 95% CI) for males and females in one of three age categories to sustain a subsequent fracture after a prior fracture in a younger age group. Bold indicates significant difference between the fracture and non-fracture groups ($p < 0.05$).

Prior fracture age category (years) ^a	Fracture age categories (years)	
	20-50	>50
Males		
0-19	1.08 (1.03, 1.14)	0.98 (0.92, 1.03)
20-50	-	1.02 (0.96, 1.08)
Females		
0-19	1.06 (1.01, 1.10)	0.87 (0.79, 0.95)
20-50	-	1.00 (0.92, 1.08)

^aInitial age category where fracture was sustained (years).