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Original Article

Incidence of Limb Fracture across Europe: Results from the European Prospective Osteoporosis Study (EPOS)

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Abstract. The aim of this population-based prospective study was to determine the incidence of limb fracture by site and gender in different regions of Europe. Men and women aged 50–79 years were recruited from population registers in 31 European centers. Subjects were invited to attend for an interviewer-administered questionnaire and lateral spinal radiographs. Subjects were subsequently followed up using an annual postal questionnaire which included questions concerning the occurrence of new fractures. Self-reported fractures were confirmed where possible by radiograph, attending physician or subject interview. There were 6451 men and 6936 women followed for a median of 3.0 years. During this time there were 140 incident limb fractures in men and 391 in women. The age-adjusted incidence of any limb fracture was 7.3/1000 person-years [pyrs] in men and 19 per 1000 pyrs in women, equivalent to a 2.5 times excess in women. Among women, the incidence of hip, humerus and distal forearm fracture, though not 'other'

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limb fracture, increased with age, while in men only the incidence of hip and humerus fracture increased with age. Among women, there was evidence of significant variation in the occurrence of hip, distal forearm and humerus fractures across Europe, with incidence rates higher in Scandinavia than in other European regions, though for distal forearm fracture the incidence in east Europe was similar to that observed in Scandinavia. Among men, there was no evidence of significant geographic variation in the occurrence of these fractures. This is the first large population-based study to characterize the incidence of limb fracture in men and women over 50 years of age across Europe. There are substantial differences in the descriptive epidemiology of limb fracture by region and gender.

Keywords: Epidemiology; Europe; Incidence; Limb fracture; Osteoporosis

Introduction

Osteoporosis is an important health problem because of its association with age-related fractures [1]. Hip, wrist and spine fractures are the most frequent osteoporotic fractures. Other limb fractures, however, account for a substantial proportion of the total number of fractures and many of these are also related to osteoporosis [2]. In contrast to the relatively detailed information concerning hip fracture occurrence [3,4] and radiographic vertebral deformity [5], relatively little is known about the descriptive epidemiology of limb fractures across Europe. Such data are important both to help determine the health and economic burden associated with osteoporosis as a whole and to help in planning population-wide strategies for prevention. Furthermore, evidence of variation in the occurrence of these fractures by age, gender and region may help provide clues to pathogenesis.

The European Prospective Osteoporosis Study (EPOS) is a multicenter, multinational population prospective study of incident fractures. The aim of this analysis was to characterize the incidence of limb fractures by age and sex across Europe, and secondly to explore the influence of geography on the occurrence of these fractures.

Subjects and Methods

Subjects

The detailed methods of the baseline survey (EVOS) have been outlined elsewhere [5,6]. In brief, men and women were recruited from population-based registers in 36 centers and invited to attend for an interviewer-administered questionnaire and lateral spinal radiographs. Stratified random sampling was used with the aim of recruiting equal numbers of men and women in each of six, 5-year bands from 50–54 years to 75 years and over. Following recruitment, subjects in 32 centers were invited to participate in a prospective survey of fractures. However, because of a low follow-up rate, data from one center was subsequently excluded from the analysis.

Ascertainment of Limb Fractures

A standardized postal questionnaire was used to ascertain the occurrence of new limb fractures. The postal questionnaire included a question which asked about the occurrence of recent fractures. If these had occurred, subjects were asked about the date and where they had attended for treatment of the fracture. Subjects were asked in addition to mark on a manikin the site of the fracture. A second postal questionnaire was sent, approximately 1 year after the first questionnaire, asking again about recent fractures. Each center was responsible for verification of self-reported fractures at their own center. A hierarchical, three-stage procedure was used. Where possible radiographic evidence was sought from the health care facility responsible for treatment of the injury. If this was not available (either because the film was not available or had not been taken), details of the injury were sought from the attending physician based on the medical records. In a proportion of subjects (15%) it was not possible to verify fractures by either method. In this case the individual subjects were, where possible, interviewed in an attempt to verify whether or not they had sustained a fracture. In some cases, however, it was not possible to obtain any further details about the injury and in this situation information concerning the site of the fracture was obtained from the questionnaire manikin. This approach to ascertaining fracture has been shown to be reasonably accurate for upper and lower limb fractures [7].

Statistical Analysis

The analysis was restricted to subjects aged 50–79 years at baseline as the proportion of the study cohort above the age of 80 years was small. Subjects contributed follow-up time (person-years) from the date of the baseline survey until limb fracture, death or the study cutoff date. In subjects who sustained more than one fracture of the same type (e.g., two distal forearm fractures), time to the first fracture event was used in the analysis. If more than one type of fracture had occurred (e.g., a hip and distal forearm fracture), depending on which fracture was being analyzed, time to the fracture of interest was used. In addition to analysis of all limb fractures, fractures were classified using the 9th edition of the International Classification of Diseases [8] into the following categories: hip (neck of femur), ICD code 820; distal forearm, ICD code 813; humerus, ICD code 812; 'other' limb, ICD codes 814–817, 821–826. Analysis was undertaken focusing on all fractures, and then separately by fracture site. All analyses were undertaken separately in men and women. Results are presented per 1000 person-years of follow-up, and by 5-year age bands. Direct standardization was used to standardize incidence rates for limb fractures to a standard European population [9]. To explore the influence of geography on the incidence of fracture, centers were grouped into four broad regional areas: Southern Europe (Greece, Italy, Portugal, Spain, Turkey), Eastern Europe (Czech Republic, Hungary, Poland, Russia, Slovakia), Western Europe (Austria, Belgium, France, Germany, The Netherlands, United Kingdom) and Scandinavia (Norway, Sweden). Differences in fracture rate between regions were assessed using Poisson regression.

Results

Subjects

Of the 16 511 subjects who participated in the baseline survey in the 31 centers that contributed to this analysis, 6451 men (mean age 63.8 years) and 6936 women (mean age 63.1 years) were followed for a median of 3.0 years (range 0.4–5.9 years). Of those recruited at baseline and in whom data concerning vital status was available there were 826 deaths.

Incidence of Limb Fracture

In total 140 men and 391 women sustained an incident limb fracture during the follow-up period. The number and type of fractures sustained in men and women is shown in Table 1. In both men and women 'other' fractures were the most frequent category and comprised: in men: hand/carpal bone (18), femoral shaft (2), patella (2), tibia/fibula (11), ankle (10), foot (19), not known (unconfirmed) (13); and in women: hand/carpal bone (35), femoral shaft (4), patella (6), tibia and fibula (33), ankle (40), foot (42), not known (unconfirmed) (16).

In men, the crude incidence rate for any limb fractures was 7.2 per 1000 person-years (pyrs) [95% confidence interval (CI) 6.1, 8.5] and in women 18.9 per 1000 pyrs (95% CI 17.1, 20.9). The age-standardized incidence rates by fracture type in men and women are shown in Table 2. In men, the overall age-standardized incidence rate for any limb fracture was 7.3 per 1000 pyrs (95% CI 6.1, 8.5) and in women, 19.0 per 1000 pyrs (95% CI 17.1, 20.8).

Influence of Age and Gender

In women the incidence of 'any' limb fracture increased with age from 14/1000 pyrs at age 50–54 years to 32/1000 pyrs at age 75–79 years (Table 3). For men, however, the incidence remained relatively constant with increasing age: 11.3/1000 pyrs at age 50–54 years and 9.4/1000 pyrs at age 75–79 years. There was variation in the pattern of incidence with age for the different fracture types. The incidence of both hip and humerus fracture increased with age in both men and women. In women, the incidence of distal forearm fracture increased progressively with age (with no evidence of plateau at age 65 years), while in men it remained low throughout life. In contrast to these patterns of incidence the incidence of all 'other' limb fractures did not increase with age in either men or women.

Table 1. Number of subjects with incident limb fracture by site and gender

	Men (n = 6451)	Women (n = 6936)
Hip	17	27
Distal forearm	34	154
Humerus	15	42
'Other' limb	75	176
Any limb fracture[a]	*140*	*391*

[a]Numbers in cells do not add up because 9 subjects incurred more than one type of limb fracture (1 man, 8 women).

Table 2. Age-standardized[a] incidence of limb fracture by fracture type and gender

	Men (n = 6451)				Women (n = 6936)			
Fracture type	Person-years at risk	No. of subjects with fracture	Incidence per 1000 person-years	95% CI	Person-years at risk	No. of subjects with fracture	Incidence per 1000 person-years	95% CI
Hip	19 694	17	0.8	(0.4, 1.0)	21 285	27	1.3	(0.8, 1.7)
Distal forearm	19 661	34	1.7	(1.1, 2.3)	21 073	154	7.3	(6.2, 8.5)
Humerus	19 690	15	0.7	(0.4, 1.1)	21 256	42	2.0	(1.4, 2.6)
'Other' limb	19 590	75	4.0	(3.1, 4.9)	21 067	176	8.4	(7.1, 9.6)
Any limb	19 494	140	7.3	(6.1, 8.5)	20 692	391	19.0	(17.1, 20.8)

[a]Age-standardized to the European population (age 50–79 years).

Table 3. Incidence of any limb fracture by age and gender

Age (years)	Men					Women				
	Subjects (*n*)	Person-years at risk	No. of subjects with fracture	Incidence per 1000 person-years	95% CI	Subjects (*n*)	Person-years at risk	No. of subjects with fracture	Incidence per 1000 person-years	95% CI
50–54	1127	3456	39	11.3	(8.0, 15.4)	1348	4133	58	14.0	(10.7, 18.1)
55–59	1260	3879	28	7.2	(4.8, 10.4)	1459	4498	64	14.2	(11.0, 18.2)
60–64	1255	3850	19	4.9	(3.0, 7.7)	1345	4033	76	18.8	(14.8, 23.6)
65–69	1147	3494	15	4.3	(2.4, 7.1)	1189	3530	81	22.9	(18.2, 28.5)
70–74	997	2908	21	7.2	(4.5, 11.0)	988	2846	59	20.7	(15.8, 26.7)
75–79	665	1909	18	9.4	(5.6, 14.9)	607	1653	53	32.0	(24.0, 41.9)

Influence of Geography

The age-standardized incidence of limb fracture by gender and type of fracture in different European regions is shown in Table 4. In both men and women the incidence of 'any' limb fracture was higher in Scandinavia and Eastern Europe than the other regions. When the individual fracture types were considered, among women, there was evidence of significant variation in the occurrence of hip, distal forearm and humerus fractures ($p < 0.05$) (Table 4). For all three the incidence was higher in Scandinavia than in other European regions, though for distal forearm fracture the incidence in Eastern Europe was similar to that observed in Scandinavia. There was no significant variation in the occurrence of all 'other' limb fractures in women though the incidence was highest in Eastern Europe. Among men, there was no evidence of significant variation in occurrence of any of the limb fracture types across Europe, though the numbers within each group were relatively small (Table 4). The geographic pattern, however, was similar to that observed in women for hip fracture, with a Scandinavian excess. As with women the incidence of distal forearm fracture and all 'other' limb fractures in men was relatively high in Eastern Europe.

Discussion

In this large prospective population-based study we have documented the incidence of the major limb fractures by age, gender and region. There was evidence in women of variation in the incidence of individual limb fracture types across Europe, with fractures of the hip and humerus being more frequent in Scandinavia than other European regions.

The study used standardized methods in both recruitment and follow-up. The study was conducted over a relatively short time period and any differences in incidence between centers due to possible secular change is therefore likely to be small. However, in interpreting the results several methodologic limitations need to be considered. In EPOS, overall follow-up was 81%. Using

Table 4. Age-standardized incidence of limb fracture by region, gender and type of fracture

Region	Men: incidence of fracture/1000 person-years[a] (95% CI)				
	Hip	Distal forearm	Humerus	'Other' limb	Any limb
Scandinavia	2.3 (0.0, 4.6)	2.1 (0.0, 4.2)	1.1 (0.0, 2.7)	4.1 (1.0, 7.1)	8.9 (4.4, 13.4)
Southern Europe	1.6 (0.0, 3.2)	1.7 (0.0, 3.4)	1.2 (0.0, 2.5)	2.0 (0.2, 3.8)	6.6 (3.4, 9.9)
Eastern Europe	0.9 (0.0, 1.7)	2.7 (1.2, 4.2)	0.4 (0.0, 1.0)	5.0 (3.0, 7.1)	9.0 (6.3, 11.8)
Western Europe	0.4 (0.0, 0.8)	1.3 (0.6, 2.0)	0.7 (0.2, 1.2)	3.9 (2.7, 5.1)	6.3 (4.8, 7.9)
	Women: Incidence of fracture/1000 person-years[a] (95% CI)				
Region	Hip*	Distal forearm*	Humerus*	'Other' limb	Any limb*
Scandinavia	4.4 (1.7, 7.0)	10.9 (6.2, 15.5)	5.2 (2.0, 8.5)	4.6 (1.5, 7.7)	24.7 (17.7, 31.7)
Southern Europe	1.4 (0.0, 2.7)	6.1 (3.3, 9.0)	1.3 (0.0, 2.6)	7.8 (4.6, 11.0)	16.8 (12.1, 21.5)
Eastern Europe	0.6 (0.0, 1.4)	10.3 (7.4, 13.1)	1.0 (0.1, 1.9)	10.2 (7.4, 13.0)	22.5 (18.2, 26.7)
Western Europe	0.8 (0.3, 1.3)	5.6 (4.3, 7.0)	1.9 (1.1, 2.8)	8.3 (6.6, 9.9)	16.7 (14.3, 19.1)

*Difference between regions: $p<0.05$.
[a]Age-standardised to the European population (age 50–79 years).

data from the baseline survey, those who were lost to follow-up were older (mean age 64.2 years vs 63.4 years) and had a higher prevalence of vertebral deformity (14.4% vs 11.4%) than those who took part in the follow-up phase. Those lost to follow-up may thus have had an increased susceptibility to osteoporotic fracture and our results may therefore underestimate the true occurrence of fracture in this population. However, because of the high follow-up rate, the degree of any underestimation is likely to be relatively small.

Not all those invited to take part in the baseline study did so. If those who participated were at lower risk of developing subsequent fracture, then it is possible that our data may represent an underestimate of the true occurrence of fracture. To assess for possible non-response bias a survey of non-responders was performed following the baseline survey. Although there were differences in aspects of lifestyle between responders and non-responders, these were not consistently in the direction of a greater or lesser risk of osteoporosis, providing some evidence against non-response bias – though we can not exclude this, and some caution is required, therefore, in interpreting the results [10].

In EPOS, incident limb fractures were ascertained using a postal questionnaire. It is possible that some individuals who had experienced a fracture did not, perhaps because of poor recall, report this. In a validation study, however, we estimated that the effect of such underreporting might be to lead to an underestimate of the true incidence of hip and distal forearm fractures by about 3% [7]. About 8% of reported fractures could not be verified, and in these cases, information concerning site of fracture was limited to the information from the postal questionnaire manikin. In a validation study using the manikin it was possible, however, to identify hip, distal forearm, upper and lower limb fractures with a high sensitivity and specificity, both in excess of 85% [7].

Comparison of the age-specific incidence rates for hip, distal forearm and humerus fractures with studies from other areas is somewhat limited because of the different methods used to ascertain fractures in the different study populations and also because of the age range studied in EPOS, with no data in the very elderly (80+ years). For wrist fracture, in the age range studied, among women the incidence in EPOS appears to be higher than has been observed in north America [11,12], Australia [13] and Japan [14]. For hip fracture, among women the rates appear to be slightly lower than those observed in America and Australia [12,13,15,16]; however, the number of hip fractures was relatively small ($n = 27$) and thus these comparisons must be interpreted with some caution.

Our data confirm previous studies which suggest that the incidence of hip and humerus fracture increases rapidly with increasing age [13,17]. For distal forearm fracture, among women the incidence increased progressively with age over the age range studied – a pattern in keeping with recent studies in the UK and Sweden [18–20]. Among men, our data are consistent with previous studies which show that the incidence of distal forearm fracture remains low until later life [11,18,19]. As observed in previous studies, the incidence of hip, humerus and distal forearm fracture was greater in women, with the female:male ratio of fracture incidence greatest for distal forearm fracture at just over 4:1 [21]. These patterns are in keeping with these fractures being ‘osteoporotic’ in type and are consistent with previous data showing a strong association between these fractures and BMD [2].

For ‘other’ fractures, the epidemiologic pattern was different, with a female excess though no increase in incidence with age. The absence of any significant age effect suggests that as a group these fractures are not osteoporotic and indeed this is in keeping with data showing no association between BMD and several limb fractures including fractures of the fingers, elbows and ankles [2]. However, the group comprises a variety of fracture types, some of which (e.g., leg) have been linked with low BMD. The numbers of subjects, however, was too small to allow exploration of the epidemiologic patterns of the individual fracture types. Broadly similar conclusions in relation to fracture type (osteoporotic/non-osteoporotic) were reported in a recent study looking at the burden of osteoporotic fractures [22].

Our study is unique in that it used standardized methods to ascertain fractures across a range of European countries. Apart from hip fracture there are relatively few data concerning the occurrence of limb fractures in a European setting. The main reason for this is that the majority of these fractures are not treated in hospital and information about their occurrence is not routinely recorded. An exception to this is in some (though not all) Scandinavian countries, where there is more detailed recording of contact with the health care system. In our study, because of the similar methods used to ascertain fracture, it is possible to make some limited determination of the geographic distribution of fractures across Europe. Because of small numbers of individuals with fracture within any individual center we pooled data from centers into four regional groups. Such an approach, however, may mask potentially important differences in occurrence of fractures *within* regions, and therefore some caution is required in interpreting the results.

Our findings are in keeping with a previous European study of hip fracture which showed an excess of fractures in Scandinavian women [3]. To date there are no comparative data for fractures of the proximal humerus. Our results suggest that the geographic distribution of these fractures is similar to that for hip fracture. Data from single-center studies suggest a higher incidence of distal forearm in women in Sweden than the UK or Yugoslavia [18,19,23]. The higher incidence of these fractures in Scandinavia may be due to regional variation in bone strength, falls or both. However, the higher prevalence of vertebral fracture in Scandinavia, a fracture not typically due to falling, suggests that differences in bone strength are more likely to explain the observations [5]. There are few data concerning the occurrence of osteoporotic fractures in Eastern Europe. Our data show that, compared with other regions, there is a relatively low incidence of hip and humerus fracture in women, though a higher incidence of distal forearm and 'other' fractures. This differs from the expected geographic pattern in which the incidence of distal forearm fracture tends to parallel that for hip fracture [24]. However, recent data suggest that the pattern for hip fracture in Eastern Europe may now be changing, with a recent secular trend towards a higher incidence [25,26].

Among men there were no statistically significant differences in fracture occurrence across Europe, however, because of small numbers of fractures within each region the study lacked statistical power to detect such differences. Although not statistically significant the geographic distribution of hip fracture was broadly similar to that in women with a Scandinavian excess. In addition the incidence of distal forearm fracture and also 'other' fractures was higher in Eastern Europe compared with the other regions.

Our data confirm the public health importance of limb fractures across Europe: in the population studied approximately 1 in 50 older women experience a limb fracture each year. Assuming that the age-specific incidence of these fractures remains constant the demographic shift towards an elderly population means that the number of individuals with these fractures and thus the associated health and economic burden will continue to rise. If the age-specific incidence increases, as has already been observed in the recent past in several European countries, the burden will be further increased [17,18,25–27].

In summary, the overall incidence of limb fracture was 7.3 and 19 per 1000 person-years in men and women respectively. Among women there is evidence of variation in the occurrence of the individual limb fracture types across Europe. Understanding of the causes of such variation may provide clues to the pathogenesis of these fractures and help in developing population-wide prevention strategies.

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