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ORIGINAL ARTICLE

Burden of non-hip, non-vertebral fractures on quality of life in postmenopausal women

The Global Longitudinal study of Osteoporosis in Women (GLOW)

C. Roux · A. Wyman · F. H. Hooven · S. H. Gehlbach · J. D. Adachi · R. D. Chapurlat · J. E. Compston · C. Cooper · A. Díez-Pérez · S. L. Greenspan · A. Z. LaCroix · J. C. Netelenbos · J. Pfeilschifter · M. Rossini · K. G. Saag · P. N. Sambrook · S. Silverman · E. S. Siris · N. B. Watts · S. Boonen · for the GLOW investigators

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Abstract
Summary Among 50,461 postmenopausal women, 1,822 fractures occurred (57% minor non-hip, non-vertebral [NHNV], 26% major NHNV, 10% spine, 7% hip) over 1 year. Spine fractures had the greatest detrimental effect on EQ-5D, followed by major NHNV and hip fractures. Decreases in physical function and health status were greatest for spine or hip fractures.
Introduction There is growing evidence that NHNV fractures result in substantial morbidity and healthcare costs. The aim of this prospective study was to assess the effect of these NHNV fractures on quality of life.

C. Roux (✉)
Department of Rheumatology, Cochin Hospital,
Paris Descartes University,
27 rue du Faubourg St. Jacques,
75659 Paris Cedex 14, France
e-mail: christian.roux@cch.ap-hop-paris.fr

A. Wyman · F. H. Hooven · S. H. Gehlbach
Center for Outcomes Research,
University of Massachusetts Medical School,
Worcester, MA, USA

J. D. Adachi
St. Joseph's Hospital, McMaster University,
Hamilton, ON, Canada

R. D. Chapurlat
Division of Rheumatology, INSERM UMR 1033,
Université de Lyon,
Hôpital E. Herriot, Hospices Civils de Lyon,
Lyon, France

J. E. Compston
School of Clinical Medicine, Addenbrooke's Hospital,
University of Cambridge,
Cambridge, UK

C. Cooper
MRC Lifecourse Epidemiology Unit, University of Southampton,
Southampton, UK

A. Díez-Pérez
Department of Medicine, Hospital del Mar–IMIM-Autonomous,
University of Barcelona,
Barcelona, Spain

A. Díez-Pérez
RETICEF, ISCIII,
Madrid, Spain

S. L. Greenspan
University of Pittsburgh,
Pittsburgh, PA, USA

A. Z. LaCroix
Fred Hutchinson Cancer Research Center,
Seattle, WA, USA

J. C. Netelenbos
Department of Endocrinology, VU University Medical Center,
Amsterdam, The Netherlands

J. Pfeilschifter
Department of Internal Medicine III,
Alfried Krupp Krankenhaus,
Essen, Germany

M. Rossini
Department of Rheumatology, University of Verona,
Verona, Italy

Methods We analyzed the 1-year incidences of hip, spine, major NHNV (pelvis/leg, shoulder/arm) and minor NHNV (wrist/hand, ankle/foot, rib/clavicle) fractures among women from the Global Longitudinal study of Osteoporosis in Women (GLOW). Health-related quality of life (HRQL) was analyzed using the EuroQol EQ-5D tool and the SF-36 health survey.
Results Among 50,461 women analyzed, there were 1,822 fractures (57% minor NHNV, 26% major NHNV, 10% spine, 7% hip) over 1 year. Spine fractures had the greatest detrimental effect on EQ-5D summary scores, followed by major NHNV and hip fractures. The number of women with mobility problems increased most for those with major NHNV and spine fractures (both +8%); spine fractures were associated with the largest increases in problems with self care (+11%), activities (+14%), and pain/discomfort (+12%). Decreases in physical function and health status were greatest for those with spine or hip fractures. Multivariable modeling found that EQ-5D reduction was greatest for spine fractures, followed by hip and major/minor NHNV. Statistically significant reductions in SF-36 physical function were found for spine fractures, and were borderline significant for major NHNV fractures.
Conclusion This prospective study shows that NHNV fractures have a detrimental effect on HRQL. Efforts to optimize the care of osteoporosis patients should include the prevention of NHNV fractures.

Keywords Non-hip, non-vertebral fractures · Postmenopausal women · Quality of life

K. G. Saag
University of Alabama–Birmingham,
Birmingham, AL, USA

P. N. Sambrook
University of Sydney–Royal North Shore Hospital, St. Leonards,
Sydney, NSW, Australia

S. Silverman
Department of Rheumatology, Cedars-Sinai/UCLA,
Los Angeles, CA, USA

E. S. Siris
Department of Medicine, Columbia University Medical Center,
New York, NY, USA

N. B. Watts
Bone Health and Osteoporosis Center, University of Cincinnati,
Cincinnati, OH, USA

S. Boonen
Leuven University Center for Metabolic Bone Diseases, Division
of Geriatric Medicine, Katholieke Universiteit Leuven,
Louvain, Belgium

Introduction

The consequences of osteoporotic fractures are increasingly recognized, but most studies have focused on hip and vertebral fractures, and the morbidity and mortality associated with these "typical" fractures. Among the different types of non-vertebral fractures, hip fractures and their clinical and economic impact have received most attention. However, growing evidence suggests that the burden of fractures at other sites (non-hip, non-vertebral [NHNV] fractures) may have been under-recognized [1, 2]. NHNV fractures occur more frequently than clinical spine or hip fractures, and carry an increased risk for subsequent fractures [3–6]. They may have different risk factors than vertebral and hip fractures [7–10] and may result in considerable morbidity and disability. Furthermore, the cost of direct medical care for NHNV fractures may exceed that for hip fracture alone [11, 12]. In a recent study, certain types of NHNV fractures were confirmed to be associated with significant excess mortality [13]. Similarly, the consequences of all types of fractures on health-related quality of life (HRQL) are well recognized [14–17], although few studies have focused on NHNV fractures [18].

The Global Longitudinal study of Osteoporosis in Women (GLOW) was established to provide a practice-based evaluation of postmenopausal osteoporosis, fractures, and related risk factors. The aims of the current analysis were to measure the 1-year incidence of NHNV fractures in a cohort of older women, and to assess the impact of these fractures on HRQL at 1 year of follow-up.

Methods

The study design of GLOW, a prospective, multinational, observational cohort study, has previously been described in detail [19]. Briefly, women were recruited through 723 primary healthcare physicians in ten countries (Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, UK, and USA). Study sites were selected on the basis of geographic distribution and the presence of lead investigators with expertise in osteoporosis and access to a clinical research team capable of managing a large cohort of subjects. These lead investigators identified primary care practices in their region that were members of local research or administrative networks and were able to supply names and addresses of their patients electronically. The composition of groups varied by region and included health-system-owned practices, private practices, independent practice associations, and health maintenance organizations. Participating physicians were defined as those who spent most of their time providing primary healthcare to patients, and included internists, family practitioners, and general practitioners.

Data were obtained using self-administered questionnaires, which were mailed to women aged ≥55 years; a 2:1 over-sampling of women ≥65 years of age has been intended. Follow-up questionnaires were sent at 1-year intervals, and this analysis uses data from the baseline and 1-year follow-up surveys. The study questionnaires were used to collect information on demographic characteristics; medical history (including fractures since age 45 with site, comorbidities); risk factors for fracture occurrence; self-report of prevention, diagnosis, and treatments of osteoporosis; HRQL; and health service access and utilization.

HRQL and functional status were assessed using the EuroQol EQ-5D tool [20] and the vitality and physical function sections of the SF-36 health survey [21]. The EQ-5D is a five-question, three-response option scale that maps each of 243 health states to a country-specific preference-based value or utility, where 1.00 represents full health and 0.00 represents a state equivalent to death. A change of 0.03 is recognized as a minimum clinically important difference in individuals with osteoporosis [22].

Women who responded to the 1-year follow-up survey were divided into subgroups according to fracture occurrence and fracture site: hip, vertebral, and NHNV fractures. We created a fracture grouping for the NHNV fractures because of the low number of some of them. This grouping was based on the published consequences of some of the NHNV fractures on increased risk of mortality [13], and our opinion on the burden of these fractures: "major" NHNV (pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow), "minor" NHNV (wrist, hand, ankle, foot, rib, and clavicle).

Statistical analysis

Continuous variables are shown as medians with 25th and 75th percentiles, or as means with standard deviations (SDs); percentages are shown for dichotomous variables. Results are shown for incident fracture groups (major, minor, spine, and hip, or by individual fracture type), with the "no fracture" group as a comparison. These categories are not mutually exclusive, as women could have experienced more than one fracture.

To estimate comparative effects of different types of fracture, we performed multiple linear regression analyses predicting 1-year EQ-5D score based on baseline EQ-5D score and fracture group, controlling for a predetermined clinically relevant set of variables. Results are expressed as mean difference in 1-year EQ-5D score with a 95% confidence interval (CI) for that difference. Identical analyses were then performed for the 1-year and baseline SF-36 physical function and vitality scores. All analyses were performed using SAS version 9.2 (SAS Inc., Cary, NC, USA).

Results

There were 51,491 women with both baseline and 1-year follow-up data. Of these, 1,030 women were excluded due to missing incident fracture information, leaving 50,461 women for this analysis.

The number of incident fractures was 1,822 and their distribution is shown in Fig. 1. Of 1,822 incident fractures, 57% were minor NHNV, 26% were major NHNV, 10% were spine, and 7% were hip fractures. The incidence of any fracture was 3.1%, spine fracture 0.4%, and hip fracture 0.3%. The incidence of all NHNV fractures was 2.7%, major NHNV fractures 0.9%, and minor NHNV fractures 2.0% (Fig. 2). Upper arm, lower leg, upper leg, and pelvis fractures accounted for 93% of major NHNV fractures; and wrist, ankle, and rib fractures made up 91% of minor NHNV fractures. The incidence of fractures according to age groups is shown in Fig. 3. Seventy women had both a major and a minor NHNV fractures; six women had both a hip and a NHNV fractures; three women had a hip, a vertebral and a NHNV fracture over 1 year.

Table 1 shows median age, age distribution, and risk factors according to the type of incident fracture reported. Women with hip fractures had the highest median age (77 years), followed by women with spine or major NHNV fractures (73 years for both), and minor fractures (69 years). Women with no incident fractures were the youngest, with a median age of 67 years. Median body mass index was similar across the fracture categories, but the proportion of

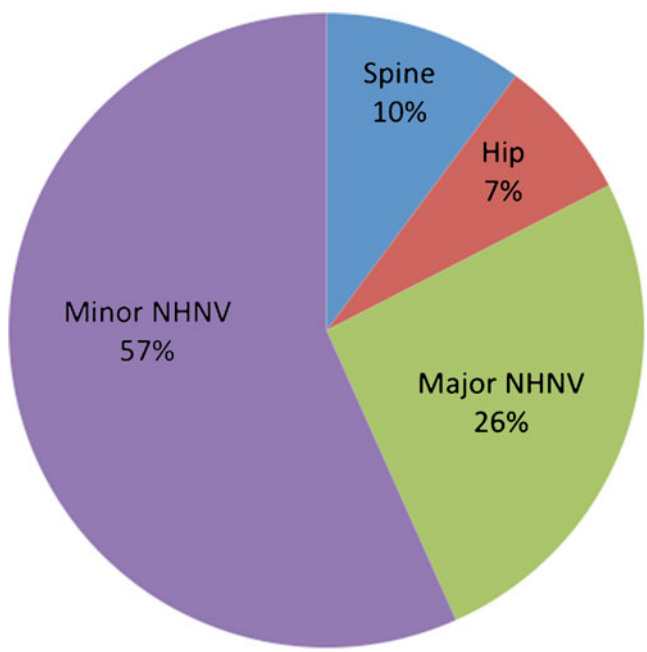

Fig. 1 Distribution of incident fracture types. *Major NHNV* pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow; *minor NHNV* wrist, hand, ankle, foot, rib, and clavicle

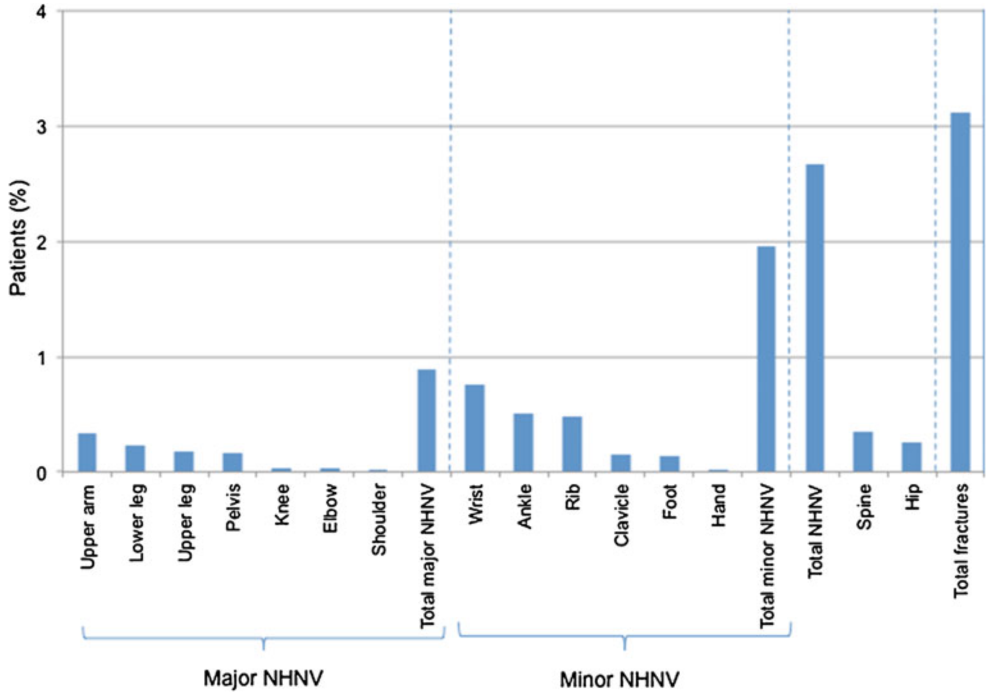

Fig. 2 Distribution of incident fracture types. *NHNV* non-hip, non-vertebral

low-weight women in each group increased from 16% in the no-fracture group, to 21% for spine fractures and 25% for hip fractures. Fewer women with major NHNV fractures were low weight (19%), although this was more than for those with minor NHNV fractures (17%) or no fracture.

Unadjusted HRQL measures at baseline and after incident fracture are shown in Table 2. Women with spine fractures experienced the greatest change in their mean EQ-5D summary score, which dropped from 0.65 at baseline to 0.58 after the fracture. Major NHNV fractures and hip fractures accounted for the next greatest drop in mean EQ-5D (from 0.70 to 0.66 and from 0.64 to 0.60, respectively), followed by minor NHNV fractures (from 0.72 to 0.70) and no fracture (no change). The change in the percentage of women reporting problems with mobility was greatest for women with major NHNV fractures or spine fractures (+8%). Spine fractures were associated with the greatest increases in problems with self care (+11%), activities (+14%), and pain/discomfort

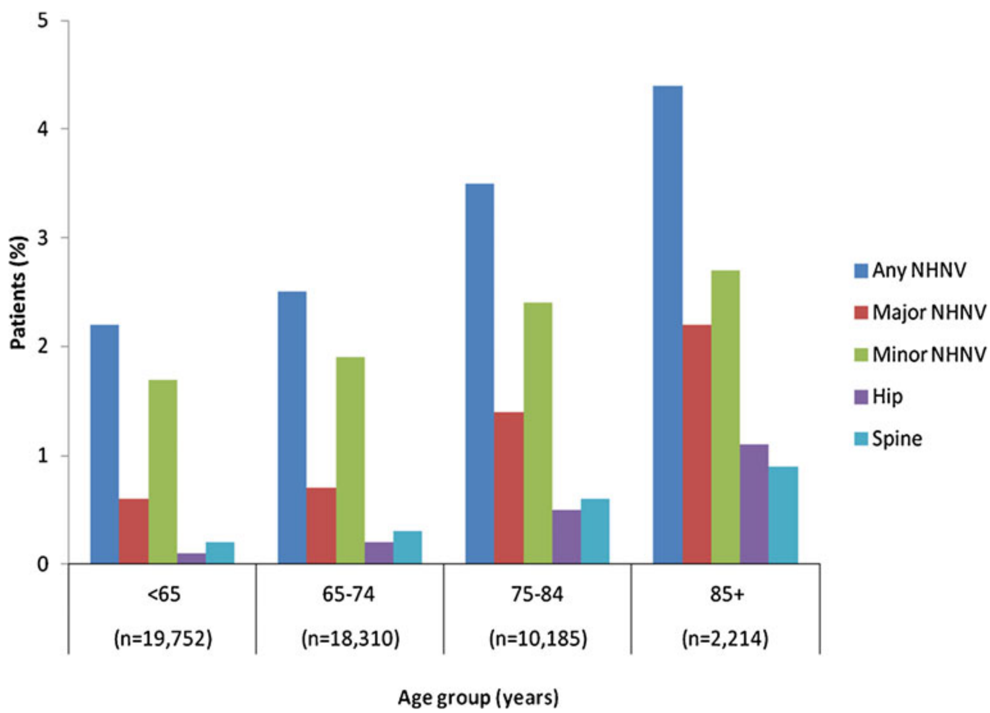

Fig. 3 One-year incidence of fractures in GLOW by age group

Table 1 Characteristics of the study population (n=50,461)

	No fracture (n=48,887)	Incident fracture type			
		Major NHNV[a] (n=448)	Minor NHNV[b] (n=982)	Spine (n=178)	Hip (n=126)
Median age, years (IQR)	67 (61, 74)	73 (63, 79)	69 (62, 77)	73 (66, 81)	77 (71, 83)
Median BMI, kg/m^2 (IQR)	26 (23, 30)	26 (23, 30)	26 (23, 30)	25 (22, 28)	25 (22, 28)
Age group,%					
<65 years	39	27	34	20	13
65-74 years	36	29	35	33	26
75-84 years	20	32	25	36	40
≥85 years	4.3	11	6.0	11	20
Risk factors for fracture, %					
Weight <125 lb (<57 kg)	16	19	17	21	25
Baseline fracture	22	50	43	56	52
Parental history of hip fracture	17	21	21	23	25
Current baseline cigarette use	8.6	10	9.9	11	7.3
Current baseline cortisone use	2.9	5.9	5.3	9.7	4.0
Secondary osteoporosis risk factors[c]	21	23	27	25	23
Alcohol >20 drinks/week	0.5	0.2	0.9	0.6	0.8

BMI body mass index, *IQR* interquartile range, *NHNV* non-hip, non-vertebral

[a] Major fractures: pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow

[b] Minor fractures: wrist, hand, ankle, foot, rib, and clavicle

[c] Baseline use of anastrozole, exemestane, or letrozole; baseline diagnosis of celiac disease, ulcerative colitis/Crohn's disease, or Type I diabetes; or menopause before age 45 years

(+12%). Increases in percentages reporting problems with self care and activities were similar for major NHNV fractures (+6% for self care; +10% for activities) and hip fractures (+5% for self care; +10% for activities). Among the different fracture categories, increases in problems reported were lowest for women with minor NHNV fractures. The increase in the percentage of women reporting fair or poor health status was greatest for spine fractures (6%), then hip and major NHNV fractures (both 5%). Decrease in physical function was greatest for spine and hip fractures (8 points), while decreases in vitality were the same for major NHNV, hip, and spine fractures (3 points).

Also reported in Table 2 are the proportions of women who reported a decrease in general health status between the baseline and 1-year surveys. The largest proportion of women to report a decrease in health status were those with a fracture of the spine (30%), followed by hip (28%), major NHNV fractures (24%), minor NHNV fractures (21%), and no fracture (19%). An increase in perception of risk of a future fracture at 1-year follow-up compared with baseline was reported by 51% of women with hip fracture, 42% with spine fractures, 40% with major NHNV fractures, 39% with minor NHNV fractures, and 21% with no incident fracture.

Table 3 shows the multivariable model predicting 1-year change in HRQL scores based on incident fracture category and controlling for age, comorbidities, and baseline fractures. The reduction in EQ-5D was greatest for spine fractures and hip fractures. The reduction for women with major or minor NHNV fractures was the same. Statistically significant reductions in SF-36 physical function and vitality were found for spine fractures, and reduction in SF-36 physical function was borderline significant for major NHNV fractures. The consequences of incident wrist fractures, the most frequent minor NHNV fractures, were weak.

Discussion

Data from cross-sectional studies have previously shown that the effect of NHNV fractures on HRQL is significant. In the Canadian Multicenter Osteoporosis Study, pelvic, lower limbs, and rib fractures were associated with very low HRQL scores [23]. Similarly, assessment of the baseline data of the GLOW study suggested that previous fractures at a variety of locations may be associated with significant reductions in quality of life [24]. Our current prospective incident fracture data confirm and extend the results of these cross-sectional studies. NHNV fractures were found to be the most common incident fractures in women aged ≥55 years, and both minor and major incident NHNV fractures found to have an impact on HRQL over 1 year, independent of baseline HRQL.

Table 2 Comparison of HRQL, functional status, and vitality measures according to incident fracture status (n=50,461)

	No fracture (n=48,887)		Incident fracture type							
			Major NHNV[a] (n=448)		Minor NHNV[b] (n=982)		Spine (n=178)		Hip (n=126)	
	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1	Baseline	Year 1
EQ-5D										
Mean summary score (SE)	0.78 (0.001)	0.78 (0.001)	0.70 (0.01)	0.66 (0.01)	0.72 (0.01)	0.70 (0.01)	0.65 (0.02)	0.58 (0.02)	0.64 (0.03)	0.60 (0.03)
Domains, problems with, %										
Mobility	27	26	46	54	38	41	48	56	57	63
Self care	5.5	6.4	17	23	11	16	17	28	23	28
Activities	26	27	44	54	39	42	52	66	57	67
Pain/discomfort	68	68	76	79	75	79	78	90	78	86
Anxiety/depression	40	41	47	49	49	49	54	58	54	54
SF-36 subscales,%										
Mean physical function score (SE)	74 (0.12)	73 (0.12)	61 (1.5)	55 (1.6)	65 (0.94)	62 (1.0)	58 (2.4)	50 (2.3)	54 (2.8)	46 (2.8)
Mean vitality score (SE)	61 (0.09)	61 (0.09)	55 (1.1)	52 (1.1)	55 (0.70)	54 (0.75)	50 (1.7)	47 (1.7)	52 (2.0)	49 (2.2)
Perception of fracture risk, %										
Increase	-	21	-	40	-	39	-	42	-	51
Decrease	-	23	-	13	-	12	-	11	-	12
Same	-	56	-	47	-	49	-	46	-	37
General health status fair/poor, %	21	22	37	42	33	35	44	50	40	45
Health status change, %										
Increase	-	17	-	19	-	18	-	14	-	18
Decrease	-	19	-	24	-	21	-	30	-	28
Same	-	64	-	57	-	60	-	56	-	55

HRQL health-related quality of life, *NHNV* non-hip non-vertebral, *SE* standard error

[a] Major fractures: pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow

[b] Minor fractures: wrist, hand, ankle, foot, rib, and clavicle

A number of studies have reported that NHNV fractures account for the majority of all fractures, up to 90% in people <80 years of age, and 50% thereafter [25, 26]. In a study by Lippuner et al. [27], limb fractures alone contributed to almost one third of all fracture-related hospital admissions. In line with these findings, NHNV fractures in our study were the most common incident fractures in women aged ≥55 years. The ratios of NHNV to hip fractures reported by Kanis et al. [2] were 21.1, 6.1, 2.8, and 1.4 in women aged 50, 60, 70, and 80 years, respectively. In our study, approximately one third of NHNV fractures occurred in women aged <65 years, which may be due to the fact that twice as many women ≥65 years were intended to be enrolled as those aged <65 years. NHNV fractures typically occurred at younger ages than vertebral and hip fractures, but their burden in our population was still dramatically high in women after the age of 70 years. For each 10-year span of age, we found the incidence of NHNV fractures to be 10-fold greater than the incidence of vertebral or hip fractures.

In addition to the effects of age and age-related determinants of fracture risk, the underlying increase in the risk of falls and decrease in bone density with age are both likely to play a major role in this high incidence of NHNV fractures. Annual fall prevalence increases with age, and NHNV fractures almost inevitably result from falls [28]. Similarly, the risk of almost all NHNV fractures is associated with low bone mineral density (BMD) [29]. Low femoral neck or hip BMD is associated with increased risk of humerus, forearm, and wrist fractures [10, 30]. Thus, beyond falls, a number of bone parameters (DXA T score and prevalent vertebral and non-vertebral fractures) can be used to assess the risk of such fractures in postmenopausal women [29, 31].

One of our key findings in women aged ≥55 years is that both minor and major incident NHNV fractures have a strong impact on HRQL as measured by EQ-5D over 1 year, independent of baseline HRQL. Women with incident major NHNV fractures also reported statistically significant reductions in HRQL following fracture as measured by SF-36 physical function index. Reductions in EQ-5D and SF-36 physical functioning for women with major NHNV fractures were of a similar magnitude to reductions for women with incident hip fractures, but lower than for women who experienced incident spine fractures.

Table 3 Multivariable models predicting adjusted mean difference in HRQL, functional status, and vitality at 1 year

	No fracture[a] (*n*=48,887)	Incident fracture type				
		Major NHNV[b,c] (*n*=448)	Minor NHNV[b,d] (*n*=632)	Wrist[b] (*n*=380)	Spine[b] (*n*=178)	Hip[b] (*n*=126)
EQ-5D (*n*=45,904)						
Mean difference	0.04	−0.06	−0.06	−0.04	−0.11	−0.07
95% CI	(0.03, 0.05)	(−0.09, −0.02)	(−0.10, −0.02)	(−0.80, 0.001)	(−0.16, −0.06)	(−0.13, −0.02)
SF-36 physical function (*n*=49,441)						
Mean difference	4.1	−3.8	−0.3	3.3	−5.4	−4.2
95% CI	(3.3, 5.0)	(−7.7, 0.4)	(−4.3, 3.6)	(−0.9, 7.5)	(−10, −0.7)	(−9.7, 1.2)
SF-36 vitality (*n*=48,952)						
Mean difference	2.7	−1.5	−1.8	−0.2	−4.5	−1.6
95% CI	(1.9, 3.5)	(−4.7, 1.7)	(−5.0, 1.4)	(−3.6, 3.2)	(−8.4, −0.5)	(−6.1, 2.9)

CI confidence interval, *HRQL* health-related quality of life, *NHNV* non-hip non-vertebral

[a] Model covariates: no incident fracture; baseline EQ-5D (or SF-36 vitality or physical function, to match the outcome); age; baseline diagnosis of lung disease, heart disease, cancer, or osteoarthritis; number of baseline fractures; major NHNV baseline fracture; minor NHNV baseline fracture; baseline hip fracture; baseline spine fracture

[b] Model covariates: major NHNV incident fracture; minor NHNV incident fracture; incident spine fracture; incident hip fracture; baseline EQ-5D [or SF-36 vitality or physical function, to match the outcome]; age; baseline diagnosis of lung disease, heart disease, cancer, or osteoarthritis; number of baseline fractures; major NHNV baseline fracture; minor NHNV baseline fracture; baseline hip fracture; baseline spine fracture; days from incident fracture and EQ-5D assessment

[c] Major fractures: pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow

[d] Minor fractures: hand, ankle, foot, rib, and clavicle

The physical function limitations and reduced HRQL among the younger women in our study could have a major impact on the number of working days lost. In fact, Fink et al. documented significant disability, as reflected by days hospitalized or confined to bed and days of reduced usual activities, because of a fracture ("limited activity days") in women with humerus, ankle, or distal forearm fracture [30]. In our multivariable analysis, women with spine fractures showed the greatest reductions in EQ-5D and SF-36 physical function and vitality scores. Although the magnitude of the change in HRQL for NHNV fractures was lower than for hip and spine fractures, it should be noted that fractures of the pelvis, upper leg, lower leg, shoulder, upper arm, knee, and elbow accounted for 26% of all incident fractures. In contrast, hip and spine fractures represented 18% of all incident fractures. The substantial number of NHNV fractures in this population, combined with the significant negative impact on HRQL has important clinical implications. As a group, these fractures are associated with significant suffering, particularly in older women, and more attention to the effects of these fractures is urgently needed.

Incident wrist fractures had little impact on HRQL, and no effect on SF36 physical function or vitality in our study. This confirms previous results [32], with the exception of studies which assessed the effect of wrist fracture in relation to specific tasks involving upper limb function [33, 34]. One study has shown that functional recovery after a wrist fracture is completed by 6 months [30] in contrast to another one showing a fair result in functional recovery in 22% of patients [35]. Our data do not suggest that, at the age of 69 years on average, wrist fracture contributes to functional decline, although we did not ask women specifically about decline in upper limb function.

Our study has some important limitations, as well as a number of strengths. Fractures were self-reported and were not confirmed radiographically. Self-report over 2 to 5 years has been shown to be accurate for hip and wrist fractures, though less so for fractures of the spine [36, 37]. We cannot confirm the diagnosis of vertebral fractures, as they were self-reported. Most vertebral fractures are not recognized, and even asymptomatic vertebral deformities could impact on daily living activities and HRQL [16]. Most studies that include vertebral fracture as an outcome will therefore underestimate the incidence of vertebral fractures and their effect on HRQL. To the extent that there is error in the reporting of other NHNV fractures, our estimates of HRQL would also be biased toward the null.

The effect of prevalent (at baseline) fractures in this study may have been attenuated by the absence of information on the time of occurrence. Had we been able to adjust for the recent timing of these fractures, we might have detected a stronger effect on HRQL for women with both a prevalent and incident fracture. Among the strengths of our study are the prospective design, the international nature of the sample, and the fact that data were collected in the same way, using the same survey questions, in all countries. We recognize, however, that while women from ten countries are included in the cohort, these results may not be generalizable to non-Western countries. The large sample size is also a strength, as few studies have had adequate statistical power to assess, prospectively, the consequences of incident NHNV fractures on HRQL.

Conclusion

In conclusion, our study demonstrates the detrimental impact of NHNV fractures on HRQL. Efforts to optimize the care of patients with osteoporosis should not be focused solely on hip and spine fractures; rather, treatment strategies should include the prevention of NHNV fractures.

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