Fracture incidence and secular trends between 1989 and 2013 in a population-based cohort: The Rotterdam Study

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Bone. *2018 Sep; 114:116-124.*

ABSTRACT

Fracture incidence needs to be evaluated over time to assess the impact of the enlarging population burden of fractures (due to increase in lifespan) and the efficacy of fracture prevention strategies. Therefore, we aimed to evaluate the association of femoral neck bone mineral density (FN-BMD) measured using dual-energy X-ray absorptiometry (DXA) at baseline with fracture risk over a long follow-up time period. Incident non-vertebral fractures were assessed in 14,613 individuals participating in the Rotterdam Study with up to 20 years of follow-up. During a mean follow-up of 10.7 ± 6.2 years, 2971 (20.3%) participants had at least one incident non-vertebral fracture. The risk for any non-vertebral fracture was 1.37 (95% Confidence Interval (CI): 1.25-1.49) and 1.42 (95%CI: 1.35-1.50) for men and women, respectively. The majority (89% in men and 79% in women) of all fractures occurred among participants with a normal or osteopenic T-score. The incidence rates per 1000 person-years for the most common fractures were 5.3 (95%CI: 5.0-5.7) for hip, 4.9 (95%CI: 4.6-5.3) for wrist and 2.3 (95%CI: 2.0-2.5) for humerus. To examine the predictive ability of BMD through follow-up time we determined fracture hazard ratios (HR) per standard deviation decrease in femoral neck BMD across five-year bins. No differences were observed, with a HR of 2.5 (95%CI: 2.0-3.1) after the first 5 years, and of 1.9 (95%CI: 1.1-3.3) after 20 years. To assess secular trends in fracture incidence at all skeletal sites we compared participants at an age of 70–80 years across two time periods: 1989–2001 (n = 2481, 60% women) and 2001–2013 (n = 2936, 58% women) and found no statistically significant difference ($p < 0.05$) between fracture incidence rates (i.e., incidence of non-vertebral fractures of 26.4 per 1000 PY (95%CI: 24.4-28.5)) between 1989 and 2001, and of 25.4 per 1000 PY (95%CI: 23.0-28.0) between 2001 and 2013. In conclusion, BMD is still predictive of future fracture over a long period of time. While no secular changes in fractures rates seem to be observed after a decade, the majority of fractures still occur above the osteoporosis threshold, emphasizing the need to improve the screening of osteopenic patients.

INTRODUCTION

Fractures of the hip, wrist and pelvis are among the most common osteoporotic fractures [1] affecting hundreds of millions of people worldwide. In the European Union, the annual costs of all osteoporotic fractures have been estimated at €37 billion[2] in 2010, of which 54% of the costs are attributed to hip fractures.[2] Due to the aging of industrialized societies, the incidence of osteoporosis and fragility fractures is expected to increase in the years to come.[3, 4]

However, not all studies show a clear increase of fractures rates. For instance, previous studies have yielded conflicting perspectives indicating that the incidence of hip fracture has either increased, plateaued, or even decreased in the last decades.[5-10] Such discrepancies may be explained by multiple factors, including: secular periods in which the fractures occur, changes in clinical practice and drug prescription or compliance, distribution of age and demographics within age and sex strata, migrations and/or geographical origin of the report.[7] For example, studies performed in the USA have reported a decline in the incidence of hip fractures between 1980 and 2000.[8,9] In contrast, in the Netherlands, an initial linear increase in hip fracture incidence during the period between 1972 and 1987[10] is now proposed to have plateaued during the following decades.[11] Moreover, recent information on incidence rates and trends for other sites of non-vertebral fractures is currently lacking despite that non-hip fractures are also associated with higher disability[12] and mortality[13] rates. Depiction of robustly-assessed overall and site-specific fracture trends is important to estimate the burden of osteoporosis and to establish proper and cost-effective prevention strategies.

Part of delineating cost-effective prevention strategies involves determining the predictive ability of fracture risk factors in time. Although fractures have a multifactorial background, apart from age, low BMI and falls, a low bone mineral density (BMD) remains one of the most important risk factors. Studies have shown that the reduction of femoral neck (FN-) BMD is essentially linear over time, comprising ~1-2% of baseline BMD per year.[14] It is well established that BMD can predict fracture risk over a period of 5–10 years[15,16] but little is known[17,18] about the predictive value of BMD over longer periods.

Altogether, our aims were to 1) evaluate the association between BMD at baseline (both continuously and using clinical cut-offs) and fracture risk over a long time period, 2) estimate the incidence of non-vertebral fractures (overall and site-specific) during 23 years of follow-up and 3) evaluate whether incidence rates have changed during two subsequent secular follow-up periods. All analyses were performed for the total group and stratified by sex, considering the well-established sexual differences in fracture rate.

MATERIALS AND METHODS

Study Population

Our study included participants from the Rotterdam Study, an ongoing population-based prospective cohort comprising 14,926 Dutch individuals aged 45 years and older examined across three population sets.[19] At its start in 1990, a total of 7983 participants aged 55 years and older were included in the initial study wave (RSI). The cohort was expanded in 2000 with 3011 participants (RSII) aged 55 years and older; and in 2006 with 3932 participants (RSIII) aged 45 years and older, or who had moved into the study area. All participants underwent an extensive home interview followed by a visit to the research center where various physical and laboratory examinations took place. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. From the 14,926 participants, 14,613 provided informed consent to undergo follow-up assessments and were included in the fracture analyses. For the BMD analysis, 3562 participants did not undergo DXA, leaving 11,051 participants for the BMD analyses.

Bone Mineral Density Measurements

FN-BMD (g/cm^2) was measured in RSI-1 (1989-1993) and RSII-1 (2000-2001) using dual energy X-ray absorptiometry (DXA) acquired with a Lunar DPX-L densitometer (Madison, WI, USA). In RSIII-1 (2006-2008), FN-BMD was measured using a GE-Lunar Prodigy bone densitometer. All scans and analyses were performed and verified by a trained technician who applied adjustments when necessary. Sex-specific T-scores (FN-BMD when compared to the young normal reference mean) were calculated using the NHANES III reference population. [20] Osteoporosis was defined according to WHO criteria[21] as a T-score below or equal to -2.5 and osteopenia as a T-score between -1.0 and -2.5. To be able to compare BMD levels with previous reports[15] differences in mean BMD across software versions in RSI-1 (DPX-L and DPX-IQ) for the calculation of T-scores were taken into account to create a uniform dataset of individuals. BMD obtained from the DPX-IQ software was recalculated using the following conversion formulas: BMD = 0.03402 + 0.9371 $*$ DPX-IQ BMD in women and BMD = 0.01588 + 0.9471 $*$ DPX-IQ BMD in men. The intercept and slope values were obtained from regressing BMD DPX-IQ values on the BMD DPX-L values across the same individuals (very similar estimates were obtained when employing different sampling sets of size 500, 1000, 2000 or 5000 individuals to determine the estimates of the calibration).

Incident Fracture Collection

The present analyses are based on follow-up data collected from baseline (1990-1993 for the first cohort, 2000–2001 for the second cohort and 2006-2008 for the third cohort) until December 31, 2012. Follow-up time was calculated as time from baseline to first fracture, death or end of follow-up period (or loss to follow-up), whichever occurred first. All fracture events were reported either by general practitioners (GPs) in the research area by means of computerized systems or through hospital records. Research physicians or trained nurses, who checked patient records regularly, retrieved information from GPs outside the research area. All events reported were verified by research physicians who independently reviewed and coded the information. Subsequently, a medical expert reviewed all inconsistencies in coded events for final classification. For the current study only non-vertebral fractures were considered, as time of event cannot accurately be assed for the vast majority of vertebral fractures.

STATISTICAL ANALYSES

All analyses were performed for the total group of participants and stratified by sex, considering the well-established sex differences in fracture risk.[22-24] First, Cox proportional hazard models adjusted for age at baseline and cohort were used to estimate the hazard ratio (HR) of first fracture associated with 1 SD decrease in FN-BMD across 1) all non-vertebral fractures, 2) for specific types of fractures and 3) all non-vertebral fractures in groups of subjects classified by WHO-based BMD cut-offs. The latter analyses were done in three age groups: below 65 years; 65-75 years; and 75 years and older. Subjects classified as having BMD in the normal range (T-score > 1.0) were used as the reference group. In order to better examine the fracture prediction we performed sensitivity analyses in which the follow-up time was stratified by 5-years categories: 0-5; 5-10; 10-15; 15-20; and > 20 years. The proportionality of hazards assumption of Cox-models was checked using correlation tests of Schoenfeld residuals. For the non-vertebral fractures analysis, we used natural splines to fit a proportional hazards model in order to smooth the nonlinear effect of age. Second, fracture incidence rates were calculated according to fracture site and additionally subdivided into three main categories: upper extremity; lower extremity; and other fractures. Incidence rates were expressed as number of fractures per 1000 person-years (PY) with 95% confidence intervals, estimated using the exact Poisson formula.[25] Third, to draw the comparison between secular periods (1989-2001 [N = 2481] and 2001-2013 [N = 2937]) incidence rates were calculated for men and women who were 70-80 years old at the start of the respective follow-up period. We used a distinct age category in order to avoid bias due to different age distribution among the follow-ups. The

70-80 years of age category was used, as it comprises the period in life with greatest exponential increase in fracture rates of most likely osteoporotic etiology. Poisson exact test was used to test the null hypothesis that the ratio between the rates was equal to 1. The trend p-value was adjusted for multiple testing. All analyses were performed using the statistical package **R version 3.1.2**.

RESULTS

Characteristics of the Study Population

Figure 1 is a flow diagram describing the selection of study participants. At baseline, the mean (± SD) age of the participants was 64.7 (±9.4) years for men and 66.5 (±10.9)

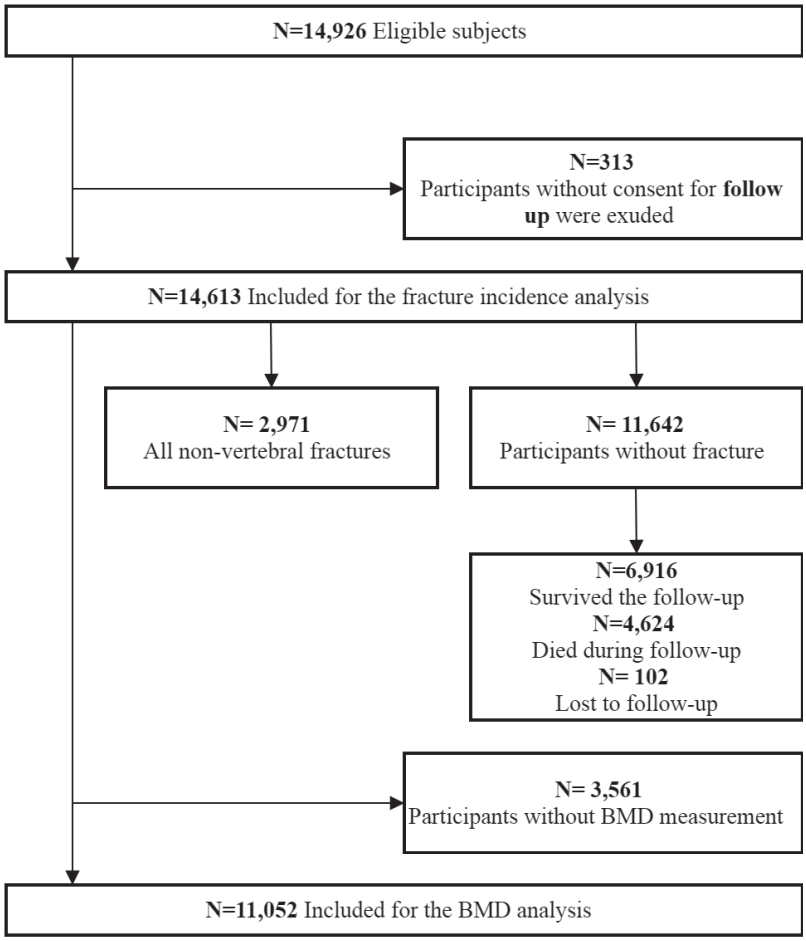

Figure 1 | Flow chart of participants in the study

years for women. The prevalence of osteoporosis (BMD T-score < -2.5) was 10.8% in women and 6.6% in men. The prevalence increased exponentially with age for all types of fractures but this relation is less prominent for wrist fractures (**Figure 2**). Above the age of 85 years, 40.9% of the women and 31.7% of the men had osteoporosis. Nearly 21% of all non-vertebral fractures occurred in women with osteoporosis and 12% in osteoporotic men (**Figure 3** and **Supplementary Table 3**). In women and men with osteoporosis, hip fractures were the most common type of fractures (38% women and 29% men). Overall, the highest fraction of all and -site-specific fractures (above 50%) occurred in men and women with osteopenia.

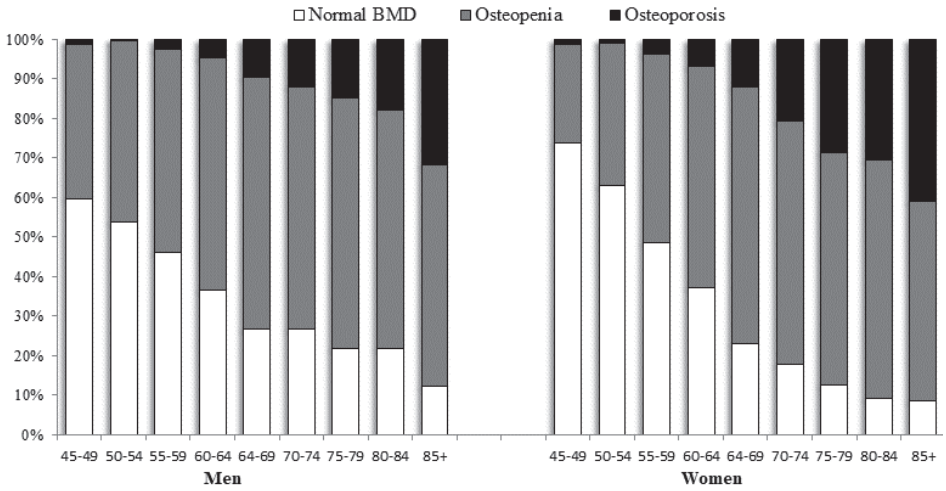

Figure 2 | Prevalence of osteoporosis and osteopenia in men and women by gender-specific T-scores. Hip fractures occurred more often in men and women above the age of 75 years. Overall, across the age distribution hip fracture incidence rates in men were similar to the rates of women 5 year younger. Furthermore, women had higher incidence rates than men in the same age category for any type of fracture.

Association between BMD and Incident Fracture

Associations of FN-BMD with non-vertebral fractures are shown in Table 1. For every SD decrease in BMD a 1.46 [95%CI: 1.34-1.46] times increased risk in non-vertebral fracture risk was observed. The associations of BMD with fracture risk were similar in women (1.42 [95%CI: 1.35-1.50]) and men (1.37 [95%CI: 1.25-1.49]). Low BMD (T-score < 1) was strongly associated with increases site-specific fracture risk at the hip, wrist and proximal humerus, with similar effects seen in women and men (**Table 1**). Individuals with osteopenia or osteoporosis had 1.4 to 4 times higher risk of non-vertebral fracture than individuals with normal BMD (**Figure 4**). Women above the age of 75 with osteoporosis had 3.8 times increased risk to develop fractures, while the risk in older women with osteopenia was 1.8 times higher than older women without

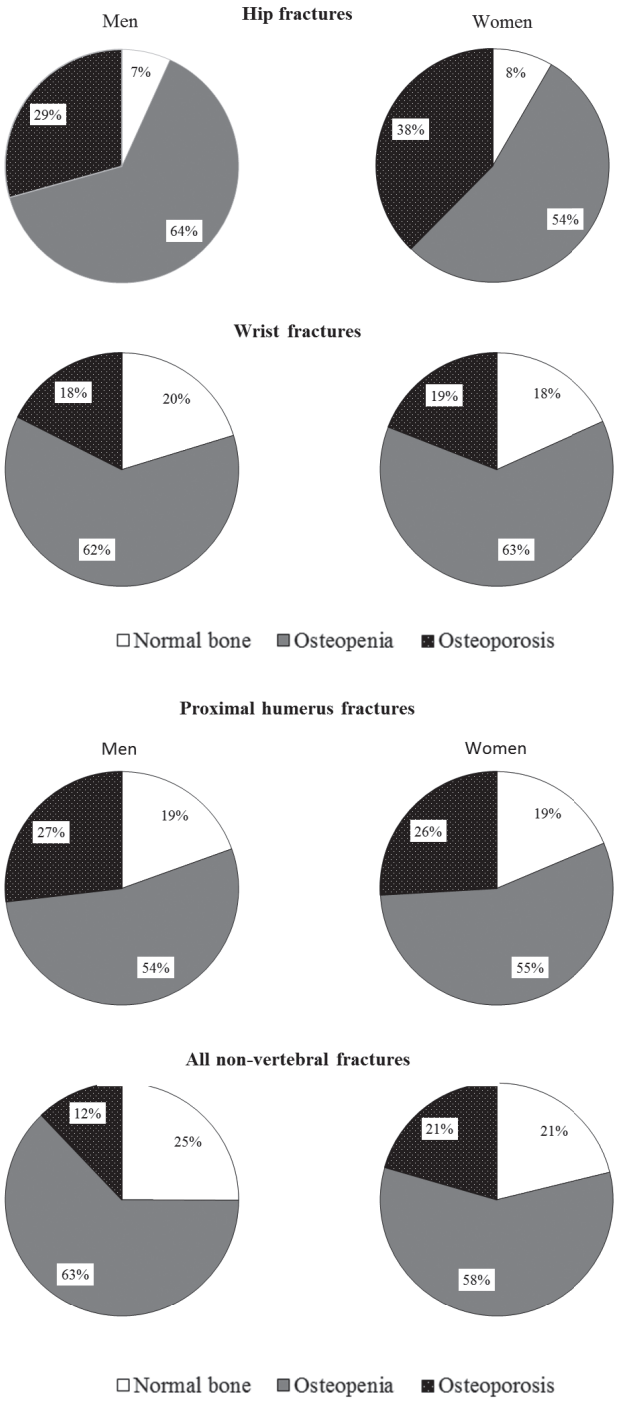

Figure 3 | Percentages of non-vertebral, hip, proximal humerus and wrist fractures that occurred in men and women with osteoporosis, osteopenia or normal BMD using gender-specific T-scores.

Table 1 | Age-adjusted hazard ratio (95%CI) for the predictive value of femoral neck BMD (g/cm^2) per one SD decrease.

Type of fracture	Total (n=11,052)			Men (n=4,777)			Women (n=6,275)		
	Number	Hazard ratio	95%CI	Number	Hazard Ratio	95%CI	Number	Hazard ratio	95%CI
Upper extremities									
Proximal humerus	261	1.59	1.38-1.83	41	1.85	1.31-2.61	220	1.55	1.33-1.81
Wrist	578	1.45	1.32-1.59	74	1.73	1.34-2.23	504	1.42	1.29-1.57
Hand	262	1.30	1.14-1.49	92	1.3	1.04-1.63	170	1.29	1.09-1.53
Other proximal arm [a]	140	1.48	1.23-1.79	43	1.3	0.94-1.79	97	1.59	1.26-2.00
Other distal arm [b]	121	1.59	1.07-1.59	20	1.36	0.84-2.23	101	1.3	1.04-1.62
Lower extremities									
Pelvis	139	1.52	1.261.84	33	1.23	0.85-1.78	106	1.63	1.30-2.04
Hip	564	2.05	1.86-2.26	133	2.3	1.89-2.82	431	1.97	1.76-2.21
Ankle	106	0.99	0.81-1.21	27	1.09	0.73-1.62	79	0.96	0.76-1.22
Metatarsal	123	1.28	1.05-1.55	21	1.82	1.12-2.94	102	1.22	0.99-1.51
Other foot [c]	165	1.14	0.97-1.35	36	1.26	0.89-1.80	129	1.12	0.93-1.35
Other proximal leg [d]	41	1.98	1.37-2.87	8	1.38	0.64-2.94	33	2.2	1.44-3.37
Other distal leg [e]	166	1.14	0.97-1.34	46	1.03	0.76-1.41	120	1.19	0.98-1.45
Other[f]	263	1.20	1.05-1.37	122	1.07	0.89-1.29	141	1.31	1.09-1.58
All non-vertebral	2,233	1.40	1.34-1.46	586	1.37	1.25-1.49	1647	1.42	1.35-1.50

[a] other proximal arm fractures include fractures of the scapula, clavicula and non-proximal fractures of the humerus

[b] other distal arm fractures of the other parts of the radius and/or ulna

[c] other foot fractures include non-metatarsal foot fractures

[d] other proximal leg fractures include non-hip fractures of the femur and patella

[e] other distal leg fractures include non-ankle fractures of the tibia and/ or fibula

[f] other fractures include skull, rib and sternum

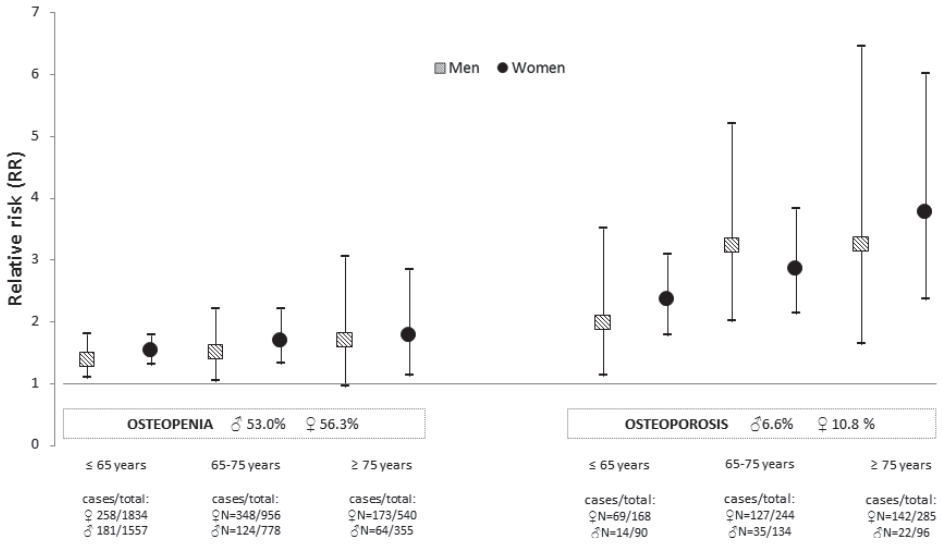

Figure 4 | Relative fracture risk comparing subjects with osteopenia or osteoporosis with normal bone subjects stratified by sex and age.

osteopenia/osteoporosis. The analysis of fracture risk over different follow-up periods confirms that BMD remains a good predictor of hip and non-vertebral fractures in time. In the first 5 years the fracture HR per SD decrease in BMD was 2.5 (95%CI: 2.0-3.1), while after 20 years the HR was 1.9 (95%CI: 1.1-3.3) (**Supplementary Table 1**).

Fracture Incidence Rates

During the 23 years of follow-up (overall mean: 10.7 ± 6.2; RSI-1 = 14.5, RSII-1 = 12.0, RSIII-1 = 5.6 years), 2971 (20.3%) participants sustained at least one non-vertebral fracture (of whom 75.4% were women). **Table 2** shows the fracture incidence rates by site and sex. Overall, the incidence of non-vertebral fractures was 12.4 [95%CI:

Table 2 | Gender and site-specific incidence rates of first non-vertebral fractures per 1000 person years.

Type of fracture	Total (n=14,613)			Men (n=6,024)			Women (n=8,589)		
	Number	Incidence rate	95%CI	Number	Incidence rate	95%CI	Number	Incidence rate	95%CI
Upper extremities									
Proximal humerus	356	2.29	2.07-2.54	59	0.96	0.74-1.23	297	3.18	2.83-3.56
Wrist	753	4.96	4.61-5.32	93	1.51	1.23-1.85	660	7.30	6.76-7.88
Hand	316	2.04	1.83-2.28	106	1.73	1.43-2.09	210	2.24	1.96-2.57
Other proximal arm [a]	195	1.25	1.08-1.44	55	0.89	0.68-1.16	140	1.48	1.26-1.75
Other distal arm [b]	155	0.99	0.85-1.16	25	0.40	0.27-0.60	130	1.38	1.16-1.64
Lower extremities									
Pelvis	194	1.24	1.08-1.43	42	0.68	0.50-0.92	152	1.61	1.37-1.88
Hip	830	5.37	5.02-5.75	185	3.01	2.60-3.47	645	6.94	6.43-7.50
Ankle	131	0.84	0.71-0.99	30	0.48	0.34-0.69	101	1.07	0.88-1.30
Metatarsal	149	0.95	0.81-1.12	24	0.39	0.26-0.58	125	1.33	1.11-1.58
Other foot [c]	194	1.24	1.08-1.43	44	0.71	0.53-0.96	150	1.59	1.36-1.87
Other proximal leg [d]	70	0.46	0.35-0.56	11	0.18	0.10-0.32	59	0.62	0.48-0.80
Other distal leg [e]	219	1.41	1.23-1.60	50	0.81	0.61-1.07	169	1.80	1.54-2.09
Other [f]	329	2.12	1.90-2.36	139	2.27	1.92-2.67	190	2.02	1.75-2.33
All non-vertebral	2,971	21.35	20.60-22.14	731	12.54	11.66-13.48	2240	27.72	26.59-28.89

[a] other proximal arm fractures include fractures of the scapula, clavicula and non-proximal fractures of the humerus
[b] other distal arm fractures of the other parts of the radius and/or ulna
[c] other foot fractures include non-metatarsal foot fractures
[d] other proximal leg fractures include non-hip fractures of the femur and patella
[e] other distal leg fractures include non-ankle fractures of the tibia and/ or fibula
[f] other fractures include skull, rib and sternum

11.6-13.4] per 1000 PY in men and 27.3 [95%CI: 26.2-28.4] per 1000 PY in women. In both men and women, the most predominant fracture sites were the wrist, hand, proximal humerus and hip. Apart from the fracture rates of the proximal humerus in men, all other non- vertebral and site-specific fracture rates increased exponentially with age (**Figure 5**).

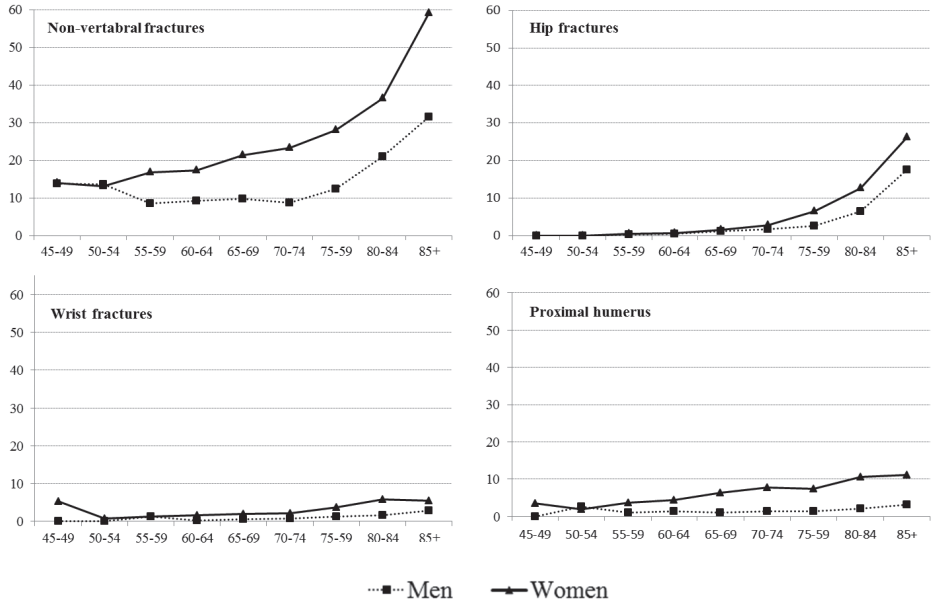

Figure 5 | Age related incidence of all non-vertebral, hip, wrist and proximal humerus fractures in men and women.

Comparing Fracture Rate between 1989 and 2001 and 2001–2013

The overall incidence of non-vertebral fractures in the period between 1989 and 2001 (25.4 per 1000 PY [95%CI: 23.0–28.0]) was similar to those observed in the period between 2001 and 2013 (26.4 per 1000 PY [95%CI: 24.4-28.5]) (**Supplementary Table 3A and B**). There was no significant change in site-specific fracture trends, with the exception of an 8.3% increased distal leg fracture incidence (p = 0.02) in men (**Figure 6**). However, this trend is not significant (0.05/14, P= 0.004) after taking multiple testing into account.

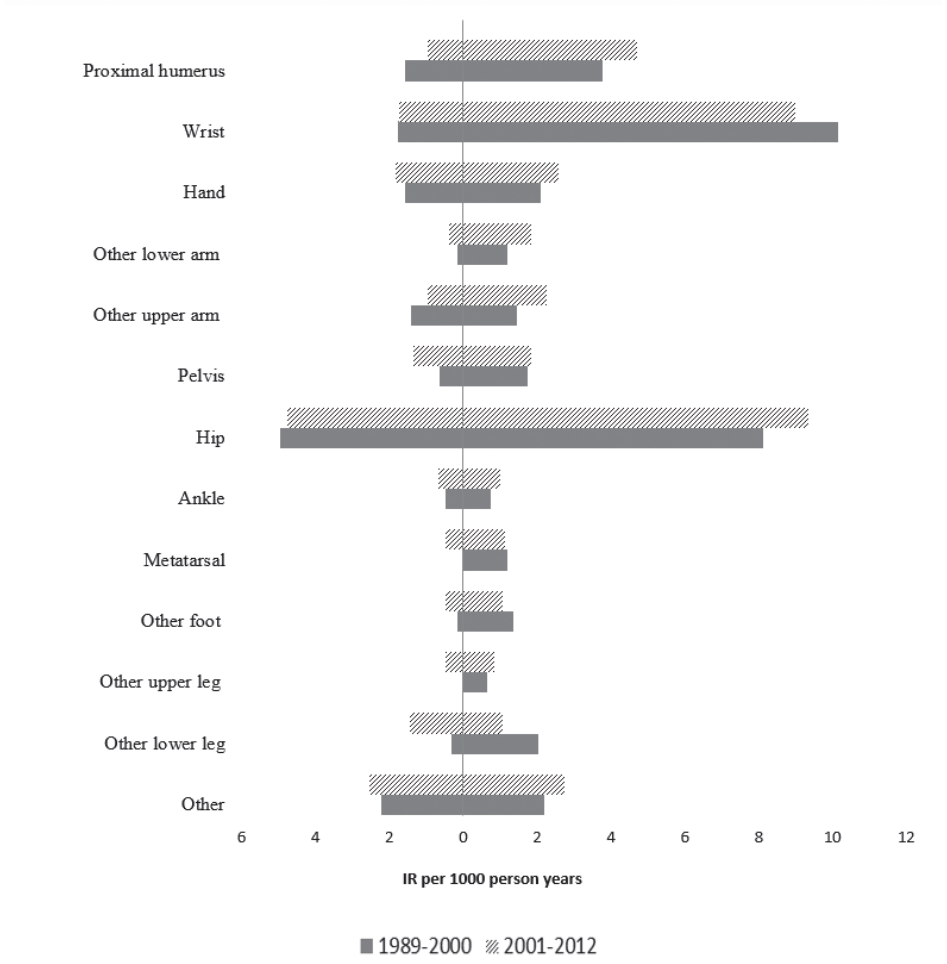

Figure 6 | Incidence of site-specific fractures in 1989 to 2001 compared with 2001 to 2013 (70–80 years old) stratified by sex

DISCUSSION

In this population-based prospective cohort, a single FN-BMD measurement at baseline remains a strong predictor of incident non-vertebral fragility fractures over a period of 20 years. The overall incidence rate of suffering non-vertebral fractures was 21.1 per 1000 PY [95%CI: 20.3-21.9] with a higher incidence rate in women than in men. The most frequent non-vertebral fractures in elderly men and women continues to be fractures of the hip, wrist, proximal humerus and hand, with most events occurring above the osteoporosis diagnostic and intervention threshold (T-score above

-2.5). We observed no secular trend changes in fracture incidence between 1989 and 2001 and 2001-2013.

In an earlier effort in the Rotterdam Study,[15] we showed an in-verse association between FN-BMD and the risk of all non-vertebral fractures during a mean 6.8-year follow-up period. After extending this follow-up period in the current study by 10 more years on average, we conclude that using one single BMD measurement is still a good predictor for fracture risk even up to 20 years after. This finding reinforces the central role of BMD in fracture etiology and prediction. Our findings corroborate with findings recently reported by Black and colleagues[17] among women of the Study of Osteoporotic Fractures showing that a single FN-BMD measurement strongly predicts long-term hip fracture up to 23 years. The fracture risk in the first five years (0–5 y) was comparable to the risk after 20 years (20-23 y). Additionally, we showed that low BMD is not only associated with hip fractures but also with fractures at other skeletal sites, among other peripheral sites. However, BMD did not have any predictive value for ankle and foot fractures. Furthermore, individuals with osteoporosis (BMD T-score < -2.5) fractured two to three times more often than individuals with normal BMD from the same sex and age group. In addition, in our study women with osteoporosis fractured more often than men, while the proportion of fractures in the osteopenia group is similar in men and women. Although BMD is an important predictor of fracture risk, the treatment indication based on T-score cut-offs alone it is not sufficient. As in our previous work, we still see that if we use a T-score of −2.5 as a diagnostic and treatment threshold, a very large proportion (> 50%) of the individuals who fracture will remain untreated; fuelling additionally the existing crisis in osteoporosis treatment.[26,27] Although there is a consensus to treat osteopenic patients presenting with prevalent low-energy fractures, the treatment of osteopenia without a fracture remains controversial. Risk assessments tools like FRAX[28] and GARVAN[29] have been developed in the last decade, which take into account other time-dependent clinical risk factors which may establish indication for pharmacotherapy. For example, age is an important risk factor and studies have found that drug-based interventions among elderly (≥65 years) women with osteopenia are cost-effective.[30] However, treatment of elderly women with osteopenia is still not part of current clinical practice recommendations and most guidelines for osteopenic patients emphasize lifestyle changes. Nevertheless, our findings encountering no significant change in the secular trends of fracture risk across periods, suggest that (at least in the Netherlands) additional steps are required to improve fracture risk prediction. Redefining intervention thresholds and targeting strategies to improve adherence to guidelines and drug compliance are some of the ways to achieve this improvement.

As reported in previous studies[10,31,32] we observed that wrist and hip fractures occur more frequently in women than in men, with a ratio of 2:1 and 5:1 for hip and

wrist fractures, respectively. The sex-specific incidence of hip fractures was similar to a previous report in the Dutch population[10] performed in 1987. Using the Dutch medical register they observed that for every 100,000 inhabitants 669 women and 308 men suffered a hip fracture. The observed sexual dimorphism in fracture risk has been mainly attributed to the rapid postmenopausal bone loss in women, accounting for 20–30% loss in cancellous bone and 5–10% loss in cortical bone.[33] Additionally, higher peak bone mass and stronger bone geometry parameters in men contribute to the sex differences.

Beside the differences in sex, large variation in hip fracture rates (up to 7-fold) has been observed across countries. Ismail and colleagues[34] estimated site-specific fracture incidence rates across Europe and found differences in rates by sex and region. In line with our study they have reported similar sex-specific hip fracture rates in Scandinavia and lower in Southern, Eastern and Western Europe. Moreover, in women the incidence rate of humerus fractures followed the same country pattern as hip fracture, while in men the incidence rate of our study was only higher than in Eastern Europe and similar to the other countries. No differences in wrist fracture incidence rates were noticed between regions. Beside falls and higher latitude, other environmental factors together with genetic factors could lead to geographical variations in incidence rates. Still, direct comparison of rates across studies should be made with caution given differences in age and sex distribution, methods for age standardization, fracture ascertainment and regional variation in general health.

In our study we provided incidence rates for different site-specific fractures. Although the major osteoporotic fractures (hip, spine and forearm) are considered the most important and prominent ones, other site-specific fractures also contribute considerably to the burden of osteoporosis. These other fractures account for 31.5% of all health care expenditure,[35] while it has also been shown that women with other types of fracture (non-hip) utilize more healthcare resources compared to women with hip fracture.[36] Altogether, gaining additional insight and knowledge about the incidence of site-specific fractures and trends in time might help in establishing better prevention strategies.

Studies in different countries have shown a steady increase in the incidence of hip fractures in the 80s and early 90s. [37-39] But recently, it has been proposed that the incidence of fracture has remained rather stable or could have even decreased in some countries (USA, Canada, Australia and Switzerland).[40-42] In our study, although there was a positive non-significant fracture trend for the majority of site-specific fractures, the incidence rates have remained rather stable over the past 20 years. Amin and colleagues[43] have also reported stabilization of the fracture incidence rates at many skeletal sites in the past two decades in the U.S. This is in contrast with findings from a recent national registry-based study in the Netherlands which observed 3-4%

increased incidence rates for wrist, hand/finger, hip/proximal leg, ankle and foot/toe fractures.[44] Moreover, Nanniga and colleagues[45] have reported increased incidence rate of pelvic fractures in the Netherlands. The different findings from the latter two studies may be attributed to a couple of factors. Firstly, the studies used hospital records to extrapolated data while we used both hospital and GP records. Next, in the study by Beerekamp et al.[44] the age range was wide and included patients ≥16 years old. In addition, their population mean age increased from 2004 to 2014 which could be one reason for the increase in the absolute number of fractures. Reason why in our study we chose a fixed age category of 70-80 years to compare between two time periods. Further, they had missing data on 7% in elderly above 70 years which could have influenced the fracture numbers. Although all events were ICD10 or ICD9 codes different group-classifications applied between the studies might have impacted the rates. Finally, our study is a cohort study and the findings might be specific for our population only. Overall, variation in fracture rates in time can be due to birth cohort effects resulting from changes in early life risk factors such as perinatal nutrition, behavioral changes in smoking and alcohol consumption, BMI, treatment of osteoporosis [bisphosphonates, calcium, vitamin D] or use of estrogen therapy. Analysis of the trends can help us identify the main factors leading to differences between countries.

Our study has several strengths. We were able to estimate the incidence and incidence trends of site-specific fractures in both men and women from the same population after a prolonged follow-up. In addition, in the Netherlands, the only way to access specialist and hospital care is consulting a GP. Therefore, checking the GPs' medical records of all participants should have resulted in a more comprehensive follow-up. One important limitation is that our study may be subject to selection bias at baseline due to non-response of subjects with impaired mobility and this could have led to an underestimation of the incidence rates. Loss to follow-up and mortality can also cause lower incidence rates, given that usually these individuals are older and more susceptible to bone loss. Competing risk of death, changes in clinical practice and bisphosphonates use could have influenced the fracture rates in both follow-up periods. However, we are not able to account for these changes in our study. Moreover, we were not able to use repeated BMD measures due to differences in densitometer per follow-up. Although single BMD measurement is associated with fracture risk over longer period in the population, repeated BMD measures may still be necessary to improve the prediction of fracture for an individual.[46]

In conclusion, BMD remains a strong predictor of hip and non-vertebral fractures over 20 years in both men and women. The majority of fractures continue to occur above the osteoporosis threshold emphasizing the need to improve the screening of osteopenic patients. Most importantly, we established there are no difference in fracture trends between the periods of 1989-2001 and 2001-2013, welcoming active

actions seeking to improve the diagnoses, treatment and prevention strategies to this costly disease.

Detailed acknowledgments and online resources can be found in the published article online

https://www.sciencedirect.com/science/article/pii/S8756328218302333?via%3Dihub

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