Impact of Osteoporotic Fracture Type and Subsequent Fracture on Mortality: The Tromsø Study

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Mini Abstract

Less is known about the impact of non-hip non-vertebral fractures (NHNV) on early death. This study demonstrated increased risk of dying following hip and NHNV fractures which was further increased by a subsequent fracture. This highlights the importance of early intervention to prevent both initial and subsequent fracture and improve survival.

Abstract

Introduction: Osteoporotic fractures are a major health concern. Limited evidence exists on their impact on mortality in ageing populations. This study examined the contribution of initial fracture type and subsequent fracture on mortality in a Norwegian population that has one of the highest rates of fractures.

Methods: The Tromsø Study is a prospective population-based cohort in Norway. Women and men aged 50+ years were followed from 1994 to 2010. All incident hip and non-hip non-vertebral fractures (NHNV) were registered. NHNV fractures were classified as either proximal or distal. Information on self-reported co-morbidities, lifestyle factors, general health and education level was collected. Multivariable Cox models were used to quantify mortality risk with incident and subsequent fractures analysed as time-dependent variables.

Results: Of 5,214 women and 4,620 men, 1,549 (30%) and 504 (11%) sustained a fracture, followed by 589 (38%) and 254 (51%) deaths over 10,523 and 2,821 person-years, respectively. There were 403 (26%) subsequent fractures in women and 68 (13%) in men. Hip fracture was associated with a two-fold increase in mortality risk (HR 2.05, 95% CI 1.73-2.42 in women, and 2.49, 95% CI 2.00-3.11 in men). Proximal NHNV fractures were associated with 49% and 81% increased mortality risk in women and men (HR 1.49 95% CI 1.21-1.84 and 1.81 95% CI 1.37-2.41), respectively. Distal NHNV fractures were not associated with mortality. Subsequent fracture was associated with 89% and 77% increased mortality risk in women and men (HR 1.89 95%CI 1.52-2.35 and 1.77 95%CI 1.16-2.71), respectively.

Conclusion: Hip, proximal NHNV and subsequent fractures were significantly associated with increased mortality risk in the elderly, highlighting the importance of early intervention.

Introduction

Osteoporotic fractures are a major and increasing cause of morbidity and loss of independence worldwide with an annual global loss of 5.8 million healthy life years to disability (1). It has been demonstrated that following an osteoporotic fracture the risk of a subsequent fracture increases by at least two-fold (2-5). Moreover, multiple studies have demonstrated an association between hip and vertebral fractures and increased risk of mortality (6-12). There is also growing evidence about the contribution of non-hip non-vertebral fractures (NHNV), the largest group of osteoporotic fractures, to increased mortality risk (12-17). In addition, there is evidence that subsequent fractures are associated with further increased risk of mortality (8, 18).

Norway has one of the highest hip fracture rates in the world (19-21). A systematic review of 63 countries presented a ten-fold variation in hip fracture risk and a ten-year probability of a major osteoporotic fracture worldwide with Denmark, Sweden and Norway exhibiting the highest rates (22). The reasons for this variation in fracture incidence are unknown. However, genetic and environmental factors are thought to play an important role (23).

In Norway, the increased risk of a subsequent fracture after initial fracture and the increased mortality risk following hip fracture has been well explored (5, 24-26). However, the impact of NHNV fractures and subsequent fractures following initial fractures on mortality have not been thoroughly examined. In a country with one of the highest life expectancies in the world and where osteoporotic fracture risk is on the rise with its ageing population, it is important to further explore and quantify the association with mortality of osteoporotic fractures and re-fracture, as potentially modifiable factors.

Therefore, based on data from Norway, the aims of this study were to examine the specific contribution of initial hip and NHNV fractures and subsequent fractures on mortality risk.

Methods

Study population and design

The Tromsø Study is a prospective, population-based cohort study in Tromsø, the largest city in Northern Norway. The study consists of seven health surveys (Tromsø 1-7) with Tromsø 1 being initiated in 1974 and Tromsø 7 completed in 2016. Participants were asked to complete questionnaires, which were supplemented by a short interview and a medical examination (27, 28). In this study, data collected in Tromsø 4 (1994/95) were used. Tromsø 4 is the largest survey. It included a total of 27,158 people (12,865 men and 14,293 women in the 25-97 age range). This study included the 5,214 women and 4,620 men from Tromsø 4 who were aged 50 years and older. The period extended from 1994-1995 to the end of 2010. Study participants were followed up until the end of the study or until they died.

Fracture and mortality data ascertainment

Fracture events were identified from the fracture registry, which is based on the radiographic archives at the University Hospital of North Norway in Tromsø. The computerized records in the radiographic archives contain the national personal identification number, date of the fracture, fracture codes and descriptions. All radiographic examinations coded "abnormal" for participants in Tromsø 4 were reviewed to ascertain the fracture code, to identify the exact fracture type, its mechanism of injury (high trauma e.g.: motor vehicle accidents, pathological fractures e.g.: cancers or minimal trauma e.g. bumps, strains and falling from standing height) and anatomical location, to distinguish consecutive fracture cases from one another and to capture any fractures that may have not been coded correctly (29, 30).
The current study included only minimal trauma fractures, which occurred following a fall from standing height or less. High trauma fractures, pathological fractures as well as fractures of the head, fingers and toes were excluded. Incident fractures were analysed according to fracture type as hip and NHNV. NHNV were classified as either proximal

(pelvis, humerus, clavicle, femur, scapula, ribs and sternum) or distal (radius, ulna, tibia, fibula, hand and foot). Vertebral fractures were not included in this study as they were not systematically collected. Mortality status was ascertained from the Population Register of Norway to which the Tromsø study is linked.

Clinical characteristics

Information was obtained from the self-administered questionnaires and physical examinations and included: age, body mass index (BMI), self-reported prior hip/forearm fractures, comorbidities (cardiovascular diseases, stroke, asthma, diabetes and hypertension), marital status [married/(single, divorced or widowed)], general health condition (good/poor), education level (junior high school, senior high school and college/university degree) and lifestyle factors such as smoking (yes/no), alcohol intake (yes/no) and hard physical activity (<1 hour/week and ≥1 hour/week).

Statistical analysis

Statistical analyses were performed using SAS, version 9.4.

Fracture and subsequent fracture were analysed as time-dependent variables, such that in the whole cohort fractured participants were considered in the no-fracture group until they had their first fracture at which point, they were followed up till the end of the study as the fracture group and in the fractured cohort those who had a subsequent fracture were considered in the no-subsequent fracture group until they had their subsequent fracture. Age was analysed as a time-dependent variable representing age at first fracture for those with only one fracture and age at subsequent fracture for those who experienced a subsequent fracture. Co-morbidities were not analysed as time-dependent variables and represented baseline information for those with single fractures and those with subsequent fractures.

Gender-specific crude mortality rates per 100 person-years were calculated for the whole

cohort for the overall period of follow up and at different time intervals (0-1, 1-2, 2-5 and >5). Age-standardised mortality ratios (SMRs) were calculated for the fracture group by comparing age and gender-specific mortality rates for each fracture type (hip and proximal and distal NHNV) with the age and gender-specific mortality rates for the no-fracture group. SMRs were also calculated for the whole follow-up period as well as for different time intervals (0-1, 1-2, 2-5 and >5 years post-fracture). The main reason for calculating SMRs was to estimate the change in mortality risks post-fracture over different time intervals. This analysis was unable to be performed using the Cox proportional hazards models (used in all other analyses) as the time-dependent Cox model which estimate risks at different time intervals could not handle the time-varying variable (fracture) that changes over time. The mortality rates and SMRs and their 95% confidence intervals were estimated assuming a Poisson distribution.

The association between fracture, subsequent fracture and mortality was examined in two ways: 1) in the whole cohort: the contribution of initial fracture type over and above other predefined risk factors on mortality risk was compared to the no-fracture group, and 2) in the fractured cohort: the contribution of subsequent fractures on post-fracture mortality after adjusting for risk factors was compared to the group with the lowest mortality risk derived from the adjusted survival curves. The reference group was those with a distal NHNV fracture and no subsequent fracture. The additional effect of subsequent fracture on post-fracture mortality for each fracture type was estimated by simply subtracting the hazard ratios for those with a single fracture only from those with a subsequent fracture. To further explore the significance of the additional effect of subsequent fracture, an additional analysis involving a direct comparison between those with a subsequent fracture versus those with a single fracture stratified by gender and fracture type was performed i.e. those with single hip fracture (referent group) versus hip fracture + subsequent fracture.

Cox proportional hazards models were used to quantify mortality risk by calculating hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for potential confounders (listed above). The proportional hazards assumptions for Cox models were tested for using Schoenfeld residuals for the time-dependent variables, Kaplan Meier curves for the categorical variables and Martingale residuals for continuous variables.

Population impact number (PIN) and case impact number (CIN) which are measures that reflect the impact of osteoporotic fractures on mortality in the whole study population were calculated. PIN is the number of those in the whole population amongst whom one death is attributable to fracture. CIN is the number of those who died amongst whom one case is attributable to fracture (31). Those measures were calculated as a function of the hazard ratios, prevalence of fracture, and incidence rate of mortality and their 95% CIs were calculated using the confidence limits of the adjusted hazard ratios. Impact measures were not computed for a statistically non-significant association between fracture and mortality (31).

Results

The study included 5,214 (53%) women and 4,620 (47%) men. The mean age was 64 ± 10 for women and 62 ± 9 years for men. The median follow-up time was 11 years (IQR, 6 to 16 years). During the follow-up 1,758 (34%) women and 1,822 (39%) men died. In the fracture cohort, 589 (38%) women and 254 (51%) men died over 10,523 and 2,821 person-years, respectively. As expected, those who died (in both the whole cohort and fracture group) were significantly ($p<0.05$) older, had more comorbidities and poorer health status. In addition, they were less likely to be married, exercised less and had lower education levels (Table 1).

Initial fracture rates, crude mortality rates and SMRs

There were 1,549 (30%) fractures in women and 504 (11%) in men over 60,376 and 56,632 person-years, respectively. NHNV fractures accounted for 75% (n=1,165) of fractures in women and 64% (n=323) in men. The majority of the NHNV fractures were distal; 75% (n=874) in women and 67% (n=218) in men. Hip fracture incidence was two-fold higher in women then in men (6.4/1000 person-years versus 3.2/1000 person-years) and NHNV fracture incidence was three-fold higher in women than in men (19.3/1000 person-years versus 5.7/1000 person-years).

Those with a fracture had a three-fold higher crude mortality rate compared to those with no fracture; in women [5.6/100 person-years (95% CI, 5.2-6.1) versus 1.9/100 person-years (95% CI, 1.8-2.1)] and in men [9.0/100 person-years (95% CI 8.0-10.2) versus 2.8/100 person-years (95% CI, 2.6-2.9)]. In general, men had higher crude mortality rates following all fracture types than women (Table 2).

The SMRs for those with any fracture in both genders were significantly increased up to five years post-fracture. The SMRs for all fracture types were highest in the first year post-fracture ranging from 1.76-6.20 in women and 1.28-8.19 in men with the highest SMRs for hip followed by proximal NHNV followed by distal NHNV. After the first year, the SMRs declined progressively and after five years only hip and proximal NHNV fractures SMRs in women remained significant (Table 2).

Mortality risk following initial fracture

In both women and men, any type of fracture was associated with a 36% (HR 1.36; 95% CI, 1.22-1.53) and a 66% (HR 1.66; 95% CI, 1.41-1.94) increased risk of mortality, respectively. Hip fracture was associated with the highest risk of mortality with more than two-fold increased risk in both genders. NHNV fractures were associated with a 15% (HR 1.15; 95% CI, 1.01-1.31) and a 28% (HR 1.28; 95% CI, 1.04-1.57) increase in mortality risk in women

and men, respectively. This excess mortality following NHNV was predominantly due to proximal NHNV fractures which were associated with 49% increased mortality risk in women (HR 1.49; 95% CI, 1.21-1.84) and 81% in men (HR 1.81; 95% CI, 1.37-2.41). Distal NHNV were not associated with mortality for either genders (Figure 1).

Mortality risk following subsequent fracture

Of 1,549 women and 504 men with incident fractures, 403 (26%) and 68 (13%) experienced a second fracture over a median of 6 years of follow up (IQR 2 to 9 years). The probability of dying over time for subjects with a single initial fracture and with an initial fracture followed by a subsequent fracture was presented using adjusted survival curves for Cox proportional hazards models. In both genders, those with distal NHNV fracture and no subsequent fracture had the lowest mortality probability while those with a hip fracture and a subsequent fracture had the highest mortality probability. For each fracture type subjects with a subsequent fracture had higher probability of dying compared to those with no subsequent fracture, particularly in women. Interestingly, women with a proximal NHNV fracture and a subsequent fracture appeared to have on average a similar probability of dying as women with a hip fracture. This effect was not observed for men (Figure 2).

The above mortality probabilities were quantified by the following adjusted hazard ratios. Compared to subjects with only a distal NHNV fracture and no subsequent fracture, in women and men any initial fracture followed by a subsequent fracture was associated with 89% (HR 1.89; 95% CI, 1.52-2.35) and 77% (HR 1.77; 95% CI, 1.16-2.71) increased mortality risks, respectively (Table 3). When analysed according to initial fracture type, a hip fracture followed by a subsequent fracture was associated with a three-fold higher mortality risk in both genders. In women, a proximal NHNV fracture followed by a subsequent fracture was associated with two-fold increased mortality risk while a distal NHNV fracture followed by a

subsequent fracture was associated with a 42% increase in mortality risk. In men, a subsequent fracture following proximal and distal NHNV fractures was associated with an increase in mortality risk, but this did not reach statistical significance, possibly due to the smaller number of fractures (Table 3).

The simple difference between hazard ratios of those with a single fracture only and those with a subsequent fracture was performed to quantify the excess mortality risk that may be contributed by subsequent fractures. A subsequent fracture in women was associated with an increase in mortality risk by ~ 92% following a hip fracture, ~ 35% following a proximal NHNV fracture and ~ 42% after a distal NHNV fracture. In men, a subsequent fracture was associated with an increase in mortality risk by ~ 83% after a hip fracture and ~ 33% after a distal NHNV fracture. However, this additional risk was not seen after a proximal NHNV fracture which may be explained by the lower number of subsequent fractures in men in this group (Table 3).

The direct comparison of a subsequent fracture versus single fracture using adjusted hazard ratios demonstrated that subsequent fracture was associated with 24% excess mortality in women but no in men. When stratified by gender and fracture type the hazard ratios were in general higher for subsequent fracture than initial fracture (ranging from a 1.2-1.5-fold increase) (Table S1). However, they were significant only for hip fracture in women. The non-significant higher mortality risks seen in other fracture types were still clinically important and the lack of significance can be explained by the smaller number of fractures in individual groups, such as proximal NHNV fractures in men.

Impact of osteoporotic fractures on mortality in the population

The PIN is the number of individuals for whom one death could be attributable to an osteoporotic fracture in the whole population. Calculation of the PIN indicates that in the

whole study population, one death would be attributable to any osteoporotic fracture for every 373 women and 449 men. To assess the relative impact, it was useful to calculate the CIN. The CIN is the number of deceased individuals among whom one death would be attributable to an osteoporotic fracture. In this study the CIN suggested that one in 10 deaths in women and one in 15 deaths in men was attributable to a fracture. Hip fractures had a similar impact on mortality in both genders (PIN=549, CIN=15 in women and PIN=548, CIN=18 in men) while NHNV fractures, specifically proximal NHNV fractures, had a higher impact on mortality in women than in men. Those results suggest that fractures in women may have a higher population impact on mortality compared to men, which is related to the higher number of NHNV fractures in women than men. For both genders the impact of hip fractures on mortality was higher than the impact of all NHNV fractures (Table 4).

Discussion

This Norwegian study is the first to our knowledge to examine the association between NHNV fractures and mortality and subsequent fractures and mortality. The study demonstrated that proximal NHNV fractures were associated with an increased mortality risk of 49% in women and 81% in men in addition to the two-fold increased mortality following hip fractures. The highest mortality rates were seen in the first year post-fracture for both hip and NHNV fractures. A subsequent fracture in women and men following any initial fracture type was associated with 89% and 77% increased mortality risk, respectively. A subsequent fracture following an initial hip fracture was associated with a three-fold increase in mortality in both genders. However, for women only, a subsequent fracture was associated with a two-fold increased mortality following an initial proximal NHNV fracture and by 42% following an initial distal NHNV fracture.

The two-fold increased mortality risk post-hip fracture observed in this study together with

the findings of the highest mortality observed in the first year post-fracture, are consistent with other studies conducted in Norway (24-26) and internationally (6, 8, 16). The increased mortality risk post-NHNV fractures especially post-proximal NHNV fractures in both genders adds to the growing evidence of the association of NHNV fractures with mortality (8, 11, 13, 16, 17, 32) and is the first large examination of this group of fractures in Norway. Similar to hip fractures, the highest mortality post-NHNV fractures was seen in the first year post-fracture. Moreover, the lack of association between distal NHNV fractures and mortality is also consistent with findings from other studies (11, 13, 16, 33), although, one study demonstrated an increased mortality risk with minor fractures in those older than 75 years (8).

In the Tromsø population similar to the CaMos population (16), the impact of fractures on mortality (PIN= 373 in women and PIN=449 in men) was greater than the impact of smoking on coronary-heart disease related deaths (PIN=1302) and lung-cancer related deaths (PIN=2564) as demonstrated by the impact measures estimated from a cohort study of British male physicians (31, 34). Moreover, the impact of hip fractures on mortality was greater than of NHNV fractures, although NHNV fractures accounted for nearly 75% of all fractures and were significantly associated with mortality. Those findings were in contrast to what was observed by Tran et al in the CaMos population (16) and may be partially explained by the higher incidence of hip fractures in the Tromsø cohort compared to the CaMos cohort (women 6.4 versus 3.5/1000 person-years and men 3.2 versus 2.6/1000 person-years, respectively).

This study also demonstrated that subsequent fractures were associated with increased mortality risk in both women and men. The greatest impact of a subsequent fracture (three-fold) on mortality risk was seen in those who had an initial hip fracture in both genders. However, in women a subsequent fracture was associated with a two-fold increase in

mortality risk post-proximal NHNV fracture and a 42% post-distal NHNV fracture. In men, there was also a consistent numerically increased mortality with subsequent fracture following proximal and distal NHNV fractures although this did not reach statistical significance likely related to the low number of subsequent fractures in men. A few studies have demonstrated an association between subsequent fractures and increased risk of mortality in both genders (8, 14, 18). Bliuc et al also reported that distal NHNV fractures were associated with mortality only in those who sustained a subsequent fracture similar to the findings of the current study. Importantly, in the current study, the additive effect of subsequent fractures to mortality risk following the different fracture types was demonstrated in adjusted survival curves and hazard ratios (by direct comparison of HRs between paired fracture groups (single fracture versus subsequent fracture). Previous studies that explored these effects used unadjusted Kaplan Meier survival curves and did not take into account comorbidities or other lifestyle factors (14, 18).

The mechanism of post-fracture mortality is not understood. Multiple risk factors, including comorbidities, have been implicated in post-hip and vertebral fractures mortality but not widely studied post-NHNV fractures. The role of comorbidities has been controversial with some studies reporting no association between comorbidities and post-fracture mortality (8, 9, 35) and others attributing up to 50% of excess mortality post-hip and vertebral fractures to concomitant medical disorders especially pulmonary and cardiac diseases (36-40). A recent study that examined the role of comorbidities on post-NHNV fracture mortality reported that adjustment for comorbidities had minimal effect on the fracture-mortality relative risks, but comorbidities contributed independently to mortality such that a woman with a humeral fracture and 1 comorbidity had a similarly reduced five-year survival as that of a woman with a hip fracture and no comorbidities (17).

Recent evidence suggests that osteoporosis treatment especially bisphosphonates, which are known to reduce fracture risk (41), may also reduce mortality risk following osteoporotic fractures (42-49). Despite this, individuals with osteoporotic fractures remain undertreated, with less than 30% of women and less than 10% of men being treated (50-52). The poor management post-fracture may be due to an underestimation of the potential premature mortality risk following the different types of fractures. This study adds to the available evidence about the increased risk of mortality and subsequent fracture following different fracture types highlighting the importance of early treatment of osteoporotic fractures.

The strengths of this study include the prospective design, the long follow-up and the large representative population. In addition, the large number of fractures in the study provided adequate power for the analyses of the association of fracture type with mortality and consequently the effect of subsequent fracture. Moreover, the availability of other collected variables enabled the examination of the effect of fracture on mortality over and above other risk factors and indicated that fracture is an independent predictor of mortality. This study has some limitations. Its observational nature allows finding an association but not a causal relation between fractures and mortality. Tromsø has few immigrants and hence the majority of the population are Caucasian limiting the generalisability of the findings to other ethnic groups. Also, as in many such studies, vertebral fractures were not registered. Nevertheless, the exclusion of those fractures would have only resulted in underestimation of the overall incident fracture and mortality rates post fracture. The misclassification would also result in increased mortality rates of the non-fractured population as unidentified vertebral fractures, known to be associated with increased mortality, would be included in the non-fractured population. In addition, the measures PIN and CIN, which quantify the excess mortality associated with fracture at a population level, are based on the assumptions that fracture has a direct cause on mortality. However, this study was only able to ascertain an association

adjusted for known variables and PIN and CIN should be viewed within this limitation. Co-morbidities were not analysed as time-dependent variables and hence individuals with subsequent fracture may have had more co-morbidities by the time of second fracture which could pose a potential bias that may result in overestimation of the mortality risks.

Conclusion

In this study there was an association between hip and proximal NHNV fractures and increased mortality risk in both genders aged 50+ years and no association of distal NHNV fractures with mortality. Mortality rates following all fracture types were highest in the first two years post-fracture. A subsequent fracture following any fracture type, in both women and men was associated with an additional impact on mortality risk such that the overall mortality risk post-fracture was higher than in those with one fracture. This was observed even in those with a distal NHNV fracture. On a population-wide basis, these fractures contribute significantly to overall mortality. This study thus demonstrates the population-level impact of fracture in the elderly and support the critical need for early identification and management to prevent both initial and subsequent fracture and potentially improve survival.

Contributors

Study design: DA, DB, TT, LAA, NE, ÅB, LJ, TC and JRC. Data Collection: LAA, NE, ÅB and LJ. Data analysis and interpretation: DA, DB, TT and JRC. Drafting of the manuscript: DA, DB, TT and JRC. Revising manuscript content: all authors. Approving final version of manuscript: all authors. We are grateful to Professor Ragnar Joakimsen for his great contribution to The Tromsø Study.

Funding

The Tromsø Study was funded by the University of Tromsø and from contributions by the National Screening Services, the Research Council of Norway, Northern Norway Regional Health Authority, Norwegian Council on Cardiovascular Diseases and Norwegian Foundation for Health and Rehabilitation.

This work was supported by the National Health Medical Research Council Australia (NHMRC project ID; DA 1114676, DB 1073430, TT 1070187 and JRC 1008219). Other funding bodies were the Bupa Health Foundation (formerly MBF Foundation) and the Mrs Gibson and Ernst Heine Family Foundation. The study sponsors had no role in the study design; collection, analyses and interpretation of the data; the writing of this report; or the decision to submit this manuscript for publication.

Conflicts of interest

DA, DB, TT, LAA, NE, ÅB, LJ, TC have no competing interests to declare. JRC has consulted for and/or given educational talks for Merck Sharp and Dohme, Amgen, Actavis and Sanofi-Aventis. JAE has consulted for and/or received research funding from Amgen, deCode, Merck Sharp and Dohme and Sanofi- Aventis.

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Figure 1. Multivariable adjusted mortality risk by gender and fracture type in the whole cohort

*Adjusted for age, BMI, comorbidities, marital status, general health condition, education level, smoking, alcohol intake and physical activities.

Figure 2. Adjusted survival curves for mortality probability after initial and subsequent fracture by gender and fracture type in the fracture cohort

Adjusted for age, BMI, comorbidities, marital status, general health condition, education level, smoking, alcohol intake and physical activity.
The distal NHNV single fracture group had the lowest death probability. The hip fracture with a subsequent fracture group had the highest death probability.
Time zero corresponds to the time of initial fracture for subjects with single fracture and time of subsequent fracture for subjects with a subsequent fracture.

Supplementary Table S1. Multivariable adjusted mortality risk following subsequent fracture by gender in fracture cohort – a paired comparison for each fracture type

Table 1. Baseline characteristics of the study population

	Women n=5214 (53%)		Men n=4620 (47%)	
	Dead* **n=1758 (34%)**	**Alive n=3456 (66%)**	**Dead*** **n=1822 (39%)**	**Alive n=2798 (61%)**
Age[a], yr	72 (9)	60 (8)	69 (9)	58 (7)
BMI kg/m²**	26 (5)	26 (4)	26 (4)	26 (3)
Prior hip/forearm fx[b]	465 (26%)	567 (17%)	191 (11%)	339 (12%)
Cardiovascular disease	441 (25%)	234 (7%)	640 (35%)	356 (13%)
Stroke	101 (6%)	47 (1%)	138 (8%)	42 (2%)
Asthma	186 (11%)	240 (7%)	169 (9%)	145 (5%)
Diabetes	144 (8%)	58 (2%)	124 (7%)	35 (1%)
Hypertension	383 (22%)	353 (10%)	365 (20%)	260 (9%)
Single/Divorced/Widowed	1028 (58%)	1239 (36%)	568 (31%)	668 (24%)
Poor health status	1158 (66%)	1589 (46%)	996 (55%)	926 (33%)
Smoking	462 (26%)	1027 (30%)	683 (38%)	877 (31%)
Alcohol (any)	408 (23%)	1572 (46%)	955 (52%)	1978 (71%)
Hard Physical Activity hr/wk				
<1hr	1650 (94%)	2944 (85%)	1508 (83%)	1927 (69%)
≥1hr	108 (6%)	512 (15%)	314 (17%)	871 (31%)
Education				
Junior high school	1362 (77%)	2021 (59%)	1025 (56%)	1128 (40%)
Senior high school	315 (18%)	908 (26%)	584 (32%)	929 (33%)
College/University	81 (5%)	527 (15%)	213 (12%)	741 (27%)
Fracture group	**n=1549 (30%)**		**n=504 (11%)**	
	n=589 (38%)	**n=960 (62%)**	**n=254 (51%)**	**n=250 (49%)**
Age, yr	74 (8)	62 (8)	71 (9)	60 (7)
BMIkg/m²**	26 (5)	26 (4)	25 (4)	26 (3)
Prior hip/forearm fracture	208 (35%)	256 (27%)	42 (17%)	39 (16%)
Cardiovascular disease	114 (19%)	77 (8%)	78 (31%)	33 (13%)
Stroke	37 (6%)	15 (2%)	23 (9%)	8 (4%)
Asthma	56 (10%)	66 (7%)	20 (8%)	10 (4%)
Diabetes	45 (8%)	15 (2%)	16 (6%)	4 (2%)
Hypertension	106 (18%)	94 (10%)	44 (17%)	28 (10%)
Single/Divorced/Widowed	348 (59%)	376 (39%)	39 (31%)	60 (24%)
Poor health status	370 (63%)	435 (45%)	128 (50%)	94 (38%)
Smoking	140 (24%)	259 (27%)	103 (41%)	81 (32%)
Alcohol (any)	126 (21%)	419 (44%)	133 (52%)	182 (73%)
Hard Physical Activity hr/wk				
<1hr	561 (95%)	827 (88%)	212 (83%)	180 (72%)
≥1hr	28 (5%)	133 (12%)	42 (17%)	70 (28%)
Education				

Junior high school	460 (78%)	575 (60%)	142 (56%)	111 (44%)
Senior high school	108 (18%)	252 (26%)	87 (34%)	77 (31%)
College/University	21 (4%)	133 (14%)	25 (10%)	62 (25%)

* Differences between dead and alive for both genders are statistically significant at P<0.05, except for BMI

** BMI, body mass index

[a] Values represent mean (SD) for continuous variables

[b] Values represent number (%) for categorical variables

Table 2. Standardised by age mortality ratios (SMRs) and crude mortality rates according to gender, fracture type and different time intervals

	Women				Men			
Fracture type	**Person-years**	**Deaths (n)**	**Crude mortality rates/100 py (95% CI)**	**SMR (95%CI)**	**Person-years**	**Deaths (n)**	**Crude mortality rates/100 py (95% CI)**	**SMR (95%CI)**
No fracture								
Overall	60377	1169	1.94 (1.83-2.05)		56633	1568	2.77 (2.64-2.91)	
0-1	5126	49	0.96 (0.72-1.27)		4563	76	1.67 (1.33-2.09)	
1-2	4941	54	1.09 (0.84-1.43)		4433	94	2.12 (1.73-2.60)	
2-5	13703	225	1.64 (1.44-1.87)		12466	312	2.50 (2.24-2.80)	
>5	36607	841	2.30 (2.15-2.46)		35171	1086	3.09 (2.91-3.28)	
Any fracture								
Overall	10524	589	5.60 (5.16-6.07)	**1.39 (1.28-1.50)**	2821	254	9.00 (7.96-10.18)	**1.62 (1.42-1.82)**
0-1	1479	119	8.05 (6.73-9.63)	**3.73 (3.06-4.39)**	451	76	16.85 (13.46-21.10)	**4.68 (3.63-574)**
1-2	1347	75	5.57 (4.44-6.98)	**2.32 (1.80-2.85)**	389	41	10.54 (7.76-14.31)	**2.71 (1.88-3.54)**
2-5	3243	172	5.30 (4.57-6.16)	**1.53 (1.31-1.76)**	870	70	8.05 (6.34-10.17)	**1.52 (1.16-1.87)**
>5	4455	223	5.01 (4.39-5.71)	1.09 (0.95-1.24)	1111	67	6.03 (4.75-7.66)	1.17 (0.89-1.45)
Hip								
Overall	1776	251	14.13 (12.49-16.00)	**2.32 (2.03-2.60)**	616	128	20.75 (17.46-24.69)	**2.55 (2.11-3.00)**
0-1	343	68	19.84 (15.64-25.16)	**6.20 (4.72-7.67)**	142	56	39.40 (30.32-51.20)	**8.19 (6.04-10.33)**
1-2	283	40	14.12 (10.36-19.25)	**3.97 (2.74-5.20)**	108	24	22.25 (14.92-33.20)	**4.54 (2.72-6.36)**
2-5	574	74	12.89 (10.27-16.19)	**2.43 (1.87-2.98)**	193	33	17.09 (12.15-24.03)	**2.17 (1.43-2.91)**
>5	576	69	11.98 (9.46-15.17)	**1.75 (1.33-2.16)**	173	15	8.66 (5.22-14.36)	1.23 (0.61-1.85)
NHNV								
Overall	8748	338	3.86 (3.47-4.30)	1.07 (0.96-1.18)	2205	126	5.72 (4.80-6.81)	1.18 (0.97-1.38)
0-1	1136	51	4.49 (3.41-5.91)	**2.43 (1.76-3.10)**	309	20	6.48 (4.18-10.04)	**2.13 (1.20-3.06)**
1-2	1064	35	3.29 (2.36-4.58)	**1.58 (1.05-2.10)**	281	17	6.05 (3.76-9.72)	1.73 (0.91-2.55)
2-5	2669	98	3.67 (3.01-4.48)	1.20 (0.96-1.44)	677	37	5.47 (3.96-7.55)	1.20 (0.81-1.58)
>5	3879	154	3.97 (3.39-4.65)	0.94 (0.79-1.08)	938	52	5.55 (4.23-7.28)	1.15 (0.84-1.47)
-Proximal								
Overall	1775	137	7.72 (6.53-9.12)	**1.60 (1.33-1.87)**	601	56	9.31 (7.16-12.10)	**1.74 (1.28-2.19)**
0-1	275	26	9.45 (6.43-13.87)	**3.83 (2.36-5.30)**	96	12	12.45 (7.07-21.92)	**3.80 (1.65-5.96)**
1-2	250	15	6.00 (3.62-9.96)	**2.18 (1.08-3.28)**	84	10	11.96 (6.43-22.22)	**3.21 (1.22-5.20)**
2-5	593	43	7.25 (5.38-9.77)	**1.77 (1.24-2.31)**	190	15	7.88 (4.75-13.07)	1.46 (0.72-2.20)
>5	657	53	8.07 (6.16-10.56)	**1.41 (1.03-1.80)**	231	19	8.22 (5.24-12.89)	1.64 (0.90-2.37)
-Distal								
Overall	6972	201	2.88 (2.51-3.31)	0.87 (0.75-1.00)	1603	70	4.37 (3.46-5.52)	0.94 (0.72-1.16)
0-1	860	25	2.91 (1.96-4.30)	**1.76 (1.07-2.45)**	212	8	3.77 (1.88-7.53)	1.28 (0.39-2.17)
1-2	814	20	2.46 (1.59-3.81)	1.31 (0.73-1.88)	198	7	3.54 (1.69-7.43)	1.04 (0.27-1.81)
2-5	2076	55	2.65 (2.03-3.45)	0.96 (0.71-1.21)	486	22	4.52 (2.98-6.87)	1.06 (0.62-1.51)
>5	3222	101	3.13 (2.58-3.81)	0.80 (0.64-0.95)	707	33	4.67 (3.32-6.57)	0.99 (0.65-1.32)

Bolded rates are significant at $p<0.05$

Table 3. Multivariable adjusted mortality risk following subsequent fracture by gender and initial fracture type in the fracture cohort

	Women			Men		
Fracture types	**Subsequent fracture (n)**	**Deaths (n)**	**Hazard ratios* (95%CI)**	**Subsequent fracture (n)**	**Deaths (n)**	**Hazard ratios* (95%CI)**
Any subsequent fracture	403	167	**1.89 (1.52-2.35)**	68	39	**1.77 (1.16-2.71)**
Hip						
-single fracture only		188	**2.15 (1.69-2.73)**		110	**2.22 (1.55-3.18)**
-subsequent fracture	94	63	**3.07 (2.25-4.20)**	23	18	**3.05 (1.72-5.42)**
Proximal NHNV						
-single fracture only		95	**1.66 (1.28-2.16)**		44	**1.88 (1.25-2.81)**
-subsequent fracture	80	42	**2.01 (1.39-2.91)**	20	12	1.28 (0.66-2.49)
Distal NHNV						
-single fracture only		139	Referent group		61	Referent group
-subsequent fracture	229	62	**1.42 (1.05-1.91)**	25	9	1.33 (0.71-2.49)

*Adjusted for age, BMI, comorbidities, marital status, general health condition, education level, smoking, alcohol intake and physical activity

Table 4. Impact of fractures on mortality by gender and fracture type

	Women		Men	
Fracture types	**PIN***	**CIN***	**PIN**	**CIN**
Any fracture	373 (254-611)	10 (7-16)	449 (316-724)	15 (11-23)
Hip	549 (406-789)	15 (11-21)	548 (387-816)	18 (13-26)
NHNV	1222 (591-18331)	31 (16-456)	1695 (818-11653)	53 (26-358)
-Proximal	1646 (960-3841)	42 (25-96)	2014 (1157-4410)	63 (37-136)
-Distal	N/A*	N/A	N/A	N/A

*PIN= population impact number and their 95% confidence intervals, PIN is the number of those in the whole population amongst whom one death is attributable to fracture.
*CIN= cases impact number and their 95% confidence intervals, CIN is the number of those who died amongst whom one case is attributable to fracture.
N/A= not applicable because distal fractures were not si