# Burden of hip fracture using disability-adjusted life-years: a pooled analysis of prospective cohorts in the CHANCES consortium

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## Summary

**Background** No studies have estimated disability-adjusted life-years (DALYs) lost due to hip fractures using real-life follow-up cohort data. We aimed to quantify the burden of disease due to incident hip fracture using DALYs in prospective cohorts in the CHANCES consortium, and to calculate population attributable fractions based on DALYs for specific risk factors.

**Methods** We used data from six cohorts of participants aged 50 years or older at recruitment to calculate DALYs. We applied disability weights proposed by the National Osteoporosis Foundation and did a series of sensitivity analyses to examine the robustness of DALY estimates. We calculated population attributable fractions for smoking, body-mass index (BMI), physical activity, alcohol intake, type 2 diabetes and parity, use of hormone replacement therapy, and oral contraceptives in women. We calculated summary risk estimates across cohorts with pooled analysis and random-effects meta-analysis methods.

**Findings** 223 880 men and women were followed up for a mean of 13 years (SD 6). 7724 (3·5%) participants developed an incident hip fracture, of whom 413 (5·3%) died as a result. 5964 DALYs (27 per 1000 individuals) were lost due to hip fractures, 1230 (20·6%) of which were in the group aged 75–79 years. 4150 (69·6%) DALYs were attributed to disability. Current smoking was the risk factor responsible for the greatest hip fracture burden (7·5%, 95% CI 5·2–9·7) followed by physical inactivity (5·5%, 2·1–8·5), history of diabetes (2·8%, 2·1–4·0), and low to average BMI (2·0%, 1·4–2·7), whereas low alcohol consumption (0·01–2·5 g per day) and high BMI had a protective effect.

**Interpretation** Hip fracture can lead to a substantial loss of healthy life-years in elderly people. National public health policies should be strengthened to reduce hip fracture incidence and mortality. Primary prevention measures should be strengthened to prevent falls, and reduce smoking and a sedentary lifestyle.

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## Introduction

Mortality has been traditionally the most common indicator for evaluation of the burden of disease in a population.[1] However, large increases in life expectancy in the past few decades have led to the development of new summary measures of population health, such as the disability-adjusted life-year (DALY), which accounts not only for mortality, but also for morbidity and quality of life.[2] One DALY can be interpreted as a year in a perfect state of health lost due to a disease. DALYs were introduced in 1993, and have been used since by WHO, the Global Burden of Disease (GBD) collaborators, and others to estimate and compare the burden of diseases and injuries worldwide.[3]

Osteoporotic fractures are common in elderly people (aged ≥65 years), and are an important cause of mortality and morbidity, especially in high-income countries.[4] Hip fracture is the most serious form of osteoporotic fracture because of the resulting high mortality, disability, need for long-term institutional care, and associated high medical costs.[5,6] In 2000, an estimated 1·6 million hip fractures occurred worldwide, and this number is expected to increase to 6·3 million by 2050.[7] Hip fractures are more prevalent in northern Europe and the USA and less prevalent in Africa and South America, with Asian countries lying somewhere between.[8] However, in the past two decades, the incidence seems to have stabilised in high-income countries, but increased in Asian countries.[7] Two studies of aggregated modelled national data have estimated the burden of disease due to hip fractures using DALYs. One of these studies was done in Iran[9] and the other was a global study showing that an estimated 1·75 million DALYs were lost globally in 1990 due to hip fractures, representing 0·1% of the total burden of disease.[5] However, no studies have calculated the burden of disease using real-life follow-up cohort data. Therefore,

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See Online for appendix

## Research in context

### Evidence before the study

We searched PubMed from 1966, to Sept 30, 2016, for published articles that investigated the burden of hip fractures using disability-adjusted life-years (DALYs), and for articles estimating population attributable fractions on the basis of DALYs for specific hip fracture risk factors. We identified two relevant studies. One of these studies was done in Iran and the other was a global study showing that an estimated 1·75 million DALYs were lost due to hip fractures, representing 0·1% of the total burden of disease, the largest part of which was in high-income countries. However, no publications calculated the burden of disease using cohort data or calculated population attributable fractions for risk factors causing loss of healthy life-years due to hip fracture.

### Added value of this study

To our knowledge, this study is the first to estimate DALYs lost due to hip fractures using data from prospective cohorts, and population attributable fractions for hip fracture risk factors. In a large cohort consortium of middle-aged and elderly Europeans and North Americans, we used real-life follow-up data to prospectively estimate hip fracture incidence, mortality, distribution of risk factors and confounding variables. 5964 DALYs (27 per 1000 individuals) were lost due to hip fractures. Disability was the predominant component of DALYs. Current smoking was the risk factor responsible for the greatest hip fracture burden followed by physical inactivity and history of diabetes.

### Implications of all the available evidence

Our findings suggest that hip fractures are an important cause primarily of disability, but also mortality, among middle-aged and older adults. Considerable opportunities exist to ameliorate the burden of hip fractures via a focus on treatments that will facilitate a rapid and complete recovery. Primary prevention measures should be strengthened to prevent falls, and individuals should be encouraged to avoid smoking and a sedentary lifestyle.

we estimated DALYs due to hip fracture in a large cohort consortium of middle-aged and elderly Europeans and North Americans, and calculated population attributable fractions for several risk factors.

## Methods

### Study design and participants

CHANCES is a consortium of 14 cohorts from Europe and the USA that was established in 2010 to produce evidence on determinants of healthy ageing in the elderly population.[10] Data for the present study were provided from six cohorts (the Cohort Of Swedish Men [COSM], European Prospective Investigation into Cancer and Nutrition [EPIC]-Elderly, Epidemiological Study on Chances of Prevention, Early Recognition and Optimised Treatment of Chronic Diseases in the Older Population [ESTHER], Nurses' Health Study [NHS], Swedish Mammography Cohort [SMC], and Tromsø Study) that had information about incident hip fractures. We included only participants aged 50 years or older at recruitment. The appendix p 1 shows detailed information about this consortium, its component studies, the harmonisation process across the cohorts, and the hip fracture assessment methods. All participants provided written informed consent and approval for the study was obtained from the ethics committees at the participating institutions.

### Estimation of disability-adjusted life-years

The DALY is a measure of overall disease burden that combines years lost due to premature mortality (years of lost life [YLL]) and years of healthy life lost due to disability (YLD).[11] To calculate the YLL, we multiplied the number of deaths due to incident hip fracture by the expected life-years remaining at the respective age of death on the basis of the Coale and Demeny model life table, West level 26.[3] To calculate the YLD, we multiplied the number of incident hip fracture cases by the duration of the disease (recorded after fracture) and a disability weight, which reflects the severity of the disease, ranging from 0 (perfect health) to 1 (death). We also calculated the ratio of YLD to YLL to show the relative difference between the two quantities. We calculated DALYs overall and separately by sex, age group (5 year groups), and participating cohort.

Besides the mortality that is directly attributed to a hip fracture, the increased all-cause excess mortality in the first year after a hip fracture has been suggested to be partly attributable to existing comorbidities, and about 25% of the all-cause mortality can be attributed to the hip fracture itself,[12] which we used in our calculations. We used the disability weights proposed by the National Osteoporosis Foundation, assigning a weight of 0·468 for the first year after the fracture, 0·17 for the second year, and discounting the weight by 10% per year for subsequent years.[13,14]

We did sensitivity analyses to examine the effect of the aforementioned assumptions in the final results. We explored different values for the excess mortality attributed to hip fractures (ie, 50%, 100%, and no excess mortality),[5] and used different disability weights as proposed in the initial GBD study,[3] the modifications proposed by Bertram and colleagues,[15] and the disability weights proposed in the Netherlands burden of disease study.[16] The estimation of DALYs traditionally includes two social value functions, an age-weighting function, and a time discount rate (3%); we did sensitivity analyses to assess the effect of omitting these functions.

### Estimation of population attributable fractions

We calculated population attributable fractions with the generalised Greenland formula,[17] which measured the proportion of hip fracture incidence in the population that can be attributed to an exposure. We used eight known or strongly suspected risk factors of hip fracture, including cigarette smoking, alcohol consumption, body-mass index (BMI), physical activity, type 2 diabetes and parity, use of hormone replacement therapy (HRT), and oral contraceptives in women. Information about assessment of these risk factors is provided in the appendix. Cox proportional hazard models were implemented to estimate the hazard ratios (HRs) and the 95% CIs by cohort for the association between the aforementioned risk factors with both the incidence and mortality of hip fractures. The HRs for hip fracture incidence were used in the calculation of population attributable fractions for YLD, whereas the HRs for mortality were used in the calculations for YLL. Those two quantities were added and then divided by the total number of DALYs to obtain the overall population attributable fractions. All the statistical models were stratified by sex and age at recruitment, and were mutually adjusted for the examined risk factors.

The models for the reproductive factors were further adjusted for age at first full-term pregnancy, breast-feeding, and menopausal status, and premenopausal women were excluded in the model for HRT. Proportionality of hazards was verified by examination of the slope of the Schoenfeld residuals. Missing values were set into separate categories and missing indicators were included in the models.

We calculated summary risk estimates across cohorts with pooled analysis and random-effects meta-analysis methods. We assessed heterogeneity between studies with the Cochran Q test and the $I^2$ statistic. All statistical analyses were done with Stata (version 11), and the population attributable fractions were calculated with the punafcc command.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

After exclusion of 1131 individuals with prevalent hip fractures, 223 880 participants from six cohorts were followed up for an average of 13 years. Table 1 shows the study and participant characteristics at recruitment. The mean age at recruitment was more than 60 years for all cohorts. The difference between the numbers of women (N=170 911) and men (N=52 969) recruited is because the large NHS and SMC cohorts recruited only women. The proportion of individuals with a BMI of less than 21·5 kg/m² at recruitment ranged from 4·9% in ESTHER to 11·4% in NHS. Regarding lifestyle factors, the proportion of current smokers ranged from 12·8% in EPIC-Elderly to 31% in Tromsø. About 80% of study participants in SMC and COSM exercised vigorously, whereas the proportion ranged from 11% to 42% in the remaining cohorts. The proportion of women who had ever used oral

| | EPIC-Elderly* (n=13 227) | ESTHER (n=9853) | Tromsø (n=10 014) | NHS (n=115 713) | SMC (n=36 777) | COSM (n=38 296) |
|---|---|---|---|---|---|---|
| Recruitment period | 1992–99 | 2000–02 | 1994–95 | 1976–77 | 1987–90 | 1997 |
| Follow-up time (years) | 10·9 (3·8) | 11 (2·3) | 13·2 (4·4) | 13·9 (6·9) | 13·6 (NR) | 13 (NR) |
| Age (years) | 65·5 (5·0) | 62·1 (6·6) | 62·9 (9·6) | 61 (0·7) | 62·6 (9·0) | 62·8 (8·5) |
| Sex | | | | | | |
| Female | 7722 (58·3%) | 5420 (55·0%) | 5279 (52·7%) | 115 713 (100%) | 36 777 (100%) | 0 |
| Male | 5505 (41·6%) | 4433 (45·0%) | 4735 (47·3%) | 0 | 0 | 38 296 (100%) |
| BMI (kg/m²) | | | | | | |
| <18·5 | 74 (0·6%) | 48 (0·5%) | 133 (1·3%) | 1200 (1%) | NR† | NR† |
| 18·5–21·5 | 592 (4·5%) | 432 (4·4%) | 846 (8·4%) | 11 996 (10·4%) | NR | NR |
| 21·5–25 | 2542 (19·2%) | 2220 (22·5%) | 3146 (31·4%) | 31 535 (27·2%) | NR | NR |
| 25–30 | 5535 (41·8%) | 4632 (47%) | 4342 (43·4%) | 34 456 (29·8%) | NR | NR |
| 30–35 | 3261 (24·7%) | 1931 (19·6%) | 1251 (12·5%) | 15 068 (13%) | NR | NR |
| ≥35 | 1158 (8·7%) | 574 (5·8%) | 266 (2·7%) | 7849 (6·8%) | NR | NR |
| Unknown | 65 (0·5%) | 16 (0·2%) | 30 (0·3%) | 13 609 (11·8%) | NR | NR |
| Smoking status | | | | | | |
| Current | 1686 (12·8%) | 1631 (16·6%) | 3108 (31%) | 17 038 (14·7%) | 8199 (22·3%) | 9148 (23·9%) |
| Former | 2500 (18·9%) | 3160 (32%) | 3558 (35·5%) | 44 700 (38·6%) | 8116 (22·1%) | 14 941 (39%) |
| Never | 8665 (65·5%) | 4793 (48·7%) | 3338 (33·4%) | 49 696 (43%) | 19 663 (53·5%) | 13 622 (35·6%) |
| Unknown | 376 (2·8%) | 269 (2·7%) | 10 (0·1%) | 4279 (3·7%) | 799 (2·1%) | 585 (1·5%) |

(Table 1 continues on next page)

| | EPIC-Elderly* (n=13 227) | ESTHER (n=9853) | Tromsø (n=10 014) | NHS (n=115 713) | SMC (n=36 777) | COSM (n=38 296) |
|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | |
| Current alcohol consumption (g per day) | | | | | | |
| 0 | 3854 (29·1%) | 2884 (29·3%) | 4856 (48·5%) | 34 942 (30·2%) | NR | NR |
| 0·01–2·5 | 4249 (32·1%) | 965 (9·8%) | 1948 (19·5%) | 19 896 (17·2%) | NR | NR |
| 2·5–5 | 1391 (10·5%) | 1278 (13%) | 1296 (12·9%) | 9301 (8%) | NR | NR |
| 5–10 | 1559 (11·8%) | 1722 (17·5%) | 1120 (11·2%) | 9613 (8·3%) | NR | NR |
| 10–15 | 574 (4·4%) | 907 (9·2%) | 424 (4·2%) | 8197 (7·1%) | NR | NR |
| ≥15 | 1575 (11·9%) | 1145 (11·6%) | 265 (2·7%) | 10 545 (9·1%) | NR | NR |
| Unknown | 25 (0·2%) | 952 (9·6%) | 105 (1%) | 23 219 (20·1%) | NR | NR |
| Vigorous physical activity | | | | | | |
| Yes | 2008 (15·2%) | 4136 (42%) | 3222 (32·2%) | 13 141 (11·4%) | 29 901 (81·3%) | 31 572 (82·4%) |
| No | 7678 (58%) | 5687 (57·7%) | 6676 (66·7%) | 86 972 (75·2%) | 1813 (4·9%) | 2373 (6·2%) |
| Unknown | 3541 (26·8%) | 30 (0·3%) | 116 (1·1%) | 15 600 (13·4%) | 5063 (13·8%) | 4351 (11·4%) |
| Diabetes | | | | | | |
| Yes | 1521 (11·5%) | 1069 (10·8%) | 364 (3·6%) | 8100 (7%) | 1571 (4·3%) | 2722 (7·1%) |
| No | 11 636 (88%) | 8213 (83·4%) | 9611 (96%) | 107 613 (93%) | 35 206 (95·7%) | 35 574 (92·9%) |
| Unknown | 70 (0·5%) | 571 (5·8%) | 39 (0·4%) | 0 | 0 | 0 |
| Age at first full-term pregnancy (years) | 24·5 (4·6) | 23·3 (4.1) | 32·9 (9.4) | 25·2 (3·4) | 23·9 (4·7) | NA |
| Ever had a full-term pregnancy | | | | | | |
| Yes | 6523 (84·5%) | 4691 (86·6%) | 4086 (77·4%) | 106 309 (91·9%) | 32 730 (89%) | NA |
| No | 608 (7·9%) | 729 (13·4%) | 383 (7·3%) | 6865 (5·9%) | 4047 (11%) | NA |
| Unknown | 591 (7·6%) | 0 (0%) | 810 (15·3%) | 2539 (2·2%) | 0 | NA |
| Ever breastfed‡ | | | | | | |
| Yes | 4911 (75·3%) | 3091 (65·9%) | 3587 (87·8%) | 58 238 (54·8%) | NR | NA |
| No | 423 (6·5%) | 1572 (33·5%) | 156 (3·8%) | 33 620 (31·6%) | NR | NA |
| Unknown | 1189 (18·2%) | 28 (0·6%) | 343 (8·4%) | 14 451 (13·6%) | NR | NA |
| Ever used oral contraceptives | | | | | | |
| Yes | 602 (7·8%) | 2988 (55·1%) | 791 (15%) | 49 552 (42·8%) | 15 047 (40·9%) | NA |
| No | 6649 (86·1%) | 2286 (42·2%) | 2110 (40%) | 60 616 (52·4%) | 20 289 (55·2%) | NA |
| Unknown | 471 (6·1%) | 146 (2·7%) | 2378 (45%) | 5545 (4·8%) | 1441 (3·9%) | NA |
| Ever used HRT | | | | | | |
| Yes | 571 (7·4%) | 2391 (48·5%) | 1244 (23·6%) | 68 724 (59·4%) | 16 886 (45·9%) | NA |
| No | 6571 (85·1%) | 2626 (44·1%) | 2517 (47·7%) | 32 384 (28%) | 18 434 (50·1%) | NA |
| Unknown | 580 (7·5%) | 403 (7·4%) | 1518 (28·7%) | 14 605 (12·6%) | 1457 (4%) | NA |
| Menopausal status | | | | | | |
| Premenopausal | 0 | 146 (2·7%) | 304 (5·8%) | 0 | 2942 (8%) | NA |
| Perimenopausal | 0 | 1134 (20·9%) | 195 (3·7%) | 0 | 0 | NA |
| Postmenopausal | 7722 (100%) | 4013 (76·4%) | 4780 (90·5%) | 115 713 (100%) | 33 316 (90·6%) | NA |
| Unknown | 0 | 0 | 0 | 0 | 519 (1·4%) | NA |

Data are mean (SD) or n (%), unless otherwise specified. EPIC=European Prospective Investigation into Cancer and Nutrition. ESTHER=Epidemiological Study on Chances of Prevention, Early Recognition and Optimised Treatment of Chronic Diseases in the Older Population. NHS=Nurses' Health Study. SMC=Swedish Mammography Cohort. COSM=Cohort of Swedish Men. NR=not reported. BMI=body-mass index. NA=not applicable. HRT=hormone replacement therapy. *EPIC-Greece and EPIC-Umea are included. †The SMC and COSM studies did not provide information about BMI and alcohol. ‡Among parous women only.

***Table 1*: Study and participant characteristics at recruitment by cohort**

contraceptives ranged from 7·8% in EPIC-Elderly to 55·1% in ESTHER, and the proportion who used HRT ranged from 7·4% in EPIC-Elderly to 59·4% in NHS.

A total of 7724 incident cases of hip fracture and 413 deaths were identified (table 2). The largest age-standardised incidence was recorded in the Tromsø study, whereas mortality was highest in SMC (table 2). In the three cohorts that included both sexes, the incidence was roughly two times higher in women than in men.

Amongst the total CHANCES population over the 13 year follow-up period, the number of DALYs lost was 5964, of which 70% was attributed to YLD rather than YLL (table 3). DALYs were three times higher in women than in men, whereas the proportion of DALYs attributed

to YLD was 52% in men and 75% in women (table 3). The group aged 70–74 years had the largest absolute number of lost YLDs, whereas the group aged 80–84 years had the largest number of lost YLLs (table 3). The contribution of YLDs to the total number of DALYs was highest in the youngest age groups, ranging from over 80% in participants aged 50–69 years to 44% in those older than 85 years (table 3).

The appendix shows the results of the sensitivity analyses after removal of the age-weighting and discounting functions, and adoption of different disability weights and excess mortality values. When the age-weighting and discounting functions were removed, the number of DALYs increased from 5964 to 11145, and the YLD to YLL ratio decreased from 2·29 to 1·56 (appendix p 3). When the excess mortality due to hip fracture was increased from 25% to 50%, the total number of DALYs increased to 6582 (appendix p 3). The most conservative approach for assignment of disability weights was that proposed by the initial GBD study,[3] which produced 2279 DALYs and increased to 3860 DALYs when the results of a review made by Bertram and colleagues[15] were included in the analysis (appendix p 4). When the disability weights from Netherlands burden of disease study were used,[16] the calculated DALYs were 4344 (appendix p 4). The appendix presents these results in further detail by sex, age group, and cohort.

The appendix provides the HRs and 95% CIs for the association of the risk factors with hip fracture incidence and mortality by cohort, sex, and overall after pooling and meta-analysis of the data from the six participating cohorts. The HRs from the pooled analyses and the meta-analyses were in high agreement (appendix pp 18–23). The results were similar when participants with missing information for any of the risk factors were excluded (data not shown). Table 4 depicts the population attributable fractions for risk factors that were statistically significant in the meta-analysis. Tobacco smoking was the risk factor responsible for the greatest hip fracture burden, followed by abstinence from vigorous physical activity (table 4). Diabetes and no use of HRT in women accounted for estimates of population attributable fractions of about 3% (95% CI 2–4) and 4% (2–6), respectively (table 4). Low BMI had a small effect, with estimates of population attributable fractions of 2% (95% CI 1–3) for a BMI of 18·5–21·5 kg/m² and 0·5% for a BMI lower than 18·5 kg/m² compared with a BMI of 21·5–25 kg/m² (table 4). By contrast, a BMI larger than 25 kg/m² had protective effects (table 4). Being overweight or obese was responsible for a reduction in DALYs that ranged from 7·2% (95% CI 4–11·2) for participants with a BMI of 25–30 kg/m², to 24·1% (14·4–32·9) for those with a BMI greater than 35 kg/m² (table 4). Low alcohol consumption (0·01–2·5 g/day) likewise led to a reduction in DALYs of 4·8% (95% CI 2·4–7·2; table 4). When we did the analysis separately by sex, alcohol consumption and BMI were no longer statistically significant in men, whereas in women the magnitude and direction of the risk estimates were similar to the overall population results (table 4). None of the remaining studied factors (ie, parity and oral contraceptive use) was significantly associated with hip fracture incidence or mortality.

| | EPIC-Elderly* | ESTHER | Tromsø | NHS | SMC | COSM |
|---|---|---|---|---|---|---|
| **Total** | | | | | | |
| Cases | 318 (290) | 104 (88) | 554 (563) | 2666 (167·2) | 2549 (531·8) | 1533 (287·9) |
| Deaths | 5 (8·3) | 1 (0·6) | 0 | 97 (6) | 145 (30·8) | 165 (30·2) |
| **Men** | | | | | | |
| Cases | 78 (138) | 37 (62·5) | 186 (473) | NA | NA | 1533 (287·9) |
| Deaths | 3 (10·4) | 0 | 0 | .. | .. | 165 (30·2) |
| **Women** | | | | | | |
| Cases | 240 (423) | 67 (107) | 368 (616) | 2666 (167·2) | 2549 (513·5) | NA |
| Deaths | 2 (6·9) | 1 (1) | 0 | 97 (6) | 145 (29·7) | .. |

Data in parentheses are age-standardised incidence per 100 000 person-years. EPIC=European Prospective Investigation into Cancer and Nutrition. ESTHER=Epidemiological Study on Chances of Prevention, Early Recognition and Optimised Treatment of Chronic Diseases in the Older Population. NHS=Nurses' Health Study. SMC=Swedish Mammography Cohort. COSM=Cohort of Swedish Men. NA=not applicable. *EPIC-Greece and EPIC-Umea are included.

***Table 2*: Hip fracture incidence and mortality**

| | Cases | Deaths | YLD | YLL | DALYs | YLD:YLL | YLD:DALYs |
|---|---|---|---|---|---|---|---|
| Total | 7724 | 413 | 4150 | 1814 | 5964 | 2·29 | 0·7 |
| Sex | | | | | | | |
| Male | 1834 | 168 | 758 | 704 | 1462 | 1·08 | 0·52 |
| Female | 5890 | 245 | 3392 | 1110 | 4502 | 3·06 | 0·75 |
| Age group (years) | | | | | | | |
| 50–59 | 82 | 1 | 109 | 25 | 134 | 4·36 | 0·81 |
| 60–64 | 501 | 5 | 577 | 81 | 658 | 7·12 | 0·88 |
| 65–69 | 874 | 11 | 785 | 129 | 914 | 6·09 | 0·86 |
| 70–74 | 1264 | 30 | 886 | 263 | 1149 | 3·37 | 0·77 |
| 75–79 | 1664 | 70 | 839 | 391 | 1230 | 2·15 | 0·68 |
| 80–84 | 1853 | 136 | 636 | 525 | 1161 | 1·21 | 0·55 |
| ≥85 | 1486 | 160 | 318 | 400 | 718 | 0·8 | 0·44 |

Disability weights were 0·468 for the first year after the fracture, 0·17 for the second year, then discounted by 10% per year for subsequent years, as proposed by the National Osteoporosis Foundation.[14] In the calculation of DALYs, we assumed that 25% of the deaths due to any cause within a year after the hip fracture were causally related. However, the table shows only the number of deaths directly linked to a hip fracture. YLD=years of life lost due to disability. YLL=years of life lost due to premature mortality. DALY=disability-adjusted life-year.

***Table 3*: DALYs for hip fracture**

## Discussion

In this study of a large cohort consortium of middle-aged and older individuals in Europe and the USA followed up for 13 years, the burden of disease due to hip fracture was 5964 DALYs or 27 DALYs per 1000 individuals, which translates to an average loss of 2·7% of the healthy life expectancy in this population. Disability predominated over mortality. Smoking, physical inactivity, and history of diabetes were the main risk factors responsible for the hip fracture burden, whereas high BMI and low alcohol consumption lessened the burden.

| | PAF (95% CI) |
|---|---|
| **Overall** | |
| Smoking (current *vs* never) | 7·5% (5·2 to 9·7) |
| Alcohol (no current use *vs* 0·01–2·5 g per day) | 4·8% (2·4 to 7·2) |
| BMI (kg/m²) | |
| <18·5 *vs* 21·5–25 | 0·56% (0·4 to 0·64) |
| 18·5–21·5 *vs* 21·5–25 | 2·0% (1·4 to 2·7) |
| 25–30 *vs* 21·5–25 | −7·2% (−11·2 to −4·0) |
| 30–35 *vs* 21·5–25 | −13·6% (−19·2 to −7·2) |
| ≥35 *vs* 21·5–25 | −24·1% (−32·9 to −14·4) |
| Vigorous activity (no *vs* yes) | 5·5% (2·1 to 8·5) |
| Diabetes (yes *vs* no) | 2·8% (2·1 to 4·0) |
| **Men** | |
| Smoking (current *vs* never) | 7·0% (4·5 to 9·0) |
| Vigorous activity (no *vs* yes) | 3·1% (2·0 to 4·4) |
| Diabetes (yes *vs* no) | 3·0% (1·6 to 4·5) |
| **Women** | |
| Smoking (current *vs* never) | 6·5% (4·6 to 8·6) |
| Alcohol (no current use *vs* 0·01–2·5 g per day) | 4·9% (2·4 to 7·3) |
| BMI (kg/m²) | |
| <18·5 *vs* 21·5–25 | 0·57% (0·5 to 0·65) |
| 18·5–21·5 *vs* 21·5–25 | 2·1% (1·4 to 2·9) |
| 25–30 *vs* 21·5–25 | −8·2% (−12·2 to −4·0) |
| 30–35 *vs* 21·5–25 | −14·7% (−20·4 to −7·3) |
| ≥35 *vs* 21·5–25 | −24·5% (−33·5 to −14·7) |
| Vigorous activity (no *vs* yes) | 1·2% (0·8 to 1·6) |
| Diabetes (yes *vs* no) | 2·1% (1·8 to 2·5) |
| Ever had HRT (no *vs* yes) | 3·8% (1·7 to 5·8) |

The risk factors were modelled with indicator variables, with the group of participants with the lowest expected population risk for hip fracture or death as the reference category. PAFs only for statistically significant risk factors are presented here. Negative values represent protective associations on the basis of the initial risk factor modelling, which were then reversed keeping the negative value to denote the change in the reference groups. The Swedish Mammography Cohort (SMC) and Cohort of Swedish Men (COSM) cohorts did not provide information about BMI and alcohol, and were therefore excluded from the relevant analyses. PAF=population attributable fraction. BMI=body-mass index. HRT=hormone replacement therapy.

***Table 4*: Proportion of total DALYs for hip fracture attributable to risk factors overall and by sex**

These findings suggest that considerable opportunities exist for improvement of the health burden related to hip fractures in developed countries. National policies should be strengthened to reduce hip fracture incidence and mortality and to prevent disability. Our estimates differ from that calculated by Johnell and Kanis (6 DALYs per 1000 individuals) for established market economies in their global burden of disease study,[5] because we only included middle-aged and older adults and the estimation was based on incident cases. Thus, our results are not representative of the burden of disease due to prevalent and incident cases across all ages. Moreover, methodological differences in the calculation of DALYs exist between the studies.[5,9] Unlike previous studies, we used real-life follow-up data of several cohorts that enable the prospective calculation of hip fracture incidence, mortality, risk factor, and confounding variables. For comparison, the burden of hip fractures in our study was smaller than that of 87 DALYs lost per 1000 individuals due to lung cancer, but was similar to the 33 DALYs and 26 DALYs lost per 1000 individuals due to breast and pancreatic cancer, respectively, as reported in another study in the CHANCES consortium.[18]

Disability predominated over mortality in our study, which is in agreement with the global burden of disease study for established market economies.[5] In view of the crisis in the treatment of osteoporosis, whereby patients are refusing effective treatments because of rare side-effects or providers are refusing to prescribe them,[19] the need to consider the effects of hip fracture interventions on reducing disability from the disease (ie, via a second hip fracture) should be emphasised. Furthermore, the effect of disability on the total burden weakened as participants aged, which was confirmed by the findings of another study.[9] A plausible reason for this decline is that older individuals are more likely to die either from natural causes or due to a disease and therefore live fewer years with the disability. That the risk of death is higher for older individuals after a hip fracture is widely accepted.[12,20] Therefore, primary prevention strategies should focus on the elderly population.

To our knowledge, this study is the first to calculate population attributable fractions for major risk factors causing loss of healthy life-years due to hip fracture. Smoking was the predominant risk factor, followed by abstaining from vigorous physical activity, no use of HRT in women, and type 2 diabetes. Although we cannot verify these attributable fractions by comparison with other studies because of the scarcity of published similar reports, the observed risk estimates were generally concordant in magnitude and direction with literature evidence from published meta-analyses.[21–25] The calculation of attributable fractions was based on risk factor information collected at the baseline of each cohort and, although this approach has the advantage of measuring the risk factors at a period of causal relevance, it might not reflect present prevalence estimates of the risk factors.

Cohort studies and meta-analyses thereof have shown that low BMI increases the risk of hip fractures even after adjustment for bone mineral density.[21,22] The exact mechanisms explaining this relationship are not clear, but a suggestion is that a low BMI, even within the normal limits of BMI classification, is associated with bone loss and hence a higher likelihood of a fracture.[26] A second hypothesis suggests that adipose tissue around the hip area can absorb part of the impact during the fall and protect against the fracture.[27] In our analysis, the protective effect of high BMI was the largest among the different BMI categories; however,

recommendation of an increase in the BMI over 25 kg/m² is inappropriate because of the association with other morbidities.

Tobacco smoking is a well-known risk factor for hip fractures, acting mostly via the associated reduction in bone mineral density or through changes in circulating concentrations of oestradiol, parathyroid hormone, and vitamin D that consequently affect calcium absorption and proliferation of bone cells.[26] The results of the present study were in agreement with a pooled analysis of ten prospective cohorts, which estimated that current smoking yielded a 65% higher risk of hip fracture than never smoking (risk ratio 1·65, 95% CI 1·34–2·03).[23] Furthermore, we confirmed that vigorous physical activity, use of HRT, and absence of type 2 diabetes were inversely associated with risk of hip fractures.[24,28,29]

Abstinence from alcohol was positively associated with the risk of hip fracture compared with low alcohol consumption (in this study defined as 0·01–2·5 g/day). Unfortunately, we could not evaluate the effect of heavy alcohol consumption because only a small proportion of our study population belonged to that category. Our results were in partial agreement with a 2014 meta-analysis in which low alcohol consumption (0·01–12·5 g/day) was associated with a lower risk of hip fracture than no consumption (relative risk 0·88, 95% CI 0·83–0·89) and high consumption (≥50 g/day) was associated with a higher risk (1·71, 1·41–2·01).[25] Low alcohol consumption has been generally associated with increased bone mineral density, whereas heavy consumption has an adverse effect on bone health.[30]

Our study has some limitations. The calculation of DALYs depends on several assumptions, and our findings should therefore be interpreted with caution. We used disability weights for hip fractures proposed by the National Osteoporosis Foundation,[13] because they are suitable for countries within the established market economies, such as those participating in our study. We did not use the disability weights proposed by WHO in our main analysis, because they have been suggested to underestimate the short-term and long-term effect of hip fractures,[15] which was shown further in our sensitivity analyses. Moreover, our study included healthy volunteers participating in well-established prospective cohorts, who might not be representative of patients with hip fracture in the general population.

Few data are available for mortality due to hip fracture worldwide. Although hip fracture is not commonly directly noted as a cause of death, many studies have reported that elderly individuals in particular have an increased risk of death after a hip fracture.[31,32] Therefore, in order not to underestimate the true effect of hip fracture, we considered that 25% of the excess mortality after the hip fracture is causally related to the fracture itself.[12] This assumption was derived from a Swedish population and it might be logical to assume that in our study the excess mortality is similar. As expected, changing assumptions concerning the excess mortality (eg, 0, 25%, 50%, 100%) after hip fracture had an effect on DALYs. Interpretation of our main results should be conservative to avoid overestimation of the effect of the DALYs. In general, the calculation of DALYs in the present study was sensitive to the underlying assumptions, but such changes were expected and have been observed in previous global burden of disease studies.[5,9]

With these reservations, our study suggests that hip fractures are an important cause primarily of disability, but also mortality among middle-aged and older adults. Considerable opportunities exist to ameliorate the burden of hip fractures via a focus on treatments that will facilitate a rapid and complete recovery. Primary prevention measures should be also strengthened to prevent falls, and individuals should be encouraged to avoid smoking and a sedentary lifestyle.

#### Contributors

KKT, DT, and AT designed the study. NP and KKT did the statistical analysis in the EPIC-Elderly, ESTHER, Tromsø, and NHS studies, and wrote the first draft of the paper. AB did the analyses in the SMC and COSM studies. EEN, PO, VB, IS, AK-N, PB, DT, and AT formed the writing team and, together with NP and KKT, finalised the paper. All other authors provided the data and critically reviewed the manuscript. All authors have read and approved the final version submitted.

#### Declaration of interests

We declare no competing interests.

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