EXTENDED REPORT

The global burden attributable to low bone mineral density

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ABSTRACT

Introduction The Global Burden of Disease Study 2010 estimated the worldwide health burden of 291 diseases and injuries and 67 risk factors by calculating disability-adjusted life years (DALYs). Osteoporosis was not considered as a disease, and bone mineral density (BMD) was analysed as a risk factor for fractures, which formed part of the health burden due to falls.

Objectives To calculate (1) the global distribution of BMD, (2) its population attributable fraction (PAF) for fractures and subsequently for falls, and (3) the number of DALYs due to BMD.

Methods A systematic review was performed seeking population-based studies in which BMD was measured by dual-energy X-ray absorptiometry at the femoral neck in people aged 50 years and over. Age- and sex-specific mean ± SD BMD values (g/cm^2) were extracted from eligible studies. Comparative risk assessment methodology was used to calculate PAFs of BMD for fractures. The theoretical minimum risk exposure distribution was estimated as the age- and sex-specific 90th centile from the Third National Health and Nutrition Examination Survey (NHANES III). Relative risks of fractures were obtained from a previous meta-analysis. Hospital data were used to calculate the fraction of the health burden of falls that was due to fractures.

Results Global deaths and DALYs attributable to low BMD increased from 103 000 and 3 125 000 in 1990 to 188 000 and 5 216 000 in 2010, respectively. The percentage of low BMD in the total global burden almost doubled from 1990 (0.12%) to 2010 (0.21%). Around one-third of falls-related deaths were attributable to low BMD.

Conclusions Low BMD is responsible for a growing global health burden, only partially representative of the real burden of osteoporosis.

INTRODUCTION

Osteoporosis is a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of bone fractures.[1] Osteoporotic fractures are defined as those occurring as the result of a low-impact trauma, with consequences ranging from chronic pain to institutionalisation and death.[2–8] For people over 50 years of age living in a developed country, the lifetime risk of sustaining any fracture is ~50% for women and 20% for men.[9] Bone strength primarily reflects the integration of bone mineral density (BMD) and bone quality. The latter is awkward to assess on a population basis, while BMD is a well-defined predictor of fracture risk[10 11] and is easily measurable. For a clinical approach, osteoporosis is defined by a threshold of 2.5 SDs below the mean BMD value of the young reference.[12 13] However, the risk of fracture due to reduced BMD is gradual over a continuum.

This paper follows the comparative risk assessment (CRA) methodology in the Global Burden of Disease (GBD) Study 2010.[14] The two primary outcome measures for the GBD work are deaths and disability-adjusted life years (DALYs), which combine the years lived with disability (YLDs) and the years lost due to premature mortality (years of life lost due to premature mortality (YLLs)).[15] Burden estimates were made for 291 diseases and injuries.[15] The burden arising from 67 risk factors was estimated by determining population attributable fractions (PAFs).[14] Osteoporosis per se was not considered as a disease, and, for the first time, BMD was included in the global burden estimates as a risk factor for fractures, which represented a proportion of the global burden from falls. We summarise the methods used to calculate the contribution of low BMD to the burden of fractures due to falls and present estimates by age and sex by world region. We also document trends in attributable burden between 1990 and 2010. Estimates of burden were limited to populations aged 50 years and older, as osteoporotic fractures represent little burden at younger ages in the general population.

This report is part of the Musculoskeletal Expert Group series within the GBD 2010 Initiative.[14–18] Extended reports on the overall methods,[19] global burden of osteoarthritis,[20] rheumatoid arthritis,[21] gout,[22] low back pain,[23] neck pain,[24] occupationally related low back pain,[25] other musculoskeletal conditions[26] and final conclusions[27] have also been published.

METHODS

Definition of the exposure variable

We performed a systematic review of Medline, Embase, CAB Abstracts, CINAHL, WHOLIS and SIGLE databases for population-based studies published from 1980 to 2010 with BMD values in g/cm^2 measured by dual-energy X-ray absorptiometry (DXA) at the femoral neck (FN). In regions with limited data, we also included other types of study (eg, non-population-based) as long as the sample was considered to be representative of the

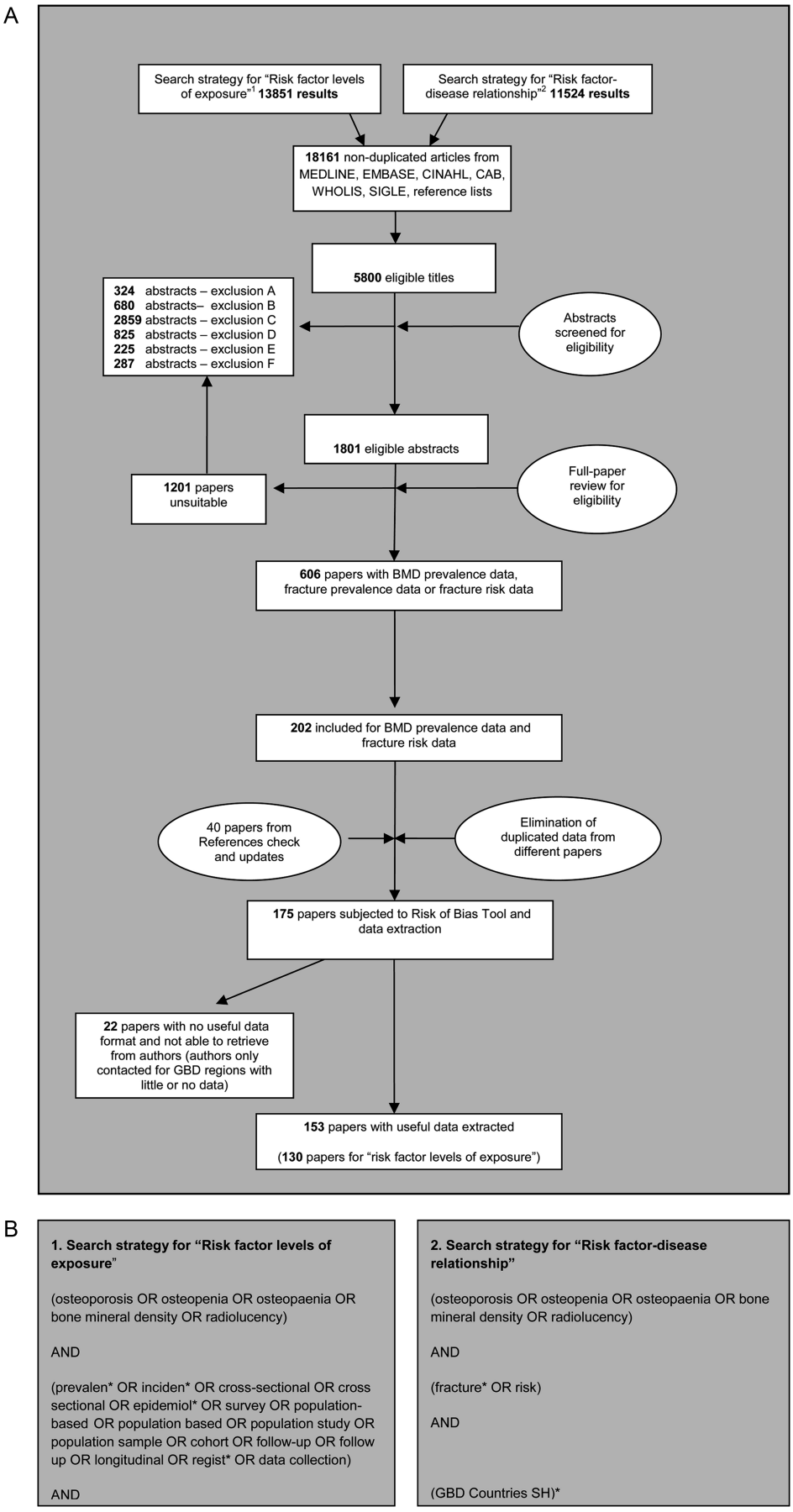

Figure 1 Summary for the Systematic Review for Low Bone Mineral Density as a Risk Factor. (A) Flowchart for the systematic review process. Exclusion criteria: A, subsample not representative of the population (ie, athletes); B, non-population-based studies (ie,clinical-based); C, no prevalence/incidence data; D, only subtypes of osteoporosis assessed (ie, steroid-induced osteoporosis); E, sample number <150; F, reviews. Final list of manuscripts used for BMD as the exposure variable can be found in Appendix 1, supplementary online file. (B) Search strategies for the systematic review. Search strategies are shown for BMD as the exposure variable (search strategy 1) and BMD as a risk factor for fractures (search strategy 2). *The whole list of the world countries was used as Subject Headings (SH) in Medline, Embase, CINAHL and CAB abstracts. GBD, global burden of disease; BMD, bone mineral density.

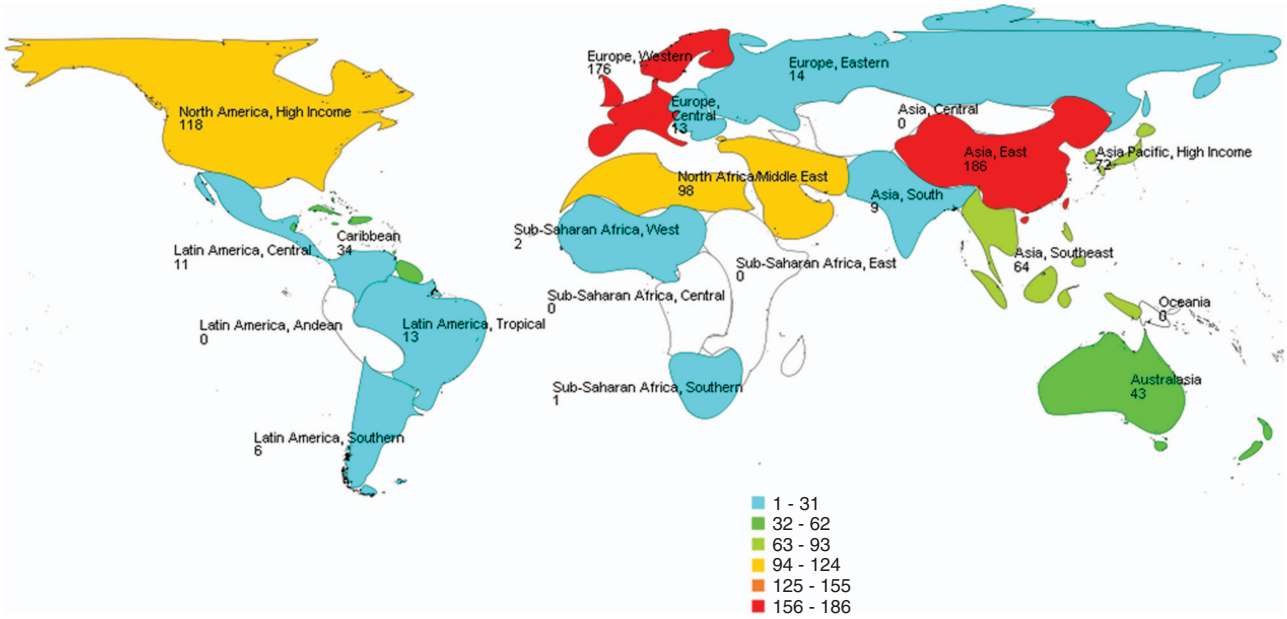

Figure 2 Number of data points of mean bone mineral density at the femoral neck measured by dual-X-ray absorptiometry by each of the 21 GBD world regions. All years (1980–2010), all ages, both sexes. Regions in white have no data. GBD, global burden of disease.

national population. Central DXA is the most validated technique for measuring BMD.[12 13] The location at the FN is justified by the evidence that the morbidity and mortality related to hip fracture (the osteoporotic outcome with the highest burden) is better predicted when BMD is measured at the FN rather than the spine or forearm.[11] Furthermore, measurement at the FN has been found to correlate well with vertebral and other osteoporotic fractures.[11]

Data extraction and processing

A database was developed and implemented in MS Excel, and information was extracted from included studies into the following predetermined fields for the exposure variable: region, country, year of publication, study type, study sample size, population description, coverage, urbanicity (rural, urban or both), start year of data collection, last year of data collection, age group start, age group end, sex, ethnicity, DXA manufacturer, DXA FN-specific coefficient of variation, and mean BMD value in g/cm^2 and SD.

All mean BMD and SD values with different DXA manufacturers (mainly Hologic, Norland and Lunar) were standardised using an international conversion formula[28] to standardise mean BMD (sBMD) and SD (sSD).

Finally, a systematic data-cleaning process was performed to identify double-counted data and inconsistencies in the values.

Search strategies and results of the systematic review for the exposure variable are shown in figures 1A,B and 2, respectively.

Modelling strategy

Eligible articles were assessed for bias using a modified version of a validated Risk of Bias (RoB) tool[29] developed for prevalence studies and adapted for osteoporosis.[30] For selection bias, the risk was considered low when most recruited subjects were included, moderate when only healthy subjects were included, and high when subjects with prior fractures were excluded. The RoB tool was not found to have significant predictive value,[30] and, consequently, all studies after the data-cleaning process were included.

As data were available for only selected country–time periods, the mean sBMD and sSD was estimated separately for all country–time periods using DisMod-MR, a Bayesian meta-regression tool developed specifically for GBD 2010.[17] The model included fixed effects for study-specific covariates, and random effects by GBD super-region, region and country. Study-specific covariates accounted for inconsistencies in the raw data—for example, data that were subnational (rather than nationally representative), or data that were collected in a non-gold-standard way (eg, non-population based). National-level covariates can be used in the model to inform the global and country-level trends, and are not study-specific; lag-distributed income per capita, mean body mass index, and availability of milk based on the Food and Agriculture Organization of the United Nations disappearance data (imports plus local production minus exports) were tested. None of these demonstrated a significant improvement in the predictive ability of the model and were therefore not included.

RELATIVE RISK ASSESSMENT: PAF OF LOW BMD TO FRACTURES

Effect size estimates

The estimates of relative risk (RR) for fractures were based on a meta-analysis of 12 population-based studies from Western Europe, USA, Canada, Japan and Australia published in 2005.[11] This study reported age- and sex-adjusted RRs for hip and non-hip fractures attributable to BMD. Our systematic review process also included searches for longitudinal population-based studies with data on RR of fracture related to FN BMD (figure 1). Data were heterogeneous in terms of BMD location measurement, fracture outcome and study design. Only eight relevant prospective studies[31–38] published since 2005 were found, with RR estimates similar to those published in the previous meta-analysis.[11]

The estimates of the gradient of risk (RR/SD) for BMD Z-scores, based on the combined data for men and women, were obtained from the authors of the meta-analysis.[11] The Z-score was established within each study population separately, which made the RRs dependent on the spread within the study

population. For our purposes this was undesirable, and therefore the 'relative' RR/SD values were converted into 'absolute' RR/0.1 g/cm^2 values (table 1) using a weighted average of the spread in BMD values for the populations that were represented in the meta-analysis, as they were estimated in the DisMod-MR output, and so derived risk estimates for men and women separately by 5-year age group.

Theoretical minimum risk exposure distribution and calculation of PAF

Comparative risk assessment (CRA) methodology[14 39] was used to estimate the proportion of fractures that are attributable to age- and sex-specific levels of BMD analysed as a continuous variable. CRA estimates are based on a counterfactual exposure distribution that would result in the lowest population risk that is theoretically possible, referred to as the theoretical minimum risk exposure distribution (TMRED).[40] The sex- and age-specific 90th percentile from the Third National Health and Nutrition Examination Survey (NHANES III),[41] the most broadly accepted standard international reference,[13] was chosen as the TMRED (table 2). The SD of the TMRED was estimated on the basis of the relationship between means and SDs from a regression of all studies in the final dataset that measured means and SDs of BMD.

Using the exposure distributions and the RR for fracture by BMD level defined above, PAFs were calculated[42] for hip fractures, non-hip vertebra fractures (fractures of vertebra occurring without hip fracture) and non-hip fractures, using the following formula:

$$\mathrm{PAF} = \frac{\int_{x=0}^{m} \mathrm{RR}(x)\mathrm{P}(x)dx - \int_{x=0}^{m} \mathrm{RR}(x)\mathrm{P}'(x)dx}{\int_{x=0}^{m} \mathrm{RR}(x)\mathrm{P}(x)dx}$$

where RR(x) is the RR at exposure level x, P(x) is the population distribution of exposure, P′(x) is the counterfactual distribution of exposure, and m the maximum exposure level.

Table 1 Relative risk (RR) of hip and non-hip fractures for each 0.1 g/cm^2 decrease in bone mineral density (BMD)

	RR/0.1 BMD unit decrease					
	Non-hip fractures			Hip fractures		
Age (years)	Mean	LCI	HCI	Mean	LCI	HCI
Men						
50–54	1.152	1.058	1.254	2.603	2.042	3.319
55–59	1.183	1.104	1.268	2.421	1.978	2.961
60–64	1.215	1.147	1.286	2.282	1.938	2.689
65–69	1.249	1.189	1.311	2.177	1.914	2.478
70–74	1.297	1.238	1.357	2.100	1.897	2.324
75–79	1.338	1.279	1.402	1.921	1.781	2.072
80+	1.371	1.302	1.444	1.730	1.627	1.840
Women						
50–54	1.158	1.061	1.265	2.697	2.096	3.470
55–59	1.201	1.114	1.296	2.629	2.109	3.278
60–64	1.237	1.162	1.317	2.466	2.062	2.951
65–69	1.286	1.216	1.358	2.412	2.084	2.792
70–74	1.342	1.274	1.413	2.315	2.064	2.596
75–79	1.398	1.327	1.475	2.118	1.942	2.311
80+	1.438	1.355	1.526	1.878	1.750	2.016

Values are RR of fracture per each 0.1 unit of BMD decrease. Units of BMD are g/cm^2. Adapted from Johnell *et al*.[11]
LCI, lower 95% CI; HCI, high 95% CI.

Table 2 Theoretical-minimum-risk exposure distribution (TMRED) for men and women aged 50 years and over

Age	Mean sBMD	SD
Women		
50–59	1.00	0.14
60–69	0.92	0.14
70–79	0.84	0.13
80+	0.78	0.13
Men		
50–59	1.09	0.16
60–69	1.06	0.16
70–79	1.02	0.16
80+	0.98	0.16

Values are expressed in g/cm^2 and correspond to the age- and sex-specific 90th centile of the mean BMD from NHANES III[41] after internationally recognised standardisation.[28]
sBMD, standardised bone mineral density.

HEALTH BURDEN OF FRACTURES AS A FRACTION OF FALLS

For attributing deaths to low BMD, the difficulty is that deaths are categorised according to cause of injury (ie, falls), not nature of injury (ie, fracture), and low BMD or osteoporosis is not coded as a cause. Fractures can be found as a consequence of many events such as road accident, assault or natural disasters. For the purposes of this analysis, estimates were restricted to fractures due to falls, where we expected most osteoporotic fractures to be coded. It was necessary to turn to hospital data from Brazil,[43] Canada,[44] Mexico[45] and the USA[46 47] to estimate the fraction of in-hospital deaths from falls that involved hip and vertebra fractures. Those with a mention of concurrent head or internal injury were excluded. Other fracture types were also excluded, as these were considered less likely to lead to death, as supported by an analysis of the Australian mortality database.[48] Among those inpatient deaths where the primary cause for admission was a fall, a large fraction, especially at older ages, involved a hip fracture; only a small proportion of deaths associated with a vertebral fracture were not also associated with a hip fracture (table 3). As this was the only data source used to determine the fraction of deaths from falls due to hip fracture or vertebra fracture, it was necessary to apply these age- and sex-specific proportions to falls to every country.

Disability from falls is estimated by the nature of the associated injury, and therefore the short- and long-term disability was estimated for fractures by site. The RRs for hip fracture

Table 3 Fraction of in-hospital deaths from falls involving hip and vertebra fractures

Sex	Age	Hip fracture (%)	Non-hip vertebra fracture (%)
Women	50–59	61.6	2.6
	60–69	73.2	1
	70–79	79.4	0.6
	80+	82.5	0.5
Men	50–59	46	8
	60–69	67.5	4.6
	70–79	79.8	0.9
	80+	84.2	0.4

Percentages express the fraction of in-hospital deaths from falls that involve hip fractures and non-hip vertebra fractures (deaths from vertebral fractures that occur without hip fracture). Calculated with in-patient hospital data from Brazil,[43] Canada,[44] Mexico[45] and the USA.[46 47]

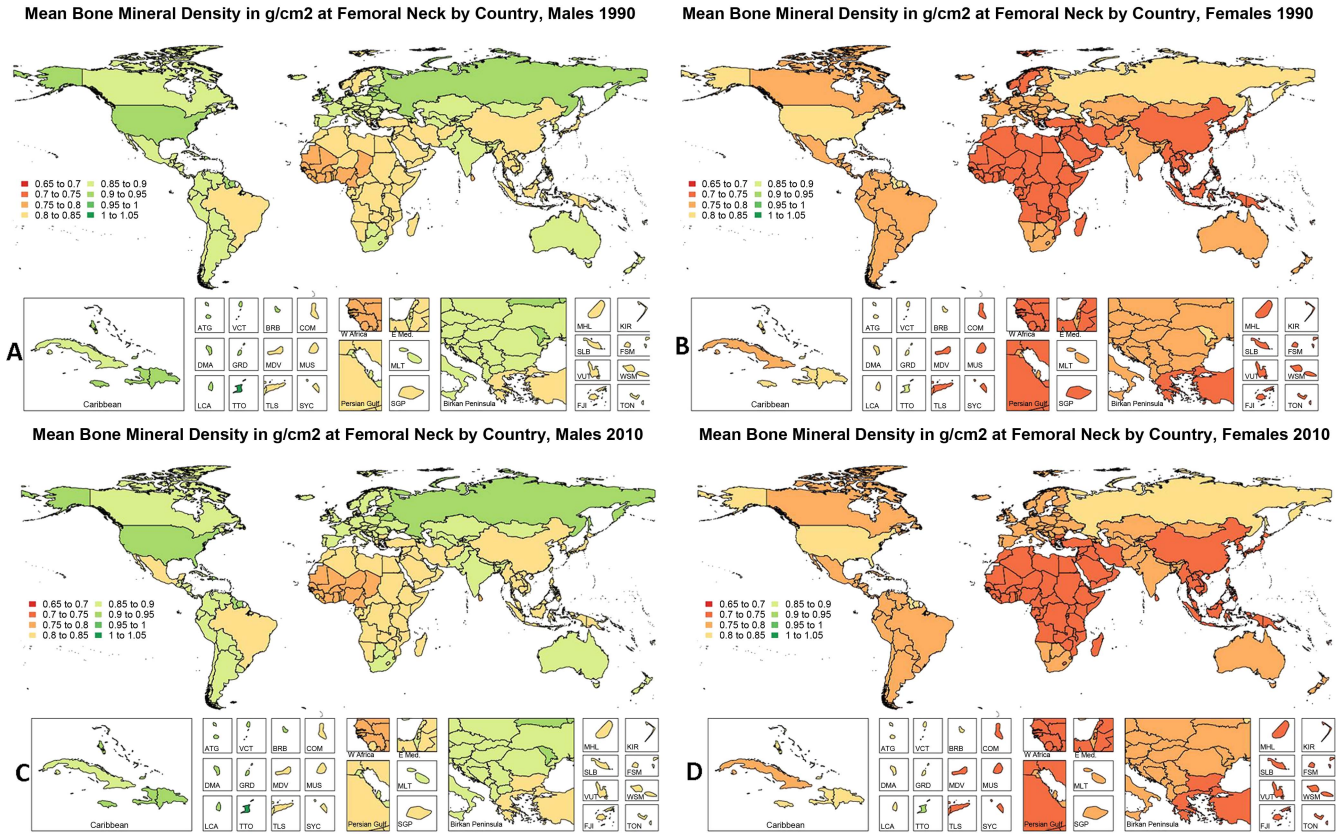

Figure 3 Word distribution of standardised bone mineral density in g/cm^2 at the femoral neck at country level. (A) Men, 1990; (B) women, 1990; (C) men, 2010; (D) women, 2010.

(table 1) were applied to the YLD estimates for hip fracture due to falls sub-cause. The RRs for non-hip fracture (table 1) were applied to YLD estimates for all other fracture sites known to be associated with osteoporosis (clavicle, scapula, humerus, skull, sternum, rib, face bone, radius or ulna, femur, patella, tibia, fibula, ankle, pelvis, vertebral, other extremities). Details on the disability weights for fracture types and methods used to calculate YLDs due to falls can be found elsewhere.[17 18]

RESULTS

There were 130 eligible articles (Appendix 1, supplementary online file), with a total of 860 data points from 49 countries and 17 world regions (figure 2). Worldwide distributions of mean BMD for people aged 50 years and over for 1990 and 2010 are shown in figure 3. Asia and Africa were the world regions with the lowest values of BMD at the FN, while high-income North America, Caribbean and Eastern Europe showed the highest BMD values for both men and women. Although age-adjusted data showed an improving trend for BMD values over time,[49] especially in Asia and Western Europe, BMD at a population level decreased in some regions as a result of the ageing of the population.

For all diseases, injuries and risk factors, data on DALYs, YLDs, YLLs and deaths can be seen online by region, country, year,

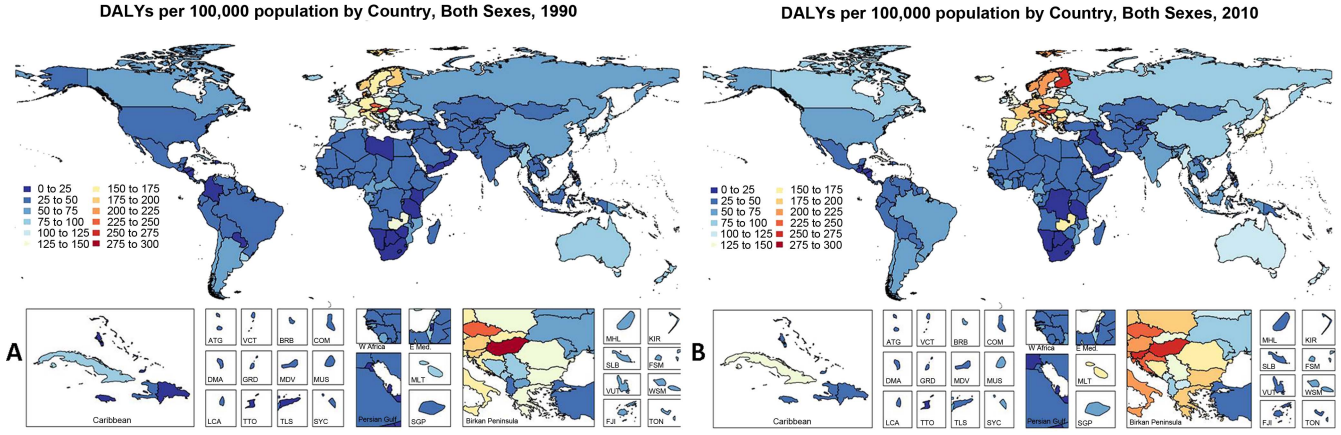

Figure 4 World distribution of disability-adjusted life years (DALYs) for low bone mineral density per 100 000 population at country level. All ages, both sexes. (A) Estimations for 1990; (B) estimations for 2010 (for all estimations for 1990, 2005 and 2010 for men and women at country, region and super-region levels, please visit http://www.healthmetricsandevaluation.org/gbd/visualizations/country).

Table 4 Global burden of low bone mineral density

Year	Sex	Deaths		DALYs		YLLs		YLDs	
		Absolute	Percentage	DALYs	Percentage	Absolute	Percentage	Absolute	Percentage
1990	Both	103 270 (90 672 to 124 230)	0.22 (0.20 to 0.27)	3 125 166 (2 588 901 to 3 811 443)	0.12 (0.10 to 0.15)	1 595 178 (1 411 360 to 1 944 972)	0.08 (0.07 to 0.10)	1 529 989 (1 044 409 to 2 121 696)	0.26 (0.19 to 0.34)
1990	Female	50 455 (40 408 to 62 110)	0.23 (0.19 to 0.29)	1 361 202 (1 101 627 to 1 685 725)	0.12 (0.10 to 0.14)	669 752 (543 744 to 809 200)	0.08 (0.07 to 0.10)	691 450 (468 513 to 989 670)	0.23 (0.16 to 0.31)
1990	Male	52 816 (43 822 to 69 605)	0.21 (0.18 to 0.28)	1 763 964 (1 448 305 to 2 207 969)	0.13 (0.11 to 0.16)	925 426 (771 153 to 1 221 801)	0.09 (0.07 to 0.12)	838 539 (569 103 to 1 184 753)	0.30 (0.22 to 0.39)
2005	Both	168 049 (125 643 to 194 351)	0.33 (0.24 to 0.37)	4 642 366 (3 674 161 to 5 641 433)	0.18 (0.15 to 0.22)	2 526 614 (1 859 581 to 2 932 549)	0.14 (0.10 to 0.16)	2 115 752 (1 446 478 to 2 971 623)	0.29 (0.21 to 0.38)
2005	Female	76 471 (51 059 to 91 865)	0.33 (0.22 to 0.39)	1 923 418 (1 465 495 to 2 382 540)	0.17 (0.13 to 0.21)	978 753 (648 292 to 1 172 601)	0.13 (0.09 to 0.15)	944 665 (637 877 to 1 337 991)	0.25 (0.18 to 0.33)
2005	Male	91 578 (59 947 to 108 685)	0.32 (0.21 to 0.39)	2 718 948 (2 020 242 to 3 341 576)	0.20 (0.15 to 0.24)	1 547 861 (1 016 485 to 1 848 546)	0.15 (0.10 to 0.18)	1 171 086 (794 783 to 1 671 341)	0.33 (0.24 to 0.44)
2010	Both	187 586 (140 636 to 219 906)	0.36 (0.27 to 0.42)	5 216 399 (4 132 978 to 6 418 307)	0.21 (0.17 to 0.25)	2 753 010 (2 031 594 to 3 242 599)	0.16 (0.12 to 0.19)	2 463 388 (1 699 328 to 3 490 237)	0.32 (0.23 to 0.41)
2010	Female	84 146 (57 863 to 102 441)	0.35 (0.25 to 0.43)	2 111 329 (1 627 353 to 2 618 461)	0.19 (0.15 to 0.23)	1 045 989 (725 341 to 1 267 368)	0.15 (0.10 to 0.18)	1 065 340 (719 873 to 1 496 345)	0.26 (0.19 to 0.35)
2010	Male	103 440 (67 743 to 124 596)	0.36 (0.24 to 0.43)	3 105 070 (2 295 173 to 3 830 642)	0.23 (0.17 to 0.28)	1 707 021 (1 089 516 to 2 077 040)	0.17 (0.11 to 0.21)	1 398 048 (961 318 to 1 998 927)	0.37 (0.27 to 0.49)

Values with 95% CI are expressed in absolute values and percentage of all GBD causes.
DALYs, disability-adjusted life years; GBD, global burden of disease; YLDs, years lived with disability; YLLs, years of life lost due to premature mortality.

age and sex (http://www.healthmetricsandevaluation.org/gbd/visualizations/country). Global deaths and DALYs attributable to low BMD increased from 103 000 and 3 125 000 in 1990 to 188 000 and 5 216 000 in 2010, respectively (table 4). The percentage of low BMD in the total global burden almost doubled from 1990 (0.12%) to 2010 (0.21%) (table 4). The fraction of the total regional burden increased in all regions except the Caribbean and Oceania. Asia East and South were the major contributors to the increase in global burden of low BMD. Rates of global DALYs per 100 000 population increased markedly from 1990 to 2010, but the increase was modest after age standardisation (table 5), which reflects population growth and ageing. Rates were higher in Western Europe, Central Europe and high-income Asia Pacific (figure 4 and table 5), while the highest age-standardised rates were more commonly found in developing regions such as Sub-Saharan Africa East and West, Oceania, Asia East and South (table 5).

The PAFs of BMD for falls were generally higher for women than men for both 1990 and 2010. In general, world regions with a low gross domestic product showed the highest PAFs (Asia East and South-East, North Africa-Middle East, Sub-Saharan Africa East and West), with the exception of Eastern Europe. However, big disparities in PAFs were observed among high-income countries, even within the same world region—for example, Scandinavian countries compared with UK (figure 5).

In 1990, global DALYs and deaths attributable to low BMD constituted 12.1% and 29.6% of all falls-related DALYs and deaths, respectively. These percentages increased slightly to 14.8% and 34.7% for 2010 estimates. Table 6 shows percentages of the falls burden due to low BMD by world region.

Low BMD ranked low in terms of attributable DALYs compared with most risk factors, such as dietary factors, high blood pressure, smoking, alcohol use, high fasting plasma glucose, high body mass index, high cholesterol and low physical activity (http://www.healthmetricsandevaluation.org/gbd/visualizations/gbd-heatmap). Globally, low BMD ranked 23rd among 25 risk factor categories for 2010 (dietary risk factors clustered into one category and occupational risk factors clustered into one category). By region, the highest ranks for low BMD were observed in Western Europe and high-income Asia Pacific, ranked 12th and 13th, respectively, followed by Central Europe, Australasia and high-income North America at 15th and Asia East at 16th.

DISCUSSION

Although age-adjusted data showed an improving trend of the global BMD values over time, the absolute burden of low BMD increased from 1990 to 2010, probably related to the global growth of the aged population. Higher age-standardised rates of DALYs and higher PAFs in developing regions probably reflect the importance of the potentially modifiable determinants of low BMD (such as nutritional factors and access to healthcare). Low BMD could be responsible for at least one-third of deaths attributable to falls, which is third in the list of major health burdens after road injuries and self-harm, as reported previously.[15] However, the contribution of low BMD to the global health burden compared with other risk factors was low, and it is likely that the burden of osteoporosis has been underestimated for several reasons.

First, the choice of an age- and sex-specific TMRED masked the important role of age and sex in fracture risk,[50] and it may explain in part the lower health burden of BMD compared with other risk factors. Given that the gradient of risk of fracture for each unit of BMD decrease is the same in men and women,[11] the use of the young female reference seems reasonable in clinical settings. In the GBD framework, however, risk factor

Table 5 Rates of DALYs per 100 000 population by GBD region in 1990 and 2010

	1990				2010			
Location	**All ages**		**Age-standardised**		**All ages**		**Age-standardised**	
Asia Pacific, high-income	80.79	(59.46 to 106.37)	65.85	(48.44 to 86.62)	138.31	(102.67 to 181.06)	63.43	(47.48 to 82.93)
Asia, Central	38.02	(26.64 to 50.90)	54.17	(37.79 to 72.72)	37.46	(26.80 to 52.41)	49.41	(35.15 to 69.01)
Asia, East	68.64	(56.02 to 84.10)	94.54	(77.36 to 116.21)	92.00	(72.58 to 113.50)	86.45	(68.28 to 106.73)
Asia, South	44.15	(32.85 to 59.10)	86.92	(65.52 to 115.84)	64.87	(42.01 to 88.54)	102.87	(66.89 to 140.05)
Asia, Southeast	45.39	(35.50 to 55.66)	85.71	(66.39 to 104.44)	62.48	(46.36 to 77.96)	84.81	(62.64 to 105.55)
Australasia	87.20	(60.27 to 124.09)	69.28	(48.18 to 98.00)	117.27	(79.24 to 164.28)	67.52	(44.60 to 94.86)
Caribbean	48.02	(35.73 to 60.13)	66.22	(49.20 to 83.01)	62.56	(46.94 to 79.73)	66.16	(49.74 to 84.60)
Europe, Central	154.51	(121.21 to 192.20)	121.69	(95.48 to 151.15)	187.81	(141.40 to 245.17)	108.44	(82.07 to 142.07)
Europe, Eastern	60.65	(39.77 to 86.20)	45.32	(29.78 to 64.35)	85.59	(54.13 to 118.30)	54.61	(34.90 to 75.23)
Europe, Western	140.64	(108.32 to 181.16)	83.04	(63.72 to 107.39)	183.26	(140.75 to 239.56)	85.86	(65.50 to 112.71)
Latin America, Andean	35.06	(25.74 to 45.51)	67.45	(49.50 to 87.44)	36.57	(27.09 to 48.39)	50.41	(37.37 to 66.73)
Latin America, Central	27.00	(21.75 to 33.29)	51.84	(41.80 to 63.95)	35.65	(28.15 to 43.87)	47.45	(37.43 to 58.41)
Latin America, Southern	63.37	(44.87 to 86.13)	64.96	(45.86 to 88.32)	63.86	(45.05 to 87.23)	50.92	(35.90 to 69.74)
Latin America, Tropical	29.45	(21.24 to 39.82)	52.47	(37.74 to 70.95)	56.82	(37.06 to 75.07)	63.95	(41.54 to 84.41)
North Africa/Middle East	30.78	(23.18 to 40.86)	66.54	(50.20 to 88.00)	37.45	(27.85 to 49.71)	60.63	(45.36 to 80.72)
North America, high-income	43.48	(28.23 to 59.15)	31.57	(20.62 to 42.99)	70.82	(43.07 to 99.00)	41.83	(25.21 to 58.36)
Oceania	56.02	(39.92 to 76.49)	147.40	(106.54 to 199.03)	41.21	(30.75 to 55.27)	91.17	(69.18 to 118.80)
Sub-Saharan Africa, Central	30.92	(23.39 to 39.60)	77.97	(59.17 to 99.77)	27.08	(20.45 to 35.20)	73.34	(55.58 to 95.12)
Sub-Saharan Africa, Eastern	37.20	(29.19 to 48.64)	96.50	(75.27 to 125.60)	42.24	(28.34 to 53.42)	103.90	(69.87 to 131.93)
Sub-Saharan Africa, Southern	15.51	(10.70 to 21.08)	36.91	(25.43 to 50.07)	22.20	(15.40 to 30.10)	38.17	(26.33 to 51.75)
Sub-Saharan Africa, Western	46.15	(37.28 to 56.03)	114.76	(92.56 to 138.91)	44.07	(36.03 to 52.63)	108.31	(87.83 to 130.19)
Global	58.95	(48.83 to 71.89)	77.89	(64.51 to 94.96)	75.71	(59.99 to 93.15)	79.87	(63.28 to 98.22)

Values with 95% CIs are rates of DALYs per 100 000 population. All ages, both sexes. Age standardisation was obtained using the global standard proposed by the WHO in 2001 (http://www.who.int/healthinfo/paper31.pdf).
DALYs, disability-adjusted life years; GBD, global burden of disease.

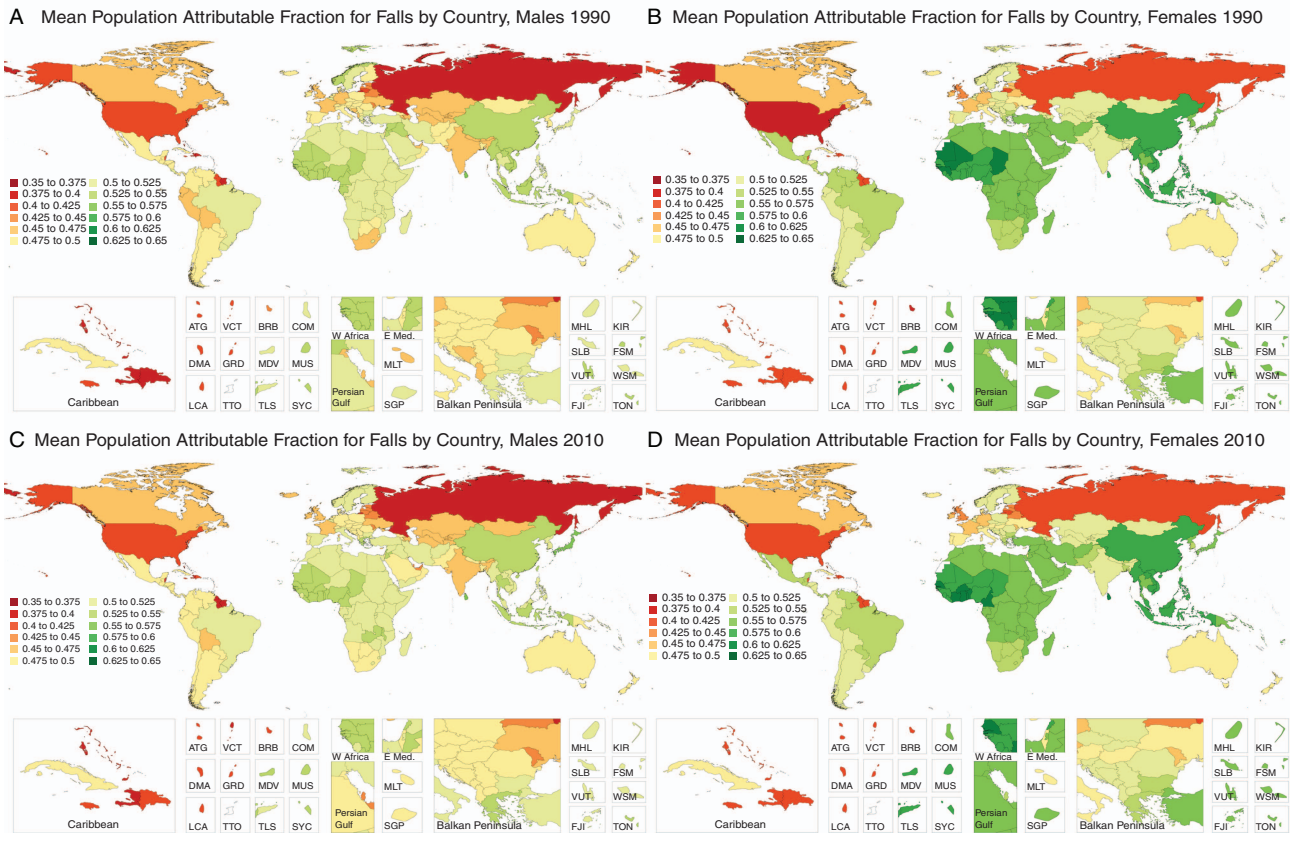

Figure 5 Age-standardized population attributable fraction (PAF) of low bone mineral density for falls. Values are expressed on 0–1 scale. (A) Men, 1990; (B) women, 1990; (C) men, 1990; (D) women, 2010. Age standardization was obtained using the global standard proposed by the WHO in 2001 (http://www.who.int/healthinfo/paper31.pdf).

Table 6 Burden of low bone mineral density as a percentage of falls-related burden by GBD region and year

Region	1990								2010							
	DALYs		YLLs		YLDs		Deaths		DALYs		YLLs		YLDs		Deaths	
Asia Pacific, high income	16.3	(13.6 to 19.3)	21.7	(18.8 to 25.8)	14.4	(11.4 to 17.6)	38.0	(33.3 to 42.9)	22.3	(18.8 to 25.8)	38.2	(32.1 to 42.6)	18.1	(14.7 to 21.5)	50.5	(44.3 to 55.6)
Asia, Central	8.0	(6.4 to 9.4)	4.9	(4.1 to 5.6)	9.7	(7.4 to 11.9)	12.7	(10.9 to 14.3)	8.5	(6.9 to 10.1)	6.0	(4.7 to 7.3)	9.7	(7.6 to 11.7)	14.0	(11.6 to 16.3)
Asia, East	13.7	(11.6 to 15.6)	14.6	(11.5 to 16.9)	12.7	(10.4 to 15.0)	32.8	(27.8 to 36.7)	17.5	(15.2 to 20.0)	21.8	(18.6 to 25.7)	14.1	(11.7 to 16.7)	39.7	(35.4 to 44.6)
Asia, South	8.9	(7.0 to 11.0)	9.1	(7.0 to 11.5)	8.7	(6.2 to 11.1)	21.6	(17.5 to 25.8)	11.9	(9.0 to 14.8)	13.7	(10.1 to 17.8)	9.2	(6.7 to 11.7)	28.3	(21.8 to 34.4)
Asia, Southeast	13.8	(11.6 to 16.2)	17.7	(14.0 to 21.6)	10.5	(8.7 to 12.4)	35.3	(30.3 to 40.8)	16.3	(13.6 to 19.1)	23.2	(19.3 to 26.8)	11.3	(9.3 to 13.3)	40.1	(35.1 to 44.9)
Australasia	15.0	(11.1 to 18.7)	27.2	(21.6 to 32.3)	12.7	(9.1 to 16.4)	40.5	(30.5 to 48.2)	17.3	(12.9 to 21.5)	35.2	(27.3 to 41.6)	14.3	(10.3 to 18.2)	44.3	(32.6 to 52.7)
Caribbean	13.6	(10.7 to 16.3)	19.0	(14.7 to 22.9)	9.4	(7.3 to 11.6)	36.8	(28.2 to 43.7)	12.6	(9.7 to 15.3)	24.8	(19.3 to 29.7)	8.3	(6.3 to 10.4)	40.3	(29.5 to 48.4)
Europe, Central	18.9	(16.0 to 21.8)	26.4	(23.2 to 29.4)	14.6	(12.0 to 17.5)	39.9	(34.2 to 44.7)	20.0	(16.9 to 23.2)	32.0	(28.1 to 35.2)	16.0	(13.2 to 19.0)	43.1	(37.1 to 47.8)
Europe, Eastern	11.1	(7.7 to 14.4)	13.8	(9.6 to 17.3)	9.7	(6.4 to 13.0)	24.0	(16.9 to 29.9)	12.7	(8.7 to 16.0)	16.1	(11.0 to 20.2)	10.3	(6.7 to 13.6)	25.9	(17.9 to 32.3)
Europe, Western	18.5	(15.8 to 21.3)	30.9	(27.0 to 34.8)	14.4	(12.1 to 16.6)	40.9	(34.6 to 46.7)	20.1	(17.0 to 23.1)	36.8	(32.5 to 40.6)	16.1	(13.4 to 19.1)	43.7	(37.1 to 48.9)
Latin America, Andean	9.3	(7.4 to 11.2)	9.6	(7.6 to 11.6)	9.1	(6.9 to 11.5)	23.4	(19.2 to 27.3)	11.7	(9.2 to 13.9)	13.4	(10.9 to 15.8)	10.8	(8.0 to 13.5)	30.2	(24.8 to 34.6)
Latin America, Central	11.0	(9.5 to 12.5)	11.4	(10.0 to 13.1)	10.5	(8.4 to 12.6)	27.5	(24.4 to 30.7)	14.7	(12.5 to 16.9)	18.7	(15.5 to 21.2)	11.5	(9.4 to 13.6)	36.1	(31.5 to 40.1)
Latin America, Southern	14.3	(10.9 to 17.5)	20.1	(16.2 to 23.8)	12.1	(8.6 to 15.6)	37.3	(29.8 to 43.1)	15.3	(12.0 to 18.7)	26.2	(21.1 to 30.8)	12.8	(9.8 to 16.0)	42.0	(33.1 to 49.0)
Latin America, Tropical	11.3	(9.1 to 13.6)	11.2	(9.0 to 14.0)	11.4	(8.8 to 14.2)	26.8	(21.8 to 32.1)	17.1	(12.9 to 20.8)	22.6	(15.8 to 27.2)	13.6	(10.3 to 16.8)	40.0	(31.7 to 46.9)
North Africa/Middle East	8.6	(7.3 to 10.0)	5.6	(4.2 to 7.0)	10.5	(8.8 to 12.2)	17.1	(13.6 to 20.7)	10.5	(9.1 to 11.9)	8.9	(7.8 to 10.3)	11.2	(9.4 to 13.1)	23.2	(20.8 to 26.0)
North America, high income	13.5	(9.4 to 17.4)	24.1	(17.3 to 30.2)	8.7	(5.7 to 11.6)	34.9	(23.1 to 43.7)	17.2	(11.4 to 22.7)	31.3	(21.8 to 39.1)	10.5	(7.0 to 13.8)	38.0	(25.0 to 47.1)
Oceania	10.2	(8.1 to 12.5)	9.2	(6.4 to 12.4)	10.8	(8.4 to 13.4)	20.9	(16.1 to 26.2)	10.7	(8.3 to 13.0)	11.6	(7.8 to 15.7)	10.0	(7.7 to 12.1)	24.5	(18.1 to 30.5)
Sub-Saharan Africa, Central	6.9	(4.0 to 12.0)	6.0	(2.6 to 14.3)	9.5	(7.4 to 11.7)	16.2	(8.7 to 30.7)	7.1	(4.6 to 11.0)	6.3	(3.1 to 13.0)	9.3	(7.3 to 11.4)	16.7	(9.9 to 28.7)
Sub-Saharan Africa, East	9.4	(6.2 to 13.1)	9.6	(5.4 to 15.0)	9.4	(7.8 to 11.0)	24.2	(15.9 to 32.0)	12.0	(9.0 to 14.4)	13.1	(8.8 to 16.2)	9.6	(8.0 to 11.4)	29.7	(22.8 to 33.9)
Sub-Saharan Africa, Southern	9.6	(7.2 to 11.8)	14.7	(11.3 to 18.2)	8.0	(5.9 to 10.2)	31.0	(24.5 to 37.1)	10.7	(8.4 to 13.1)	17.6	(13.8 to 21.7)	8.8	(6.5 to 11.0)	34.9	(28.0 to 41.3)
Sub-Saharan Africa, West	5.1	(3.3 to 9.1)	4.1	(2.6 to 8.7)	10.9	(8.9 to 13.0)	13.9	(9.8 to 23.1)	6.7	(5.1 to 9.0)	5.7	(4.1 to 8.4)	10.8	(9.0 to 12.6)	18.3	(14.0 to 23.7)
Global	12.1	(11.1 to 13.2)	12.7	(11.3 to 14.7)	11.5	(10.3 to 12.8)	29.6	(27.4 to 32.0)	14.8	(13.4 to 16.0)	17.3	(15.4 to 19.1)	12.7	(11.4 to 13.9)	34.7	(32.2 to 37.1)

Values with 95% CI represent low bone mineral density burden expressed as the percentage of falls-related burden. All ages, both sexes.
DALYs, disability-adjusted life years; YLDs, years lived with disability; GBD, global burden of disease; YLLs, years of life lost due to premature mortality.

analysis focuses on modifiable risk factors. The TMRED should be possible at the population level and supported by convincing epidemiological evidence of a continuous risk reduction to that exposure distribution.[16] Longitudinal studies[51 52] have demonstrated that a small percentage of older people can maintain their bone mass over time in the absence of risk factors for osteoporosis. However, the extent to which the differences in BMD observed by age and sex are modifiable is not certain. Men have a higher BMD than women, women show faster rates of bone loss after menopause than men,[52–54] and there is no definitive evidence that individuals can maintain their young peak bone mass as they age. There is also a significant genetic component to the ability to retain bone mass.[55 56] On the basis of this evidence, we used a TMRED that was age- and sex-specific. In order to enable worldwide comparisons, an international reference standard is recommended,[57] and the choice of an American reference (NHANES III) might lead to overestimates or underestimates of the risk depending on the world region. However, NHANES III is the reference used in the meta-analysis from which we derived the risk relationship between BMD and fractures.[11] Further research into the modifiability of BMD would help to inform the choice of TMRED.

Separating deaths due to specific fractures from overall deaths due to falls was not straightforward. Osteoporotic fractures are defined as those occurring as the result of a low-impact trauma, but hospital data on falls-related deaths did not include the nature of the injury. Our review did not find prospective population studies with data on mortality due to falls-related fractures covering both sexes and all ages over 50 years. Most of the studies reporting deaths from falls-related fractures were carried out retrospectively from medical charts and death certificates, or they were restricted to frail older populations. This made it difficult to determine what percentage of all falls in a population leads to a fracture-related death.

Hip fracture and clinical vertebral fractures have been shown to be the first and second most important sites, respectively, for osteoporotic fracture-related deaths.[5 58 59] For our mortality analysis, we used in-hospital data, and other fracture types were excluded, as they were less likely to be the underlying cause of death. However, this may have contributed to underestimation of the mortality burden given the evidence that other osteoporotic fracture sites are related to a higher risk of long-term mortality compared with age- and sex-matched peers.[5 60 61] A prospective population-based study conducted over an 18-year period in Australia[5] showed that the fall-fracture event was likely to be missed out as an underlying cause for some deaths that occurred a long time after the fall, particularly in non-hip and non-vertebral fractures. However, long-term mortality after fractures is tedious to interpret within the scope of the GBD Study. Previous studies have demonstrated that mortality is highly related to baseline frailty,[62–65] and it is hard to estimate what percentage of the excess mortality is really due to the fracture event.

As the exposure variable-measuring method, DXA is considerably more expensive and technically more complicated than measurement systems for other risk factors such as hypertension or body mass index. Consequently, the availability of DXA scans is limited,[66] leading to a possible selection bias towards countries with better access to DXA scans. Selecting the FN as the location of the fracture further restricted the number of papers that could be included. Furthermore, the application of standardisation equations among different DXA manufacturers[28] is unlikely to have removed all differences, especially between models from the same manufacturer.[67 68] In addition, BMD has low sensitivity in identifying fracture risk,[69] being purely a quantitative value that does not account for other mechanical properties known to influence bone strength, and consequently leading to an underestimation of the burden associated with osteoporosis.

Another important limitation is selection bias in the source studies. Most of the studies excluded subjects with a history of fracture, bone metabolism diseases, or receiving treatments that might affect bone metabolism. We expected to find discrepancies in the BMD values among different study groups depending on the exclusion or inclusion of such subjects, but linear regression models failed to prove this assumption. The reasons for this are not fully apparent, but it might be related to the heterogeneity among studies. We recommend including patients with previous fractures or a diagnosed bone disease in similar future studies. This is particularly important in elderly populations, as the percentage of individuals with a history of previous fragility fractures is high and excluding such subjects makes the sample not truly representative of the real population and underestimates the real risk.

CONCLUSION

This analysis demonstrates that low BMD is a growing global health burden. However, this is likely to reflect only a small part of the true burden of osteoporosis, given that BMD cannot reflect other important components of bone strength. For future studies of GBD, we strongly recommend a focus on osteoporosis as a disease rather than a risk factor. Health information systems should be better equipped to detect fragility fractures and long-term mortality related to them. The information provided could be used to better inform targeted clinical and public health prevention and management programmes.

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Contributors LSR was the leader for the Osteoporosis Working Group and led the writing of the article. EC, TV, SSL, RN, LV, DH, JMN and LM reviewed the different drafts of the article, sent comments and suggested changes. LSR performed most of the systematic review process and coordinated the extraction data team formed by ES, NW, MM, JSC, YL, NK, JMN, CSH and CK. DH, LSR, TV, LV, RN, JMN and LM developed the Risk of Bias Tool adapted to low bone mineral density as a risk factor in the GBD Study. LSR, LV, RN, EC, TV, LM and SSL developed the estimates of risk-specific exposure, theoretical-minimum-risk exposure distribution, and RR inputs, and checked and interpreted results. TV and SSL were members of the core team for the GBD Study and supervised all the estimates analysis. LM was the MSK Expert Group Leader and led the networking with world experts and supervised the overall work; ES and DH coordinated the Osteoporosis Working Team within the rest of the MSK Expert Group and the GBD Study Group.

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REFERENCES

1 NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;285:785–95.
2 Bertram M, Norman R, Kemp L, *et al*. Review of the long-term disability associated with hip fractures. *Inj Prev* 2011;17:365–70.
3 Naves Diaz M, Diaz Lopez JB, Rodriguez Rebollar A, *et al*. Effect of vertebral fracture on health related quality of life in a Spanish population older than 54 years. *Med Clin (Barc)* 2001;116:533–5.
4 Kaukonen JP, Karaharju EO, Porras M, *et al*. Functional recovery after fractures of the distal forearm. Analysis of radiographic and other factors affecting the outcome. *Ann Chir Gynaecol* 1988;77:27–31.
5 Bliuc D, Nguyen ND, Milch VE, *et al*. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;301:513–21.
6 Kanis JA, Oden A, Johnell O, *et al*. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int* 2004;15:108–12.
7 Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897–902.
8 Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726–33.
9 Sanders KM, Nicholson GC, Ugoni AM, *et al*. Health burden of hip and other fractures in Australia beyond 2000. Projections based on the Geelong Osteoporosis Study. *Med J Aust* 1999;170:467–70.
10 Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312:1254–9.
11 Johnell O, Kanis JA, Oden A, *et al*. Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 2005;20:1185–94.
12 WHO Study Group. *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis*. Geneva, Switzerland: World Health Organization, 1994.
13 Official positions. The International Society for Clinical Densitometry. 2007. http://www.iscd.org.
14 Lim SS, Vos T, Flaxman AD, *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–60.
15 Murray CJ, Vos T, Lozano R, *et al*. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2197–223.
16 The GBD Study 2010. http://www.globalburden.org.
17 Vos T, Flaxman AD, Naghavi M, *et al*. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2163–96.
18 Salomon JA, Vos T, Hogan DR, *et al*. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2129–43.
19 Hoy D, Smith E, Cross M, *et al*. The global burden of musculoskeletal conditions for 2010: an overview of methods. *Ann Rheum Dis* 2014;73:982–9.
20 Cross M, Smith E, Hoy D, *et al*. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1323–30.
21 Cross M, Smith E, Hoy D, *et al*. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1316–22.
22 Smith E, Hoy D, Cross M, *et al*. The global burden of gout: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1470–6.
23 Hoy D, March L, Brooks P, *et al*. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:968–74.
24 Hoy D, March L, Woolf A, *et al*. The global burden of neck pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1309–15.
25 Driscoll T, Jacklyn G, Orchard J, *et al*. The global burden of occupationally-related low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:975–81.
26 Smith E, Hoy D, Cross M, *et al*. The global burden of other musculoskeletal disorders: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1462–9.
27 Hoy D, Smith E, Blyth F, *et al*. Reflecting on the global burden of musculoskeletal conditions: lessons learnt, next steps. *Ann Rheum Dis* 2014; in press.
28 Lu Y, Fuerst T, Hui S, *et al*. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. *Osteoporos Int* 2001;12:438–44.
29 Hoy D, Brooks P, Woolf A, *et al*. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65:934–9.
30 Sanchez-Riera L, Wilson N, Hoy D, *et al*. Use of a quality assessment tool for a systematic review on osteoporosis prevalence. *Osteoporos Int* 2010;21(Suppl 1): S276.
31 Abrahamsen B, Vestergaard P, Rud B, *et al*. Ten-year absolute risk of osteoporotic fractures according to BMD T score at menopause: the Danish Osteoporosis Prevention Study. *J Bone Miner Res* 2006;21:796–800.
32 Hartl F, Tyndall A, Kraenzlin M, *et al*. Discriminatory ability of quantitative ultrasound parameters and bone mineral density in a population-based sample of postmenopausal women with vertebral fractures: results of the Basel Osteoporosis Study. *J Bone Miner Res* 2002;17:321–30.
33 Kung AW, Lee KK, Ho AY, *et al*. Ten-year risk of osteoporotic fractures in postmenopausal Chinese women according to clinical risk factors and BMD T-scores: a prospective study. *J Bone Miner Res* 2007;22:1080–7.
34 Lopes JB, Danilevicius CF, Takayama L, *et al*. Prevalence and risk factors of radiographic vertebral fracture in Brazilian community-dwelling elderly. *Osteoporos Int* 2011;22:711–19.
35 McLean RR, Jacques PF, Selhub J, *et al*. Plasma B vitamins, homocysteine, and their relation with bone loss and hip fracture in elderly men and women. *J Clin Endocrinol Metab* 2008;93:2206–12.
36 Blaizot S, Delmas PD, Marchand F, *et al*. Risk factors for peripheral fractures vary by age in older men—the prospective MINOS study. *Osteoporos Int* 2011;22:1755–64.
37 Jacobs JW, Da Silva JA, Armbrecht G, *et al*. Prediction of vertebral fractures is specific for gender and site of bone mineral density measurement. *J Rheumatol* 2010;37:149–54.
38 Cauley JA, Lui LY, Ensrud KE, *et al*. Bone mineral density and the risk of incident nonspinal fractures in black and white women. *JAMA* 2005;293:2102–8.
39 Ezzati M, Hoorn SV, Lopez AD, *et al*. Comparative Quantification of Mortality and Burden of Disease Attributable to Selected Risk Factors 2006.
40 Ezzati M, Hoorn SV, Lopez AD, *et al*. Comparative quantification of mortality and burden of disease attributable to selected risk factors. *Source: global burden of disease and risk factors*. Washington, DC: World Bank, 2006. Chapter 4, pp 241–68.
41 Looker AC, Wahner HW, Dunn WL, *et al*. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int* 1998;8:468–86.
42 Barendregt JJ, Veerman JL. Categorical versus continuous risk factors and the calculation of potential impact fractions. *J Epidemiol Community Health* 2010;64:209–12.
43 Ministry of Health (Brazil). Brazil Hospital Information System 2006–2009.
44 Canadian Institute for Health Information (CIHI). Canada Discharge Abstract Database 1994–2009.
45 Ministry of Health (Mexico). Mexico Ministry of Health Hospital Discharges 2000–2009.
46 Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality (AHRQ). United States State Inpatient Databases 2003–2008.
47 National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), US Census Bureau. United States National Hospital Discharge Survey 1979–2009.
48 http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3303.0Main+Features12003?OpenDocument
49 Sanchez-Riera L, Wilson N, Kamalaraj N, *et al*. Osteoporosis and fragility fractures. *Best Pract Res Clin Rheumatol* 2010;24:793–810.
50 Kanis JA, Johnell O, Odén A, *et al*. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int* 2001;12: 989–95.
51 Cauley JA, Lui LY, Barnes D, *et al*. Successful skeletal aging: a marker of low fracture risk and longevity. The Study of Osteoporotic Fractures (SOF). *J Bone Miner Res* 2009;24:134–43.
52 Burger H, de Laet CE, van Daele PL, *et al*. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. *Am J Epidemiol* 1998;147:871–9.
53 Yoshimura N, Kinoshita H, Danjoh S, *et al*. Bone loss at the lumbar spine and the proximal femur in a rural Japanese community, 1990–2000: the Miyama study. *Osteoporos Int* 2002;13:803–8.
54 Jones G, Nguyen T, Sambrook P, *et al*. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. *BMJ* 1994;309:691–5.
55 Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. *J Bone Miner Res* 1997;12:2076–81.
56 Harris M, Nguyen TV, Howard GM, *et al*. Genetic and environmental correlations between bone formation and bone mineral density: a twin study. *Bone* 1998;22: 141–5.

57 Kanis JA, McCloskey EV, Johansson H, *et al*. A reference standard for the description of osteoporosis. *Bone* 2008;42:467–75.
58 Ioannidis G, Papaioannou A, Hopman WM, *et al*. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. *CMAJ* 2009;181:265–71.
59 Browner WS, Pressman AR, Nevitt MC, *et al*. Mortality following fractures in older women. The study of osteoporotic fractures. *Arch Intern Med* 1996;156: 1521–5.
60 Morin S, Lix LM, Azimaee M, *et al*. Mortality rates after incident non-traumatic fractures in older men and women. *Osteoporos Int* 2011;22:2439–48.
61 Melton LJ III, Achenbach SJ, Atkinson EJ, *et al*. Long-term mortality following fractures at different skeletal sites: a population-based cohort study. *Osteoporos Int* 2013;24:1689–96.
62 Patel KV, Brennan KL, Brennan ML, *et al*. Association of a modified frailty index with mortality after femoral neck fracture in patients aged 60 years and older. *Clin Orthop Relat Res* 2014;472:1010–17.
63 Ensrud KE, Ewing SK, Taylor BC, *et al*. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* 2007;62:744–51.
64 Cawthon PM, Marshall LM, Michael Y, *et al*. Frailty in older men: prevalence, progression, and relationship with mortality. *J Am Geriatr Soc* 2007;55:1216–23.
65 Tosteson AN, Gottlieb DJ, Radley DC, *et al*. Excess mortality following hip fracture: the role of underlying health status. *Osteoporos Int* 2007;18:1463–72.
66 International Osteoporosis Foundation. Osteoporosis in the European Union in 2008. 10 years of progress and on-going challenges. 2008. http:// wwwiofbonehealthorg/publications/eu-policy-report-of-2008html
67 Barthe N, Braillon P, Ducassou D, *et al*. Comparison of two Hologic DXA systems (QDR 1000 and QDR 4500/A). *Br J Radiol* 1997;70:728–39.
68 Henzell S, Dhaliwal SS, Price RI, *et al*. Comparison of pencil-beam and fan-beam DXA systems. *J Clin Densitom* 2003;6:205–10.
69 Siris ES, Chen YT, Abbott TA, *et al*. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 2004;164:1108–12.