Estimating the Direct Economic Burden of Osteoporotic Fractures in a Multinational Study: A Real-World Data Perspective

Alireza Moayyeri, MD, PhD[1]; Hector Sanz, PhD[2]; Joshua Warden, MSc[1]; Siin Kim, PhD[3]; Hae Sun Suh, PhD[3]; Rafael Pinedo-Villanueva, PhD[4]; Nicholas C. Harvey, PhD[5]; Jeffrey R. Curtis, MD, MPH[6]; Stuart Silverman, MD, FACP, FACR[7]; Eric J. Yeh, PhD[8]

[1]UCB Pharma, Slough, UK; [2]IQVIA, Falls Church, Virginia, USA; [3]Kyung Hee University, Seoul, South Korea; [4]University of Oxford, Oxford, UK; [5]University of Southampton, Southampton, UK; [6]University of Alabama at Birmingham, Birmingham, Alabama, USA; [7]Cedars-Sinai Medical Center, Los Angeles, California, USA; [8]Amgen Inc. Thousand Oaks, California, USA

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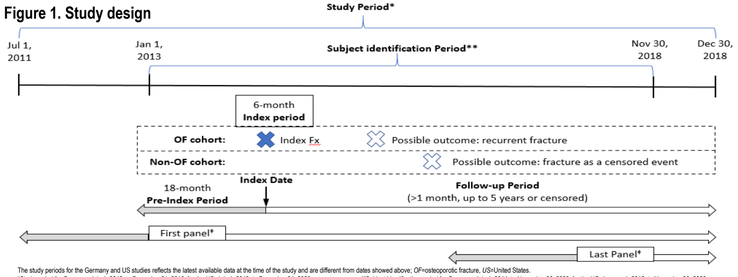
Background & Objective

- It is challenging to assess economic burden of osteoporotic fractures (OF) across countries, partially due to differences in country-specific healthcare and payer systems, socioeconomic determinants of health, geopolitical factors, national wealth, health status of the population, as well as differences across studies in fracture sites of interest, data availability and methodology
- We used a standardized methodology to assess the direct economic burden of OF in women aged >50 years in Australia, Germany, South Korea, Spain and the US

Study Design & Methods

Figure 1. Study design



The study periods for the Germany and US studies reflects the latest available data at the time of the study and are different from dates showed above; OF=osteoporotic fracture, US=United States.
*Study period for Germany: July 1, 2013, to December 31, 2018; for the US: July 1, 2013, to December 31, 2020. ; **Subject identification period for Germany: July 1, 2014, to November 30, 2020; for the US: January 1, 2015, to November 30, 2020.
†There were 12 panels during the subject identification period, each panel had 6-month panel to identify subjects, except the last panel which had a 5-month period to allow a 1-month follow-up period.

- Propensity Score Matching (1 OF to 3 non-OF cohorts) was based on multivariate logistic regression with the following baseline characteristics: geographic region, race/ethnicity (if available), pre-index use of glucocorticoid, hormone replacement therapy, anti-osteoporosis drugs, residence (i.e., living at home or in an institution), Charlson Comorbidity Index, comorbidities (osteoporosis diagnosis, cardiac disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, diabetes, depression, anxiety), and number of pre-index hospitalizations
- All-cause healthcare resource utilization (HCRU) and costs are presented as a rate on per person-year basis as the frequency of utilizations or total costs divided by the total follow-up time (in years) contributed by each woman; costs are presented in 2021 USD (US) or 2018 USD (other countries), adjusted by country-specific consumer price index
- The adjusted rate ratio (OF vs. non-OF) was assessed using negative binomial regression models with log-link function and person-years as offset for all-cause HCRU person-year rates, or generalized linear models with gamma distribution and log-link function for all-cause costs; both adjusted for baseline characteristics with a standardized difference ≥10% after matching and residence at index date

Table 1. Baseline demographic and clinical characteristics

Country		Australia		Germany		South Korea		Spain		US	
Cohort		OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF
N		4,809	13,921	11,452	34,090	47,238	134,813	25,214	75,308	193,262	570,864
Age, mean (SD)		75.4 (11.6)	75.3 (11.7)	76.6 (10.1)	76.7 (10.0)	71.2 (11.1)	70.8 (11.1)	73.3 (11.9)	73.2 (11.9)	63.3 (9.2)	63.1 (9.2)
Follow-up, months, median (Q1-Q3)		31 .0 (15.0-49.0)	33 .0 (16.0-51.0)	26.5 (13.1-40.2)	24.6 (12.3-38.4)	34.6 (16.9-52.6)	35.0 (17.4-52.8)	34.0 (16.0-52.0)	32.0 (16.0-50.0)	18.1 (7.9-34.2)	19.1 (8.6-35.6)
Glucocorticoids		11.3%	11.3%	14.3%	12.4%	57.3%	55.4%	4.8%	4.5%	36.5%	35.5%
HRT		13.9%	15.7%	9.9%	9.2%	5.1%	4.3%	0.1%	<0.1%	6.2%	5.6%
OP med		6.4%	8.0%	5.9%	5.7%	19.8%	17.9%	10.7%	10.4%	7.1%	7.1%
CCI	0-1	92.8%	93.6%	55.4%	54.0%	57.0%	58.5%	74.1%	72.0%	81.9%	82.9%
	2-3	6.3%	5.7%	35.6%	35.6%	30.6%	30.0%	21.8%	23.5%	13.9%	13.2%
	>3	0.9%	0.8%	9.0%	10.3%	12.3%	11.6%	4.1%	4.5%	4.2%	3.9%
OP diagnosis		21.6%	22.9%	4.6%	4.2%	15.0%	13.3%	3.9%	3.9%	11.3%	11.2%
Cardiac disease		23.7%	27.8%	81.6%	85.2%	59.1%	58.7%	18.5%	17.8%	52.7%	53.7%
CeVD		5.6%	6.3%	22.9%	24.2%	18.0%	17.9%	2.5%	2.6%	7.7%	7.6%
Diabetes		12.5%	14.8%	8.9%	8.4%	29.4%	27.9%	4.1%	4.2%	16.4%	16.0%
Fall		9.7%	5.6%	NA	NA	0.1%	0.1%	7.4%	1.9%	7.7%	3.0%
Index OF	Hip	26.2%	NA	32.7%	NA	8.5%	NA	12.5%	NA	7.9%	NA
	Vertebral	5.9%	NA	18.7%	NA	42.4%	NA	18.1%	NA	11.9%	NA
	Radius-Ulna	29.2%	NA	11.2%	NA	30.4%	NA	24.0%	NA	31.4%	NA
	Others	38.7%	NA	37.4%	NA	18.7%	NA	45.4%	NA	48.8%	NA

CCI=Charlson Comorbidity Index, CeVD= cerebrovascular disease; HRT= hormone replacement therapy, NA=not available, OF=osteoporotic fracture, OP= osteoporosis, Q1=25th percentile, Q3=75th percentile, SD=standard deviation, US=United States.

Main Results

- OF cohorts had significantly higher all-cause HCRU and all-cause costs than non-OF cohorts in all 5 countries
- The approach to present data as adjusted rate ratios within each country facilitates comparable relative comparisons across countries

Table 2 Adjusted rate ratios of HCRU between OF and non-OF cohorts by country and service type

Country	Australia		Germany		South Korea		Spain		US	
Cohort	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF
Number of patients	4809	13,921	11,452	34,090	47,238	134,813	25,214	75,308	193,262	570,864
Inpatient admissions[a]	2.10 (1.98-2.23)		1.16 (1.13-1.18)		3.18 (3.10-3.27)		2.13 (2.08-2.19)		3.90 (3.84-3.95)	
Nights stayed at hospital	4.11 (3.76-4.50)		1.71 (1.64-1.78)		4.70 (4.54-4.85)		4.04 (3.85-4.24)		11.52 (11.23-11.82)	
All-type outpatient visit rate[b]	1.19 (1.16-1.22)		NA		NA		1.27 (1.26-1.29)		2.00 (1.99-2.01)	
Outpatient GP visit rate[c]	1.10 (1.07-1.13)		1.11 (1.08-1.14)		NA		1.26 (1.25-1.28)		1.32 (1.31-1.33)	
Outpatient specialist visit rate[d]	1.21 (1.17-1.25)		1.02 (1.00-1.04)		1.81 (1.78-1.85)		1.08 (1.05-1.12)		2.29 (2.27-2.30)	
Other outpatient service rate[e]	1.20 (1.16-1.24)		1.21 (1.20-1.23)		1.02 (1.01-1.03)		1.28 (1.27-1.30)		1.93 (1.92-1.94)	
Emergency room visit rate[f]	1.21 (1.14-1.29)		1.04 (1.02-1.06)		1.82 (1.77-1.87)		NA		3.19 (3.17-3.22)	
Home visit rate[g]	1.29 (1.22-1.37)		1.27 (1.24-1.30)		NA		1.91 (1.85-1.98)		4.74 (4.68-4.80)	
Prescription rate[h]	1.04 (1.01-1.07)		NA		1.45 (1.44-1.46)		1.07 (1.06-1.08)		1.19 (1.18-1.20)	

Parenthesis indicates 95% confidence interval
GP= general practice or primary care, NA=not available, OF=osteoporotic fracture
[a]At least one overnight stay in the hospital as an inpatient.
[b]All outpatient-types combined: primary care, specialist, and others.
[c]Outpatient primary care visit: office/clinic visit general physician or primary care physician.
[d]Outpatient specialist visit: office/clinic visit to specialist (e.g., rheumatologist, orthopedist).
[e]Other outpatient services: clinic/facility visit for lab/radiology, skilled nursing facility, physical/occupational rehabilitation services and any other ancillary services.
[f]Emergency room visit: care received in the emergency department.
[g]Home visit information is based on home visits or domiciliary care visits.
[h]Prescription: is based on all filled pharmacy prescription claims including refill prescriptions.

Table 3 Adjusted rate ratios of all-cause costs between OF and non-OF cohorts by country and service type

Country	Australia		Germany		South Korea		Spain		US	
Cohort	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF
N	4809	13,921	11,452	34,090	47,238	134,813	25,214	75,308	193,262	570,864
Total costs of care[a]	1.83 (1.77-1.90)		1.38 (1.35-1.41)		2.87 (2.80-2.94)		1.66 (1.64-1.69)		3.11 (3.09-3.13)	
Total medical costs[b]	2.00 (1.93-2.08)		1.42 (1.38-1.46)		NA		1.85 (1.82-1.88)		3.69 (3.67-3.72)	
Total pharmacy costs[c]	1.11 (1.07-1.15)		1.27 (1.24-1.30)		NA		1.26 (1.25-1.28)		1.13 (1.12-1.14)	
Total medical inpatient costs[d]	1.59 (1.52-1.67)		1.61 (1.52-1.70)		1.99 (1.93-2.05)		NA		2.17 (2.14-2.20)	
Total emergency room costs[e]	1.04 (0.99-1.08)		NA		1.54 (1.38-1.72)		NA		1.74 (1.72-1.76)	
Total outpatient costs[f]	1.23 (1.20-1.26)		1.04 (1.02-1.06)		1.28 (1.26-1.29)		1.31 (1.29-1.33)		2.52 (2.50-2.53)	

Parenthesis indicates 95% confidence interval; NA=not available, OF=osteoporotic fracture
[a]Total medical and total pharmacy costs are considered.
[b]Total medical cost: the sum of total inpatient, outpatient, and ER.
[c]Total pharmacy cost: total cost of filled prescriptions.
[d]Total medical inpatient cost: total cost of services from all inpatient claims.
[e]Emergency room cost: total cost of services from all ER claims.
[f]Total medical outpatient cost: total cost of services from all outpatient claims (excluding ER, and including visits, diagnostics, and procedures).

Conclusions

- These results demonstrated the substantial economic burden of OF across the five participating countries
- More efforts, including wider use of more intensive bone-forming and anti-resorptive therapies, should be made to alleviate the burden
- The adjusted rate ratio approach pioneered in this study minimized potential concern of methodological variance when data were compared across countries

Additional Results

Table 1S Data source characteristics and components across countries

Country		Australia	Germany	South Korea[a]	Spain[a]	US[a]
Main Database		45 and Up Study linked to administrative claims	InGef	NHIS	SIDIAP linked to hospital admin data	PharMetrics Plus
Type of database	EMR				Main	
	Claims	Linked	Main	Main		Main
	Survey	Main				
Sampling approach of the database(s)		Prospective survey cohort study linked to regional/national administrative claims	Individuals insured in 60 SHI	National administrative claims of inpatient and outpatient visits	Primary care data linked to regional hospital admissions data	Predominantly commercially managed/self-insured health plans
Regional Coverage		√	√		√	
National coverage				√		√
Data components	Mortality					
	Use of supportive equipment					
	Rehabilitation facility use					
	Nursing home use					
	Falls					
		Prescription information[b] Hospitalization claims, primary care, ER claims, Home visits are available for all countries.				

[a]Race/ethnicity not available; [b]For South Korea, pharmacy costs were summed with medical costs due to data limitations
EMR electronic medical records, ER emergency room, NHIS National Health Insurance Service, SHI statutory health insurances, SIDIAP Information System for Research in Primary Care, US United States.

Available | Not available

- Table 2S & 3S present unadjusted HCRU and costs of care during the follow-up period, but it is challenging to directly compare across countries

Table 2S Healthcare resources utilization during the follow-up period per 100 person-years,[a] by country and cohort

Country	Australia		Germany		South Korea		Spain		US	
Cohort	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF
N	4809	13,921	11,452	34,090	47,238	134,813	25,214	75,308	193,262	570,864
Total person-years	12,820	37,851	25,376	71,855	138,505	398,550	73,112	212,600	370,996	1,139,594
Inpatient admissions[b]	NA	NA	94	83	NA	NA	NA	NA	33	12
Inpatient admissions excluding ER/A&E	87	41	54	49	131	58	5	3	NA	NA
Inpatient admissions including ER/A&E	117	64	40	33	15	5	26	15	NA	NA
Inpatient admission nights at hospital	803	321	1022	756	2504	1101	189	89	317	92
Outpatient primary care visit[c]	1437	1335	1274	1148	NA	NA	1560	1319	303	239
Outpatient specialist visits[d]	455	392	1451	1428	1026	665	32	29	1282	764
Other outpatient services[e]	2705	2349	284	294	2223	2112	185	145	3361	2285
Emergency room visit[f]	36	28	40	33	11	6	21	12	70	29
Home visits[g]	587	458	444	261	NA	NA	227	164	872	373
Use of supportive equipment[h]	NA/NC	NA/NC	480	323	0	0	NA/NC	NA/NC	27	77
Prescriptions[i]	4793	4643	3216	2677	124	87	4376	3977	2930	2438

ER/A&E=emergency room/accident & emergency room, NA/NC=not applicable/not collected, OF=osteoporotic fracture, US=United States, [a]N cases/total person-years) x 100; [b]Inpatient admissions: at least one overnight stay in the hospital as an inpatient; [c]Outpatient primary care visit: office/clinic visit general practice or primary care physician; [d]Outpatient specialist visit: office/clinic visit to specialist (e.g., rheumatologist, orthopedist).; [e]Other outpatient services: clinic/facility visit for lab/radiology, skilled nursing facility, physical/occupational rehabilitation services and any other ancillary services.; [f]Emergency room visit: care received in the emergency department; [g]Home visit information is based on home visits or domiciliary care visits. Categories considered include family medicine, general internal medicine, general practice, geriatric medicine, and other; [h]Supportive equipment: any described supportive equipment or mobility aids will be considered such as canes, crutches, wheelchairs, or mobility scooters; [i]Prescription: is based on all filled pharmacy prescription claims.

Table 3S Costs of care (USD)[1] during the follow-up period by country and cohort

Country	Australia		Germany		South Korea		Spain		US	
Cohort	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF	OF	Non-OF
N	4,809	13,921	11,452	34,090	47,238	134,813	25,214	75,308	193,262	570,864
Total person-years	12,820	37,851	25,376	71,855	138,505	398,550	73,112	212,600	370,996	1,139,594
Total cost of care[a]	11,752	7570	6584	5192	3553	1892	6158	4397	32,852	10,494
Total medical cost[b]	10,294	6227	5207	4012	NA	NA	3944	2676	29,370	7747
Total pharmacy cost[c]	1458	1343	1164	1149	NA	NA	2214	1721	3482	2746
Total medical inpatient cost[d]	7547	3945	1377	1180	2681	1190	1960	1067	16,070	2776
Total emergency room cost[e]	230	211	NA/NC	NA/NC	37	20	NA/NC	NA/NC	1566	325
Total outpatient cost[f]	2517	2071	4043	2863	835	683	NA/NC	NA/NC	11,734	4646
Total outpatient visit cost	1030	910	NA/NC	NA/NC	NA/NC	NA/NC	1985	1609	2584	1236
Total outpatient diagnostic/procedure cost	1487	1161	NA/NC	NA/NC	NA/NC	NA/NC	NA/NC	NA/NC	9150	3410

NA/NC=not applicable/not collected, OF=osteoporotic fracture, US=United States, USD=US dollar. [1]mean per 100 person-years; [a]Total medical and total pharmacy costs are considered; [b]Total medical cost: the sum of total inpatient, outpatient, emergency room costs; [c]Total pharmacy cost: total cost of filled prescriptions; [d]Total medical inpatient cost: total cost of services from all inpatient claims; [e]Emergency room/accident & emergency cost: total cost of services from all emergency room claims (not resulting in hospitalizations); [f]Total medical outpatient cost: total cost of services from all outpatient claims (excluding emergency room, and including visits, diagnostics, and procedures).

Disclosures & Funding Statement

Conflict of interest: **Alireza Moayyeri** is an employee of UCB Pharma and holds UCB stocks; **Hector Sanz** is an employee of IQVIA; **Joshua Warden** is an employee of UCB Pharma with no UCB stock; **Siin Kim** has no conflict of interest; **Hae Sun Suh** received a research grant from Amgen Inc. to conduct the South Korean study of this work at Kyung Hee University; **Rafael Pinedo-Villanueva** received research funding from the UK NIHR, the International Osteoporosis Foundation, Kyowa Kirin Services, Fondation privée des HUG (Geneva, Switzerland), Amgen Inc., and the Royal Osteoporosis Society, and lecture fees and/or consulting honoraria from Amgen Inc., UCB, Kyowa Kirin Services, Astellas, the International Osteoporosis Foundation, and Meras BioPharma; **Nicholas C. Harvey** reported personal fees, consultancy, lecture fees, and honoraria from Alliance for Better Bone Health, Amgen Inc., MSD, Eli Lilly, UCB, Kyowa Kirin, Servier, Shire, Consilient Healthcare, and Internis Pharmaceuticals, outside the submitted work; **Jeffrey R. Curtis** reported consulting fees and research grants from Amgen Inc.; **Stuart Silverman** received research grants, consulting fees, and honoraria from Amgen Inc., and honoraria from Radius Health; **Eric J. Yeh** is an employee of Amgen Inc. and holds Amgen stock.
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***Correspondence:** **Eric J. Yeh PhD eyeh01@amgen.com**;

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