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Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a study protocol for a multi-country, observational study

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Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a study protocol for a multi-country, observational study

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Abstract

Introduction Hip fractures are associated with a high burden of morbidity and mortality. Globally, there is wide variation in the incidence of hip fracture in people aged 50 years and older. Longitudinal and cross-geographical comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However, systematic reviews of studies that utilise different methods and study periods do not permit direct comparison across geographical regions. Thus, the objective of this study is to investigate global secular trends in hip fracture incidence, mortality, and use of post-fracture treatment across Asia, Oceania, North and South America, and Western and Northern Europe using a unified methodology applied to health records.

Methods and analysis This retrospective cohort study will use a common protocol and analytical common data model (ACDM) approach to examine incidence of hip fracture across population-based databases in different geographical regions and healthcare settings. The study period will be from 2005 to 2018 subject to data availability in study sites. Patients aged 50 years and older and hospitalised due to hip fracture during the study period will be included. The primary outcome will be expressed as the annual incidence of hip fracture. Secondary outcomes will be the pharmacological treatment rate and mortality within 12 months following initial hip fracture by year. For the primary outcome, crude and standardised incidence of hip fracture will be reported. Linear regression will be used to test for time trends in the annual incidence. For secondary outcomes, the crude mortality and standardised mortality ratio will be reported.

Ethics and dissemination Each participating site will follow the relevant local ethics and regulatory frameworks for study approval. The results of the study will be submitted for peer-reviewed scientific publications and presented at scientific conferences.

Keywords: Hip Fractures, Osteoporosis, Incidence, Mortality, Internationality

Strengths and limitations of this study

- This study will involve countries/regions across Asia, Oceania, North and South America, Western and Northern Europe.
- The study will use a common protocol and an analytical common data model to ensure consistency in data analysis and validity in cross-geographical comparisons.
- This study will build a global real-world data platform to efficiently collaborate across multiple institutions.
- Several databases will capture only treatments in the public reimbursement system, hence the treatment rates might be underestimated by not including patients in the private payment system.
- Though most of the data sources will be representative of the country-specific population, a few data sources will be representative of local hospitals and regional population.

Introduction

Hip fractures are a leading cause of high morbidity (30% - 50% of patients lose functional independence) [1 2] and mortality (approximately 22% mortality rate at one year).[3] Globally, there is wide variation in the incidence of hip fracture in people aged 50 years and older[4], ranging from an age-standardised rate of over 500 cases per 100,000 adults (e.g. Denmark) to less than 100 cases per 100,000 adults (e.g. South Africa). Secular trends in the incidence of hip fracture have been suggested to follow the level of urbanisation.[1]

Following a hip fracture, individuals are at greater risk of another osteoporotic fracture relative to those without a fracture. For example, in a study that included over 96,000 U.S. postmenopausal women who sustained a hip fracture, 8% had another clinical fracture within 1 year, 15% within 2 years, and 25% within 5 years.[5] To reduce the risk of a subsequent fracture, clinical guidelines from American and European societies for bone and osteoporosis recommend pharmacological treatment to reduce fracture risk after a hip fracture.[6 7] Irrespective of guidelines, treatment rates in post-fracture populations have been reported to be low in several geographical regions (16 – 21% of patients receiving pharmacological treatment)[8 9] and appear to be decreasing in both the U.S.[10] and Europe.[11] Given that pharmacological treatments have demonstrated a 30%-50% reduction in subsequent fracture,[12] many fractures occurring nowt are preventable.[13]

Longitudinal and cross-geographical comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However, global reports are typically systematic literature reviews based upon studies representing a heterogeneity of methods and study periods, making it a challenge to examine and compare data between geographical regions. For hip fracture specifically, the current available reports on hip fracture incidence are based on 20-year old data in some geographical regions.[1 14] Thus, we will investigate the global secular trends in hip fracture for incidence, mortality, and use of post-fracture treatment across Asia, Oceania, North and South America, Western and Northern Europe using a unified methodology applied to health records.

This study will use a common protocol and an analytical common data model (ACDM) approach to examine incidence of hip fracture using population-based databases from different geographical regions and healthcare settings. The concept of ACDM is to standardise a limited set of extracted variables into a common data structure, allowing the use of common analytics and methods across multiple datasets.[15] Thus, the quality of data analyses in each study site can be controlled by using standardised methodology including definition, calculation, and standardisation. This approach will provide high quality and comparable data on hip fracture and, therefore, is superior to data from systematic reviews of individual studies that have applied diverse methodologies.[1 4] The standardisation of estimates can facilitate cross-geography comparisons. In addition, this study will build a global real-world data platform to efficiently collaborate across multiple institutions.

Hypothesis and Objectives

This is an estimation study and no hypothesis will be tested. The study aim is to characterise hip fracture incidence estimates by year and assess the trend among men and women aged 50 years and older within multiple countries.

Primary objective

- To estimate the annual incidence of hip fracture and evaluate the trend during 2005 - 2018 (Objective 1).

Secondary objective

- To estimate the proportion of patients using a pharmacological treatment for osteoporosis within 12 months following their initial hip fracture by calendar year (Objective 2).
- To estimate the mortality rate within 12 months following patients' initial hip fracture by calendar year (Objective 3).

Methods and analysis

Study design

This is a retrospective cohort study based on healthcare databases from multiple sites representing numerous geographical regions. To enable consistent analysis and reporting across different databases in different regions and healthcare settings, a common protocol, statistical analysis plan (SAP), and an analytical common data model (ACDM) will be used to obtain aggregated data from each database. The study will consist of annual cohorts of patients who experience hip fracture from each database. Each site will convert their raw data into an ACDM format and apply the common statistical code provided by the study coordinator (University of Hong Kong) to perform the analysis. The study coordinator will not receive any patient-level data from the sites. Instead, each site will conduct the analysis locally and share aggregated results with the study coordinator.

Data source

This study will obtain aggregated data from the participating sites. All included sites will use patient-level electronic health data derived from the respective national or regional administrative databases, clinical databases, or registry databases. The study period will be from 1 January 2005 to 31 December 2018, subject to data availability in each study site. A full list of participating sites and databases is provided in Table 1.

The study sites will contribute aggregated data on diagnosis, medications, mortality, and other data associated with hip fracture in a defined population. Depending on the data capability to address study questions (i.e., fit-for-purpose), the study sites will contribute aggregated data for some or all of the objectives. Study sites can contribute incidence estimates for objective 1 for data sources of population-based data (i.e., a defined denominator). If complete prescription data are available, study sites can contribute the treatment rates for objective 2. Study sites can contribute the mortality rates for objective 3 if their database contains death data or

can link to death registries.

Study population

Patients aged 50 years and older and hospitalised due to hip fracture from 1 January 2005 to 31 December 2018 will be included. Patients will be excluded if they meet any of the following criteria: i) had a diagnosis of hip fracture within 12 months before the initial hip fracture; ii) had missing sex or age information; or iii) had less than 12 months continuous observation period in the data source prior to the start of the calendar year.

Identification of the 12 months observation period in the data source depends on the type of data source. For a database of medical claims, the patient's enrolment date should precede the hip fracture by at least 12 months. For a database of hospital electronic medical records (EMRs), the patient's first event (e.g. medical visit or prescription) in the database should precede the hip fracture by at least 12 months.

Baseline and Follow-up period

The index date will be defined as the date of admission for the initial hip fracture. The baseline period will be the 1-year period before the index date (not including the index date).

For the primary objective of hip fracture incidence, there is no follow-up of patients. For the secondary objectives of post-fracture treatment and mortality, each patient will be followed from the index date until another hip fracture episode, 12 months, death, disenrollment from database, 31 December 2018 or the end of data available in a database, whichever is earliest.

Outcome assessment

Hip fracture episodes will be defined as an in-patient diagnosis with ICD-9/-10 codes or equivalent codes of other diagnostic coding systems. Hip fracture is a major clinical event that almost always requires hospitalization and is generally accurately coded.[16-18] The diagnosis codes to identify hip fracture are subject to local clinical practice; the sites will use their own standard or validated algorithms for identifying hip fracture. The algorithms for hip fracture used by each site, and positive predictive values where available, are provided in Table 2. Most data sources have inpatient data. If inpatient diagnoses are not available, for example, in databases from general practice (e.g., Netherlands), the documented hip fracture will be used. Patients may have multiple hip fracture episodes during the study period. The initial hip fracture will be defined as the first occurrence of hip fracture without any inpatient or outpatient hip fracture diagnosis during the 1-year baseline period. All the hip fracture episodes including the initial hip fracture and any subsequent new episodes (contralateral or ipsilateral) will be considered in the calculation of hip fracture incidence. Subsequent new episodes are defined by no inpatient hip fracture diagnosis in the 180-days prior. (i.e., wash-out period). A study design schema for defining hip fracture episodes is illustrated in Figure 1.

Pharmacological treatments for fracture prevention include medications that are recommended for secondary prevention of osteoporotic fractures. These medications will be identified with prescription/dispensing of the

medications classified using the WHO Anatomical Therapeutic Chemical (ATC) Classification System codes whenever possible or equivalent codes of other drug coding systems used at the study site.

Date or month of death will be extracted. The cause of death (defined by ICD-9/-10 codes, or equivalent codes of other classification systems used at the study sites) will be included if available.

Covariate assessment

Sex and date or month of birth (or age at index date) will be captured. In addition, history of osteoporosis treatment defined as at least one prescription/dispensing record of any anti-osteoporosis medication during the 1-year baseline period will be captured.

For the secondary objective of treatment following hip fracture, patients will be considered as "ever use" if the patient had a history of osteoporosis treatment; and patient will be considered as "new use" if the patient did not have a history of osteoporosis treatment.

Statistical analysis

Microsoft Excel®, R, Statistical Analysis System (SAS) (SAS Inc., United States) will be used for data management and analyses. The proportion of missing data will be reported, but missing data will not be imputed. Patients with missing age or sex information will be excluded during the selection procedure. The number of study variables collected per patient is small and the impact of missing data is expected to be minimal and not likely to impact the reliability of the results.

Description of Patient Characteristics

Description of baseline characteristics will include age, sex, and history of anti-osteoporosis medications. Discrete variables will be summarised using frequencies and proportions, and continuous variables will be summarised using means and standard deviation or medians and interquartile range, as appropriate. Age will be categorised into 5-year age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80 or above.

Primary objective: Incidence of hip fracture

Population data will be used as the denominator (i.e., population at-risk) to calculate the annual incidence of hip fracture. The population of each calendar year will be defined as people i) aged 50 years and older, ii) with known sex, iii) enrolled/registered in the database on 1 January of that year, and iv) with a 1-year baseline period. If the population in the database is unknown, the national/regional population reported by the government will be used. The mid-year population of the database or the reported national/regional population aged 50 years and older of each calendar year will be used as the denominator.

Similar to prior studies,[19-21] the incidence (per 1,000 persons) rate per calendar year of hip fractures will be calculated as the sum of new hip fracture episodes in a year divided by the population at-risk on 1 Jan of that year. In addition, age- and sex-standardised incidence will be calculated to facilitate cross-geography

comparisons. The world population estimates in 2020 reported by the United Nations (https://population.un.org/wpp/Download/Standard/Population/) will be used as a standard.

A linear regression model will be used to test for time trends in the annual incidence in each site, assuming a linear trend for the hip fracture incidence, throughout the study period. The annual incidence as a dependent variable and the calendar year as a predictor variable will be fitted into the model. A two-tailed $P<0.05$ will be considered statistically significant.

Secondary objective: Treatment proportion

Similar to a prior study,[22] we will use the Kaplan-Meier method to estimate the treatment proportion within 3, 6, and 12 months of fracture and 95% confidence intervals (CI), censoring patients on another hip fracture episode, 12 months, death, disenrollment from database, 31 December 2018, or the end of data available in a database; whichever is earliest.

The description of the treatment proportion will include i) the treatment proportion by year of initial hip fracture; ii) the treatment proportion for new medication users (treatment-naive), defined as those with no prescriptions filled for osteoporosis medications within 12 months prior to their hip fracture (i.e., during the baseline period); and iii) the treatment proportion by the type of treatment (see Table 3 for details).

Secondary objective: One-year mortality following hip fracture

Similar to a prior study,[20] the one-year mortality (per 100 patients) rate per calendar year of initial hip fracture will be calculated as the sum of patients who died of any cause during the 12-month follow-up period divided by the sum of patients with an initial hip fracture. An additional analysis using the Kaplan-Meier method to account for censoring will be included as well. In addition, the mortality will be ascertained for the first 3 months and the first 6 months after the initial hip fracture. Age- and sex- standardized mortality will be calculated to facilitate cross-geography comparisons. Global age- and sex-specific mortality as reported by WHO will be used as a standard.

Additional analysis

Sensitivity analyses will be performed to evaluate the robustness of the results from the primary analysis. In the primary analysis, a wash-out period of 180 days is used to define a new episode of hip fracture. In the sensitivity analysis, a shorter (90 days) and a longer (365 days) wash-out period will be used. In addition, the requirement of at least 12-months continuous observation period may not capture fractures in a given year among those with less than a year of prior observation. Thus, a sensitivity analysis by removing this requirement will be conducted to evaluate if this requirement affects the estimates.

Fractures may occur in patients for reasons other than osteoporosis. In databases where the information is available, we will repeat the analysis in the subgroup excluding patients with any of the following criteria: i) concurrent diagnosis of high trauma fractures (high trauma is defined as vehicle accident or fall from greater

than standing height); ii) bone metastasis during the 1-year baseline period; iii) Paget's disease during the 1-year baseline period; or iv) osteogenesis imperfecta during the 1-year baseline period.

Subgroup analysis will be conducted. Estimates of hip fracture incidence and mortality will be stratified by sex and age (in 5-years age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80 or above).

Sample size

The estimated sample size in the databases ranges from several hundred hip fractures per year to tens of thousands of hip fractures per year. For example, the data source for Hong Kong, a region of 7.2 million people with 2.8 million adults aged 50+, has approximately 9,300 hip fractures per year in adults aged 50+ (a crude rate of 330 fractures per 100,000). The estimated samples sizes for each database are provided in Table 4.

Limitations

In general, most of the databases were built for administrative or reimbursement purposes rather than research purposes. The databases represent a variety of data sources, healthcare settings, and coding practices each of which will have different features and limitations.

Measurement Errors/Misclassifications

The study will use prescription/dispensing data to assess treatment, which is only a proxy for the patient taking their medication. The actual treatment with certain medications, such as oral bisphosphonates, may therefore be overestimated. In addition, use of zoledronic acid is not expected to be captured in all databases. For example, in countries where zoledronic acid is administered in hospitals or outpatient clinics, some databases do not readily capture medication administered in the hospital setting. In such circumstances, patients may be misclassified as having no treatment even though they were exposed to zoledronic acid.

The database for Hong Kong does not capture clinical records from private clinics/hospitals, though it is expected that most of the cases will be admitted to public hospitals via emergency service.

Several databases will capture only treatments in the public reimbursement system (Hong Kong, New Zealand, South Korea, Taiwan, and others), hence the treatment rates might be underestimated by not including patients in the private payment system.

Information Bias

Since hip fracture is a major clinical event that almost always requires hospitalisation, only hospital diagnoses of hip fracture will be considered in most databases (except when inpatient diagnoses are not available in the database). Fractures may occur in patients for reasons other than osteoporosis (e.g, trauma, bone metastasis,

Paget's disease, osteogenesis imperfect). Eligibility criteria for the study have been kept broad for the practical purpose of applying consistent definitions across multiple databases. To inform interpretation, we will conduct a sensitivity analysis excluding patients with these four criteria in those databases able to support the analysis.

Selection Bias

All patients who fulfill the eligibility criteria in each database will be included. All data sources are based on population databases, some of which cover the whole country from birth to death, and therefore selection bias is not expected to be a major issue. The Japan database has no patients aged 75+ years and limited number of aged >60 years compared to national statistics. Some databases are hospital-based or single province (e.g., China) and the representativeness of each database will be discussed when interpreting the results.

Patient and public involvement

The study will involve analysis of data collected from existing databases and there is no direct patient involvement. However, several researchers involved in this study routinely consult with patients in the design, development and reporting of research at a national level. Patients may be involved in presentations and dissemination of the results at a national level.

Ethics and dissemination

Each participating site will follow the relevant local ethics and regulatory frameworks for study approval (Table 5). All data to be used in this study are taken from existing anonymised records. In addition, participating sites will only share aggregated data with the study coordinators.

The results of the study will be submitted for peer-reviewed scientific publications and presented in scientific conferences. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Authors' contributions

C.W.S., T.C.L., J.O., C.B., J.L., C.L.C., K.K.M., I.C.W. designed the study. C.W.S and T.C.L. drafted and edited the protocol. All the authors had critical revision on the protocols. I.C.W. is the correspondence author and takes responsibility for the integrity of the study.

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Competing Interest

I.C.W, S.W, K.M.V, A.M.T, H.T.S, J.Y.S, D.P.A, M.M.A, E.C.L, K.K, C.D.P, M.C, A.H.Y.C, J.S.B had financial support from Amgen Inc. for the submitted work.

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Figure 1 Study design schema for estimating incidence of hip fracture (Objective 1).

Table 1 List of participating countries/regions and databases

Country / Region	Database	Data Type	Objectives planning to contribute
Asia-Pacific			
Australia	Linked hospital databases in the State of Victoria	EMR	1,2,3
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	EMR	1,2,3
Japan	Japanese Medical Data Center (JMDC)	Claims	1,2,3
South Korea	Health Insurance Review and Assessment Service (HIRA)	National Claims	1,2,3
New Zealand	National Minimum Dataset. Ministry of Health national databases	National Data	1,2,3
Singapore	Singapore Ministry of Health Central Claims Processing System	National Claims, Registries	1,3
Taiwan	National Health Insurance Database (NHID)	National Claims	1,2,3
Thailand	Hospital databases or central data from National Health Security Office	EMR or National Data	1,2,3
Western Europe			
France	SNDS	Claims	1,2,3
Germany	German sickness funds (WIG2)	Claims	1,2,3
Italy	Pool of databases from 4 different regions (Lazio, Napoli, Umbria, Torino)	Claims	1,2,3
Netherlands	Integrated Primary Care Information (IPCI) database	EMR (primary care)	1,2,3
Spain	Spanish Centralized Hospital Discharge Database (CMBD)	EMR	1
UK	Clinical Practice Research Datalink (CPRD)	EMR (primary care)	1,2,3
Northern Europe			
Denmark	Danish National Prescription Registry, Danish National Patient Register, Danish Civil Registration system, Cause of Death register	National Registries	1,2,3
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	National Registries	1,2,3
South & North America			
Brazil	DATASUS	Claims	1,2,3
Canada	The Canadian Chronic Disease Surveillance System (CCDSS)	Physician billing, hospitalization and prescription drug databases	1,2,3
US	Medicare FFS 20%	National Claims	1,2,3
US	Optum	Claims	1,2,3

Table 2 Diagnosis codes for hip fractures in each study site

Study Site	Coding System	Code	Validation
Australia	ICD10	S72.0, S72.1, S72.2	For all hip fracture records identified by admission, sensitivity was 93%-94% and PPV was 72%-80%[1]
Hong Kong	ICD9	820	PPV 100%[2]
Japan	ICD10	S7200, S7201, S7210, S7211, S7220, S7221, S7230, S7231, S7240, S7241, S7270, S7271, S7290, S7291	No study for hip fracture but a small study on subtrochanteric fracture (ICD-10 code S72.2, 11 cases) and femoral shaft fracture (ICD-10 code S72.3, 28 cases) showed sensitivity ~82% and PPV 100%.[3]
South Korea	ICD10	S72.0, S72.1	Algorithm included i) age ≥50; ii) ICD-10 codes (S72.0, S72.1); iii) Procedure codes (N0601, N0991, N0981, N0641, N0652, N0654, N0715). Sensitivity (93.1%), PPV (77.4%)[4]
New Zealand	ICD10/ ICD10-AM	ICD10: S72.0, S72.1, S72.2 ICD10-AM: S71.81 (Equivalent to ICD10 S72.01)	Nil
Singapore	ICD9/ICD10	ICD9: 820, 820.0, 820.2, 820.8 ICD10: S7200, S7201, S7210, S7211, S7220, S7221	Nil
Taiwan	ICD9/ICD10	ICD9: 73314, 82003, 82009, 82020, 82021, 82022, 8208 ICD10: M84451A, M84452A, M84459A, M80851A, M80852A, S72001A, S72002A, S72011A, S72012A, S72041A, S72042A, S72052A, S72091A, S72092A, S72101A, S72102A, S72111A, S72112A, S72121A, S72122A, S72141A,	99% (unpublished)

		S72142A, S72144A, S72145A, S7221XA, S7222XA	
Thailand	ICD10	S72.0, S72.1, S72.2, S32.4	Nil
Denmark	ICD10	S72.0, S72.1, S72.2	Nil
Finland	ICD10	S72.0, S72.1, S72.2	86.3% for detailed hip fracture diagnosis (88% for femoral neck, 96% for trochanteric and 63% for subtrochanteric fracture)[4]
France	ICD10	S72.0, S72.1, S72.2	Nil
Germany	ICD10	S72.0, S72.1, S72.2	Nil
Italy	ICD9	820	Nil
Netherlands	ICPC	L75, L75.01	Nil
Spain	ICD9	820	Nil
UK	ICD10	S72.0, S72.1, S72.2	Nil
Brazil	ICD10	S72.0, S72.1, S72.2	Nil
Canada	ICD9/ICD10	ICD9: 820 ICD10: S72.0, S72.1, S72.2	Nil
US (Medicare) US (Optum)	ICD9/ICD10	820/S72.0, S72.1, S72.2	Nil (The algorithm has been used in the literature and many research projects although it has not been formally validated. We believe the accuracy is good because (1) most hip fractures need hospitalisation and (2) the diagnosis codes in Medicare inpatient claims are accurate.)

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Table 3 Type of anti-osteoporosis medications

Type	Drug
Oral bisphosphonates	Alendronate Ibandronate (oral) Risedronate Clodronate Etidronate Pamidronate
IV bisphosphonates	Ibandronate (IV) Zoledronate
Denosumab	Denosumab
Parathyroid hormone analogue	Teriparatide
Others	Calcitonin Strontium ranelate Raloxifene Hormone replacement therapy

410 Table 4 Sample size estimation in each database

Country/ Region	Database	Number of patients in database	Number of people aged 50+*		Number of people with OP**		Number of incident hip fractures per year***	
Asia-Pacific			**Women**	**Men**	**Women (22.1% of age 50+)**	**Men (6.6% of age 50+)**	**Women (0.45% of age 50+)**	**Men (0.20% of age 50+)**
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	7M	1.5M (21%)	1.3M (19%)	325K	88K	6615	2660
Japan	Japanese Medical Data Center (JMDC)	3.9M	418K (11%)	550K (14%)	92K	36K	1882	1101
South Korea	Health Insurance Review and Assessment Service (HIRA)	50M	9M (18%)	3.3M (16%)	2M	518K	40500	6600
Taiwan	National Health Insurance Database (NHID)	25M	3.5M (14%)	3.5M (14%)	774K	231K	15750	7000
Australia	Linked hospital databases in the State of Victoria	90,000 hip fracture episodes	(17%)	(16%)	--		--	--
New Zealand	National Minimum Dataset.	36,000 episodes of care	(70%)	(30%)	--		--	--
Thailand	Hospital databases or central data from National Health Security Office	47M	8.8M (19%)	7.4M (16%)	1.9M	585K	39608	14705
Singapore	Singapore Ministry of Health Central Claims Processing System	TBD	(16%)	(17%)				
Western Europe								
UK	Clinical Practice Research Datalink (CPRD)	4.6M	874K (19%)	782K (17%)	193K	52K	3933	1564
Netherlands	Integrated Primary Care Information (IPCI) database	2.4M	480K (20%)	432K (18%)	106K	29K	2160	864
Italy	Pool of databases from 4 different regions (Lazio, Napoli, Umbria, Torino)	10M	2.3M (23%)	1.9M (19%)	508K	125K	10350	3800
Germany	German sickness funds (WIG2)	4.5M	1.0M (23%)	0.9M (20%)	229K	69K	4658	1800
Spain	Spanish Centralized Hospital Discharge	TBC	1.2M	1.02				

	Database (CMBD)		(20%)	(17%)				
France	SNDS	66M	14M (21%)	11M (17%)	3.1M	274M	63000	22440
Northern Europe								
Denmark	Danish National Prescription Registry, Danish National Patient Register	5.8M	1.2M (20%)	1.0M (18%)	256K	29K	5220	2088
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	5.4M	1.2M (22%)	1.0M (19%)	264K	38K	5346	2052
South & North America								
Brazil	DATASUS	209M	25M (12%)	21M (10%)	5.5M	4M	1.1M	0.4M
Canada	The Canadian Chronic Disease Surveillance System (CCDSS)	36.7M	7.3M	6.8M	1.6M	50K	32K	13K
US	Medicare FFS 20%	TBD	(18%)	(16%)				
US	Optum	TBD	(18%)	(16%)				

TBD To be determined

*Proportions taken from 2015 data from https://www.populationpyramid.net/

**Based on Hernlund et al, Archives of OP 2013. Table 24 Estimated number of men and women with osteoporosis (defined as a T-score of −2.5 SD or less at the femoral neck) and prevalence in the population aged over 50 years in the EU27, 2010

***Based on Hernlund et al, Archives of OP 2013. Table 27: Estimated number of incident fractures stratified by age and fracture type in the EU27, 2010

Table 5 Ethics statement in each participating site

Country/Region	Ethnics statement
Asia-Pacific	
Australia	The study using Victorian linked health data has been approved by the Australian Institute of Health and Welfare and will be reviewed by the Monash University Human Research Ethics Committee
Hong Kong	The study is approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)
Japan	The study protocol is approved by the Ethics Committee of the Nihon University School of Pharmacy
South Korea	The study protocol is approved by Institutional Review Board of Sungkyunkwan University (SKKU IRB)
Singapore	Ethics approval is not required for the analysis of anonymised administrative data under Singapore's Human Biomedical Research Act
New Zealand	The study was reviewed on the NZ Health and Disability Ethics Committee online site and considered out of scope for review given the retrospective nature of the database study
Taiwan	The study protocol is approved by The National Cheng Kung University Hospital
Thailand	The study protocol is approved by the Ethical Review Board of Ubon Ratchathani University
Western Europe	
UK	The protocol is approved by an Independent Scientific Advisory Committee (ISAC) for access to CPRD data
Netherlands	The study protocol is approved by the IPCI Review Board
Italy	The study protocol is approved by the Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino
Germany	Ethics approval is not required
France	The study protocol is under review by the National Institute of Health Data (INDS) and pending approval by the French data protection commission (Commission Nationale de l'Informatique et des Libertés - CNIL)
Spain	The study protocol is under review by the ethics committee
Northern Europe	
Denmark	The study protocol is approved by Danish Data Protection Agency
Finland	The study protocol is under review by the Health and Social Data Permit Authority Findata
South & North America	
Brazil	The study protocol is under review by The National Commission for Research Ethics (CONEP) and Institutional ethics committees (CEP)
Canada	Ethics approval is not required
US (Optum)	The study protocol is under review by the ethics committee
US (Medicare)	The study protocol is under review by the ethics committee

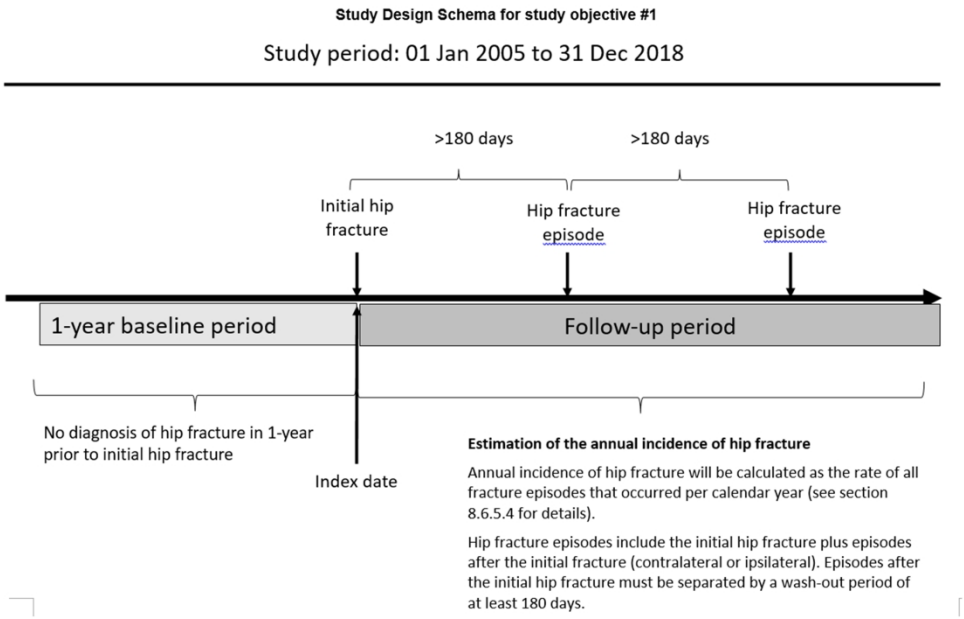

Figure 1 Study design schema

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Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a study protocol for a multi-country, observational study

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Keywords:	Calcium & bone < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, EPIDEMIOLOGY, PUBLIC HEALTH

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Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a study protocol for a multi-country, observational study

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Abstract

Introduction Hip fractures are associated with a high burden of morbidity and mortality. Globally, there is wide variation in the incidence of hip fracture in people aged 50 years and older. Longitudinal and cross-geographical comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However, systematic reviews of studies that utilise different methods and study periods do not permit direct comparison across geographical regions. Thus, the objective of this study is to investigate global secular trends in hip fracture incidence, mortality, and use of post-fracture pharmacological treatment across Asia, Oceania, North and South America, and Western and Northern Europe using a unified methodology applied to health records.

Methods and analysis This retrospective cohort study will use a common protocol and an analytical common data model (ACDM) approach to examine incidence of hip fracture across population-based databases in different geographical regions and healthcare settings. The study period will be from 2005 to 2018 subject to data availability in study sites. Patients aged 50 years and older and hospitalised due to hip fracture during the study period will be included. The primary outcome will be expressed as the annual incidence of hip fracture. Secondary outcomes will be the pharmacological treatment rate and mortality within 12 months following initial hip fracture by year. For the primary outcome, crude and standardised incidence of hip fracture will be reported. Linear regression will be used to test for time trends in the annual incidence. For secondary outcomes, the crude mortality and standardised mortality incidence will be reported.

Ethics and dissemination Each participating site will follow the relevant local ethics and regulatory frameworks for study approval. The results of the study will be submitted for peer-reviewed scientific publications and presented at scientific conferences.

Keywords: Hip Fractures, Osteoporosis, Incidence, Mortality, Internationality

Strengths and limitations of this study

- This study will involve countries/regions across Asia, Oceania, North and South America, Western and Northern Europe.
- The study will use a common protocol and an analytical common data model to ensure consistency in data analysis and validity in cross-geographical comparisons.
- This study will build a global real-world data platform to efficiently collaborate across multiple institutions.
- Several databases will capture only treatments in the public reimbursement system. Hence the treatment rates might be underestimated by not including patients in the private payment system.
- Though most of the data sources will be representative of the country-specific population, a few data sources will be representative of local hospitals and regional population.

Introduction

Hip fracture is a leading cause of high morbidity (30% - 50% of patients lose functional independence) [1 2] and mortality (approximately 22% mortality rate at one year).[3] Globally, there is wide variation in the incidence of hip fracture in people aged 50 years and older[4], ranging from an age-standardised rate of over 500 cases per 100,000 adults (e.g. Denmark) to less than 100 cases per 100,000 adults (e.g. South Africa). Secular trends in the incidence of hip fracture have been suggested to follow the level of urbanisation.[1]

Following a hip fracture, individuals are at greater risk of another osteoporotic fracture relative to those without a fracture. For example, in a study that included over 96,000 U.S. postmenopausal women who sustained a hip fracture, 8% had another clinical fracture within 1 year, 15% within 2 years, and 25% within 5 years.[5] To reduce the risk of a subsequent fracture, clinical guidelines from American and European societies for bone and osteoporosis recommend pharmacological treatment to reduce fracture risk after a hip fracture.[6 7] Irrespective of guidelines, treatment rates in post-fracture populations have been reported to be low in several geographical regions (16 – 21% of patients received pharmacological treatment)[8 9] and appear to be decreasing in both the U.S.[10] and Europe.[11] Given that pharmacological treatments have demonstrated a 30%-50% reduction in subsequent fracture,[12] many fractures occurring now are preventable.[13]

Longitudinal and cross-geographical comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However, global reports are typically systematic literature reviews based upon studies representing a heterogeneity of methods and study periods, making it a challenge to examine and compare data between geographical regions. For hip fracture specifically, the current available reports on hip fracture incidence are based on 20-year-old data in some geographical regions.[1 14] Thus, we will investigate the global secular trends in hip fracture for incidence, mortality, and use of post-fracture pharmacological treatment across Asia, Oceania, North and South America, Western and Northern Europe using a unified methodology applied to health records.

This study will use a common protocol and an analytical common data model (ACDM) approach to examine incidence of hip fracture using population-based databases from different geographical regions and healthcare settings. The concept of ACDM is to standardise a limited set of extracted variables into a common data structure, allowing the use of common analytics and methods across multiple datasets.[15] Thus, the quality of data analyses in each study site can be controlled by using standardised methodologies including definition, calculation, and standardisation. This approach will provide high quality and comparable data on hip fracture and, therefore, is superior to data from systematic reviews of individual studies that have applied diverse methodologies.[1 4] The standardisation of estimates can facilitate cross-geographical comparisons. In addition, this study will build a global real-world data platform to efficiently collaborate across multiple institutions.

Hypothesis and Objectives

This is an estimation study and no hypothesis will be tested. The study aim is to characterise hip fracture incidence estimates by year and assess the trend among men and women aged 50 years and older within multiple countries. We aim to investigate the between-country and between-region differences in hip fracture incidence, mortality and pharmacological treatment rate. This may in turn lead to research into environmental, sociodemographic and biological explanatory factors for geographical variations in incidence and mortality of hip fracture.

Primary objective

- To estimate the annual incidence of hip fracture and evaluate the trend during 2005 - 2018 (Objective 1).

Secondary objective

- To estimate the proportion of patients using a pharmacological treatment for osteoporosis within 12 months following their initial hip fracture by calendar year (Objective 2).
- To estimate the mortality rate within 12 months following patients' initial hip fracture by calendar year (Objective 3).

Methods and analysis

The study is in the common data model development phase. We plan to start the data analysis in the second quarter of 2021. The study will end in the first quarter of 2022.

Study design

This is a retrospective cohort study based on healthcare databases from multiple sites representing numerous geographical regions. To enable consistent analysis and reporting across different databases in different regions and healthcare settings, a common protocol, statistical analysis plan (SAP), and an analytical common data model (ACDM) will be used to obtain aggregated data from each database. The study will consist of annual cohorts of patients who experience hip fracture from each database. Each site will convert their raw data into an ACDM format and apply the common statistical code provided by the study coordinator (University of Hong Kong, HKU) to perform the analysis. The study coordinator will not receive any patient-level data from the sites. Instead, each site will conduct the analysis locally using a centrally developed analytic plan and share aggregated results with the study coordinator for the analysis of the pooled data.

Data source

This study will obtain aggregated data from the participating sites. All included sites will use patient-level electronic health data derived from the respective national or regional administrative databases, clinical databases, or registry databases. The study period will be from 1 January 2005 to 31 December 2018, subject to data availability in each study site. A full list of participating sites and databases is provided in Table 1.

The study sites will contribute aggregated data on diagnosis, medications, mortality, and other data associated with hip fracture in a defined population. Depending on the data capability to address study questions (i.e., fit-for-purpose), the study sites will contribute aggregated data for some or all of the objectives. Study sites can contribute incidence estimates for objective 1 for data sources of population-based data (i.e., a defined denominator). If complete prescription data are available, study sites can contribute the treatment rates for objective 2. Study sites can contribute the mortality rates for objective 3 if their database contains death data or can link to death registries.

Study population

Patients aged 50 years and older and hospitalised due to hip fracture from 1 January 2005 to 31 December 2018 will be included. We use 50 years old as a cut-off age because women generally enter menopause at 50 years old and their risk of osteoporosis and fractures after then increases.[11 16] Patients will be excluded if they meet any of the following criteria: i) had a diagnosis of hip fracture within 12 months before the initial hip fracture; ii) had missing sex or age information; or iii) had less than 12 months continuous observation period in the data source prior to the start of the calendar year.

Identification of the 12 months observation period in the data source depends on the type of data source. For a database of medical claims, the patient's enrolment date should precede the hip fracture by at least 12 months. For a database of hospital electronic medical records (EMRs), the patient's first event (e.g., medical visit or prescription) in the database should precede the hip fracture by at least 12 months.

Baseline and Follow-up period

The index date will be defined as the date of admission for the initial hip fracture. The baseline period will be the 1-year period before the index date (not including the index date).

For the primary objective of hip fracture incidence, there is no follow-up of patients. For the secondary objectives of post-fracture pharmacological treatment and mortality, each patient will be followed from the index date until another hip fracture episode, 12 months, death, disenrollment from database, 31 December 2019 or the end of data availability in a database, whichever is earliest.

Outcome assessment

Hip fracture episodes will be defined as an in-patient diagnosis with ICD-9/-10 codes or equivalent codes of other diagnostic coding systems. Hip fracture is a major clinical event that almost always requires hospitalization and is generally accurately coded.[17-19] The diagnosis codes to identify hip fracture are subject to local clinical practice; the sites will use their own standard or validated algorithms for identifying hip fracture. The algorithms for hip fracture used by each site, and positive predictive values where available, are provided in Table 2. Most data sources have inpatient data. If inpatient diagnoses are not available, for example, in databases from general practice (e.g., Netherlands), the documented hip fracture will be used. Patients may have

multiple hip fracture episodes during the study period. The initial hip fracture will be defined as the first occurrence of hip fracture without any inpatient or outpatient hip fracture diagnosis during the 1-year baseline period. All the hip fracture episodes including the initial hip fracture and any subsequent new episodes (contralateral or ipsilateral) will be considered in the calculation of hip fracture incidence. Subsequent new episodes are defined by no inpatient hip fracture diagnosis in the 180 days prior. (i.e., wash-out period). A study design schema for defining hip fracture episodes is illustrated in Figure 1.

Pharmacological treatments for fracture prevention include medications that are recommended for secondary prevention of osteoporotic fractures. These medications will be identified with prescription/dispensing of the medications classified using the WHO Anatomical Therapeutic Chemical (ATC) Classification System codes whenever possible or equivalent codes of other drug coding systems used at the study site.

Date or month of death will be extracted. The cause of death (defined by ICD-9/-10 codes, or equivalent codes of other classification systems used at the study sites) will be included if available.

Covariate assessment

Sex and date or month of birth (or age at index date) will be captured. In addition, history of osteoporosis treatment defined as at least one prescription/dispensing record of any anti-osteoporosis medication during the 1-year baseline period will be captured.

For the secondary objective of treatment following hip fracture, patients will be considered as "ever use" if the patient had a history of osteoporosis treatment; and patient will be considered as "new use" if the patient did not have a history of osteoporosis treatment.

Statistical analysis

Microsoft Excel®, R, Statistical Analysis System (SAS) (SAS Inc., United States) will be used for data management and analyses. The proportion of missing data will be reported, but missing data will not be imputed. Patients with missing age or sex information will be excluded during the selection procedure. The number of study variables collected per patient is small and the impact of missing data is expected to be minimal and not likely to impact the reliability of the results.

Description of Patient Characteristics

Description of baseline characteristics will include age, sex, and history of anti-osteoporosis medications. Discrete variables will be summarised using frequencies and proportions, and continuous variables will be summarised using means and standard deviation or medians and interquartile range, as appropriate. Age will be categorised into 5-year age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above.

Primary objective: Incidence of hip fracture

Population data will be used as the denominator (i.e., population at-risk) to calculate the annual incidence of hip

fracture. The population of each calendar year will be defined as people i) aged 50 years and older, ii) with known sex, iii) enrolled/registered in the database on 1 January of that year, and iv) with a 1-year baseline period. If the population in the database is unknown, the national/regional population reported by the government will be used. The mid-year population of the database or the reported national/regional population aged 50 years and older of each calendar year will be used as the denominator.

Similar to prior studies,[20-22] the incidence (per 100,000 persons) rate per calendar year of hip fractures will be calculated as the sum of new hip fracture episodes in a year divided by the population at-risk on 1 January of that year. In addition, age- and sex-standardised incidence will be calculated to facilitate cross-geographical comparisons. The world population estimates in 2020 reported by the United Nations (https://population.un.org/wpp/Download/Standard/Population/) will be used as a standard.

A linear regression model will be used to test for time trends in the annual incidence in each site, assuming a linear trend for the hip fracture incidence, throughout the study period. The annual incidence as a dependent variable and the calendar year as a predictor variable will be fitted into the model. A two-tailed $P<0.05$ will be considered statistically significant.

Secondary objective: Treatment proportion

Similar to a prior study,[23] we will use the Kaplan-Meier method to estimate the treatment proportion within 3, 6, and 12 months of fracture and 95% confidence intervals (CI), censoring patients on another hip fracture episode, 12 months, death, disenrollment from database, 31 December 2019, or the end of data availability in a database; whichever is earliest.

The description of the treatment proportion will include i) the treatment proportion by year of initial hip fracture; ii) the treatment proportion for new medication users (treatment-naive), defined as those with no prescription filled for osteoporosis medications within 12 months prior to their hip fracture (i.e., during the baseline period); and iii) the treatment proportion by the type of treatment (see Table 3 for details).

Secondary objective: One-year mortality following hip fracture

Similar to a prior study,[21] the 1-year mortality (per 100 patients) rate per calendar year of initial hip fracture will be calculated as the sum of patients who died of any cause during the 12-month follow-up period divided by the sum of patients with an initial hip fracture. An additional analysis using the Kaplan-Meier method to account for censoring will be included as well. In addition, the mortality will be ascertained for the first 3 months and the first 6 months after the initial hip fracture. Age- and sex- standardized mortality will be calculated to facilitate cross-geographical comparisons. The world population estimates in 2020 reported by the United Nations will be used as a standard.

Additional analysis

Sensitivity analyses will be performed to evaluate the robustness of the results from the primary analysis. In the

primary analysis, a wash-out period of 180 days is used to define a new episode of hip fracture. In the sensitivity analysis, a shorter (90 days) and a longer (365 days) wash-out period will be used. In addition, the requirement of at least 12-month continuous observation period may not capture fractures in a given year among those with less than a year of prior observation. Thus, a sensitivity analysis by removing this requirement will be conducted to evaluate if this requirement affects the estimates.

Fractures may occur in patients for reasons other than osteoporosis. In databases where the information is available, we will repeat the analysis in the subgroup excluding patients with any of the following criteria: i) concurrent diagnosis of high trauma fractures (high trauma is defined as vehicle accident or fall from greater than standing height); ii) bone metastasis during the 1-year baseline period; iii) Paget's disease during the 1-year baseline period; or iv) osteogenesis imperfecta during the 1-year baseline period.

Given the high mortality in the first year after hip fracture, death could be a competing risk event leading to overestimation of treatment probability. Therefore, a competing risk analysis using the cumulative incidence function approach will be performed to estimate the marginal probability of treatment with adjustment for competing risk of death.

Subgroup analysis will be conducted. Estimates of hip fracture incidence and mortality will be stratified by sex and age (in 5-years age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above).

Analytical common data model (ACDM)

The ACDM will be created to increase validity and consistency of data analysis using multi-databases. The sites will convert de-identified subject-level data into table formats in ACDM and use standard programming codes to conduct the statistical analysis and generate aggregate-level data. The ACDM will be co-developed by HKU and Amgen, Inc. R and SAS programming codes will be developed by the programming team in HKU and Amgen, Inc, respectively. To ensure quality assurance, at least two programmers will be involved to cross check the codes. The R and SAS programming codes will run on the same sample dataset and the results should be a 100% match. It is expected that the development of ACDM and programming codes will take around 2-3 months. Since the data structure varies across databases, HKU will discuss with the sites if any modification of the ACDM and programming codes will be needed. All the site-specific modifications will be documented. Sharing of the script as open-source code will be subject to journal requirement when the results are published.

Sample size

The estimated sample size in the databases ranges from several hundred hip fractures per year to tens of thousands of hip fractures per year. For example, the data source for Hong Kong, a region of 7.2 million people with 2.8 million adults aged 50+, has approximately 9,300 hip fractures per year in adults aged 50+ (a crude

rate of 330 fractures per 100,000). The estimated samples sizes for each database are provided in Table 4.

Limitations

In general, most of the databases were built for administrative or reimbursement purposes rather than research purposes. The databases represent a variety of data sources, healthcare settings, and coding practices each of which will have different features and limitations. The strengths and limitations of different type of databases have been discussed elsewhere.[24] The features of the databases in this study are shown in Table 1. A majority of databases have a high (over 90%) population coverage and official census data will be used as denominator. Databases with lower population coverage will use the actual number of individuals in the databases as denominator (Japan, UK and US). The databases in Italy do not link to national/regional death registry. National prescription data are only available in Australia, Denmark, Finland, New Zealand, South Korea, and Taiwan.

Measurement Errors/Misclassifications

The study will use prescription/dispensing data to assess treatment, which is only a proxy for the patient taking their medication. The actual treatment with certain medications, such as oral bisphosphonates, may therefore be overestimated. In addition, use of zoledronic acid is not expected to be captured in all databases. For example, in countries where zoledronic acid is administered in hospitals or outpatient clinics, some databases do not readily capture medication administered in the hospital setting. In such circumstances, patients may be misclassified as having no treatment even though they were exposed to zoledronic acid.

The database for Hong Kong does not capture clinical records from private clinics/hospitals, though it is expected that most of the cases will be admitted to public hospitals via emergency service.

Several databases will capture only treatments in the public reimbursement system (Hong Kong, South Korea, Taiwan, and others), hence the treatment rates might be underestimated by not including patients in the private payment system. Similarly, non-reimbursed medications cannot be captured in the reimbursement system, leading to potential underestimation of treatment rates.

Information Bias

Since hip fracture is a major clinical event that almost always requires hospitalisation, only hospital diagnoses of hip fracture will be considered in most databases (except when inpatient diagnoses are not available in the database). Fractures may occur in patients for reasons other than osteoporosis (e.g, trauma, bone metastasis, Paget's disease, osteogenesis imperfect). Eligibility criteria for the study have been kept broad for the practical purpose of applying consistent definitions across multiple databases. To inform interpretation, we will conduct a sensitivity analysis excluding patients with these four criteria in those databases able to support the analysis.

Selection Bias

All patients who fulfil the eligibility criteria in each database will be included. A majority of the databases cover over 90% of the population (e.g., Finland, Hong Kong, South Korea, and others.) (see Table 1) and therefore selection bias is not expected to be a major issue in these databases. However, a few data sources will be representative of local hospitals with limited population coverage (e.g. Thailand), leading to potential selection bias. For instance, the Japanese database has no subjects aged 75+ years and limited number of subjects aged >60 years compared to national statistics. Given that Japan has a large population of the oldest adults and the mean age for hip fracture is around 70-80 years, underestimation of the population incidence of hip fracture in Japan would be expected. However, the data would be still representative of the population under 75 years old. Although these sites have limited data for population estimates, the results are still informative for cross-geographical comparisons. More importantly, the site participation in this study can facilitate global cooperation, and also raise the awareness of the need for standardised high-quality national data for research.

Patient and public involvement

The study will involve retrospective analysis of secondary data collected from databases. Patients are de-identified and there is no direct patient involvement. Thus, patient consent is not required. However, several researchers involved in this study routinely consult with patients in the design, development and reporting of research at a national level. Patients may be involved in presentations and dissemination of the results at a national level.

Ethics and dissemination

Each participating site will follow the relevant local ethics and regulatory frameworks for study approval. The status of ethics approval in each site is listed in Supplementary Table. All data to be used in this study are taken from existing anonymised records. In addition, participating sites will only share aggregated data with the study coordinators.

The results of the study will be submitted for peer-reviewed scientific publications and presented in scientific conferences. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Authors' contributions

CWS co-developed and wrote the protocol. TCL co-developed, drafted, reviewed and commented on the protocol. JO, CB, JL, CLC, KKM co-developed, reviewed and commented on the protocol. SB, JSB, KB, PBL,

AHYC, MC, CYD, CDP, GG, SH, JH, HEJ, DPK, KK, ECCL, EML, JNL, MMA, NM, NO, ABP, DPA, JYS, HTS, KBT, AMT, KMCV, GHMW, SW, HZ reviewed and commented on the protocol. ICW is the principal investigator of the study, takes responsibility for the integrity of the study, co-developed, reviewed, and commented on the protocol.

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Competing Interest

I.C.W, S.W, K.M.V, A.M.T, H.T.S, J.Y.S, D.P.A, M.M.A, E.C.L, K.K, C.D.P, M.C, A.H.Y.C, J.S.B had financial support from Amgen Inc. for the submitted work.

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Figure 1 Study design schema for estimating incidence of hip fracture (Objective 1).

447 Table 1 List of participating countries/regions and databases

448

Country/ Region	Database	Data nature and healthcare setting	Population coverage	Study period	Denominator	Data source for medical conditions	Data source for medication use	Data source for death
Asia-Pacific								
Victoria, Australia	Linked hospital databases in the State of Victoria	EMR data from all Victorian public and private hospitals	100% (26 % of Australian population)	2012-2018	Mid-year population in the state of Victoria	Inpatient diagnosis	Dispensed and reimbursed data from Australia's Pharmaceutical Benefits Scheme	Death Registry
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	EMR data from all public hospitals and clinics	90%	2005-2018	Mid-year population in Hong Kong	Inpatient and outpatient diagnosis	Dispensed data in public hospitals and clinics	Death registry
Japan	Japanese Medical Data Center (JMDC)	Claims data from >200 medical institutions	6%	2005-2018	Number of individuals in the database at start of year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	TBC
South Korea	Health Insurance Review and Assessment Service (HIRA)	National Claims	97%	2008-2018	Mid-year population in South Korea	Inpatient and outpatient diagnosis	Dispensed data in hospitals and reimbursed data in pharmacy claims	National mortality registration data
New Zealand	Ministry of Health national databases	National data	98%	2005-2018	Mid-year population in New Zealand	Inpatient and outpatient diagnosis	National pharmaceutical claims database for all subsidised medicines in New Zealand	National death registration data (mortality dataset)
Singapore	Singapore Ministry of Health Central Claims Processing System	National Claims, Registries	100%	2005-2017	Mid-year population in Singapore	Inpatient diagnosis	NA	National death registration data

Taiwan	National Health Insurance Database (NHID)	National Claims	99%	2005-2018	Mid-year population in Taiwan	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	Cause of death registry
Thailand	Central data from National Health Security Office	National Data	67%	2014-2018	Mid-year population in Thailand	Inpatient diagnosis	Reimbursed data	National Data
	Hospital databases	EMR	Varies across hospitals	Varies across hospitals	Mid-year population in EMR	Inpatient diagnosis	Diagnosis and dispensed data	EMR
Western Europe								
France	SNDS	National Claims	99%	2006-2018	Mid-year population in France	Inpatient diagnosis	Reimbursed data in outpatients	National death registry
Germany	German sickness funds (WIG2)	Claims	5%	2012-2018	Mid-year population in Italy	Inpatient diagnosis	Reimbursed data in pharmacy claims	TBC
Italy	Pool of databases from 5 different regions (Lazio, Napoli, Umbria, Piemonte, Marche)	Claims	TBC	2012-2018 (Marche and Umbria) 2015-2018 (Piemonte, Napoli, Lazio)	Mid-year population in Italy	Inpatient diagnosis	Reimbursed data in pharmacy claims	NA
Netherlands	Integrated Primary Care Information (IPCI) database	Primary care EMR from >700 general practices (GP)	10%	2005-2018	Number of individuals in the database at start of year	GP diagnosis	GP prescription	NA
Spain	Spanish Centralized Hospital Discharge Database (CMBD)	EMR in all public and private hospitals	99.5%	2005-2018	Mid-year population in Spain	Inpatient diagnosis	NA	NA
UK	Clinical Practice Research Datalink (CPRD)	Primary care EMR from >650 GP	24%	2005-2018	Number of individuals in the database at start of year	Inpatient diagnosis	GP prescription	Office for National Statistics
Northern Europe								

Denmark	Danish National Prescription Registry, Danish National Patient Register, Danish Civil Registration system, Cause of Death register	National Registries	100%	2005-2018	Mid-year population in Denmark	Inpatient and outpatient diagnosis	Dispensed data at community pharmacies	National death registry
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	National Registries	100%	2005-2018	Population of Finland at the turn of the year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacies	National death registry
South & North America								
Brazil	DATASUS	National Data	70%	2005-2018	Mid-year population in Brazil	Inpatient and outpatient diagnosis	TBC	National mortality information system
Canada	The Canadian Chronic Disease Surveillance System (CCDSS)	Physician billing, hospitalization and prescription drug databases from all Canadian provinces and territories	97%	incidence, mortality : 2005-2017 Treatment: 2005-2016 *by fiscal year from April 1 to March 31	Number of individuals with valid health insurance at start of year	Inpatient diagnosis	Provincial /Territorial Drug Plan Databases	Provincial /Territorial Health Registries
US	Medicare fee-for-service 20%	National Claims for patients covered by Medicare	Medicare covers more than 90% of population ≥65 years; about 70% in the Medicare fee-for-service program. The data will be used for this study is a 20% random sample.	2007-2018	Number of individuals in the database at start of year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	Medicare death report and national social security death master file
US	Optum	Claims database for commercial-insured population	TBC	2005-2018	Number of individuals in the database at start of year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	TBC

Table 2 Diagnosis codes for hip fractures in each study site

Study Site	Coding System	Code	Validation
Australia	ICD10	S72.0, S72.1, S72.2	For all hip fracture records identified by admission, sensitivity was 93%-94% and PPV was 72%-80%[17]
Hong Kong	ICD9	820	PPV 100%[18]
Japan	ICD10	S7200, S7201, S7210, S7211, S7220, S7221, S7230, S7231, S7240, S7241, S7270, S7271, S7290, S7291	No study for hip fracture but a small study on subtrochanteric fracture (ICD-10 code S72.2, 11 cases) and femoral shaft fracture (ICD-10 code S72.3, 28 cases) showed sensitivity ~82% and PPV 100%.[25]
South Korea	ICD10	S72.0, S72.1	Algorithm included i) age ≥50; ii) ICD-10 codes (S72.0, S72.1); iii) Procedure codes (N0601, N0991, N0981, N0641, N0652, N0654, N0715). Sensitivity (93.1%), PPV (77.4%)[26]
New Zealand	ICD10	ICD10: S72.0, S72.1, S72.2	Nil
Singapore	ICD9/ICD10	ICD9: 820, 820.0, 820.2, 820.8 ICD10: S7200, S7201, S7210, S7211, S7220, S7221	Nil
Taiwan	ICD9/ICD10	ICD9: 73314, 82003, 82009, 82020, 82021, 82022, 8208 ICD10: M84451A, M84452A, M84459A, M80851A, M80852A, S72001A, S72002A, S72011A, S72012A, S72041A, S72042A, S72052A, S72091A, S72092A, S72101A, S72102A, S72111A, S72112A, S72121A, S72122A, S72141A, S72142A, S72144A, S72145A, S7221XA,	99% (unpublished)

		S7222XA	
Thailand	ICD10	S72.0, S72.1, S72.2, S32.4	Nil
Denmark	ICD10	S72.0, S72.1, S72.2	PPV was 90%, 92%, and 83% for fracture of the neck of femur, trochanteric fracture, and subtrochanteric fracture, respectively. Joining trochanteric and subtrochanteric fracture resulted in a PPV of 97%[27]
Finland	ICD10	S72.0, S72.1, S72.2	Sensitivity and PPV for femoral neck fracture 96.7% and 88.1%, for trochanteric fracture 68.6% and 96.0% and subtrochanteric fracture 83.3% and 62.5%[19]
France	ICD10	S72.0, S72.1, S72.2	Nil
Germany	ICD10	S72.0, S72.1, S72.2	Nil
Italy	ICD9	820	Nil
Netherlands	ICPC	L75, L75.01	Nil
Spain	ICD9	820	Nil
UK	ICD10	S72.0, S72.1, S72.2	Nil
Brazil	ICD10	S72.0, S72.1, S72.2	Nil
Canada	ICD9/ICD10	ICD9: 820 ICD10: S72.0, S72.1, S72.2	Validation has been done in one province (Manitoba). No significance difference in ascertainment between administrative data and clinically-validated cases[28]
US (Medicare) US (Optum)	ICD9/ICD10	820/S72.0, S72.1, S72.2	Nil (The algorithm has been used in the literature and many research projects although it has not been formally validated. We believe the accuracy is good because (1) most hip fractures need hospitalisation and (2) the diagnosis codes in Medicare inpatient claims are accurate.)

451

Table 3 Type of anti-osteoporosis medications

Type	Drug
Oral bisphosphonates	Alendronate Ibandronate (oral) Risedronate Clodronate Etidronate Pamidronate
IV bisphosphonates	Ibandronate (IV) Zoledronate
Denosumab	Denosumab
Parathyroid hormone analogue	Teriparatide
Others	Calcitonin Strontium ranelate Raloxifene Hormone replacement therapy

454 Table 4 Sample size estimation in each database

Country/ Region	Database	Number of patients in database	Number of people aged 50+*		Number of people with OP**		Number of incident hip fractures per year***	
Asia-Pacific			**Women**	**Men**	**Women (22.1% of age 50+)**	**Men (6.6% of age 50+)**	**Women (0.45% of age 50+)**	**Men (0.20% of age 50+)**
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	7M	1.5M (21%)	1.3M (19%)	325K	88K	6615	2660
Japan	Japanese Medical Data Center (JMDC)	3.9M	418K (11%)	550K (14%)	92K	36K	1882	1101
South Korea	Health Insurance Review and Assessment Service (HIRA)	50M	9M (18%)	3.3M (16%)	2M	518K	40500	6600
Taiwan	National Health Insurance Database (NHID)	25M	3.5M (14%)	3.5M (14%)	774K	231K	15750	7000
Australia	Linked hospital databases in the State of Victoria	90,000 hip fracture episodes	(17%)	(16%)	--		--	--
New Zealand	Ministry of Health national databases	36,000 episodes of care	(70%)	(30%)	--		--	--
Thailand	Hospital databases or central data from National Health Security Office	47M	8.8M (19%)	7.4M (16%)	1.9M	585K	39608	14705
Singapore	Singapore Ministry of Health Central Claims Processing System	TBD	(16%)	(17%)				
Western Europe								
UK	Clinical Practice Research Datalink (CPRD)	4.6M	874K (19%)	782K (17%)	193K	62K	3933	1564
Netherlands	Integrated Primary Care Information (IPCI) database	2.4M	480K (20%)	432K (18%)	106K	29K	2160	864
Italy	Pool of databases from 5 different regions (Lazio, Napoli, Umbria, Piemonte, Marche	10M	2.3M (23%)	1.9M (19%)	508K	125K	10350	3800
Germany	German sickness funds (WIG2)	4.5M	1.0M (23%)	0.9M (20%)	229K	69K	4658	1800
Spain	Spanish Centralized Hospital Discharge	TBC	1.2M	1.02				

	Database (CMBD)		(20%)	(17%)				
France	SNDS	66M	14M (21%)	11M (17%)	3.1M	274M	63000	22440
Northern Europe								
Denmark	Danish National Prescription Registry, Danish National Patient Register	5.8M	1.2M (20%)	1.0M (18%)	256K	29K	5220	2088
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	5.4M	1.2M (22%)	1.0M (19%)	264K	38K	5346	2052
South & North America								
Brazil	DATASUS	209M	25M (12%)	21M (10%)	5.5M	4M	1.1M	0.4M
Canada	The Canadian Chronic Disease Surveillance System (CCDSS)	36.7M	7.3M	6.8M	1.6M	150K	32K	13K
US	Medicare fee-for-service 20%	TBD	(18%)	(16%)				
US	Optum	TBD	(18%)	(16%)				

TBD To be determined

*Proportions taken from 2015 data from https://www.populationpyramid.net/

**Based on Hernlund et al, Archives of OP 2013. Table 24 Estimated number of men and women with osteoporosis (defined as a T-score of −2.5 SD or less at the femoral neck) and prevalence in the population aged over 50 years in the EU27, 2010

***Based on Hernlund et al, Archives of OP 2013. Table 27: Estimated number of incident fractures stratified by age and fracture type in the EU27, 2010

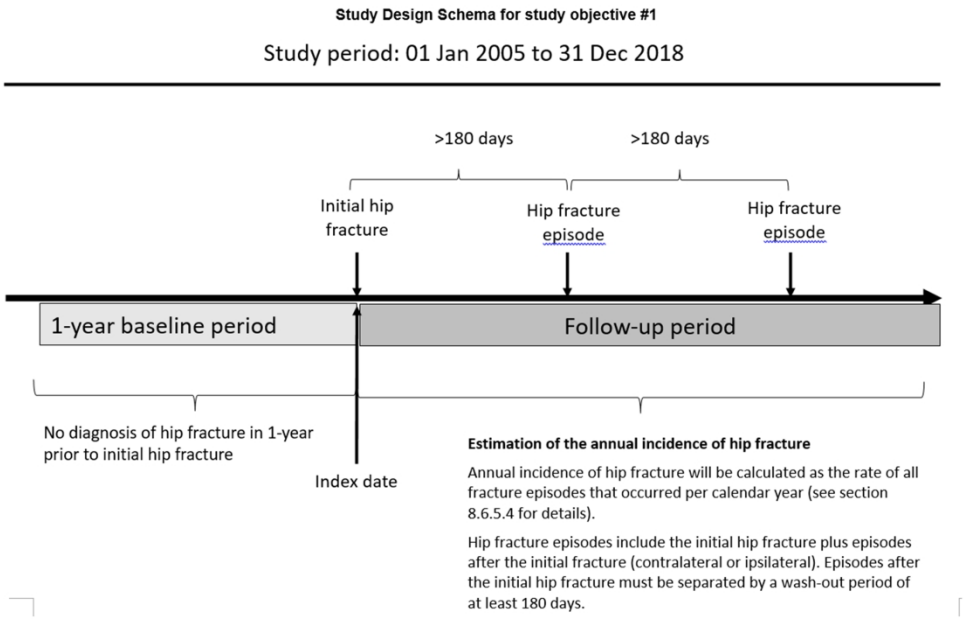

Figure 1 Study design schema

299x190mm (300 x 300 DPI)

Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a study protocol for a multi-country, observational study

Supplementary file

Supplementary Table Ethics approvals in each participating site

Country/Region	Ethics statement	Reference number, if any
Asia-Pacific		
Australia	The study using Victorian linked health data has been approved by the Australian Institute of Health and Welfare and will be reviewed by the Monash University Human Research Ethics Committee	
Hong Kong	The study is approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)	UW 19-154
Japan	The study protocol is approved by the Ethics Committee of the Nihon University School of Pharmacy	
South Korea	The study protocol is approved by Institutional Review Board of Sungkyunkwan University (SKKU IRB)	SKKU 2020-07-017
Singapore	Ethics approval is not required for the analysis of anonymised administrative data under Singapore's Human Biomedical Research Act	
New Zealand	The study was reviewed on the NZ Health and Disability Ethics Committee online site and considered out of scope for review given the retrospective nature of the database study and use of de-identified health information	
Taiwan	The study protocol is approved by The National Cheng Kung University Hospital	B-EX-109-030
Thailand	The study protocol is approved by the Ethical Review Board of Ubon Ratchathani University	UBU-REG-39/2563
Western Europe		
UK	The protocol is approved by an Independent Scientific Advisory Committee (ISAC) for access to CPRD data	
Netherlands	The study protocol is approved by the IPCI Review Board	IPCI 5/2020
Italy	The study protocol is approved by the Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino	
Germany	Ethics approval is not required	
France	The study protocol is approved by the National Institute of Health Data (INDS) and pending approval by the French data protection commission (Commission Nationale de l'Informatique et des Libertés - CNIL)	921079
Spain	The study protocol is under review by the ethics committee	
Northern Europe		
Denmark	The study protocol is approved by Danish Data Protection	

	Agency	
Finland	The study protocol is approved by the Health and Social Data Permit Authority Findata	REMS 2020/503
South & North America		
Brazil	The study protocol is under review by The National Commission for Research Ethics (CONEP) and Institutional ethics committees (CEP)	
Canada	Ethics approval is not required	
US (Optum)	The study protocol is under review by the ethics committee	
US (Medicare)	The study protocol has be approved by Office of Human Subjects Research, Hennepin Healthcare Research Institute	20-2342X

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Global epidemiology of hip fractures; a study protocol using a common analytical platform among multiple countries

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Global epidemiology of hip fractures; a study protocol using a common analytical platform among multiple countries

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Abstract

Introduction Hip fractures are associated with a high burden of morbidity and mortality. Globally, there is wide variation in the incidence of hip fracture in people aged 50 years and older. Longitudinal and cross-geographical comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However, systematic reviews of studies that utilise different methods and study periods do not permit direct comparison across geographical regions. Thus, the objective of this study is to investigate global secular trends in hip fracture incidence, mortality, and use of post-fracture pharmacological treatment across Asia, Oceania, North and South America, and Western and Northern Europe using a unified methodology applied to health records.

Methods and analysis This retrospective cohort study will use a common protocol and an analytical common data model (ACDM) approach to examine incidence of hip fracture across population-based databases in different geographical regions and healthcare settings. The study period will be from 2005 to 2018 subject to data availability in study sites. Patients aged 50 years and older and hospitalised due to hip fracture during the study period will be included. The primary outcome will be expressed as the annual incidence of hip fracture. Secondary outcomes will be the pharmacological treatment rate and mortality within 12 months following initial hip fracture by year. For the primary outcome, crude and standardised incidence of hip fracture will be reported. Linear regression will be used to test for time trends in the annual incidence. For secondary outcomes, the crude mortality and standardised mortality incidence will be reported.

Ethics and dissemination Each participating site will follow the relevant local ethics and regulatory frameworks for study approval. The results of the study will be submitted for peer-reviewed scientific publications and presented at scientific conferences.

Keywords: Hip Fractures, Osteoporosis, Incidence, Mortality, Internationality

Strengths and limitations of this study

- This study will involve countries/regions across Asia, Oceania, North and South America, Western and Northern Europe.
- The study will use a common protocol and an analytical common data model to ensure consistency in data analysis and validity in cross-geographical comparisons.
- This study will build a global real-world data platform to efficiently collaborate across multiple institutions.
- Several databases will capture only treatments in the public reimbursement system. Hence the treatment rates might be underestimated by not including patients in the private payment system.
- Though most of the data sources will be representative of the country-specific population, a few data sources will be representative of local hospitals and regional population.

Introduction

Hip fracture is a leading cause of high morbidity (30% - 50% of patients lose functional independence) [1 2] and mortality (approximately 22% mortality rate at one year).[3] Globally, there is wide variation in the incidence of hip fracture in people aged 50 years and older[4], ranging from an age-standardised rate of over 500 cases per 100,000 adults (e.g. Denmark) to less than 100 cases per 100,000 adults (e.g. South Africa). Secular trends in the incidence of hip fracture have been suggested to follow the level of urbanisation.[1]

Following a hip fracture, individuals are at greater risk of another osteoporotic fracture relative to those without a fracture. For example, in a study that included over 96,000 U.S. postmenopausal women who sustained a hip fracture, 8% had another clinical fracture within 1 year, 15% within 2 years, and 25% within 5 years.[5] To reduce the risk of a subsequent fracture, clinical guidelines from American and European societies for bone and osteoporosis recommend pharmacological treatment to reduce fracture risk after a hip fracture.[6 7] Irrespective of guidelines, treatment rates in post-fracture populations have been reported to be low in several geographical regions (16 – 21% of patients received pharmacological treatment)[8 9] and appear to be decreasing in both the U.S.[10] and Europe.[11] Given that pharmacological treatments have demonstrated a 30%-50% reduction in subsequent fracture,[12] many fractures occurring now are preventable.[13]

Longitudinal and cross-geographical comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However, global reports are typically systematic literature reviews based upon studies representing a heterogeneity of methods and study periods, making it a challenge to examine and compare data between geographical regions. For hip fracture specifically, the current available reports on hip fracture incidence are based on 20-year-old data in some geographical regions.[1 14] Thus, we will investigate the global secular trends in hip fracture for incidence, mortality, and use of post-fracture pharmacological treatment across Asia, Oceania, North and South America, Western and Northern Europe using a unified methodology applied to health records.

This study will use a common protocol and an analytical common data model (ACDM) approach to examine incidence of hip fracture using population-based databases from different geographical regions and healthcare settings. The concept of ACDM is to standardise a limited set of extracted variables into a common data structure, allowing the use of common analytics and methods across multiple datasets.[15] Thus, the quality of data analyses in each study site can be controlled by using standardised methodologies including definition, calculation, and standardisation. This approach will provide high quality and comparable data on hip fracture and, therefore, is superior to data from systematic reviews of individual studies that have applied diverse methodologies.[1 4] The standardisation of estimates can facilitate cross-geographical comparisons. In addition, this study will build a global real-world data platform to efficiently collaborate across multiple institutions.

Hypothesis and Objectives

This is an estimation study and no hypothesis will be tested. The study aim is to characterise hip fracture incidence estimates by year and assess the trend among men and women aged 50 years and older within multiple countries. We aim to investigate the between-country and between-region differences in hip fracture incidence, mortality and pharmacological treatment rate. This may in turn lead to research into environmental, sociodemographic and biological explanatory factors for geographical variations in incidence and mortality of hip fracture.

Primary objective

- To estimate the annual incidence of hip fracture and evaluate the trend during 2005 - 2018 (Objective 1).

Secondary objective

- To estimate the proportion of patients using a pharmacological treatment for osteoporosis within 12 months following their initial hip fracture by calendar year (Objective 2).
- To estimate the mortality rate within 12 months following patients' initial hip fracture by calendar year (Objective 3).

Methods and analysis

The study is in the common data model development phase. We plan to start the data analysis in the second quarter of 2021. The study will end in the first quarter of 2022.

Study design

This is a retrospective cohort study based on healthcare databases from multiple sites representing numerous geographical regions. To enable consistent analysis and reporting across different databases in different regions and healthcare settings, a common protocol, statistical analysis plan (SAP), and an analytical common data model (ACDM) will be used to obtain aggregated data from each database. The study will consist of annual cohorts of patients who experience hip fracture from each database. Each site will convert their raw data into an ACDM format and apply the common statistical code provided by the study coordinator (University of Hong Kong, HKU) to perform the analysis. The study coordinator will not receive any patient-level data from the sites. Instead, each site will conduct the analysis locally using a centrally developed analytic plan and share aggregated results with the study coordinator for the analysis of the pooled data.

Data source

This study will obtain aggregated data from the participating sites. All included sites will use patient-level electronic health data derived from the respective national or regional administrative databases, clinical databases, or registry databases. The study period will be from 1 January 2005 to 31 December 2018, subject to data availability in each study site. A full list of participating sites and databases is provided in Table 1.

The study sites will contribute aggregated data on diagnosis, medications, mortality, and other data associated with hip fracture in a defined population. Depending on the data capability to address study questions (i.e., fit-for-purpose), the study sites will contribute aggregated data for some or all of the objectives. Study sites can contribute incidence estimates for objective 1 for data sources of population-based data (i.e., a defined denominator). If complete prescription data are available, study sites can contribute the treatment rates for objective 2. Study sites can contribute the mortality rates for objective 3 if their database contains death data or can link to death registries.

Study population

Patients aged 50 years and older and hospitalised due to hip fracture from 1 January 2005 to 31 December 2018 will be included. We use 50 years old as a cut-off age because women generally enter menopause at 50 years old and their risk of osteoporosis and fractures after then increases.[11 16] Patients will be excluded if they meet any of the following criteria: i) had a diagnosis of hip fracture within 12 months before the initial hip fracture; ii) had missing sex or age information; or iii) had less than 12 months continuous observation period in the data source prior to the start of the calendar year.

Identification of the 12 months observation period in the data source depends on the type of data source. For a database of medical claims, the patient's enrolment date should precede the hip fracture by at least 12 months. For a database of hospital electronic medical records (EMRs), the patient's first event (e.g., medical visit or prescription) in the database should precede the hip fracture by at least 12 months.

Baseline and Follow-up period

The index date will be defined as the date of admission for the initial hip fracture. The baseline period will be the 1-year period before the index date (not including the index date).

For the primary objective of hip fracture incidence, there is no follow-up of patients. For the secondary objectives of post-fracture pharmacological treatment and mortality, each patient will be followed from the index date until another hip fracture episode, 12 months, death, disenrollment from database, 31 December 2019 or the end of data availability in a database, whichever is earliest.

Outcome assessment

Hip fracture episodes will be defined as an in-patient diagnosis with ICD-9/-10 codes or equivalent codes of other diagnostic coding systems. Hip fracture is a major clinical event that almost always requires hospitalization and is generally accurately coded.[17-19] The diagnosis codes to identify hip fracture are subject to local clinical practice; the sites will use their own standard or validated algorithms for identifying hip fracture. The algorithms for hip fracture used by each site, and positive predictive values where available, are provided in Table 2. Most data sources have inpatient data. If inpatient diagnoses are not available, for example, in databases from general practice (e.g., Netherlands), the documented hip fracture will be used. Patients may have

multiple hip fracture episodes during the study period. The initial hip fracture will be defined as the first occurrence of hip fracture without any inpatient or outpatient hip fracture diagnosis during the 1-year baseline period. All the hip fracture episodes including the initial hip fracture and any subsequent new episodes (contralateral or ipsilateral) will be considered in the calculation of hip fracture incidence. Subsequent new episodes are defined by no inpatient hip fracture diagnosis in the 180 days prior. (i.e., wash-out period). A study design schema for defining hip fracture episodes is illustrated in Figure 1.

Pharmacological treatments for fracture prevention include medications that are recommended for secondary prevention of osteoporotic fractures. These medications will be identified with prescription/dispensing of the medications classified using the WHO Anatomical Therapeutic Chemical (ATC) Classification System codes whenever possible or equivalent codes of other drug coding systems used at the study site.

Date or month of death will be extracted. The cause of death (defined by ICD-9/-10 codes, or equivalent codes of other classification systems used at the study sites) will be included if available.

Covariate assessment

Sex and date or month of birth (or age at index date) will be captured. In addition, history of osteoporosis treatment defined as at least one prescription/dispensing record of any anti-osteoporosis medication during the 1-year baseline period will be captured.

For the secondary objective of treatment following hip fracture, patients will be considered as "ever use" if the patient had a history of osteoporosis treatment; and patient will be considered as "new use" if the patient did not have a history of osteoporosis treatment.

Statistical analysis

Microsoft Excel®, R, Statistical Analysis System (SAS) (SAS Inc., United States) will be used for data management and analyses. The proportion of missing data will be reported, but missing data will not be imputed. Patients with missing age or sex information will be excluded during the selection procedure. The number of study variables collected per patient is small and the impact of missing data is expected to be minimal and not likely to impact the reliability of the results.

Description of Patient Characteristics

Description of baseline characteristics will include age, sex, and history of anti-osteoporosis medications. Discrete variables will be summarised using frequencies and proportions, and continuous variables will be summarised using means and standard deviation or medians and interquartile range, as appropriate. Age will be categorised into 5-year age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above.

Primary objective: Incidence of hip fracture

Population data will be used as the denominator (i.e., population at-risk) to calculate the annual incidence of hip

fracture. The population of each calendar year will be defined as people i) aged 50 years and older, ii) with known sex, iii) enrolled/registered in the database on 1 January of that year, and iv) with a 1-year baseline period. If the population in the database is unknown, the national/regional population reported by the government will be used. The mid-year population of the database or the reported national/regional population aged 50 years and older of each calendar year will be used as the denominator.

Similar to prior studies,[20-22] the incidence (per 100,000 persons) rate per calendar year of hip fractures will be calculated as the sum of new hip fracture episodes in a year divided by the population at-risk on 1 January of that year. In addition, age- and sex-standardised incidence will be calculated to facilitate cross-geographical comparisons. The world population estimates in 2020 reported by the United Nations (https://population.un.org/wpp/Download/Standard/Population/) will be used as a standard.

A linear regression model will be used to test for time trends in the annual incidence in each site, assuming a linear trend for the hip fracture incidence, throughout the study period. The annual incidence as a dependent variable and the calendar year as a predictor variable will be fitted into the model. A two-tailed $P<0.05$ will be considered statistically significant.

Secondary objective: Treatment proportion

Similar to a prior study,[23] we will use the Kaplan-Meier method to estimate the treatment proportion within 3, 6, and 12 months of fracture and 95% confidence intervals (CI), censoring patients on another hip fracture episode, 12 months, death, disenrollment from database, 31 December 2019, or the end of data availability in a database; whichever is earliest.

The description of the treatment proportion will include i) the treatment proportion by year of initial hip fracture; ii) the treatment proportion for new medication users (treatment-naive), defined as those with no prescription filled for osteoporosis medications within 12 months prior to their hip fracture (i.e., during the baseline period); and iii) the treatment proportion by the type of treatment (see Table 3 for details).

Secondary objective: One-year mortality following hip fracture

Similar to a prior study,[21] the 1-year mortality (per 100 patients) rate per calendar year of initial hip fracture will be calculated as the sum of patients who died of any cause during the 12-month follow-up period divided by the sum of patients with an initial hip fracture. An additional analysis using the Kaplan-Meier method to account for censoring will be included as well. In addition, the mortality will be ascertained for the first 3 months and the first 6 months after the initial hip fracture. Age- and sex- standardized mortality will be calculated to facilitate cross-geographical comparisons. The world population estimates in 2020 reported by the United Nations will be used as a standard.

Additional analysis

Sensitivity analyses will be performed to evaluate the robustness of the results from the primary analysis. In the

primary analysis, a wash-out period of 180 days is used to define a new episode of hip fracture. In the sensitivity analysis, a shorter (90 days) and a longer (365 days) wash-out period will be used. In addition, the requirement of at least 12-month continuous observation period may not capture fractures in a given year among those with less than a year of prior observation. Thus, a sensitivity analysis by removing this requirement will be conducted to evaluate if this requirement affects the estimates.

Fractures may occur in patients for reasons other than osteoporosis. In databases where the information is available, we will repeat the analysis in the subgroup excluding patients with any of the following criteria: i) concurrent diagnosis of high trauma fractures (high trauma is defined as vehicle accident or fall from greater than standing height); ii) bone metastasis during the 1-year baseline period; iii) Paget's disease during the 1-year baseline period; or iv) osteogenesis imperfecta during the 1-year baseline period.

Given the high mortality in the first year after hip fracture, death could be a competing risk event leading to overestimation of treatment probability. Therefore, a competing risk analysis using the cumulative incidence function approach will be performed to estimate the marginal probability of treatment with adjustment for competing risk of death.

Age- and sex-specific estimates of hip fracture incidence and mortality will be provided in 5-years age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above.

Analytical common data model (ACDM)

The ACDM will be created to increase validity and consistency of data analysis using multi-databases. The sites will convert de-identified subject-level data into table formats in ACDM and use standard programming codes to conduct the statistical analysis and generate aggregate-level data. The ACDM will be co-developed by HKU and Amgen, Inc. R and SAS programming codes will be developed by the programming team in HKU and Amgen, Inc, respectively. To ensure quality assurance, at least two programmers will be involved to cross check the codes. The R and SAS programming codes will run on the same sample dataset and the results should be a 100% match. It is expected that the development of ACDM and programming codes will take around 2-3 months. Since the data structure varies across databases, HKU will discuss with the sites if any modification of the ACDM and programming codes will be needed. All the site-specific modifications will be documented. Sharing of the script as open-source code will be subject to journal requirement when the results are published.

Sample size

The estimated sample size in the databases ranges from several hundred hip fractures per year to tens of thousands of hip fractures per year. For example, the data source for Hong Kong, a region of 7.2 million people with 2.8 million adults aged 50+, has approximately 9,300 hip fractures per year in adults aged 50+ (a crude

rate of 330 fractures per 100,000). The estimated samples sizes for each database are provided in Table 4.

Limitations

In general, most of the databases were built for administrative or reimbursement purposes rather than research purposes. The databases represent a variety of data sources, healthcare settings, and coding practices each of which will have different features and limitations. The strengths and limitations of different type of databases have been discussed elsewhere.[24] The features of the databases in this study are shown in Table 1. A majority of databases have a high (over 90%) population coverage and official census data will be used as denominator. Databases with lower population coverage will use the actual number of individuals in the databases as denominator (Japan, UK and US). The databases in Italy do not link to national/regional death registry. National prescription data are only available in Australia, Denmark, Finland, New Zealand, South Korea, and Taiwan.

Measurement Errors/Misclassifications

The study will use prescription/dispensing data to assess treatment, which is only a proxy for the patient taking their medication. The actual treatment with certain medications, such as oral bisphosphonates, may therefore be overestimated. In addition, use of zoledronic acid is not expected to be captured in all databases. For example, in countries where zoledronic acid is administered in hospitals or outpatient clinics, some databases do not readily capture medication administered in the hospital setting. In such circumstances, patients may be misclassified as having no treatment even though they were exposed to zoledronic acid.

The database for Hong Kong does not capture clinical records from private clinics/hospitals, though it is expected that most of the cases will be admitted to public hospitals via emergency service.

Several databases will capture only treatments in the public reimbursement system (Hong Kong, South Korea, Taiwan, and others), hence the treatment rates might be underestimated by not including patients in the private payment system. Similarly, non-reimbursed medications cannot be captured in the reimbursement system, leading to potential underestimation of treatment rates.

Information Bias

Since hip fracture is a major clinical event that almost always requires hospitalisation, only hospital diagnoses of hip fracture will be considered in most databases (except when inpatient diagnoses are not available in the database). Fractures may occur in patients for reasons other than osteoporosis (e.g, trauma, bone metastasis, Paget's disease, osteogenesis imperfect). Eligibility criteria for the study have been kept broad for the practical purpose of applying consistent definitions across multiple databases. To inform interpretation, we will conduct a sensitivity analysis excluding patients with these four criteria in those databases able to support the analysis.

Selection Bias

All patients who fulfil the eligibility criteria in each database will be included. A majority of the databases cover over 90% of the population (e.g., Finland, Hong Kong, South Korea, and others.) (see Table 1) and therefore selection bias is not expected to be a major issue in these databases. However, a few data sources will be representative of local hospitals with limited population coverage (e.g. Thailand), leading to potential selection bias. For instance, the Japanese database has no subjects aged 75+ years and limited number of subjects aged >60 years compared to national statistics. Given that the Japan data source does not contain the oldest adults at highest risk for hip fracture, the current protocol will provide an underestimation of the overall population incidence of hip fracture in Japan. However, the age subgroup analysis will provide a reasonable measure of incidence in the population under 75 years old. Therefore, we will exclude Japan data in the estimation of overall population incidence but will include it only in the age-specific analysis. Although these sites have limited data for population estimates, the results are still informative for cross-geographical comparisons. More importantly, the site participation in this study can facilitate global cooperation, and also raise the awareness of the need for standardised high-quality national data for research.

Patient and public involvement

The study will involve retrospective analysis of secondary data collected from databases. Patients are de-identified and there is no direct patient involvement. However, several researchers involved in this study routinely consult with patients in the design, development and reporting of research at a national level. Patients may be involved in presentations and dissemination of the results at a national level. Each participating site will be responsible for obtaining ethical clearances in accordance with current regulations within their local jurisdiction.

Ethics and dissemination

Each participating site will follow the relevant local ethics and regulatory frameworks for study approval. The status of ethics approval in each site is listed in Supplementary Table. All data to be used in this study are taken from existing anonymised records. In addition, participating sites will only share aggregated data with the study coordinators.

The results of the study will be submitted for peer-reviewed scientific publications and presented in scientific conferences. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Authors' contributions

CWS co-developed and wrote the protocol. TCL co-developed, drafted, reviewed and commented on the protocol. JO, CB, JL, CLC, KKM co-developed, reviewed and commented on the protocol. SB, JSB, KB, PBL, AHYC, MC, CYD, CDP, GG, SH, JI, HEJ, DPK, KK, ECCL, EML, JNL, MMA, NM, NO, ABP, DPA, JYS, HTS, KBT, AMT, KMCV, GHMW, SW, HZ reviewed and commented on the protocol. ICW is the principal investigator of the study, takes responsibility for the integrity of the study, co-developed, reviewed, and commented on the protocol.

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Competing Interest

I.C.W, S.W, K.M.V, A.M.T, H.T.S, J.Y.S, D.P.A, M.M.A, E.C.L, K.K, C.D.P, M.C, A.H.Y.C, J.S.B had financial support from Amgen Inc. for the submitted work.

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Figure 1 Study design schema for estimating incidence of hip fracture (Objective 1).

449 Table 1 List of participating countries/regions and databases

450

Country/ Region	Database	Data nature and healthcare setting	Population coverage	Study period	Denominator	Data source for medical conditions	Data source for medication use	Data source for death
Asia-Pacific								
Victoria, Australia	Linked hospital databases in the State of Victoria	EMR data from all Victorian public and private hospitals	100% (26 % of Australian population)	2012-2018	Mid-year population in the state of Victoria	Inpatient diagnosis	Dispensed and reimbursed data from Australia's Pharmaceutical Benefits Scheme	Death Registry
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	EMR data from all public hospitals and clinics	90%	2005-2018	Mid-year population in Hong Kong	Inpatient and outpatient diagnosis	Dispensed data in public hospitals and clinics	Death registry
Japan	Japanese Medical Data Center (JMDC)	Claims data from >200 medical institutions	6%	2005-2018	Number of individuals in the database at start of year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	TBC
South Korea	Health Insurance Review and Assessment Service (HIRA)	National Claims	97%	2008-2018	Mid-year population in South Korea	Inpatient and outpatient diagnosis	Dispensed data in hospitals and reimbursed data in pharmacy claims	National mortality registration data
New Zealand	Ministry of Health national databases	National data	98%	2005-2018	Mid-year population in New Zealand	Inpatient and outpatient diagnosis	National pharmaceutical claims database for all subsidised medicines in New Zealand	National death registration data (mortality dataset)
Singapore	Singapore Ministry of Health Central Claims Processing System	National Claims, Registries	100%	2005-2017	Mid-year population in Singapore	Inpatient diagnosis	NA	National death registration data

Taiwan	National Health Insurance Database (NHID)	National Claims	99%	2005-2018	Mid-year population in Taiwan	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	Cause of death registry
Thailand	Central data from National Health Security Office	National Data	67%	2014-2018	Mid-year population in Thailand	Inpatient diagnosis	Reimbursed data	National Data
	Hospital databases	EMR	Varies across hospitals	Varies across hospitals	Mid-year population in EMR	Inpatient diagnosis	Diagnosis and dispensed data	EMR
Western Europe								
France	SNDS	National Claims	99%	2006-2018	Mid-year population in France	Inpatient diagnosis	Reimbursed data in outpatients	National death registry
Germany	German sickness funds (WIG2)	Claims	5%	2012-2018	Mid-year population in Italy	Inpatient diagnosis	Reimbursed data in pharmacy claims	TBC
Italy	Pool of databases from 5 different regions (Lazio, Napoli, Umbria, Piemonte, Marche)	Claims	TBC	2012-2018 (Marche and Umbria) 2015-2018 (Piemonte, Napoli, Lazio)	Mid-year population in Italy	Inpatient diagnosis	Reimbursed data in pharmacy claims	NA
Netherlands	Integrated Primary Care Information (IPCI) database	Primary care EMR from >700 general practices (GP)	10%	2005-2018	Number of individuals in the database at start of year	GP diagnosis	GP prescription	NA
Spain	Spanish Centralized Hospital Discharge Database (CMBD)	EMR in all public and private hospitals	99.5%	2005-2018	Mid-year population in Spain	Inpatient diagnosis	NA	NA
UK	Clinical Practice Research Datalink (CPRD)	Primary care EMR from >650 GP	24%	2005-2018	Number of individuals in the database at start of year	Inpatient diagnosis	GP prescription	Office for National Statistics
Northern Europe								

Denmark	Danish National Prescription Registry, Danish National Patient Register, Danish Civil Registration system, Cause of Death register	National Registries	100%	2005-2018	Mid-year population in Denmark	Inpatient and outpatient diagnosis	Dispensed data at community pharmacies	National death registry
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	National Registries	100%	2005-2018	Population of Finland at the turn of the year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacies	National death registry
South & North America								
Brazil	DATASUS	National Data	70%	2005-2018	Mid-year population in Brazil	Inpatient and outpatient diagnosis	TBC	National mortality information system
Canada	The Canadian Chronic Disease Surveillance System (CCDSS)	Physician billing, hospitalization and prescription drug databases from all Canadian provinces and territories	97%	incidence, mortality : 2005-2017 Treatment: 2005-2016 *by fiscal year from April 1 to March 31	Number of individuals with valid health insurance at start of year	Inpatient diagnosis	Provincial /Territorial Drug Plan Databases	Provincial /Territorial Health Registries
US	Medicare fee-for-service 20%	National Claims for patients covered by Medicare	Medicare covers more than 90% of population ≥65 years; about 70% in the Medicare fee-for-service program. The data will be used for this study is a 20% random sample.	2007-2018	Number of individuals in the database at start of year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	Medicare death report and national social security death master file
US	Optum	Claims database for commercial-insured population	TBC	2005-2018	Number of individuals in the database at start of year	Inpatient and outpatient diagnosis	Reimbursed data in pharmacy claims	TBC

452 Table 2 Diagnosis codes for hip fractures in each study site

Study Site	Coding System	Code	Validation
Australia	ICD10	S72.0, S72.1, S72.2	For all hip fracture records identified by admission, sensitivity was 93%-94% and PPV was 72%-80%[17]
Hong Kong	ICD9	820	PPV 100%[18]
Japan	ICD10	S7200, S7201, S7210, S7211, S7220, S7221, S7230, S7231, S7240, S7241, S7270, S7271, S7290, S7291	No study for hip fracture but a small study on subtrochanteric fracture (ICD-10 code S72.2, 11 cases) and femoral shaft fracture (ICD-10 code S72.3, 28 cases) showed sensitivity ~82% and PPV 100%.[25]
South Korea	ICD10	S72.0, S72.1	Algorithm included i) age ≥50; ii) ICD-10 codes (S72.0, S72.1); iii) Procedure codes (N0601, N0991, N0981, N0641, N0652, N0654, N0715). Sensitivity (93.1%), PPV (77.4%)[26]
New Zealand	ICD10	ICD10: S72.0, S72.1, S72.2	Nil
Singapore	ICD9/ICD10	ICD9: 820, 820.0, 820.2, 820.8 ICD10: S7200, S7201, S7210, S7211, S7220, S7221	Nil
Taiwan	ICD9/ICD10	ICD9: 73314, 82003, 82009, 82020, 82021, 82022, 8208 ICD10: M84451A, M84452A, M84459A, M80851A, M80852A, S72001A, S72002A, S72011A, S72012A, S72041A, S72042A, S72052A, S72091A, S72092A, S72101A, S72102A, S72111A, S72112A, S72121A, S72122A, S72141A, S72142A, S72144A, S72145A, S7221XA,	99% (unpublished)

		S7222XA	
Thailand	ICD10	S72.0, S72.1, S72.2, S32.4	Nil
Denmark	ICD10	S72.0, S72.1, S72.2	PPV was 90%, 92%, and 83% for fracture of the neck of femur, trochanteric fracture, and subtrochanteric fracture, respectively. Joining trochanteric and subtrochanteric fracture resulted in a PPV of 97%[27]
Finland	ICD10	S72.0, S72.1, S72.2	Sensitivity and PPV for femoral neck fracture 96.7% and 88.1%, for trochanteric fracture 68.6% and 96.0% and subtrochanteric fracture 83.3% and 62.5%[19]
France	ICD10	S72.0, S72.1, S72.2	Nil
Germany	ICD10	S72.0, S72.1, S72.2	Nil
Italy	ICD9	820	Nil
Netherlands	ICPC	L75, L75.01	Nil
Spain	ICD9	820	Nil
UK	ICD10	S72.0, S72.1, S72.2	Nil
Brazil	ICD10	S72.0, S72.1, S72.2	Nil
Canada	ICD9/ICD10	ICD9: 820 ICD10: S72.0, S72.1, S72.2	Validation has been done in one province (Manitoba). No significance difference in ascertainment between administrative data and clinically-validated cases[28]
US (Medicare) US (Optum)	ICD9/ICD10	820/S72.0, S72.1, S72.2	Nil (The algorithm has been used in the literature and many research projects although it has not been formally validated. We believe the accuracy is good because (1) most hip fractures need hospitalisation and (2) the diagnosis codes in Medicare inpatient claims are accurate.)

453

Table 3 Type of anti-osteoporosis medications

Type	Drug
Oral bisphosphonates	Alendronate Ibandronate (oral) Risedronate Clodronate Etidronate Pamidronate
IV bisphosphonates	Ibandronate (IV) Zoledronate
Denosumab	Denosumab
Parathyroid hormone analogue	Teriparatide
Others	Calcitonin Strontium ranelate Raloxifene Hormone replacement therapy

456 Table 4 Sample size estimation in each database

Country/ Region	Database	Number of patients in database	Number of people aged 50+*		Number of people with OP**		Number of incident hip fractures per year***	
Asia-Pacific			**Women**	**Men**	**Women (22.1% of age 50+)**	**Men (6.6% of age 50+)**	**Women (0.45% of age 50+)**	**Men (0.20% of age 50+)**
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	7M	1.5M (21%)	1.3M (19%)	325K	88K	6615	2660
Japan	Japanese Medical Data Center (JMDC)	3.9M	418K (11%)	550K (14%)	92K	36K	1882	1101
South Korea	Health Insurance Review and Assessment Service (HIRA)	50M	9M (18%)	3.3M (16%)	2M	518K	40500	6600
Taiwan	National Health Insurance Database (NHID)	25M	3.5M (14%)	3.5M (14%)	774K	231K	15750	7000
Australia	Linked hospital databases in the State of Victoria	90,000 hip fracture episodes	(17%)	(16%)	--		--	--
New Zealand	Ministry of Health national databases	36,000 episodes of care	(70%)	(30%)	--		--	--
Thailand	Hospital databases or central data from National Health Security Office	47M	8.8M (19%)	7.4M (16%)	1.9M	585K	39608	14705
Singapore	Singapore Ministry of Health Central Claims Processing System	TBD	(16%)	(17%)				
Western Europe								
UK	Clinical Practice Research Datalink (CPRD)	4.6M	874K (19%)	782K (17%)	193K	62K	3933	1564
Netherlands	Integrated Primary Care Information (IPCI) database	2.4M	480K (20%)	432K (18%)	106K	29K	2160	864
Italy	Pool of databases from 5 different regions (Lazio, Napoli, Umbria, Piemonte, Marche	10M	2.3M (23%)	1.9M (19%)	508K	125K	10350	3800
Germany	German sickness funds (WIG2)	4.5M	1.0M (23%)	0.9M (20%)	229K	69K	4658	1800
Spain	Spanish Centralized Hospital Discharge	TBC	1.2M	1.02				

	Database (CMBD)		(20%)	(17%)				
France	SNDS	66M	14M (21%)	11M (17%)	3.1M	274M	63000	22440
Northern Europe								
Denmark	Danish National Prescription Registry, Danish National Patient Register	5.8M	1.2M (20%)	1.0M (18%)	256K	29K	5220	2088
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	5.4M	1.2M (22%)	1.0M (19%)	264K	38K	5346	2052
South & North America								
Brazil	DATASUS	209M	25M (12%)	21M (10%)	5.5M	4M	1.1M	0.4M
Canada	The Canadian Chronic Disease Surveillance System (CCDSS)	36.7M	7.3M	6.8M	1.6M	150K	32K	13K
US	Medicare fee-for-service 20%	TBD	(18%)	(16%)				
US	Optum	TBD	(18%)	(16%)				

TBD To be determined

*Proportions taken from 2015 data from https://www.populationpyramid.net/

**Based on Hernlund et al, Archives of OP 2013. Table 24 Estimated number of men and women with osteoporosis (defined as a T-score of −2.5 SD or less at the femoral neck) and prevalence in the population aged over 50 years in the EU27, 2010

***Based on Hernlund et al, Archives of OP 2013. Table 27: Estimated number of incident fractures stratified by age and fracture type in the EU27, 2010

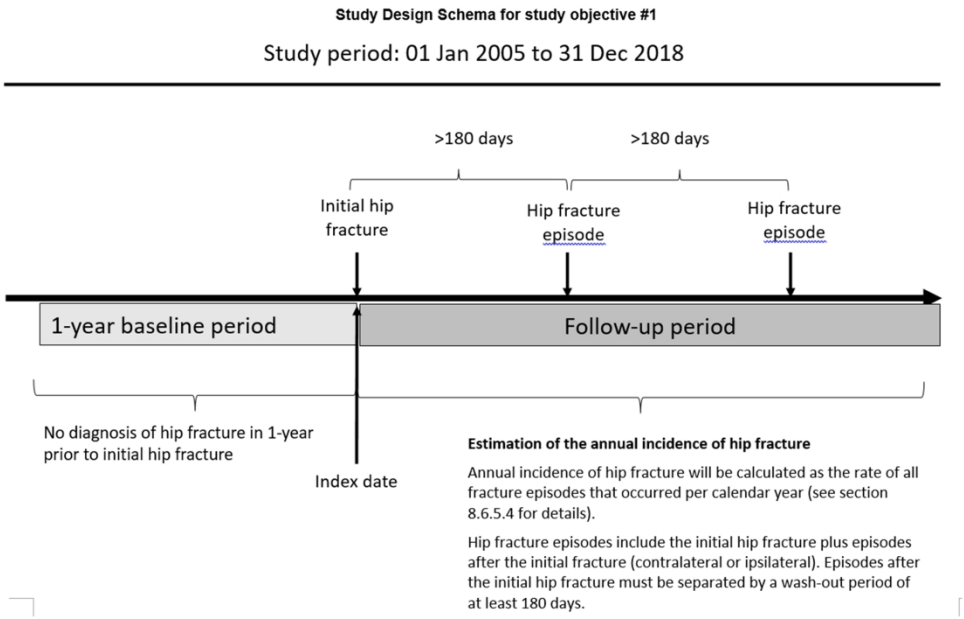

Figure 1 Study design schema

299x190mm (300 x 300 DPI)

Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a study protocol for a multi-country, observational study

Supplementary file

Supplementary Table Ethics approvals in each participating site

Country/Region	Ethics statement	Reference number, if any
Asia-Pacific		
Australia	The study using Victorian linked health data has been approved by the Australian Institute of Health and Welfare and will be reviewed by the Monash University Human Research Ethics Committee	
Hong Kong	The study is approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)	UW 19-154
Japan	The study protocol is approved by the Ethics Committee of the Nihon University School of Pharmacy	
South Korea	The study protocol is approved by Institutional Review Board of Sungkyunkwan University (SKKU IRB)	SKKU 2020-07-017
Singapore	Ethics approval is not required for the analysis of anonymised administrative data under Singapore's Human Biomedical Research Act	
New Zealand	The study was reviewed on the NZ Health and Disability Ethics Committee online site and considered out of scope for review given the retrospective nature of the database study and use of de-identified health information	
Taiwan	The study protocol is approved by The National Cheng Kung University Hospital	B-EX-109-030
Thailand	The study protocol is approved by the Ethical Review Board of Ubon Ratchathani University	UBU-REG-39/2563
Western Europe		
UK	The protocol is approved by an Independent Scientific Advisory Committee (ISAC) for access to CPRD data	
Netherlands	The study protocol is approved by the IPCI Review Board	IPCI 5/2020
Italy	The study protocol is approved by the Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino	
Germany	Ethics approval is not required	
France	The study protocol is approved by the National Institute of Health Data (INDS) and pending approval by the French data protection commission (Commission Nationale de l'Informatique et des Libertés - CNIL)	921079
Spain	The study protocol is under review by the ethics committee	
Northern Europe		
Denmark	The study protocol is approved by Danish Data Protection	

	Agency	
Finland	The study protocol is approved by the Health and Social Data Permit Authority Findata	REMS 2020/503
South & North America		
Brazil	The study protocol is under review by The National Commission for Research Ethics (CONEP) and Institutional ethics committees (CEP)	
Canada	Ethics approval is not required	
US (Optum)	The study protocol is under review by the ethics committee	
US (Medicare)	The study protocol has be approved by Office of Human Subjects Research, Hennepin Healthcare Research Institute	20-2342X