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

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3 **57 Abstract**
4

5 **58 Introduction** Hip fractures are associated with a high burden of morbidity and mortality. Globally, there is wide
6 variation in the incidence of hip fracture in people aged 50 years and older. Longitudinal and cross-geographical
7 59 comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However,
8 60 systematic reviews of studies that utilise different methods and study periods do not permit direct comparison
9 61 across geographical regions. Thus, the objective of this study is to investigate global secular trends in hip
10 62 fracture incidence, mortality, and use of post-fracture treatment across Asia, Oceania, North and South America,
11 63 and Western and Northern Europe using a unified methodology applied to health records.
12 64

13 **65 Methods and analysis** This retrospective cohort study will use a common protocol and analytical common data
14 model (ACDM) approach to examine incidence of hip fracture across population-based databases in different
15 66 geographical regions and healthcare settings. The study period will be from 2005 to 2018 subject to data
16 67 availability in study sites. Patients aged 50 years and older and hospitalised due to hip fracture during the study
17 68 period will be included. The primary outcome will be expressed as the annual incidence of hip fracture.
18 69 Secondary outcomes will be the pharmacological treatment rate and mortality within 12 months following initial
19 70 hip fracture by year. For the primary outcome, crude and standardised incidence of hip fracture will be reported.
20 71 Linear regression will be used to test for time trends in the annual incidence. For secondary outcomes, the crude
21 72 mortality and standardised mortality ratio will be reported.
22 73

23 **74 Ethics and dissemination** Each participating site will follow the relevant local ethics and regulatory
24 frameworks for study approval. The results of the study will be submitted for peer-reviewed scientific
25 75 publications and presented at scientific conferences.
26 76

27 **77 Keywords:** Hip Fractures, Osteoporosis, Incidence, Mortality, Internationality
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3 78 **Strengths and limitations of this study**
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- 5 79 • This study will involve countries/regions across Asia, Oceania, North and South America, Western and
6 Northern Europe.
7 80
8 81 • The study will use a common protocol and an analytical common data model to ensure consistency in data
9 analysis and validity in cross-geographical comparisons.
10 82
11 83 • This study will build a global real-world data platform to efficiently collaborate across multiple institutions.
12
13 84 • Several databases will capture only treatments in the public reimbursement system, hence the treatment
14 rates might be underestimated by not including patients in the private payment system.
15 85
16 86 • Though most of the data sources will be representative of the country-specific population, a few data sources
17 will be representative of local hospitals and regional population.
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88 Introduction

89 Hip fractures are a leading cause of high morbidity (30% - 50% of patients lose functional independence)^{1 2}
90 and mortality (approximately 22% mortality rate at one year).³ Globally, there is wide variation in the incidence
91 of hip fracture in people aged 50 years and older⁴, ranging from an age-standardised rate of over 500 cases per
92 100,000 adults (e.g. Denmark) to less than 100 cases per 100,000 adults (e.g. South Africa). Secular trends in
93 the incidence of hip fracture have been suggested to follow the level of urbanisation.¹

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

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

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

119 Hypothesis and Objectives

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3 121 This is an estimation study and no hypothesis will be tested. The study aim is to characterise hip fracture
4 122 incidence estimates by year and assess the trend among men and women aged 50 years and older within multiple
5 123 countries.

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9 124 Primary objective

- 10
11 125 • To estimate the annual incidence of hip fracture and evaluate the trend during 2005 - 2018 (Objective 1).
12

13 126 Secondary objective

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15 127 • To estimate the proportion of patients using a pharmacological treatment for osteoporosis within 12 months
16 128 following their initial hip fracture by calendar year (Objective 2).
17
18 129 • To estimate the mortality rate within 12 months following patients' initial hip fracture by calendar year
19 130 (Objective 3).
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23 131 24 25 132 **Methods and analysis**

26 27 133 **Study design**

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29 134 This is a retrospective cohort study based on healthcare databases from multiple sites representing numerous
30 135 geographical regions. To enable consistent analysis and reporting across different databases in different regions
31 136 and healthcare settings, a common protocol, statistical analysis plan (SAP), and an analytical common data
32 137 model (ACDM) will be used to obtain aggregated data from each database. The study will consist of annual
33 138 cohorts of patients who experience hip fracture from each database. Each site will convert their raw data into
34 139 an ACDM format and apply the common statistical code provided by the study coordinator (University of Hong
35 140 Kong) to perform the analysis. The study coordinator will not receive any patient-level data from the sites.
36 141 Instead, each site will conduct the analysis locally and share aggregated results with the study coordinator.
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42 43 142 **Data source**

44
45 143 This study will obtain aggregated data from the participating sites. All included sites will use patient-level
46 144 electronic health data derived from the respective national or regional administrative databases, clinical
47 145 databases, or registry databases. The study period will be from 1 January 2005 to 31 December 2018, subject to
48 146 data availability in each study site. A full list of participating sites and databases is provided in Table 1.
49

50
51 147 The study sites will contribute aggregated data on diagnosis, medications, mortality, and other data associated
52 148 with hip fracture in a defined population. Depending on the data capability to address study questions (i.e., fit-
53 149 for-purpose), the study sites will contribute aggregated data for some or all of the objectives. Study sites can
54 150 contribute incidence estimates for objective 1 for data sources of population-based data (i.e., a defined
55 151 denominator). If complete prescription data are available, study sites can contribute the treatment rates for
56 152 objective 2. Study sites can contribute the mortality rates for objective 3 if their database contains death data or
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3 153 can link to death registries.

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5 154 **Study population**

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8 155 Patients aged 50 years and older and hospitalised due to hip fracture from 1 January 2005 to 31 December 2018
9 156 will be included. Patients will be excluded if they meet any of the following criteria: i) had a diagnosis of hip
10 157 fracture within 12 months before the initial hip fracture; ii) had missing sex or age information; or iii) had less
11 158 than 12 months continuous observation period in the data source prior to the start of the calendar year.

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15 159 Identification of the 12 months observation period in the data source depends on the type of data source. For a
16 160 database of medical claims, the patient's enrolment date should precede the hip fracture by at least 12 months.
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18 161 For a database of hospital electronic medical records (EMRs), the patient's first event (e.g. medical visit or
19 162 prescription) in the database should precede the hip fracture by at least 12 months.

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22 163 **Baseline and Follow-up period**

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24 164 The index date will be defined as the date of admission for the initial hip fracture. The baseline period will be
25 165 the 1-year period before the index date (not including the index date).

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28 166 For the primary objective of hip fracture incidence, there is no follow-up of patients. For the secondary
29 167 objectives of post-fracture treatment and mortality, each patient will be followed from the index date until
30 168 another hip fracture episode, 12 months, death, disenrollment from database, 31 December 2018 or the end of
31 169 data available in a database, whichever is earliest.

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35 170 **Outcome assessment**

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37 171 Hip fracture episodes will be defined as an in-patient diagnosis with ICD-9/-10 codes or equivalent codes of
38 172 other diagnostic coding systems. Hip fracture is a major clinical event that almost always requires
39 173 hospitalization and is generally accurately coded.¹⁶⁻¹⁸ The diagnosis codes to identify hip fracture are subject to
40 174 local clinical practice; the sites will use their own standard or validated algorithms for identifying hip fracture.

41
42
43 175 The algorithms for hip fracture used by each site, and positive predictive values where available, are provided
44 176 in Table 2. Most data sources have inpatient data. If inpatient diagnoses are not available, for example, in
45 177 databases from general practice (e.g., Netherlands), the documented hip fracture will be used. Patients may have
46 178 multiple hip fracture episodes during the study period. The initial hip fracture will be defined as the first
47 179 occurrence of hip fracture without any inpatient or outpatient hip fracture diagnosis during the 1-year baseline
48 180 period. All the hip fracture episodes including the initial hip fracture and any subsequent new episodes
49 181 (contralateral or ipsilateral) will be considered in the calculation of hip fracture incidence. Subsequent new
50 182 episodes are defined by no inpatient hip fracture diagnosis in the 180-days prior. (i.e., wash-out period). A study
51 183 design schema for defining hip fracture episodes is illustrated in Figure 1.

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58 184 Pharmacological treatments for fracture prevention include medications that are recommended for secondary
59 185 prevention of osteoporotic fractures. These medications will be identified with prescription/dispensing of the

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3 186 medications classified using the WHO Anatomical Therapeutic Chemical (ATC) Classification System codes
4
5 187 whenever possible or equivalent codes of other drug coding systems used at the study site.
6

7 188 Date or month of death will be extracted. The cause of death (defined by ICD-9/-10 codes, or equivalent codes
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9 189 of other classification systems used at the study sites) will be included if available.
10

11 190 **Covariate assessment**

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13 191 Sex and date or month of birth (or age at index date) will be captured. In addition, history of osteoporosis
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15 192 treatment defined as at least one prescription/dispensing record of any anti-osteoporosis medication during the
16
17 193 1-year baseline period will be captured.
18

19 194 For the secondary objective of treatment following hip fracture, patients will be considered as “ever use” if the
20
21 195 patient had a history of osteoporosis treatment; and patient will be considered as “new use” if the patient did
22
23 196 not have a history of osteoporosis treatment.
24

24 197 **Statistical analysis**

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26 198 Microsoft Excel®, R, Statistical Analysis System (SAS) (SAS Inc., United States) will be used for data
27
28 199 management and analyses. The proportion of missing data will be reported, but missing data will not be imputed.
29
30 200 Patients with missing age or sex information will be excluded during the selection procedure. The number of
31
32 201 study variables collected per patient is small and the impact of missing data is expected to be minimal and not
33
34 202 likely to impact the reliability of the results.
35

35 203 Description of Patient Characteristics

36
37 204 Description of baseline characteristics will include age, sex, and history of anti-osteoporosis medications.
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39 205 Discrete variables will be summarised using frequencies and proportions, and continuous variables will be
40
41 206 summarised using means and standard deviation or medians and interquartile range, as appropriate. Age will be
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43 207 categorised into 5-year age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80 or above.
44

44 208 Primary objective: Incidence of hip fracture

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46 209 Population data will be used as the denominator (i.e., population at-risk) to calculate the annual incidence of hip
47
48 210 fracture. The population of each calendar year will be defined as people i) aged 50 years and older, ii) with
49
50 211 known sex, iii) enrolled/registered in the database on 1 January of that year, and iv) with a 1-year baseline
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52 212 period. If the population in the database is unknown, the national/regional population reported by the
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54 213 government will be used. The mid-year population of the database or the reported national/regional population
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56 214 aged 50 years and older of each calendar year will be used as the denominator.
57

58 215 Similar to prior studies,¹⁹⁻²¹ the incidence (per 1,000 persons) rate per calendar year of hip fractures will be
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60 216 calculated as the sum of new hip fracture episodes in a year divided by the population at-risk on 1 Jan of that
61
62 217 year. In addition, age- and sex-standardised incidence will be calculated to facilitate cross-geography

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3 218 comparisons. The world population estimates in 2020 reported by the United Nations
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5 219 (<https://population.un.org/wpp/Download/Standard/Population/>) will be used as a standard.
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7 220 A linear regression model will be used to test for time trends in the annual incidence in each site, assuming a
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9 221 linear trend for the hip fracture incidence, throughout the study period. The annual incidence as a dependent
10 222 variable and the calendar year as a predictor variable will be fitted into the model. A two-tailed $P < 0.05$ will be
11
12 223 considered statistically significant.
13

14 224 Secondary objective: Treatment proportion

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16 225 Similar to a prior study,²² we will use the Kaplan-Meier method to estimate the treatment proportion within 3,
17
18 226 6, and 12 months of fracture and 95% confidence intervals (CI), censoring patients on another hip fracture
19
20 227 episode, 12 months, death, disenrollment from database, 31 December 2018, or the end of data available in a
21 228 database; whichever is earliest.
22

23 229 The description of the treatment proportion will include i) the treatment proportion by year of initial hip fracture;
24
25 230 ii) the treatment proportion for new medication users (treatment-naive), defined as those with no prescriptions
26
27 231 filled for osteoporosis medications within 12 months prior to their hip fracture (i.e., during the baseline period);
28 232 and iii) the treatment proportion by the type of treatment (see Table 3 for details).
29

30 233 Secondary objective: One-year mortality following hip fracture

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32 234 Similar to a prior study,²⁰ the one-year mortality (per 100 patients) rate per calendar year of initial hip fracture
33
34 235 will be calculated as the sum of patients who died of any cause during the 12-month follow-up period divided
35
36 236 by the sum of patients with an initial hip fracture. An additional analysis using the Kaplan-Meier method to
37 237 account for censoring will be included as well. In addition, the mortality will be ascertained for the first 3 months
38
39 238 and the first 6 months after the initial hip fracture. Age- and sex- standardized mortality will be calculated to
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41 239 facilitate cross-geography comparisons. Global age- and sex-specific mortality as reported by WHO will be
42 240 used as a standard.
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44 241 Additional analysis

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46 242 Sensitivity analyses will be performed to evaluate the robustness of the results from the primary analysis. In the
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48 243 primary analysis, a wash-out period of 180 days is used to define a new episode of hip fracture. In the sensitivity
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50 244 analysis, a shorter (90 days) and a longer (365 days) wash-out period will be used. In addition, the requirement
51 245 of at least 12-months continuous observation period may not capture fractures in a given year among those with
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53 246 less than a year of prior observation. Thus, a sensitivity analysis by removing this requirement will be conducted
54
55 247 to evaluate if this requirement affects the estimates.
56

57 248 Fractures may occur in patients for reasons other than osteoporosis. In databases where the information is
58 249 available, we will repeat the analysis in the subgroup excluding patients with any of the following criteria: i)
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60 250 concurrent diagnosis of high trauma fractures (high trauma is defined as vehicle accident or fall from greater

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3 251 than standing height); ii) bone metastasis during the 1-year baseline period; iii) Paget's disease during the 1-
4
5 252 year baseline period; or iv) osteogenesis imperfecta during the 1-year baseline period.

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7 253 Subgroup analysis will be conducted. Estimates of hip fracture incidence and mortality will be stratified by sex
8
9 254 and age (in 5-years age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80 or above).

10 11 255 12 13 256 **Sample size**

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15 257 The estimated sample size in the databases ranges from several hundred hip fractures per year to tens of
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17 258 thousands of hip fractures per year. For example, the data source for Hong Kong, a region of 7.2 million people
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19 259 with 2.8 million adults aged 50+, has approximately 9,300 hip fractures per year in adults aged 50+ (a crude
20 260 rate of 330 fractures per 100,000). The estimated samples sizes for each database are provided in Table 4.
21

22 261 23 24 25 262 **Limitations**

26
27 263 In general, most of the databases were built for administrative or reimbursement purposes rather than research
28
29 264 purposes. The databases represent a variety of data sources, healthcare settings, and coding practices each of
30 265 which will have different features and limitations.
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32 266 Measurement Errors/Misclassifications

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35 267 The study will use prescription/dispensing data to assess treatment, which is only a proxy for the patient taking
36 268 their medication. The actual treatment with certain medications, such as oral bisphosphonates, may therefore be
37
38 269 overestimated. In addition, use of zoledronic acid is not expected to be captured in all databases. For example,
39 270 in countries where zoledronic acid is administered in hospitals or outpatient clinics, some databases do not
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41 271 readily capture medication administered in the hospital setting. In such circumstances, patients may be
42 272 misclassified as having no treatment even though they were exposed to zoledronic acid.
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45 273 The database for Hong Kong does not capture clinical records from private clinics/hospitals, though it is
46 274 expected that most of the cases will be admitted to public hospitals via emergency service.
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49 275 Several databases will capture only treatments in the public reimbursement system (Hong Kong, New Zealand,
50 276 South Korea, Taiwan, and others), hence the treatment rates might be underestimated by not including patients
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52 277 in the private payment system.
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54 278 Information Bias

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56 279 Since hip fracture is a major clinical event that almost always requires hospitalisation, only hospital diagnoses
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58 280 of hip fracture will be considered in most databases (except when inpatient diagnoses are not available in the
59 281 database). Fractures may occur in patients for reasons other than osteoporosis (e.g. trauma, bone metastasis,
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282 Paget's disease, osteogenesis imperfect). Eligibility criteria for the study have been kept broad for the practical
283 purpose of applying consistent definitions across multiple databases. To inform interpretation, we will conduct
284 a sensitivity analysis excluding patients with these four criteria in those databases able to support the analysis.

285 Selection Bias

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

292 **Patient and public involvement**

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

298 **Ethics and dissemination**

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

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

307 **Authors' contributions**

308 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
309 edited the protocol. All the authors had critical revision on the protocols. I.C.W. is the correspondence author
310 and takes responsibility for the integrity of the study.

Funding statement

This work was supported by Amgen Inc. Award/Grant number is not applicable.

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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3 386 Figure 1 Study design schema for estimating incidence of hip fracture (Objective 1).
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For peer review only

388 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

390 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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408 Table 3 Type of anti-osteoporosis medications

Type	Drug
Oral bisphosphonates	Alendronate
	Ibandronate (oral)
	Risedronate
	Clodronate
	Etidronate
IV bisphosphonates	Pamidronate
	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***	
			Women	Men	Women (22.1% of age 50+)	Men (25.6% of age 50+)	Women (0.45% of age 50+)	Men (0.20% of age 50+)
Asia-Pacific								
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	7M	1.5M (21%)	1.3M (19%)	325K	28K	6615	2660
Japan	Japanese Medical Data Center (JMDC)	3.9M	418K (11%)	550K (14%)	92K	6K	1882	1101
South Korea	Health Insurance Review and Assessment Service (HIRA)	50M	9M (18%)	3.3M (16%)	2M	18K	40500	6600
Taiwan	National Health Insurance Database (NHID)	25M	3.5M (14%)	3.5M (14%)	774K	31K	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	85K	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	2K	3933	1564
Netherlands	Integrated Primary Care Information (IPCI) database	2.4M	480K (20%)	432K (18%)	106K	9K	2160	864
Italy	Pool of databases from 4 different regions (Lazio, Napoli, Umbria, Torino)	10M	2.3M (23%)	1.9M (19%)	508K	25K	10350	3800
Germany	German sickness funds (WIG2)	4.5M	1.0M (23%)	0.9M (20%)	229K	9K	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	74M	63000	22440
Northern Europe								
Denmark	Danish National Prescription Registry, Danish National Patient Register	5.8M	1.2M (20%)	1.0M (18%)	256K	9K	5220	2088
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	5.4M	1.2M (22%)	1.0M (19%)	264K	8K	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%)				

411 TBD To be determined

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

413 **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
414 the femoral neck) and prevalence in the population aged over 50 years in the EU27, 2010

415 ***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

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418 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

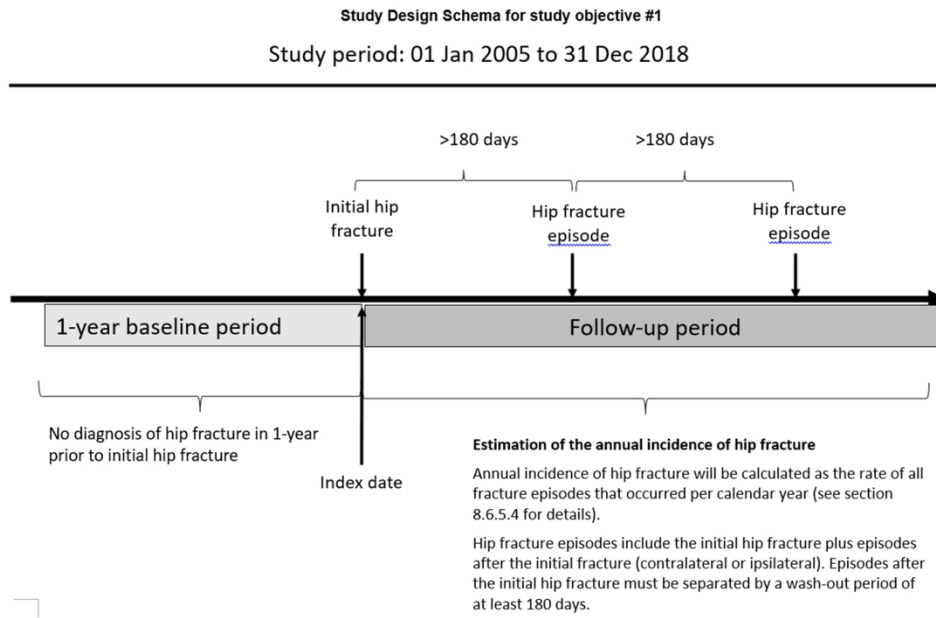


Figure 1 Study design schema

299x190mm (300 x 300 DPI)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047258.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Apr-2021
Complete List of Authors:	<p>SING, CHOR WING; University of Hong Kong, Pharmacology and Pharmacy Lin, Tzu-Chieh; Amgen Inc, Center for Observational Research Bartholomew, Sharon; Public Health Agency of Canada, Centre for Surveillance and Applied Research Bell, J Simon; Monash University, Centre for Medicine Use and Safety Bennett, Corina; Amgen Inc, Center for Observational Research Beyene, Kebede; The University of Auckland Faculty of Medical and Health Sciences, School of Pharmacy Bosco-Lévy, Pauline ; University of Bordeaux, Bordeaux PharmacoEpi Chan, Amy; The University of Auckland School of Pharmacy Chandran, Manju; Singapore General Hospital, Osteoporosis and Bone Metabolism Unit, Department of Endocrinology Cheung, Ching-Lung; University of Hong Kong Faculty of Medicine, Department of Pharmacology and Pharmacy Doyon, Caroline; Public Health Agency of Canada, Centre for Surveillance and Applied Research Droz, Cécile ; Université de Bordeaux, Ganesan, Ganga; Ministry of Health Singapore Hartikainen, Sirpa ; University of Eastern Finland School of Pharmacy Ilomaki, Jenni; Monash University, Centre for Medicine Use and Safety Jeong, Han Eol; Sungkyunkwan University School of Pharmacy Kiel, Douglas; Institute for Aging Research, Hebrew Senior Life, Beth Israel Deaconess Medical Center, Harvard Medical School Kubota, Kiyoshi; NPO Drug Safety Research Unit Japan Lai, Edward Chia-Cheng; National Cheng Kung University, Institute of Clinical Pharmacy and Pharmaceutical Sciences Lange, Jeff; Amgen Inc, Center for Observational Research Lewiecki, E; New Mexico Clinical Research & Osteoporosis Center, Liu, Jiannong; Hennepin Healthcare Research Institute, Chronic Disease Research Group Man, Kenneth; University College London, Research Department of Practice and Policy, UCL School of Pharmacy; The University of Hong Kong, Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy Mendes de Abreu, Mirhelen; Universidade Federal do Rio de Janeiro, Rheumatology Service, Internal Medicine Department, School of Medicine Moore, Nicolas; Universite de Bordeaux, Pharmacologie Clinique</p>

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Primary Subject Heading :	Global health
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Keywords :	Calcium & bone < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, EPIDEMIOLOGY, PUBLIC HEALTH

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

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3 **Abstract**
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5 **Introduction** Hip fractures are associated with a high burden of morbidity and mortality. Globally, there is wide
6 variation in the incidence of hip fracture in people aged 50 years and older. Longitudinal and cross-geographical
7 comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However,
8 systematic reviews of studies that utilise different methods and study periods do not permit direct comparison
9 across geographical regions. Thus, the objective of this study is to investigate global secular trends in hip
10 fracture incidence, mortality, and use of post-fracture pharmacological treatment across Asia, Oceania, North
11 and South America, and Western and Northern Europe using a unified methodology applied to health records.
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17 **Methods and analysis** This retrospective cohort study will use a common protocol and an analytical common
18 data model (ACDM) approach to examine incidence of hip fracture across population-based databases in
19 different geographical regions and healthcare settings. The study period will be from 2005 to 2018 subject to
20 data availability in study sites. Patients aged 50 years and older and hospitalised due to hip fracture during the
21 study period will be included. The primary outcome will be expressed as the annual incidence of hip fracture.
22 Secondary outcomes will be the pharmacological treatment rate and mortality within 12 months following initial
23 hip fracture by year. For the primary outcome, crude and standardised incidence of hip fracture will be reported.
24 Linear regression will be used to test for time trends in the annual incidence. For secondary outcomes, the crude
25 mortality and standardised mortality incidence will be reported.
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32 **Ethics and dissemination** Each participating site will follow the relevant local ethics and regulatory
33 frameworks for study approval. The results of the study will be submitted for peer-reviewed scientific
34 publications and presented at scientific conferences.
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37 **Keywords:** Hip Fractures, Osteoporosis, Incidence, Mortality, Internationality
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3 78 **Strengths and limitations of this study**
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- 5 79 • This study will involve countries/regions across Asia, Oceania, North and South America, Western and
6 Northern Europe.
7 80
8 81 • The study will use a common protocol and an analytical common data model to ensure consistency in data
9 analysis and validity in cross-geographical comparisons.
10 82
11 83 • This study will build a global real-world data platform to efficiently collaborate across multiple institutions.
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13 84 • Several databases will capture only treatments in the public reimbursement system. Hence the treatment
14 rates might be underestimated by not including patients in the private payment system.
15 85
16 86 • Though most of the data sources will be representative of the country-specific population, a few data sources
17 will be representative of local hospitals and regional population.
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88 Introduction

89 Hip fracture is a leading cause of high morbidity (30% - 50% of patients lose functional independence)^{1 2} and
90 mortality (approximately 22% mortality rate at one year).³ Globally, there is wide variation in the incidence of
91 hip fracture in people aged 50 years and older⁴, ranging from an age-standardised rate of over 500 cases per
92 100,000 adults (e.g. Denmark) to less than 100 cases per 100,000 adults (e.g. South Africa). Secular trends in
93 the incidence of hip fracture have been suggested to follow the level of urbanisation.¹

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

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

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

121 Hypothesis and Objectives

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3 122 This is an estimation study and no hypothesis will be tested. The study aim is to characterise hip fracture
4 123 incidence estimates by year and assess the trend among men and women aged 50 years and older within multiple
5 124 countries. We aim to investigate the between-country and between-region differences in hip fracture incidence,
6 125 mortality and pharmacological treatment rate. This may in turn lead to research into environmental,
7 126 sociodemographic and biological explanatory factors for geographical variations in incidence and mortality of
8 127 hip fracture.
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13 128 Primary objective

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16 129 • To estimate the annual incidence of hip fracture and evaluate the trend during 2005 - 2018 (Objective 1).

17 18 130 Secondary objective

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20 131 • To estimate the proportion of patients using a pharmacological treatment for osteoporosis within 12 months
21 132 following their initial hip fracture by calendar year (Objective 2).
- 22
23 133 • To estimate the mortality rate within 12 months following patients' initial hip fracture by calendar year
24 134 (Objective 3).

25 26 27 135 28 29 30 136 **Methods and analysis**

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32 137 The study is in the common data model development phase. We plan to start the data analysis in the second
33 138 quarter of 2021. The study will end in the first quarter of 2022.

34 35 36 139 **Study design**

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38 140 This is a retrospective cohort study based on healthcare databases from multiple sites representing numerous
39 141 geographical regions. To enable consistent analysis and reporting across different databases in different regions
40 142 and healthcare settings, a common protocol, statistical analysis plan (SAP), and an analytical common data
41 143 model (ACDM) will be used to obtain aggregated data from each database. The study will consist of annual
42 144 cohorts of patients who experience hip fracture from each database. Each site will convert their raw data into
43 145 an ACDM format and apply the common statistical code provided by the study coordinator (University of Hong
44 146 Kong, HKU) to perform the analysis. The study coordinator will not receive any patient-level data from the
45 147 sites. Instead, each site will conduct the analysis locally using a centrally developed analytic plan and share
46 148 aggregated results with the study coordinator for the analysis of the pooled data.
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52 53 149 **Data source**

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55 150 This study will obtain aggregated data from the participating sites. All included sites will use patient-level
56 151 electronic health data derived from the respective national or regional administrative databases, clinical
57 152 databases, or registry databases. The study period will be from 1 January 2005 to 31 December 2018, subject to
58 153 data availability in each study site. A full list of participating sites and databases is provided in Table 1.
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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

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3 187 multiple hip fracture episodes during the study period. The initial hip fracture will be defined as the first
4 188 occurrence of hip fracture without any inpatient or outpatient hip fracture diagnosis during the 1-year baseline
5 189 period. All the hip fracture episodes including the initial hip fracture and any subsequent new episodes
6 190 (contralateral or ipsilateral) will be considered in the calculation of hip fracture incidence. Subsequent new
7 191 episodes are defined by no inpatient hip fracture diagnosis in the 180 days prior. (i.e., wash-out period). A study
8 192 design schema for defining hip fracture episodes is illustrated in Figure 1.

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11 193 Pharmacological treatments for fracture prevention include medications that are recommended for secondary
12 194 prevention of osteoporotic fractures. These medications will be identified with prescription/dispensing of the
13 195 medications classified using the WHO Anatomical Therapeutic Chemical (ATC) Classification System codes
14 196 whenever possible or equivalent codes of other drug coding systems used at the study site.

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17 197 Date or month of death will be extracted. The cause of death (defined by ICD-9/-10 codes, or equivalent codes
18 198 of other classification systems used at the study sites) will be included if available.

19 200 **Covariate assessment**

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22 200 Sex and date or month of birth (or age at index date) will be captured. In addition, history of osteoporosis
23 201 treatment defined as at least one prescription/dispensing record of any anti-osteoporosis medication during the
24 202 1-year baseline period will be captured.

25
26 203 For the secondary objective of treatment following hip fracture, patients will be considered as “ever use” if the
27 204 patient had a history of osteoporosis treatment; and patient will be considered as “new use” if the patient did
28 205 not have a history of osteoporosis treatment.

29 206 **Statistical analysis**

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31 207 Microsoft Excel®, R, Statistical Analysis System (SAS) (SAS Inc., United States) will be used for data
32 208 management and analyses. The proportion of missing data will be reported, but missing data will not be imputed.
33 209 Patients with missing age or sex information will be excluded during the selection procedure. The number of
34 210 study variables collected per patient is small and the impact of missing data is expected to be minimal and not
35 211 likely to impact the reliability of the results.

36 212 Description of Patient Characteristics

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38 213 Description of baseline characteristics will include age, sex, and history of anti-osteoporosis medications.
39 214 Discrete variables will be summarised using frequencies and proportions, and continuous variables will be
40 215 summarised using means and standard deviation or medians and interquartile range, as appropriate. Age will be
41 216 categorised into 5-year age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above.

42 217 Primary objective: Incidence of hip fracture

43 218 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-naïve), 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

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3 252 primary analysis, a wash-out period of 180 days is used to define a new episode of hip fracture. In the sensitivity
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5 253 analysis, a shorter (90 days) and a longer (365 days) wash-out period will be used. In addition, the requirement
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7 254 of at least 12-month continuous observation period may not capture fractures in a given year among those with
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9 255 less than a year of prior observation. Thus, a sensitivity analysis by removing this requirement will be conducted
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11 256 to evaluate if this requirement affects the estimates.

12 257 Fractures may occur in patients for reasons other than osteoporosis. In databases where the information is
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14 258 available, we will repeat the analysis in the subgroup excluding patients with any of the following criteria: i)
15 259 concurrent diagnosis of high trauma fractures (high trauma is defined as vehicle accident or fall from greater
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17 260 than standing height); ii) bone metastasis during the 1-year baseline period; iii) Paget's disease during the 1-
18 261 year baseline period; or iv) osteogenesis imperfecta during the 1-year baseline period.

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20 262 Given the high mortality in the first year after hip fracture, death could be a competing risk event leading to
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22 263 overestimation of treatment probability. Therefore, a competing risk analysis using the cumulative incidence
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24 264 function approach will be performed to estimate the marginal probability of treatment with adjustment for
25 265 competing risk of death.

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27 266 Subgroup analysis will be conducted. Estimates of hip fracture incidence and mortality will be stratified by sex
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29 267 and age (in 5-years age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above).

30 31 268 32 33 269 **Analytical common data model (ACDM)**

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35 270 The ACDM will be created to increase validity and consistency of data analysis using multi-databases. The sites
36 271 will convert de-identified subject-level data into table formats in ACDM and use standard programming codes
37 272 to conduct the statistical analysis and generate aggregate-level data. The ACDM will be co-developed by HKU
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39 273 and Amgen, Inc. R and SAS programming codes will be developed by the programming team in HKU and
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41 274 Amgen, Inc, respectively. To ensure quality assurance, at least two programmers will be involved to cross check
42 275 the codes. The R and SAS programming codes will run on the same sample dataset and the results should be a
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44 276 100% match. It is expected that the development of ACDM and programming codes will take around 2-3 months.
45 277 Since the data structure varies across databases, HKU will discuss with the sites if any modification of the
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47 278 ACDM and programming codes will be needed. All the site-specific modifications will be documented. Sharing
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49 279 of the script as open-source code will be subject to journal requirement when the results are published.

50 51 52 280 53 54 281 **Sample size**

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56 282 The estimated sample size in the databases ranges from several hundred hip fractures per year to tens of
57 283 thousands of hip fractures per year. For example, the data source for Hong Kong, a region of 7.2 million people
58 284 with 2.8 million adults aged 50+, has approximately 9,300 hip fractures per year in adults aged 50+ (a crude

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3 285 rate of 330 fractures per 100,000). The estimated samples sizes for each database are provided in Table 4.
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7 287 **Limitations**

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10 288 In general, most of the databases were built for administrative or reimbursement purposes rather than research
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12 289 purposes. The databases represent a variety of data sources, healthcare settings, and coding practices each of
13 290 which will have different features and limitations. The strengths and limitations of different type of databases
14
15 291 have been discussed elsewhere.²⁴ The features of the databases in this study are shown in Table 1. A majority
16 292 of databases have a high (over 90%) population coverage and official census data will be used as denominator.
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18 293 Databases with lower population coverage will use the actual number of individuals in the databases as
19
20 294 denominator (Japan, UK and US). The databases in Italy do not link to national/regional death registry. National
21 295 prescription data are only available in Australia, Denmark, Finland, New Zealand, South Korea, and Taiwan.
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23 296 Measurement Errors/Misclassifications

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25 297 The study will use prescription/dispensing data to assess treatment, which is only a proxy for the patient taking
26 298 their medication. The actual treatment with certain medications, such as oral bisphosphonates, may therefore be
27 299 overestimated. In addition, use of zoledronic acid is not expected to be captured in all databases. For example,
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29 300 in countries where zoledronic acid is administered in hospitals or outpatient clinics, some databases do not
30 301 readily capture medication administered in the hospital setting. In such circumstances, patients may be
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32 302 misclassified as having no treatment even though they were exposed to zoledronic acid.
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36 303 The database for Hong Kong does not capture clinical records from private clinics/hospitals, though it is
37 304 expected that most of the cases will be admitted to public hospitals via emergency service.
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40 305 Several databases will capture only treatments in the public reimbursement system (Hong Kong, South Korea,
41 306 Taiwan, and others), hence the treatment rates might be underestimated by not including patients in the private
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43 307 payment system. Similarly, non-reimbursed medications cannot be captured in the reimbursement system,
44 308 leading to potential underestimation of treatment rates.
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46 309 Information Bias

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49 310 Since hip fracture is a major clinical event that almost always requires hospitalisation, only hospital diagnoses
50 311 of hip fracture will be considered in most databases (except when inpatient diagnoses are not available in the
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52 312 database). Fractures may occur in patients for reasons other than osteoporosis (e.g. trauma, bone metastasis,
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54 313 Paget's disease, osteogenesis imperfect). Eligibility criteria for the study have been kept broad for the practical
55 314 purpose of applying consistent definitions across multiple databases. To inform interpretation, we will conduct
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57 315 a sensitivity analysis excluding patients with these four criteria in those databases able to support the analysis.
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59 316 Selection Bias

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3 317 All patients who fulfil the eligibility criteria in each database will be included. A majority of the databases
4 318 cover over 90% of the population (e.g., Finland, Hong Kong, South Korea, and others.) (see Table 1) and
5 319 therefore selection bias is not expected to be a major issue in these databases. However, a few data sources will
6 320 be representative of local hospitals with limited population coverage (e.g. Thailand), leading to potential
7 321 selection bias. For instance, the Japanese database has no subjects aged 75+ years and limited number of subjects
8 322 aged >60 years compared to national statistics. Given that Japan has a large population of the oldest adults and
9 323 the mean age for hip fracture is around 70-80 years, underestimation of the population incidence of hip fracture
10 324 in Japan would be expected. However, the data would be still representative of the population under 75 years
11 325 old. Although these sites have limited data for population estimates, the results are still informative for cross-
12 326 geographical comparisons. More importantly, the site participation in this study can facilitate global cooperation,
13 327 and also raise the awareness of the need for standardised high-quality national data for research.
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23 329 **Patient and public involvement**

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26 330 The study will involve retrospective analysis of secondary data collected from databases. Patients are de-
27 331 identified and there is no direct patient involvement. Thus, patient consent is not required. However, several
28 332 researchers involved in this study routinely consult with patients in the design, development and reporting of
29 333 research at a national level. Patients may be involved in presentations and dissemination of the results at a
30 334 national level.
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34 335 35 36 336 **Ethics and dissemination**

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39 337 Each participating site will follow the relevant local ethics and regulatory frameworks for study approval. The
40 338 status of ethics approval in each site is listed in Supplementary Table. All data to be used in this study are taken
41 339 from existing anonymised records. In addition, participating sites will only share aggregated data with the study
42 340 coordinators.
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46 341 The results of the study will be submitted for peer-reviewed scientific publications and presented in scientific
47 342 conferences. Authorship of any publications resulting from this study will be determined on the basis of the
48 343 International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting,
49 344 Editing, and Publication of Scholarly Work in Medical Journals.
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53 345 54 55 346 **Authors' contributions**

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57 347 CWS co-developed and wrote the protocol. TCL co-developed, drafted, reviewed and commented on the
58 348 protocol. JO, CB, JL, CLC, KKM co-developed, reviewed and commented on the protocol. SB, JSB, KB, PBL,
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3 349 AHYC, MC, CYD, CDP, GG, SH, JH, HEJ, DPK, KK, ECCL, EML, JNL, MMA, NM, NO, ABP, DPA, JYS,
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5 350 HTS, KBT, AMT, KMCV, GHMW, SW, HZ reviewed and commented on the protocol. ICW is the principal
6
7 351 investigator of the study, takes responsibility for the integrity of the study, co-developed, reviewed, and
8
9 352 commented on the protocol.

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12 354 **Funding statement**

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15 355 This work was supported by Amgen Inc. Award/Grant number is not applicable.

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17 356

18 19 357 **Competing Interest**

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21 358 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
22
23 359 financial support from Amgen Inc. for the submitted work.

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27 361 **References**

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3 445 Figure 1 Study design schema for estimating incidence of hip fracture (Objective 1).
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447 Table 1 List of participating countries/regions and databases

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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								

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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

450 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.)

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3 452 Table 3 Type of anti-osteoporosis medications
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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

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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***	
			Women	Men	Women (22.1% of age 50+)	Men (5.6% of age 50+)	Women (0.45% of age 50+)	Men (0.20% of age 50+)
Asia-Pacific								
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	7M	1.5M (21%)	1.3M (19%)	325K	28K	6615	2660
Japan	Japanese Medical Data Center (JMDC)	3.9M	418K (11%)	550K (14%)	92K	6K	1882	1101
South Korea	Health Insurance Review and Assessment Service (HIRA)	50M	9M (18%)	3.3M (16%)	2M	18K	40500	6600
Taiwan	National Health Insurance Database (NHID)	25M	3.5M (14%)	3.5M (14%)	774K	31K	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	85K	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	22K	3933	1564
Netherlands	Integrated Primary Care Information (IPCI) database	2.4M	480K (20%)	432K (18%)	106K	9K	2160	864
Italy	Pool of databases from 5 different regions (Lazio, Napoli, Umbria, Piemonte, Marche)	10M	2.3M (23%)	1.9M (19%)	508K	25K	10350	3800
Germany	German sickness funds (WIG2)	4.5M	1.0M (23%)	0.9M (20%)	229K	9K	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	74M	63000	22440
Northern Europe								
Denmark	Danish National Prescription Registry, Danish National Patient Register	5.8M	1.2M (20%)	1.0M (18%)	256K	9K	5220	2088
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	5.4M	1.2M (22%)	1.0M (19%)	264K	8K	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 fee-for-service 20%	TBD	(18%)	(16%)				
US	Optum	TBD	(18%)	(16%)				

455 TBD To be determined

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

457 **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
458 the femoral neck) and prevalence in the population aged over 50 years in the EU27, 2010

459 ***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

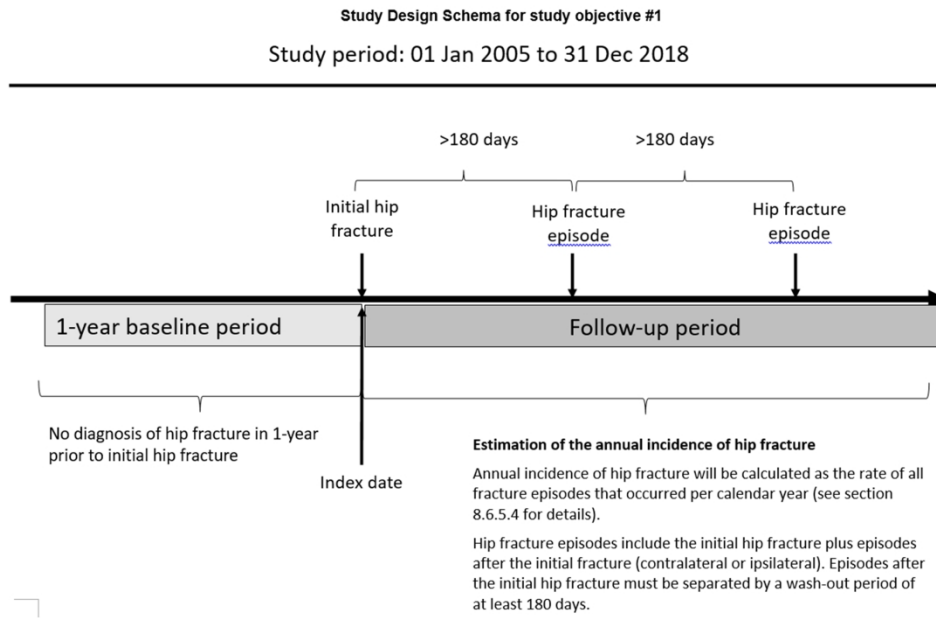


Figure 1 Study design schema

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

BMJ Open

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

Journal:	<i>BMJ Open</i>
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1
2
3 **Abstract**
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57 **Introduction** Hip fractures are associated with a high burden of morbidity and mortality. Globally, there is wide
58 variation in the incidence of hip fracture in people aged 50 years and older. Longitudinal and cross-geographical
59 comparisons of health data can provide insights on aetiology, risk factors, and healthcare practices. However,
60 systematic reviews of studies that utilise different methods and study periods do not permit direct comparison
61 across geographical regions. Thus, the objective of this study is to investigate global secular trends in hip
62 fracture incidence, mortality, and use of post-fracture pharmacological treatment across Asia, Oceania, North
63 and South America, and Western and Northern Europe using a unified methodology applied to health records.

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

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

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

77 **Strengths and limitations of this study**

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

87 Introduction

88 Hip fracture is a leading cause of high morbidity (30% - 50% of patients lose functional independence)^{1 2} and
89 mortality (approximately 22% mortality rate at one year).³ Globally, there is wide variation in the incidence of
90 hip fracture in people aged 50 years and older⁴, ranging from an age-standardised rate of over 500 cases per
91 100,000 adults (e.g. Denmark) to less than 100 cases per 100,000 adults (e.g. South Africa). Secular trends in
92 the incidence of hip fracture have been suggested to follow the level of urbanisation.¹

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

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

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

120 Hypothesis and Objectives

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3 121 This is an estimation study and no hypothesis will be tested. The study aim is to characterise hip fracture
4 122 incidence estimates by year and assess the trend among men and women aged 50 years and older within multiple
5 123 countries. We aim to investigate the between-country and between-region differences in hip fracture incidence,
6 124 mortality and pharmacological treatment rate. This may in turn lead to research into environmental,
7 125 sociodemographic and biological explanatory factors for geographical variations in incidence and mortality of
8 126 hip fracture.

13 127 Primary objective

- 15 128 • To estimate the annual incidence of hip fracture and evaluate the trend during 2005 - 2018 (Objective 1).

18 129 Secondary objective

- 20 130 • To estimate the proportion of patients using a pharmacological treatment for osteoporosis within 12 months
21 131 following their initial hip fracture by calendar year (Objective 2).
- 23 132 • To estimate the mortality rate within 12 months following patients' initial hip fracture by calendar year
24 133 (Objective 3).

29 135 **Methods and analysis**

31 136 The study is in the common data model development phase. We plan to start the data analysis in the second
32 137 quarter of 2021. The study will end in the first quarter of 2022.

35 138 **Study design**

37 139 This is a retrospective cohort study based on healthcare databases from multiple sites representing numerous
38 140 geographical regions. To enable consistent analysis and reporting across different databases in different regions
39 141 and healthcare settings, a common protocol, statistical analysis plan (SAP), and an analytical common data
40 142 model (ACDM) will be used to obtain aggregated data from each database. The study will consist of annual
41 143 cohorts of patients who experience hip fracture from each database. Each site will convert their raw data into
42 144 an ACDM format and apply the common statistical code provided by the study coordinator (University of Hong
43 145 Kong, HKU) to perform the analysis. The study coordinator will not receive any patient-level data from the
44 146 sites. Instead, each site will conduct the analysis locally using a centrally developed analytic plan and share
45 147 aggregated results with the study coordinator for the analysis of the pooled data.

52 148 **Data source**

54 149 This study will obtain aggregated data from the participating sites. All included sites will use patient-level
55 150 electronic health data derived from the respective national or regional administrative databases, clinical
56 151 databases, or registry databases. The study period will be from 1 January 2005 to 31 December 2018, subject to
57 152 data availability in each study site. A full list of participating sites and databases is provided in Table 1.

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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

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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.

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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.

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Baseline and Follow-up period

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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).

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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.

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Outcome assessment

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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

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3 186 multiple hip fracture episodes during the study period. The initial hip fracture will be defined as the first
4 187 occurrence of hip fracture without any inpatient or outpatient hip fracture diagnosis during the 1-year baseline
5 188 period. All the hip fracture episodes including the initial hip fracture and any subsequent new episodes
6 189 (contralateral or ipsilateral) will be considered in the calculation of hip fracture incidence. Subsequent new
7 190 episodes are defined by no inpatient hip fracture diagnosis in the 180 days prior. (i.e., wash-out period). A study
8 191 design schema for defining hip fracture episodes is illustrated in Figure 1.
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13 192 Pharmacological treatments for fracture prevention include medications that are recommended for secondary
14 193 prevention of osteoporotic fractures. These medications will be identified with prescription/dispensing of the
15 194 medications classified using the WHO Anatomical Therapeutic Chemical (ATC) Classification System codes
16 195 whenever possible or equivalent codes of other drug coding systems used at the study site.
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20 196 Date or month of death will be extracted. The cause of death (defined by ICD-9/-10 codes, or equivalent codes
21 197 of other classification systems used at the study sites) will be included if available.
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24 198 **Covariate assessment**

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26 199 Sex and date or month of birth (or age at index date) will be captured. In addition, history of osteoporosis
27 200 treatment defined as at least one prescription/dispensing record of any anti-osteoporosis medication during the
28 201 1-year baseline period will be captured.
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32 202 For the secondary objective of treatment following hip fracture, patients will be considered as “ever use” if the
33 203 patient had a history of osteoporosis treatment; and patient will be considered as “new use” if the patient did
34 204 not have a history of osteoporosis treatment.
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37 205 **Statistical analysis**

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39 206 Microsoft Excel®, R, Statistical Analysis System (SAS) (SAS Inc., United States) will be used for data
40 207 management and analyses. The proportion of missing data will be reported, but missing data will not be imputed.
41 208 Patients with missing age or sex information will be excluded during the selection procedure. The number of
42 209 study variables collected per patient is small and the impact of missing data is expected to be minimal and not
43 210 likely to impact the reliability of the results.
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48 211 Description of Patient Characteristics

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50 212 Description of baseline characteristics will include age, sex, and history of anti-osteoporosis medications.
51 213 Discrete variables will be summarised using frequencies and proportions, and continuous variables will be
52 214 summarised using means and standard deviation or medians and interquartile range, as appropriate. Age will be
53 215 categorised into 5-year age bands: 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above.
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57 216 Primary objective: Incidence of hip fracture

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59 217 Population data will be used as the denominator (i.e., population at-risk) to calculate the annual incidence of hip
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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-naïve), 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

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3 251 primary analysis, a wash-out period of 180 days is used to define a new episode of hip fracture. In the sensitivity
4 252 analysis, a shorter (90 days) and a longer (365 days) wash-out period will be used. In addition, the requirement
5 253 of at least 12-month continuous observation period may not capture fractures in a given year among those with
6 254 less than a year of prior observation. Thus, a sensitivity analysis by removing this requirement will be conducted
7 255 to evaluate if this requirement affects the estimates.

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12 256 Fractures may occur in patients for reasons other than osteoporosis. In databases where the information is
13 257 available, we will repeat the analysis in the subgroup excluding patients with any of the following criteria: i)
14 258 concurrent diagnosis of high trauma fractures (high trauma is defined as vehicle accident or fall from greater
15 259 than standing height); ii) bone metastasis during the 1-year baseline period; iii) Paget's disease during the 1-
16 260 year baseline period; or iv) osteogenesis imperfecta during the 1-year baseline period.

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20 261 Given the high mortality in the first year after hip fracture, death could be a competing risk event leading to
21 262 overestimation of treatment probability. Therefore, a competing risk analysis using the cumulative incidence
22 263 function approach will be performed to estimate the marginal probability of treatment with adjustment for
23 264 competing risk of death.

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27 265 Age- and sex-specific estimates of hip fracture incidence and mortality will be provided in 5-years age bands:
28 266 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74, 75 – 79, 80-84, 85 or above.

29 30 31 267 32 33 268 **Analytical common data model (ACDM)**

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36 269 The ACDM will be created to increase validity and consistency of data analysis using multi-databases. The sites
37 270 will convert de-identified subject-level data into table formats in ACDM and use standard programming codes
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39 271 to conduct the statistical analysis and generate aggregate-level data. The ACDM will be co-developed by HKU
40 272 and Amgen, Inc. R and SAS programming codes will be developed by the programming team in HKU and
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42 273 Amgen, Inc, respectively. To ensure quality assurance, at least two programmers will be involved to cross check
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44 274 the codes. The R and SAS programming codes will run on the same sample dataset and the results should be a
45 275 100% match. It is expected that the development of ACDM and programming codes will take around 2-3 months.
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47 276 Since the data structure varies across databases, HKU will discuss with the sites if any modification of the
48 277 ACDM and programming codes will be needed. All the site-specific modifications will be documented. Sharing
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50 278 of the script as open-source code will be subject to journal requirement when the results are published.

51 52 279 53 54 280 **Sample size**

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57 281 The estimated sample size in the databases ranges from several hundred hip fractures per year to tens of
58 282 thousands of hip fractures per year. For example, the data source for Hong Kong, a region of 7.2 million people
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60 283 with 2.8 million adults aged 50+, has approximately 9,300 hip fractures per year in adults aged 50+ (a crude

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3 284 rate of 330 fractures per 100,000). The estimated samples sizes for each database are provided in Table 4.
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6 7 8 286 **Limitations**

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10 287 In general, most of the databases were built for administrative or reimbursement purposes rather than research
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12 288 purposes. The databases represent a variety of data sources, healthcare settings, and coding practices each of
13 289 which will have different features and limitations. The strengths and limitations of different type of databases
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15 290 have been discussed elsewhere.²⁴ The features of the databases in this study are shown in Table 1. A majority
16 291 of databases have a high (over 90%) population coverage and official census data will be used as denominator.
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18 292 Databases with lower population coverage will use the actual number of individuals in the databases as
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20 293 denominator (Japan, UK and US). The databases in Italy do not link to national/regional death registry. National
21 294 prescription data are only available in Australia, Denmark, Finland, New Zealand, South Korea, and Taiwan.
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23 295 Measurement Errors/Misclassifications

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25 296 The study will use prescription/dispensing data to assess treatment, which is only a proxy for the patient taking
26 297 their medication. The actual treatment with certain medications, such as oral bisphosphonates, may therefore be
27 298 overestimated. In addition, use of zoledronic acid is not expected to be captured in all databases. For example,
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29 299 in countries where zoledronic acid is administered in hospitals or outpatient clinics, some databases do not
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31 300 readily capture medication administered in the hospital setting. In such circumstances, patients may be
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33 301 misclassified as having no treatment even though they were exposed to zoledronic acid.
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36 302 The database for Hong Kong does not capture clinical records from private clinics/hospitals, though it is
37 303 expected that most of the cases will be admitted to public hospitals via emergency service.
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40 304 Several databases will capture only treatments in the public reimbursement system (Hong Kong, South Korea,
41 305 Taiwan, and others), hence the treatment rates might be underestimated by not including patients in the private
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43 306 payment system. Similarly, non-reimbursed medications cannot be captured in the reimbursement system,
44 307 leading to potential underestimation of treatment rates.
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46 308 Information Bias

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48 309 Since hip fracture is a major clinical event that almost always requires hospitalisation, only hospital diagnoses
49 310 of hip fracture will be considered in most databases (except when inpatient diagnoses are not available in the
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51 311 database). Fractures may occur in patients for reasons other than osteoporosis (e.g. trauma, bone metastasis,
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53 312 Paget's disease, osteogenesis imperfect). Eligibility criteria for the study have been kept broad for the practical
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55 313 purpose of applying consistent definitions across multiple databases. To inform interpretation, we will conduct
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57 314 a sensitivity analysis excluding patients with these four criteria in those databases able to support the analysis.
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59 315 Selection Bias

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3 316 All patients who fulfil the eligibility criteria in each database will be included. A majority of the databases
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5 317 cover over 90% of the population (e.g., Finland, Hong Kong, South Korea, and others.) (see Table 1) and
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7 318 therefore selection bias is not expected to be a major issue in these databases. However, a few data sources will
8 319 be representative of local hospitals with limited population coverage (e.g. Thailand), leading to potential
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10 320 selection bias. For instance, the Japanese database has no subjects aged 75+ years and limited number of subjects
11 321 aged >60 years compared to national statistics. Given that the Japan data source does not contain the oldest
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13 322 adults at highest risk for hip fracture, the current protocol will provide an underestimation of the overall
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15 323 population incidence of hip fracture in Japan. However, the age subgroup analysis will provide a reasonable
16 324 measure of incidence in the population under 75 years old. Therefore, we will exclude Japan data in the
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18 325 estimation of overall population incidence but will include it only in the age-specific analysis. Although these
19 326 sites have limited data for population estimates, the results are still informative for cross-geographical
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21 327 comparisons. More importantly, the site participation in this study can facilitate global cooperation, and also
22 328 raise the awareness of the need for standardised high-quality national data for research.
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24 329 25 26 27 330 **Patient and public involvement**

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29 331 The study will involve retrospective analysis of secondary data collected from databases. Patients are de-
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31 332 identified and there is no direct patient involvement. However, several researchers involved in this study
32 333 routinely consult with patients in the design, development and reporting of research at a national level. Patients
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34 334 may be involved in presentations and dissemination of the results at a national level. Each participating site will
35 335 be responsible for obtaining ethical clearances in accordance with current regulations within their local
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37 336 jurisdiction.
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39 337 40 41 338 **Ethics and dissemination**

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43 339 Each participating site will follow the relevant local ethics and regulatory frameworks for study approval. The
44 340 status of ethics approval in each site is listed in Supplementary Table. All data to be used in this study are taken
45 341 from existing anonymised records. In addition, participating sites will only share aggregated data with the study
46
47 342 coordinators.
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51 343 The results of the study will be submitted for peer-reviewed scientific publications and presented in scientific
52 344 conferences. Authorship of any publications resulting from this study will be determined on the basis of the
53
54 345 International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting,
55 346 Editing, and Publication of Scholarly Work in Medical Journals.
56

57 347 58 59 60 348 **Authors' contributions**

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3 349 CWS co-developed and wrote the protocol. TCL co-developed, drafted, reviewed and commented on the
4 protocol. JO, CB, JL, CLC, KKM co-developed, reviewed and commented on the protocol. SB, JSB, KB, PBL,
5 350 AHYC, MC, CYD, CDP, GG, SH, JI, HEJ, DPK, KK, ECCL, EML, JNL, MMA, NM, NO, ABP, DPA, JYS,
6 351 HTS, KBT, AMT, KMCV, GHMW, SW, HZ reviewed and commented on the protocol. ICW is the principal
7 investigator of the study, takes responsibility for the integrity of the study, co-developed, reviewed, and
8 352 commented on the protocol.
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13 355 14 15 **Funding statement** 16 356

17
18 357 This work was supported by Amgen Inc. Award/Grant number is not applicable.
19
20 358
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22 359 **Competing Interest** 23

24
25 360 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
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31 363 **References** 32

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3 447 Figure 1 Study design schema for estimating incidence of hip fracture (Objective 1).
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449 Table 1 List of participating countries/regions and databases

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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.)

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3 454 Table 3 Type of anti-osteoporosis medications
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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

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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***	
			Women	Men	Women (22.1% of age 50+)	Men (5.6% of age 50+)	Women (0.45% of age 50+)	Men (0.20% of age 50+)
Asia-Pacific								
Hong Kong	Clinical Data Analysis and Reporting System (CDARS)	7M	1.5M (21%)	1.3M (19%)	325K	28K	6615	2660
Japan	Japanese Medical Data Center (JMDC)	3.9M	418K (11%)	550K (14%)	92K	6K	1882	1101
South Korea	Health Insurance Review and Assessment Service (HIRA)	50M	9M (18%)	3.3M (16%)	2M	18K	40500	6600
Taiwan	National Health Insurance Database (NHID)	25M	3.5M (14%)	3.5M (14%)	774K	31K	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	85K	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	22K	3933	1564
Netherlands	Integrated Primary Care Information (IPCI) database	2.4M	480K (20%)	432K (18%)	106K	9K	2160	864
Italy	Pool of databases from 5 different regions (Lazio, Napoli, Umbria, Piemonte, Marche)	10M	2.3M (23%)	1.9M (19%)	508K	25K	10350	3800
Germany	German sickness funds (WIG2)	4.5M	1.0M (23%)	0.9M (20%)	229K	9K	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	74M	63000	22440
Northern Europe								
Denmark	Danish National Prescription Registry, Danish National Patient Register	5.8M	1.2M (20%)	1.0M (18%)	256K	9K	5220	2088
Finland	Finnish Prescription Register, Care Register for Health Care, Causes of Death Register	5.4M	1.2M (22%)	1.0M (19%)	264K	8K	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 fee-for-service 20%	TBD	(18%)	(16%)				
US	Optum	TBD	(18%)	(16%)				

457 TBD To be determined

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

459 **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
460 the femoral neck) and prevalence in the population aged over 50 years in the EU27, 2010

461 ***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

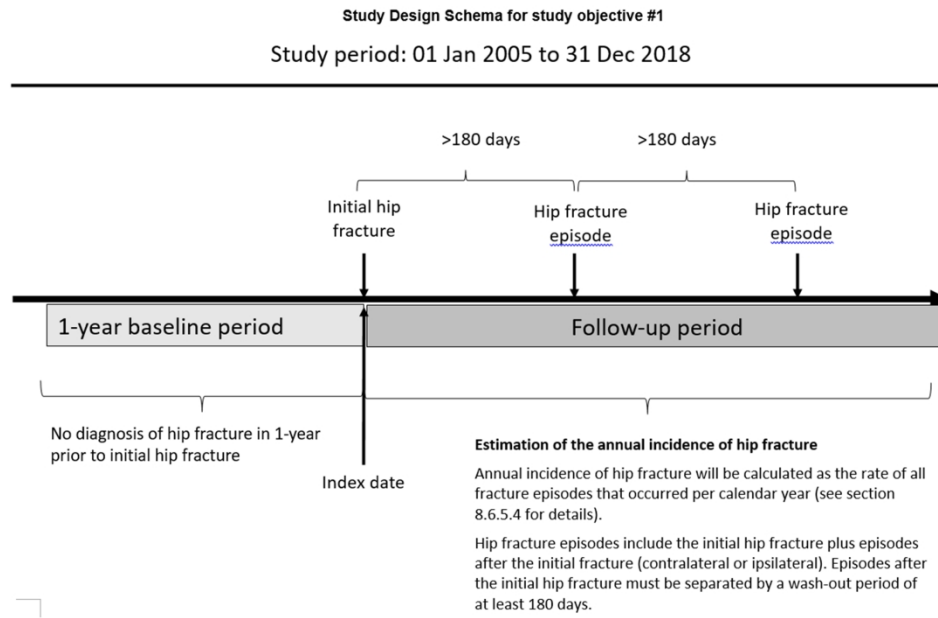


Figure 1 Study design schema

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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

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