Predicting imminent fractures in patients with a recent fracture or starting oral bisphosphonate therapy: development and international validation of prognostic models

Running title: Imminent fracture risk prediction tool

Authors

Sara Khalid[1] (MSc, PhD)*, Marta Pineda Moncusí[9] (MSc, PhD)*, Leena El-Hussein[1] (MSc), Antonella Delmestri (PhD)[1], Martin Ernst[4], Christopher Smith[4], Cesar Libanati[5] *(MD),* Emese Toth[5] (MSc), Muhammad K Javaid[1](MD, PhD, Professor), Cyrus Cooper [1,8] (MD, PhD, Professor), Bo Abrahamsen✉ [1,4,6,7](MD, PhD, Professor), Daniel Prieto-Alhambra [1,2,3,8] (MD, PhD, Professor)

*Joint first authors, ✉ Corresponding author

Affiliations

1- Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Nuffield Orthopaedic Centre, University of Oxford, UK.

2 - Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gorina (IDIAPJ Gol), CIBERFES, Barcelona, Spain.

3 - Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jbmr.4414

4 - Department of Public Health, Clinical Pharmacology and Pharmacy, University of Sourthern Denmark, Odense, Denmark

5 - UCB Biopharma Sprl, Brussels, Belgium

6 - Open Patient Data Explorative Network, University of Southern Denmark and Odense University Hospital, Odense, Denmark.

7 - Department of Medicine, Holbæk Hospital, Holbæk, Denmark

8 - MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton

9 - IMIM (Hospital del Mar Research Institute), Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Barcelona, Spain

FUNDING The study was sponsored by UCB Pharma.

CONFLICT OF INTEREST

SK, MPM, LE and AD has no conflict to declare. ME reports institutional grants from UCB, during the conduct of the study. CS has nothing to disclose. CL reports being employed by UCB Pharma. ET is an employee of UCB Pharma, who sponsored the study. MKJ reports personal fees from Amgen, Consilient Health, Kyowa Kirin Hakin, UCB, Abbvie and grant support from Kyowa Kirin Hakin and Amgen outside the submitted work. CC reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. BA reports grants from UCB during the conduct of the study; and personal

fees from UCB, personal fees from Amgen, grants from Novartis, personal fees from Eli Lilly, personal fees from Kyowa Kirin, grants from Kyowa Kirin and personal fees from Pharmacosmos, outside the submitted work. DPA reports grants and other from AMGEN, grants, non-financial support and other from UCB Biopharma, and grants from Les Laboratoires Servier, outside the submitted work; and Janssen, on behalf of IMI-funded EHDEN and EMIF consortiums, and Synapse Management Partners have supported training programmes organised by DPA's department and open for external participants.

Abstract

The availability of anti-osteoporosis medications with rapid onset and high potency requires tools to identify patients at high imminent fracture risk (IFR). There are few tools that predict a patient's IFR. We aimed to develop and validate tools for target patients with a recent fracture or initiating oral bisphosphonate therapy. Models for two separate cohorts, those with incident fragility fracture (IFx) and with incident oral bisphosphonate prescription (OBP), were developed in primary care records from Spain (SIDIAP database), UK (Clinical Practice Research Datalink GOLD), and Denmark (Danish Health Registries). Separate models were developed for hip, major, and any fracture outcomes. Only variables present in all databases were included in Lasso regression models for the development and logistic regression models for external validation. Discrimination was tested using area under curve (AUC) and calibration was assessed using observed vs predicted risk plots stratified by age, sex, and previous fracture history. The development analyses included 35,526 individuals in the IFx and 41,401 in OBP cohorts, with 671,094 in IFx and 330,256 in OBP for the validation analyses. Both the IFx and OBP models demonstrated similarly good performance for hip fracture at 1 year (with AUCs of 0.79 (95% CI 0.75 to 0.82) and 0.87 (0.83 to 0.91) in Spain, 0.71 (0.71 to 0.72) and 0.73 (0.72 to 0.74) in the UK, and 0.70 (0.70 to 0.70) and 0.69 (0.68 to 0.70) in Denmark), and lower discrimination for major osteoporotic and any fracture sites. Calibration was good across all three countries with similar discrimination and calibration for the 2-year models. The proposed IFR prediction models could be used to identify more precisely patients at high imminent risk of fracture and inform anti-osteoporosis treatment selection. The freely available model parameters permit local validation and implementation.

KEY WORDS (5): Osteoporosis, Anti-resorptive, Fracture prevention, Fracture risk assessment, Prognostic model.

Introduction

Osteoporosis is a global public health issue for both women and men, leading to bone fragility and increased fracture risk. In 2010, it was estimated that 22 million women and 5.5 million men had osteoporosis in Europe, with an occurrence of 3.5 million new fragility fractures[1] each year. The EU27 study valued the cost of incident and prior fragility fractures around € 37 billion in 2010, and estimated an increase of 25% by 2025[1]. Despite the availability of highly effective treatments to reduce fracture risk, national reimbursement for medications, and multiple guidelines, the treatment gap of eligible individuals receiving treatment with osteoporosis drugs is estimated to be 73% for women and 63% for men in the EU[2], and by 2030 a 23% increase in fractures is expected amounting to €47 billion in costs[3].

Based on cost, oral bisphosphonates are generally considered to be first-line agents. Recent clinical studies demonstrated differences in fracture reduction when comparing anabolic therapies with oral bisphosphonates[4]. Incorporating these treatment benefits into routine clinical care requires an approach based on baseline risk and treating to target[5]. Previous fracture is a strong predictor of fracture risk[6]. The fracture risk is highest in the first 2 years, a period known as the imminent risk period[7]. Imminent fracture risk is central to the categorisation of very high-risk and for personalisation of anti-osteoporosis treatment choice[8 9].

Predictive fracture risk tools including FRAX®[10], Garvan[11] and QFracture®[12] are widely used for identification of patients at high-risk of fracture. These tools incorporate the increased risk of a previous fracture, but do not take into account the recency of fracture or the fracture location[7]. Using a simulated cohort, probability ratios have been recently proposed to adjust the 10 years FRAX® score based on the presence of prior

fracture within a 2-year interval by gender and age [13]. While studies have identified independent predictors of imminent hip fracture risk[14], no models for imminent fracture risk have been specifically designed using a multi-country approach, which provides an opportunity to assess how well a proposed tool performs across populations. Further, the existing tools are for treatment naïve patients. A tool that assesses the risk of imminent fracture for new users of oral bisphosphonates can be of use for clinicians to determine patients for which oral bisphosphonates may not be the best choice of treatment given the onset of effect versus imminent risk. Hence, we aimed to develop and externally validate international models to predict imminent risk of hip, major or any fractures, in two different cohorts: patients with incident fracture of osteoporotic sites, and incident users of oral bisphosphonates.

Methods

This analysis forms part of the Multinational Observational Database Study on Imminent Osteoporotic Fracture Risk (the IFRISK study) that has been previously described[15]. Patient-level data were extracted from 3 data sources:

(1) the Catalan Information System for Research in Primary Care "Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària" (SIDIAP) database of primary care records linked to pharmacy invoice and hospital admissions[16] for 5.8 million people;

(2) the UK Clinical Practice Research Datalink (CPRD GOLD), which is a primary care database of over 19 million people representative of the UK population, [17] linked to computerised hospital records (Hospital Episode Statistics) and death records (Office for National Statistics), and

(3) the Danish Health Registries (DHR) database which includes the National Prescriptions Database, the National Hospital Discharge Register and the National Cause of Death register[18]. This database includes records for over 5 million people.

The study was approved by the Independent Scientific Advisory Committee (Ref. 19_080), the IDIAP.J Gol Clinical Research Ethics Committee (Ref. P17/152) and Statistics Denmark (Ref 706638).

Populations

Two retrospective cohort studies were constructed to identify patients with an index event of an incident fracture (IFx) or incident use of oral bisphosphonates (OBP). The IFx cohort included individuals with an incident fracture documented in GP records, inpatients and outpatients records in the above databases at any site except face, skull and digits. Fracture records at the same site within the 6 months after the index fracture were considered duplicates (i.e. the same fracture recoded more than once) and were omitted. The OBP cohort included incident users of oral bisphosphonates (alendronate, clodronate, etidronate, ibandronate, pamidronate, risedronate, tiludronate, zoledronate) without any anti-osteoporotic drug (except calcium and vitamin D supplements) recorded in the previous year.

Patients were included if they were aged 50 years or more at the time of the index event, did not have a history of breast cancer, prostatic cancer, bone metastasis or a diagnosis of Paget disease of the bone. Patients registered in a database less than one year before their index date were not included, to ensure baseline characteristics were recorded.

Study period and outcomes

The study period was from January 1, 1995 to December 31, 2016 in DHR; from January 1, 1995 to December 31, 2018 in CPRD databases; and from January 1, 2006 to December 31, 2016 in SIDIAP. To ensure maximum coverage, the study period dates were based on the earliest and latest dates of data availability.

The following outcomes were predicted: hip fracture; major osteoporotic fractures (for sites including hip, thoracic/ lumbar spine, proximal humerus and distal forearm), or fracture at any site, excluding skull, face, and digits. Patients were followed from the index date (first fracture for the IFx cohort, and first use of bisphosphonates for the OBP cohort) until the earliest of the following events: 1. fracture outcome, or 2. censoring at death[19], migration out of catchment area, end of data availability, or the completion of one and two years since index date. The model considered whether or not an outcome had occurred in a one- or two-year period, and as such the resulting models were outcome-count based and not time-to-event based.

Candidate Variables

Potential predictors were described using the International Classification of Disease version 10 (ICD10) and Anatomical Therapeutic Classification System (ATC) codes in the DHR and SIDIAP databases, and using Read, OPCS and ICD10 codes in the CPRD databases. Eighty-two candidate variables to be considered for inclusion in the prediction model were identified from previous literature (listed in Supplementary Data). These included risk factors of imminent fracture and predictors of fracture while on bisphosphonate therapy, as well as risk factors included in QFracture® and FRAX® prediction tools[10,12,14,20,21]. For demographic and diagnoses variables any time before index date was considered, and for drug use, a lookback period of 12 months before

index date was used. The SIDIAP, CPRD and DHR datasets were examined for identical or equivalent variables to create a list of common variables. An identical variable was one which was recorded using exactly the same definition in all datasets, such as age and gender. An equivalent variable was one for which a proxy definition was used in the absence of the exact variable in a dataset. For a given candidate variable, if neither the exact nor an equivalent variable was recorded in any one of the databases, it was not included. For instance, alcohol use was coded differently in the three databases and was not included. Body mass index, which also had more than 50% missing data in CPRD and SIDIAP, was not available at all in the DHR dataset and so was not included. Ultimately, the variables commonly reported by all three databased (listed in Supplementary Data) were entered into the prediction models.

Statistical methods

Separate models were created for the IFx and OPB cohorts. Models were developed using the SIDIAP dataset and externally validated in the CPRD and DHR datasets, to assess generalisability to external datasets (Figure 1). The SIDIAP dataset was randomly split into a development set containing 80% of the patients and a test set containing the remaining 20%. Further, to focus the models on older adults, the internal and external validation analyses were restricted to patients who were 50 years or older, considered a clinically relevant age range for determining imminent fracture risk.

A descriptive assessment of the common variables against the outcome was done including checking for variables with near-zero variance and high collinearity. The key predictors were selected using least absolute shrinkage and selection operator (LASSO) regression[22] to the development set, a commonly used technique for variable selection in fixed-time models, which enables selection by assigning higher weights to the more

predictive variables. Next, the selected predictors were combined into a logistic regression model fitted to the development set to learn the model coefficients. The resulting model was applied to the test set for internal validation, and to the CPRD and DHR datasets for external validation.

Discrimination was assessed using Area under ROC curve (AUC). Calibration was assessed by plotting observed versus predicted risks, stratified by age and gender. Intercepts for the DHR and CPRD calibration curves were recalibrated to account for differences in baseline risk[20]. The models were then tested in specific subgroups - bisphosphonate use in IFx and by sex in both IFx and OBP cohorts. An AUC for external validation of ≥0.7 was used as a threshold for acceptability of each model. For an outcome, separate models were generated for the prediction of risk after one year and two years of follow-up.

Analyses were performed in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines[23]. All analyses were performed R version 3.5.3. The same R script was used to perform the analysis for each database, and it was independently checked by 3 analysts, one from each country,

Results

The numbers of patients in the IFx and OBP cohorts are shown in Figure 2. A total of 82 candidate variables were identified, of which 48 common variables were found (listed in Supplementary Data). A baseline comparison of the common variables in the SIDIAP, CPRD, and DHR datasets for the hip fracture model is shown in Table 1, with those for major fracture and any fracture shown in Supplemental Table 1. The prevalence of certain conditions and co-morbidities differed between datasets, reflecting

differences in populations and also coding practice and in particular the larger number of patients with chronic conditions such as diabetes who are treated in general practice (CPRD and SIDIAP) versus requiring contacts to hospital clinics (DHR). This resulted in a requirement for calibration as will be shown below.

The number of fractures after one and two years of follow up are summarised in Supplemental Figure. The rates of hip, major and any fractures were substantially higher in the IFx cohort compared with the OBP cohort. After index fracture the incidence rates of fracture were higher per 1,000 patient years in the first year compared to the first two years, reflecting the higher imminent risk of fracture in the first year that follows an index fracture event, a trend that has previously been described [7,24]. Rates of fracture were highest in CPRD and lowest in SIDIAP, with DHR intermediate for IFx cohorts. For the OBP cohorts, DHR was highest, CPRD intermediate and SIDIAP lowest.

Model development and validation

For the hip fracture model, the development and test sets in the IFx cohort from the SIDIAP dataset included 35,526 and 8,881 patients, respectively, and in the OBP cohort 41,401 and 10,350 patients, respectively. Details of the SIDIAP dataset split into training and test sets, stratified by outcome, and for each cohort, can be found in Supplemental Table 2. Out of the three outcomes (hip, major, and any fractures), the models for hip fracture after one year of follow-up had the highest AUCs (AUC 0.70 to 0.87) for both internal validations using the SIDIAP test dataset and external validations, using the CPRD and DHR datasets (Figure 3, Supplemental table 3). Model discrimination tended to be better (i.e. higher AUC) for the OBP cohort than the IFx and for the outcomes of hip fracture compared to major and all fracture. Models for two

years of follow-up had a similar performance to those at 1 year (Figure 3, Supplemental table 3). Models for both 1- and 2-year follow-up had good overall calibration performance (Figure 4), also when stratified by age and gender (Figure 5). In general, prediction was marginally better in women than in men but the difference in AUC was small.

Table 2 shows the predictors included in the final models for the IFx and OBP cohorts at 1- and 2-year follow-up, for each outcome. Supplemental table 4 shows the final models incorporating all included variables. For the IFx cohort, the predictors of hip fracture after 1 year were age, sex, proton pump inhibitor use, and dementia. For OBP cohort, the predictors were age, history of prior fracture, chronic obstructive pulmonary disease, anticoagulant use, antiepileptic use, benzodiazepine use, systemic steroids use, heparin use, cerebrovascular disease, dementia, and renal disease.

Model equations for the hip, major and any fracture outcomes are reported in Table 3, and final models intercepts (after recalibration for DHR and CPRD) are shown in Supplemental Table 3. Explanation of how to calculate an estimate for an individual has been included in the supplementary file entitled *Using the Model Equations.*

The pre-planned sensitivity analyses by gender in the IFx and OBP cohorts, and previous oral bisphosphonates use in the IFx cohorts yielded similar findings, as shown in Supplemental Tables 5a-b, with the equations' intercepts in Supplemental Tables 6a-b.

Discussion

In this study, we have developed and validated a prediction tool to estimate the risk of imminent fracture for patients with incident fracture of osteoporotic sites, and another for patients with incident use of oral bisphosphonates. The first scenario is similar to the fracture liaison service (secondary prevention), the second approximates newly diagnosed and treated osteoporosis and is dominated by primary prevention. The models have good predictive power and validity (discrimination and calibration) across three large real-world European populations in hip fracture prediction models, and a low to acceptable discrimination for major and any type of fracture models. These models enable estimation of the risk of imminent fracture using routinely collected predictors in those with incident fractures as well as in those initiating oral bisphosphonate therapy. All equations produced in this study are supplied in the article supplement to permit others to use and evaluate freely the prediction tool in their respective populations.

Given the high proportion and burden from fractures[25], there is a clinical need for treatment strategies that reduce imminent fractures. Imminent fracture risk tools offer the potential to personalise risk assessment and treatment recommendations in the years following a significant event. For example, oral bisphosphonates, which are the mainstay of osteoporosis therapy today, are effective in reducing risk, but take over 12 months to demonstrate significant reductions in non-vertebral fracture risk[26]. In contrast, some therapies have been shown to significantly reduce fracture risk within 12 months and to have superior fracture risk reductions over oral bisphosphonates[27,28]. The prediction of imminent risk of fracture in those initiating oral bisphosphonate therapy could be integrated into consultation to inform co-decision making between clinicians and patients.

Predicting the short-term increase in fracture risk at the patient-level poses challenges. For instance, Miller et al. generated a classification tool for 12-month fracture risk limited to women with a T score of -1 to -2.5, as measured at peripheral sites[29]. History of previous fracture was identified as a key predictor of high risk and with no further differentiation of the level of risk or recency of fracture. Online risk tools such as FRAX®[10], Garvan[11] and QFracture®[12] are available to predict fracture risk at 5 or 10 years. QFracture permits risk calculation over shorter intervals, but was developed in individuals without including information about the recency or the type of fracture. Additionally, Qfracture has not been validated in countries outside of the UK[30]. FRAX® and Garvan were not developed to calculate fracture risk within the imminent risk period. Extrapolating the 10-year risk to the 2-year risk can significantly underestimate risk[7]. For example the risk of re-fracture after a humeral fracture in women at 2 years ranges from 7.6% to 23.2%[7,21,24,31-34]. These rates are up to 3-fold higher, depending on age and sex, than the 2-year expected risk from extrapolation of the 10-year risk from FRAX®, even with the recently published FRAX® multipliers for fracture probability by sex and fracture site[13]. The clinical consequence of this is that a proportion of patients with a recent fracture will not be correctly identified as being at very high risk of fracture over the next 2 years and not recommended potent anti-osteoporosis therapy. The differences in observed from the risk at 2 years extrapolated from the predicted 10 year risk, reflect the non-linear impact of fracture recency on fracture risk[35] with up to half the expected fractures over 10 years known to occur within this 2-year window[7]. Another consideration is the impact of including mortality over 10 years when estimating fracture risk over 2 years. This may account for the unexpected finding that the proportion of individuals classified at very high risk is relatively stable across age bands with FRAX®[13], in contrast to the findings from our

analyses. These considerations differentiate individuals at high imminent fracture risk compared with high fracture risk and have important implications for treatment decisions. Another approach for predicting short term fracture risk is to apply machine learning techniques on the temporal sequence of ICD codes held in a US electronic health record system that has demonstratable good discrimination[36]. Fundamental limitations include lack of interpretability of the model, and that of reproducibility: it is unclear if and how the model needs to be recalibrated given our observation of the significant differences in ICD coding between countries.

For most models, there was consistency of variables, such as age, sex and proton pump inhibitor use across the outcomes of hip, major and any fracture sites. The predictors for 1 year were also broadly similar to those for 2 years. When comparing IFx and OBP cohorts, in the latter there were more variables that were independently predictive of imminent fracture risk, and that may relate to medication adherence itself[37]. The inclusion or lack of some variables in the models might be considered unexpected. However, causality is not a requirement of a strong predictor in a mathematical model, and therefore the results of these models should be interpreted with caution. For instance, it is not implied that any steroid user is at a high risk of imminent fracture. Thus the selected variables simply represent the combination of factors that, when adjusted for each other, provide the best prediction set after regularization[38,39].

We were expecting models to perform better in women than in men due in part to the lower prevalence and greater heterogeneity of the fracture population in men. For example, in Denmark, only 20% of male hip fractures had experienced a prior osteoporotic fracture in the last ten years before breaking their hip, while this was the case for 40% of women with hip fractures[40]. However, the risk prediction using the present algorithm was not materially affected by the relative difference in fracture

history between the two genders. As regards the difference in performance of the algorithm for predicting MOF or predicting hip fractures, this is likely driven by the difference in fracture mechanism with hip fractures being particularly strongly associated with proxy measures for frailty and impaired balance.

The main strengths of this study are the large sample size used and validation of the models using data sources from three countries that are highly representative of the diversity of wider national/regional populations and the diversity of data structure and health services. Despite the differences in the data sources, discrimination for the imminent hip fracture models were between 0.70 and 0.87, indicating acceptable to excellent discrimination, and comparable to the 10-year hip fracture prediction from FRAX® (AUC with BMD= 0.78 (0.75, 0.81) and AUC without BMD=0.77 (0.73, 0.80))[41]. We noted that prediction of major osteoporotic fractures was somewhat more challenging. Specifically, the discriminatory ability for major osteoporotic fractures was low to acceptable (AUC between 0.56 and 0.70), and similar to FRAX® (AUC with BMD 0.67 (0.65,0.69); AUC without BMD 0.65 (0.63,0.67). In order to reduce chances of inter-analyst discrepancy as well as programming errors, a single R script was used that had been independently cross-checked by three programmers. The model parameters have been included in the supplementary materials, which would permit these models to be freely validated and used in other settings.

In addition, the main contributions of the proposed models compared to the current clinical tools are: 1) we have focused on predict fractures at short-term, which has not been done before; 2) we have conducted an external international validation while developing the proposed models, again, which has not been done, and 3) these equations can be implemented in electronic medical records etc for automatic calculation. This is new and enables population-based screening ‘with a click.

The results of this study should be viewed in the light of some limitations. A possible bias due to potential misclassification of risk factors or outcomes of interest in primary care or hospital records cannot be ruled out, although linkage of primary care and hospital data minimizes incompleteness in the recording of outcomes. Differences in variables codes and/or outcome classification between SIDIAP, CPRD and DHR could limit the application of the model in other populations. We consider likely that the consultation threshold is lower for General Practice than for hospital clinics, though the exact thresholds will vary between healthcare systems. In order to diminish this effect, we carefully selected a list of potential predictors that were as similar as possible among data sources. Unfortunately, levels of trauma are not routinely recorded in the utilised data sources. The vast majority of fractures seen in osteoporosis patients are however likely classifiable as 'fragility related'. We have previously validated fractures in the general population in one of the contributing data sources, and found that most fractures recorded in people age 60-65+ are not trauma-related [42]. Another consideration is that this is a predictive model based on optimising estimates of imminent risk rather than a causal model based on establish determinants of bone health and should therefore be applied with care in clinical decision-making. It is possible that the mechanisms of imminent risk identify patients with fracture risks that are not reversible by anti-osteoporosis medication. However evidence from trials that recruited patients based only on specific fractures and no other skeletal risk factors, such as bone mineral density, have reassuringly demonstrated similar and robust effectiveness of anti-osteoporosis therapies across a wide demographic[43].

In summary, we have developed, validated, and presented the models for estimating the imminent risk of hip, major and any fractures in patients in the two most pertinent clinical settings for decision-making, i.e. patients consulting following a recent fracture,

such as the in the context of the fracture liaison service, and those starting oral bisphosphonate therapy (a first drug scenario). The outputs of the prediction model could be used to identify groups of patients at very high risk of imminent fracture who may benefit most from potent rapidly acting anti-osteoporosis medications.

ACKNOWLEDGMENTS

The authors would like to acknowledge Paloma O'Dogherty for project management, and CPRD, SIDIAP, and Statistics Denmark for their support, and UCB Pharma for funding this study.

AUTHORS' ROLES

Study design: DPA, BA, ET. CPRD data management and advanced curation: AD. Data analysis: SK, DPA, MPM, LE, ME, CS. Data interpretation: SK, MPM, MKJ, DPA, BA, ET, CL. Drafting manuscript: SK, MPM, DPA, MKJ. Revising manuscript content: all authors. Approving final version of manuscript: all authors. DPA takes responsibility for the integrity of the data analysis.

FUNDING The study was sponsored by UCB Pharma.

References

1. Svedbom A, Hernlund E, Ivergard M, et al. Osteoporosis in the European Union: a compendium of country-specific reports. *Archives of osteoporosis.* 2013;8:137.

2. Borgström F, Karlsson L, Ortsäter G, et al. Fragility fractures in Europe: burden, management and opportunities. *Archives of osteoporosis.* Apr 19 2020;15(1):59.

3. International-Osteoporosis-Foundation. Broken bones, broken lives: a roadmap to solve the fragility fracture crisis in Europe. 2018; https://www.iofbonehealth.org/broken-bones-broken-lives. Accessed 12/10/2020, 2020.

4. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *The New England journal of medicine.* Oct 12 2017;377(15):1417-1427.

5. Lewiecki EM, Cummings SR, Cosman F. Treat-to-target for osteoporosis: is now the time? *J Clin Endocrinol Metab.* Mar 2013;98(3):946-953.

6. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res.* Apr 2000;15(4):721-739.

7. Kanis JA, Johansson H, Oden A, et al. Characteristics of recurrent fractures. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Aug 2018;29(8):1747-1757.

8. Compston JE, Drake MT. Defining Very High Fracture Risk: Is FRAX Fit for Purpose? *J Bone Miner Res.* Jul 22 2020.

9. Pinedo-Villanueva R, Charokopou M, Toth E, et al. Imminent fracture risk assessments in the UK FLS setting: implications and challenges. *Archives of osteoporosis.* Feb 2 2019;14(1):12.

10. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAXtrade mark and the assessment of fracture probability in men and women from the UK. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Feb 22 2008.

11. Ahmed LA, Nguyen ND, Bjørnerem Å, et al. External validation of the Garvan nomograms for predicting absolute fracture risk: the Tromsø study. *PLoS One.* 2014;9(9):e107695-e107695.

12. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *BMJ.* Nov 19 2009;339:b4229.

13. Kanis JA, Johansson H, Harvey NC, et al. Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Jul 1 2020.

14. Bonafede M, Shi N, Barron R, Li X, Crittenden DB, Chandler D. Predicting imminent risk for fracture in patients aged 50 or older with

osteoporosis using US claims data. *Archives of osteoporosis.* Dec 2016;11(1):26.

15. Skjødt MK, Khalid S, Ernst M, et al. Secular trends in the initiation of therapy in secondary fracture prevention in Europe: a multi-national cohort study including data from Denmark, Catalonia, and the United Kingdom. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Aug 2020;31(8):1535-1544.

16. Premaor MO, Compston JE, Fina Aviles F, et al. The association between fracture site and obesity in men: a population-based cohort study. *J Bone Miner Res.* Aug 2013;28(8):1771-1777.

17. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International journal of epidemiology.* Jun 2015;44(3):827-836.

18. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *International journal of epidemiology.* Jun 1 2017;46(3):798-798f.

19. Delmestri A, Prieto-Alhambra D. CPRD GOLD and linked ONS mortality records: Reconciling guidelines. *International journal of medical informatics.* Apr 2020;136:104038.

20. Prieto-Alhambra D, Pages-Castella A, Wallace G, et al. Predictors of fracture while on treatment with oral bisphosphonates: a population-based cohort study. *J Bone Miner Res.* Jan 2014;29(1):268-274.

21. Banefelt J, Akesson KE, Spangeus A, et al. Risk of imminent fracture following a previous fracture in a Swedish database study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Mar 2019;30(3):601-609.

22. Tibshirani R. Regression Shrinkage and Selection Via the Lasso. *Journal of the Royal Statistical Society: Series B (Methodological).* 1996;58(1):267-288.

23. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *J Clin Epidemiol.* Feb 2015;68(2):134-143.

24. van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. *Annals of the rheumatic diseases.* Jan 2009;68(1):99-102.

25. Roux C, Wyman A, Hooven FH, et al. Burden of non-hip, non-vertebral fractures on quality of life in postmenopausal women: the Global Longitudinal study of Osteoporosis in Women (GLOW). *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Dec 2012;23(12):2863-2871.

26. Inderjeeth CA, Chan K, Kwan K, Lai M. Time to onset of efficacy in fracture reduction with current anti-osteoporosis treatments. *Journal of bone and mineral metabolism.* Sep 2012;30(5):493-503.

27. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet.* Jan 20 2018;391(10117):230-240.

28. Cosman F, Crittenden DB, Ferrari S, et al. Romosozumab FRAME Study: A Post Hoc Analysis of the Role of Regional Background Fracture Risk on Nonvertebral Fracture Outcome. *J Bone Miner Res.* Aug 2018;33(8):1407-1416.

29. Miller PD, Barlas S, Brenneman SK, et al. An approach to identifying osteopenic women at increased short-term risk of fracture. *Archives of internal medicine.* May 24 2004;164(10):1113-1120.

30. Collins GS, Michaëlsson K. Fracture risk assessment: state of the art, methodologically unsound, or poorly reported? *Curr Osteoporos Rep.* Sep 2012;10(3):199-207.

31. van Helden S, Cals J, Kessels F, Brink P, Dinant GJ, Geusens P. Risk of new clinical fractures within 2 years following a fracture. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2006;17(3):348-354.

32. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *Jama.* Jan 24 2007;297(4):387-394.

33. Balasubramanian A, Zhang J, Chen L, et al. Risk of subsequent fracture after prior fracture among older women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Jan 2019;30(1):79-92.

34. Toth E, Banefelt J, Åkesson K, Spångeus A, Ortsäter G, Libanati C. History of Previous Fracture and Imminent Fracture Risk in Swedish Women Aged 55 to 90 Years Presenting With a Fragility Fracture. *J Bone Miner Res.* 2020:10.1002/jbmr.3953.

35. Johansson H, Siggeirsdottir K, Harvey NC, et al. Imminent risk of fracture after fracture. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Mar 2017;28(3):775-780.

36. Almog YA, Rai A, Zhang P, et al. Crystal Bone: Predicting Short-Term Fracture Risk From Electronic Health Records With Deep Learning. *J Med Internet Res.* Sep 12 2020.

37. Hiligsmann M, Cornelissen D, Vrijens B, et al. Determinants, consequences and potential solutions to poor adherence to anti-osteoporosis treatment: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF). *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Aug 7 2019.

38. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ.* Feb 23 2009;338:b375.

39. Zalpuri S, Middelburg RA, van de Watering L, Vamvakas E, Zwaginga JJ, van der Bom JG. Association vs. causality in transfusion medicine: understanding multivariable analysis in prediction vs. etiologic research. *Transfusion medicine reviews.* Apr 2013;27(2):74-81.

40. Frederiksen A, Abrahamsen B, Johansen PB, Sorensen HA. Danish, national cross-sectional observational study on the prevalence of prior major osteoporotic fractures in adults presenting with hip fracture-limitations and scope for fracture liaison services in prevention of hip fracture. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Jan 2018;29(1):109-114.

41. Beaudoin C, Moore L, Gagné M, et al. Performance of predictive tools to identify individuals at risk of non-traumatic fracture: a systematic review, meta-analysis, and meta-regression. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* Apr 2019;30(4):721-740.

42. Martinez-Laguna D, Soria-Castro A, Carbonell-Abella C, et al. Validation of fragility fractures in primary care electronic medical records: A population-based study. *Reumatologia clinica.* Sep - Oct 2019;15(5):e1-e4.

43. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *The New England journal of medicine.* Nov 1 2007;357(18):1799-1809.

Tables

Table 1 Baseline characteristics of patients in the development set, and the internal and external validation sets, for the hip fracture outcome.

		IFx				OBP			
Variable		Development set hip fracture	Internal validation set hip fracture (SIDIAP test set)	External validation set CPRD	External validation set DHR	Development set hip fracture	Internal validation set hip fracture (SIDIAP test set)	External validation set CPRD	External validation set DHR
		n=35526	n=8881	n=148,077	n=514,139	n=41401	n=10350	n=115,896	n=204,010
Age , mean (SD)		71.6 (12.5)	71.6 (12.4)	73.0 (12.6)	70.8 (12.4)	69.1 (10.2)	69.1 (10.2)	73.7 (10.6)	71.0 (10.0)
Sex (n(%))	Male	11519 (32.4)	2840 (32.0)	41147 (27.8)	354660 (69.0)	7834 (18.9)	1951 (18.9)	23634 (20.4)	166888 (82.0)
	Female	24007 (67.6)	6041 (68.0)	106930 (72.2)	159479 (31.0)	7834 (81.1)	8399 (81.1)	92262 (79.6)	37122 (18.0)
Anxiety or Obsessive-Compulsive Disorder (n(%))		6205 (17.5)	1558 (17.5)	15098 (10.2)	1996 (0.4)	6847 (16.5)	1659 (16.0)	11614 (10.0)	997 (0.49)
Rheumatoid arthritis diagnosis (n(%))		403 (1.1)	107 (1.2)	2733 (1.9)	8949 (1.7)	952 (2.3)	230 (2.2)	4704 (4.1)	10854 (5.3)
Asthma diagnosis (n(%))		1583 (4.5)	378 (4.3)	13891 (9.4)	11497 (2.2)	2147 (5.2)	530 (5.1)	13708 (11.8)	9973 (4.9)
Diagnosis of cancer (n(%))		2226 (6.3)	569 (6.4)	12674 (8.6)	36100 (7.0)	2161 (5.2)	547 (5.3)	10627 (9.2)	16930 (8.3)
Diabetes mellitus II diagnosis (n(%))		7762 (21.8)	1908 (21.5)	10377 (7.01)	31057 (6.04)	6150 (14.9)	1564 (15.1)	7287 (6.3)	11144 (5.5)
Epilepsy diagnosis (n(%))		532 (1.5)	120 (1.4)	3180 (2.2)	9199 (1.8)	382 (0.9)	89 (0.9)	2072 (1.8)	3588 (1.8)
Spondyloarthropathy diagnosis (n(%))		91 (0.3)	13 (0.1)	713 (0.48)	568 (0.11)	99 (0.2)	28 (0.3)	755 (0.7)	465 (0.2)
Prior fracture (n(%))		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10471 (25.3)	2607 (25.2)	29841 (25.7)	68965 (33.8)
Cardiovascular disease (n(%))		6711 (18.9)	1643 (18.5)	30307 (20.5)	94023 (18.3)	6388 (15.4)	1618 (15.6)	24245 (20.9)	42209 (20.7)
Chronic obstructive pulmonary disease (n(%))		2305 (6.5)	586 (6.6)	8511 (5.8)	27371 (5.3)	2102 (5.1)	544 (5.3)	10163 (8.8)	25357 (12.4)
Parkinson's disease (n(%))		1251 (3.5)	306 (3.4)	1847 (1.3)	6589 (1.3)	899 (2.2)	242 (2.3)	1198 (1.0)	2547 (1.3)
Systemic lupus diseae (n(%))		49 (0.1)	7 (0.1)	146 (0.1)	487 (0.1)	85 (0.2)	25 (0.2)	287 (0.25)	696 (0.34)

Anticoagulants use (n(%))		2507 (7.1)	648 (7.3)	7294 (4.9)	32337 (6.3)	2344 (5.7)	586 (5.7)	6583 (5.7)	16410 (8.0)
Antiepileptics use (n(%))		3397 (9.6)	805 (9.1)	6561 (4.4)	41725 (8.1)	4121 (10.0)	1035 (10.0)	5132 (4.4)	19053 (9.3)
Non-benzodiazepine hypnotics use (n(%))		715 (2.0)	164 (1.8)	14586 (9.9)	7786 (1.5)	1050 (2.5)	267 (2.6)	12067 (10.4)	4067 (2.0)
Beta-blockers use (n(%))		5051 (14.2)	1217 (13.7)	25123 (17.0)	117399 (22.8)	5165 (12.5)	1320 (12.8)	20376 (17.6)	55598 (27.3)
Benzodiazepines use (n(%))		13102 (36.9)	3250 (36.6)	8859 (6.0)	205964 (40.1)	18134 (43.8)	4517 (43.6)	7354 (6.35)	90559 (44.4)
Hormone contraceptives use (n(%))		9 (0.0)	2 (0.0)	4 (0.0)	13261 (2.6)	13 (0.0)	2 (0.0)	1 (0.0)	6817 (3.3)
Systemic steroids use (n(%))		2992 (8.4)	721 (8.1)	12771 (8.6)	126905 (24.7)	5303 (12.8)	1362 (13.2)	33876 (29.2)	91192 (44.7)
Heparin use (n(%))		1933 (5.4)	463 (5.2)	600 (0.4)	2002 (0.4)	2741 (6.6)	681 (6.6)	826 (0.7)	1353 (0.7)
Hormonal replace treatment (n(%))		889 (2.5)	224 (2.5)	3555 (2.4)	108712 (21.1)	2458 (5.9)	618 (6.0)	5001 (4.3)	68476 (33.6)
Proton pump inhibitors use (n(%))		17761 (50.0)	4430 (49.9)	0.25 (0.4)	138413 (26.9)	23920 (57.8)	6005 (58.0)	0.33 (0.5)	79535 (39.0)
Chronic liver disease (n(%))		1989 (5.6)	521 (5.9)	1057 (0.7)	8004 (1.56)	1829 (4.4)	436 (4.2)	991 (0.9)	4164 (2.0)
Gastrointestinal conditions (n(%))		217 (0.6)	66 (0.7)	1439 (1.0)	5234 (1.0)	254 (0.6)	51 (0.5)	2447 (2.1)	4033 (2.0)
Other endocrine conditions (n(%))		615 (1.7)	158 (1.8)	1249 (0.8)	11089 (2.2)	793 (1.9)	198 (1.9)	1658 (1.4)	8945 (4.4)
Previous bisphosphonates use (n(%))		1810 (5.1)	468 (5.3)	13623 (9.2)	23286 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Charlson Comorbidity Index variables (n(%))	Myocardial infarction diagnosis	989 (2.8)	248 (2.8)	3803 (2.6)	21471 (4.2)	814 (2.0)	209 (2.0)	2921 (2.5)	9132 (4.5)
	Other heart conditions diagnosis	2412 (6.8)	568 (6.4)	5772 (3.9)	25395 (4.9)	1594 (3.9)	413 (4.0)	4221 (3.6)	11077 (5.4)
	Atherosclerosis diagnosis	1217 (3.4)	295 (3.3)	4258 (2.9)	21021 (4.1)	920 (2.2)	252 (2.4)	3470 (3.0)	10973 (5.4)
	Cerebrovascular disease	3135 (8.8)	738 (8.3)	4922 (3.32)	49495 (9.6)	2275 (5.5)	576 (5.6)	3363 (2.9)	18512 (9.1)
	Dementia diagnosis	2494 (7.0)	586 (6.6)	5108 (3.5)	15004 (2.9)	995 (2.4)	249 (2.4)	2017 (1.7)	3375 (1.7)
	Emphysema diagnosis	5333 (15.0)	1307 (14.7)	18092 (12.2)	39021 (7.6)	5496 (13.3)	1389 (13.4)	17724 (15.3)	32564 (16.0)
	Diagnosis of rheumatoid arthritis with	771 (2.2)	202 (2.3)	6829 (4.61)	14976 (2.9)	1796 (4.3)	459 (4.4)	15578 (13.4)	21096 (10.3)

	rheumatoid factor								
	Gastric ulcer diagnosis	1274 (3.6)	329 (3.7)	2261 (1.5)	18979 (3.7)	1398 (3.4)	335 (3.2)	1752 (1.5)	9111 (4.5)
	Liver disease	1885 (5.3)	478 (5.4)	542 (0.4)	7181 (1.4)	1701 (4.1)	403 (3.9)	529 (0.5)	3721 (1.8)
	Diagnosis of diabetes without complications	7659 (21.6)	1879 (21.2)	14472 (9.8)	29259 (5.7)	6066 (14.7)	1543 (14.9)	9834 (8.5)	10713 (5.3)
	Diagnosis of diabetes with complications	362 (1.0)	100 (1.1)	3524 (2.4)	10690 (2.1)	207 (0.5)	57 (0.6)	2089 (1.8)	3278 (1.6)
	Paraplegia diagnosis	138 (0.4)	41 (0.5)	238 (0.2)	1527 (0.3)	81 (0.2)	21 (0.2)	152 (0.1)	752 (0.4)
	Renal disease	2813 (7.9)	719 (8.1)	15954 (10.8)	6309 (1.23)	1638 (4.0)	415 (4.0)	12248 (10.6)	2145 (1.05)
	Diagnosis of cancer	2164 (6.1)	558 (6.3)	5789 (3.9)	28870 (5.6)	2118 (5.1)	534 (5.2)	5255 (4.5)	13713 (6.7)
	Severe liver failure diagnosis	134 (0.4)	30 (0.3)	186 (0.1)	1904 (0.4)	96 (0.2)	17 (0.2)	103 (0.1)	889 (0.4)
	Diagnosis of metastatic cancer	126 (0.4)	33 (0.4)	345 (0.2)	2722 (0.5)	90 (0.2)	22 (0.2)	366 (0.3)	1137 (0.6)
	Diagnosis of AIDS	41 (0.1)	15 (0.2)	4 (0.0)	145 (0.0)	28 (0.1)	8 (0.1)	5 (0.0)	54 (0.0)

Abbreviations: IFx, Incident Fracture cohort; OBP, Oral Bisphosphonates cohort; SIDIAP, Catalan Information System for Research in Primary Care; CPRD, UK Clinical Practice Research Datalink; DHR, Danish Health Registries.

Table 2: Predictors (main models)

Cohort		IFx OR (95%CI)					
Predictor		One year			Two years		
		Hip	Major	Any	Hip	Major	Any
Age		1.07 (1.06 to 1.09)	1.01 (1.01 to 1.02)	1.01 (1.01 to 1.02)	1.07 (1.07 to 1.08)	1.02 (1.02 to 1.02)	1.01 (1.01 to 1.02)
Sex (male)		0.74 (0.56 to 0.98)	0.76 (0.67 to 0.87)	0.84 (0.76 to 0.93)	X	0.72 (0.65 to 0.80)	0.78 (0.72 to 0.86)
Proton pump inhibitors use		1.25 (0.99 to 1.57)	1.17 (1.04 to 1.31)	1.12 (1.02 to 1.24)	X	1.20 (1.09 to 1.31)	1.15 (1.06 to 1.25)
	Dementia diagnosis	1.67 (1.25 to 2.23)	X	X	1.63 (1.31 to 2.02)	X	X

	Diagnosis of diabetes type 2 without complications	X	1.23 (1.08 to 1.40)	1.27 (1.14 to 1.41)	X	X	1.18 (1.08 to 1.29)
Abbreviations: IFx, Incident Fracture cohort; OR, Odds Ratio; CI, Confidence interval							

Cohort		OBP OR (95%CI)					
Predictor		One year			Two years		
		Hip	Major	Any	Hip	Major	Any
Age		1.10 (1.08 to 1.12)	1.05 (1.04 to 1.05)	1.04 (1.04 to 1.05)	1.10 (1.09 to 1.12)	1.04 (1.04 to 1.05)	1.04 (1.03 to 1.04)
Sex (male)		X	0.64 (0.52 to 0.78)	0.59 (0.50 to 0.71)	X	0.58 (0.49 to 0.69)	0.58 (0.50 to 0.66)
Anxiety or Obsessive-Compulsive Disorder		X	1.36 (1.15 to 1.62)	1.24 (1.07 to 1.43)	X	1.23 (1.06 to 1.42)	1.18 (1.05 to 1.33)
Diabetes mellitus II diagnosis		X	1.01 (0.25 to 4.15)	0.96 (0.30 to 3.07)	1.49 (1.18 to 1.88)	1.16 (1.01 to 1.34)	1.11 (0.98 to 1.25)
Prior fracture		1.77 (1.34 to 2.33)	1.21 (1.04 to 1.41)	1.24 (1.09 to 1.40)	1.43 (1.15 to 1.79)	1.16 (1.03 to 1.31)	1.25 (1.13 to 1.39)
Chronic obstructive pulmonary disease		1.58 (1.02 to 2.44)	X	X	1.50 (0.96 to 2.35)	1.25 (0.94 to 1.65)	X
Parkinson's disease		X	X	1.48 (1.11 to 1.96)	X	X	1.54 (1.22 to 1.94)
Anticoagulants use		1.32 (0.87 to 2.01)	X	X	X	1.12 (0.91 to 1.38)	X
Antiepileptics use		1.54 (1.06 to 2.23)	1.32 (1.08 to 1.61)	1.34 (1.13 to 1.58)	X	1.19 (1.00 to 1.40)	1.24 (1.08 to 1.43)
Benzodiazepines use		0.78 (0.59 to 1.02)	X	X	X	1.07 (0.95 to 1.20)	1.02 (0.92 to 1.12)
Systemic steroids use		1.20 (0.84 to 1.70)	X	X	X	X	1.07 (0.94 to 1.22)
Heparin use		1.42 (0.94 to 2.13)	X	1.39 (1.15 to 1.69)	1.37 (1.00 to 1.89)	1.17 (0.97 to 1.43)	1.36 (1.16 to 1.59)
Hormonal replace treatment		X	0.53 (0.36 to 0.79)	0.68 (0.51 to 0.91)	X	0.66 (0.49 to 0.87)	0.75 (0.60 to 0.94)
Proton pump inhibitors use		X	1.07 (0.92 to 1.24)	1.06 (0.93 to 1.20)	1.05 (0.84 to 1.32)	1.11 (0.98 to 1.25)	1.06 (0.96 to 1.18)
Chronic liver disease		X	X	1.37 (1.08 to 1.75)	X	1.34 (1.06 to 1.70)	1.38 (1.14 to 1.67)
	Atherosclerosis diagnosis	X	X	X	X	X	1.45 (1.13 to 1.85)
	Cerebrovascular disease	1.35 (0.91 to 2.01)	X	X	1.35 (0.99 to 1.84)	1.19 (0.97 to 1.46)	1.14 (0.96 to 1.36)
	Dementia diagnosis	2.32 (1.54 to 3.50)	1.65 (1.23 to 2.20)	1.30 (1.00 to 1.70)	2.09 (1.50 to 2.90)	1.38 (1.07 to 1.78)	X
	Emphysema diagnosis	X	X	1.14 (0.97 to 1.33)	1.17 (0.83 to 1.65)	1.06 (0.88 to 1.29)	1.19 (1.05 to 1.35)
	Diagnosis of diabetes type 2 without complications	1.40 (1.03 to 1.90)	1.24 (0.30 to 5.10)	1.26 (0.39 to 4.04)	X	X	X

	Renal disease	1.47 (0.97 to 2.23)	X	X	1.37 (0.98 to 1.92)	X	X
Abbreviations: OBP, Oral Bisphosphonates cohort; OR, Odds Ratio; CI, Confidence interval							

Table 3 Model Equations

Predictor	IFx Beta Coefficient						OBP Beta Coefficient					
	One year			Two years			One year			Two years		
	Hip	Major	Any	Hip	Major	Any	Hip	Major	Any	Hip	Major	Any
Intercept	-5.311	-3.362	-2.998	-4.596	-2.925	-2.559	-6.054	-4.051	-3.700	-5.513	-3.638	-3.210
Age	0.071	0.013	0.012	0.071	0.019	0.014	0.096	0.044	0.042	0.098	0.043	0.038
Sex (male)	-0.298	-0.273	-0.173	X	-0.328	-0.243	X	-0.450	-0.521	X	-0.542	-0.550
Anxiety or Obsessive-Compulsive Disorder	X	X	X	X	X	X	X	0.309	0.211	X	0.205	0.167
Rheumatoid arthritis diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
Asthma diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
Diagnosis of cancer	X	X	X	X	X	X	X	X	X	X	X	X
Diabetes mellitus II diagnosis	X	X	X	X	X	X	X	0.013	-0.042	0.397	0.151	0.100
Epilepsy diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
Spondyloarthropathy diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
Prior fracture	X	X	X	X	X	X	0.569	0.193	0.213	0.360	0.151	0.226
Cardiovascular disease	X	X	X	X	X	X	X	X	X	X	X	X
Chronic obstructive pulmonary disease	X	X	X	X	X	X	0.457	X	X	0.407	0.219	X
Parkinson's disease	X	X	X	X	X	X	X	X	0.392	X	X	0.432
Systemic lupus diseae	X	X	X	X	X	X	X	X	X	X	X	X
Anticoagulants use	X	X	X	X	X	X	0.278	X	X	X	0.116	X
Antiepileptics use	X	X	X	X	X	X	0.429	0.279	0.293	X	0.172	0.218
Non-benzodiazepine hypnotics use	X	X	X	X	X	X	X	X	X	X	X	X
Beta-blockers use	X	X	X	X	X	X	X	X	X	X	X	X
Benzodiazepines use	X	X	X	X	X	X	-0.250	X	X	X	0.063	0.017
Hormone contraceptives use	X	X	X	X	X	X	X	X	X	X	X	X
Systemic steroids use	X	X	X	X	X	X	0.178	X	X	X	X	0.069
Heparin use	X	X	X	X	X	X	0.349	X	0.332	0.317	0.160	0.307
Hormonal replace treatment	X	X	X	X	X	X	X	-0.626	-0.389	X	-0.420	-0.284
Proton pump inhibitors use	0.221	0.155	0.114	X	0.178	0.143	X	0.065	0.054	0.047	0.101	0.062
Chronic liver disease	X	X	X	X	X	X	X	X	0.318	X	0.292	0.322
Gastrointestinal conditions	X	X	X	X	X	X	X	X	X	X	X	X
Other endocrine conditions	X	X	X	X	X	X	X	X	X	X	X	X

Previous bisphosphonates use		X	X	X	X	X	X	X	X	X	X	X	X
Previous use of other anti-osteoporotic drugs		X	X	X	X	X	X	X	X	X	X	X	X
Charlson Comorbidity Index variables	Myocardial infarction diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
	Other heart conditions diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
	Atherosclerosis diagnosis	X	X	X	X	X	X	X	X	X	X	X	0.369
	Cerebrovascular disease	X	X	X	X	X	X	0.303	X	X	0.301	0.172	0.131
	Dementia diagnosis	0.511	X	X	0.488	X	X	0.843	0.499	0.262	0.736	0.321	X
	Emphysema diagnosis	X	X	X	X	X	X	X	X	0.130	0.157	0.061	0.173
	Diagnosis of rheumatoid arthritis with rheumatoid factor	X	X	X	X	X	X	X	X	X	X	X	X
	Gastric ulcer diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
	Liver disease	X	X	X	X	X	X	X	X	X	X	X	X
	Diagnosis of diabetes without complications	X	X	X	X	X	X	0.333	0.213	0.228	X	X	X
	Diagnosis of diabetes with complications	X	0.206	0.236	X	X	0.165	X	X	X	X	X	X
	Paraplegia diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
	Renal disease	X	X	X	X	X	X	0.385	X	X	0.315	X	X
	Diagnosis of cancer	X	X	X	X	X	X	X	X	X	X	X	X
	Severe liver failure diagnosis	X	X	X	X	X	X	X	X	X	X	X	X
	Diagnosis of metastatic cancer	X	X	X	X	X	X	X	X	X	X	X	X
	Diagnosis of AIDS	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: IFx, Incident Fracture cohort; OBP, Oral Bisphosphonates cohort; SIDIAP, Catalan Information System for Research in Primary Care; CPRD, UK Clinical Practice Research Datalink; DHR, Danish Health Registries.

Figure legends

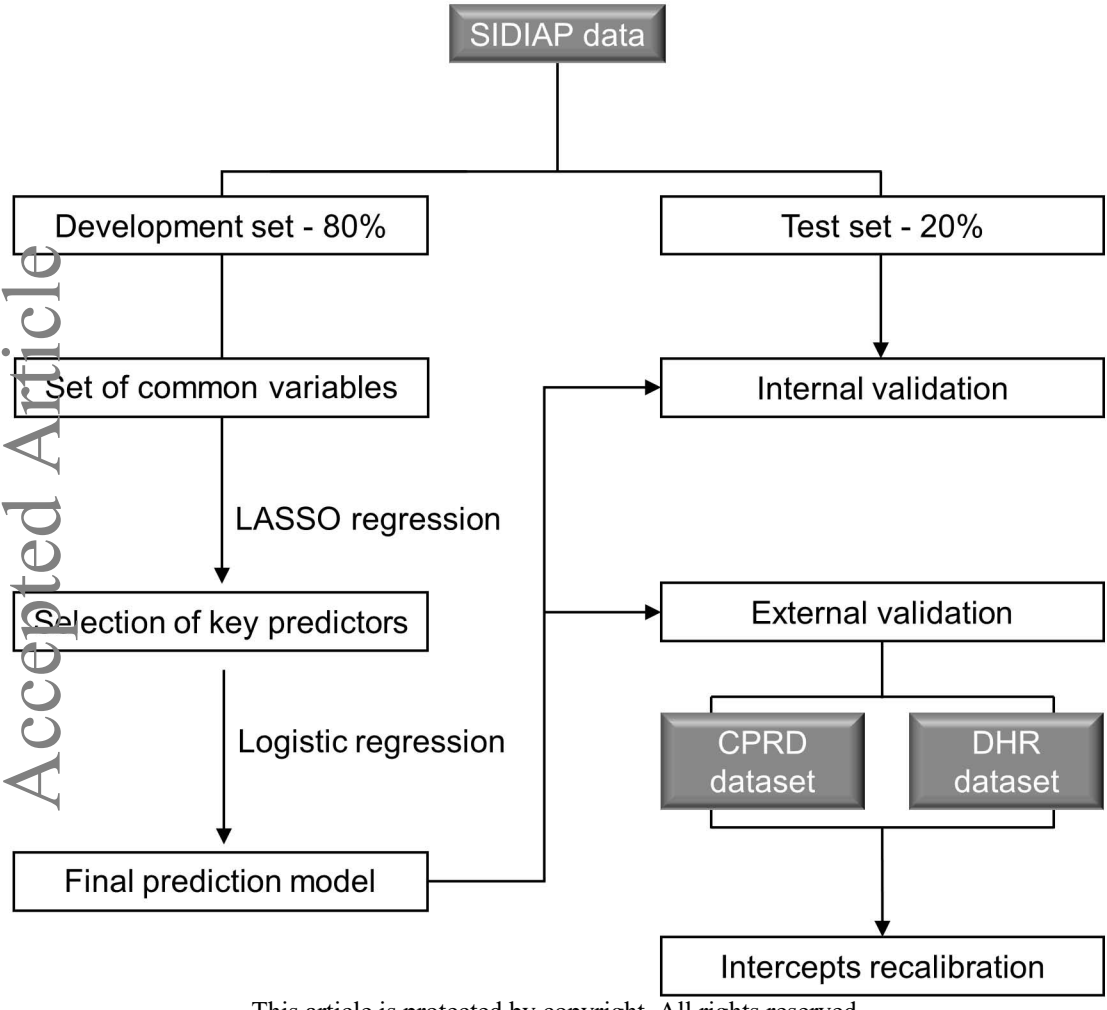
Figure 1. Steps in the development and validation of the prediction model. Abbreviations: SIDIAP, Catalan Information System for Research in Primary Care; CPRD, UK Clinical Practice Research Datalink; DHR, Danish Health Registries.

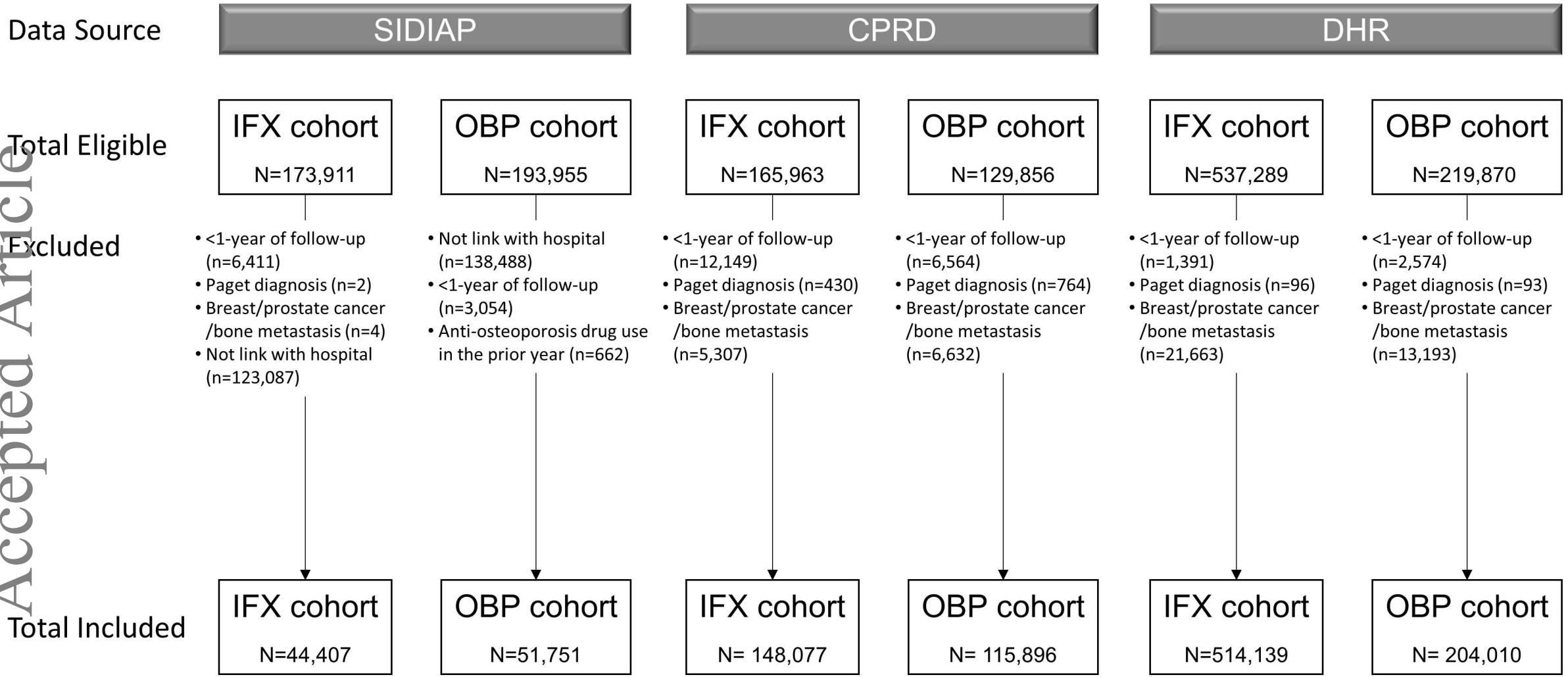
Figure 2. Study flow chart. Abbreviations: SIDIAP, Catalan Information System for Research in Primary Care; CPRD, UK Clinical Practice Research Datalink; DHR, Danish Health Registries; IFx, Incident Fracture cohort; OBP, Oral Bisphosphonates cohort.

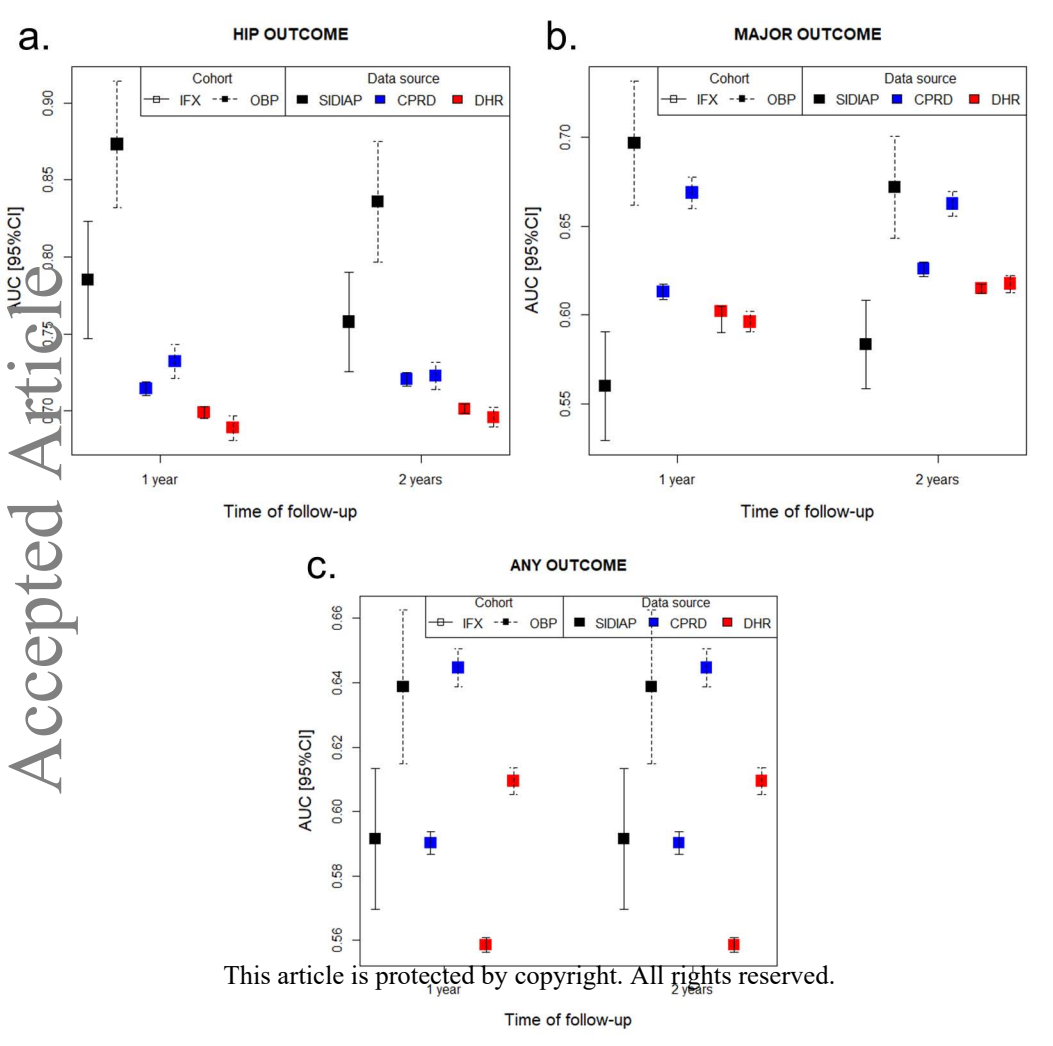
Figure 3. Area under ROC curve for internal and external validation. Prediction models for a) hip fracture, b) major fracture and c) any type of fracture. Models were internally validated using SIDIAP cohort, and externally validated by CPRD and DHR cohorts. Abbreviations: IFx, Incident Fracture cohort; OBP, Oral Bisphosphonates cohort; SIDIAP, Catalan Information System for Research in Primary Care; CPRD, UK Clinical Practice Research Datalink; DHR, Danish Health Registries.

Figure 4. Calibration curves for internal and external validation. a) One-year hip fracture model for IFx cohort, b) one-year hip fracture model for OBP cohort, c) two-years hip fracture model for IFx cohort, d) two-years hip fracture model for OBP cohort. Models were internally validated using SIDIAP cohort, and externally validated by CPRD and DHR cohorts. Abbreviations: IFx, Incident Fracture cohort; OBP, Oral Bisphosphonates cohort; SIDIAP, Catalan Information System for Research in Primary Care; CPRD, UK Clinical Practice Research Datalink; DHR, Danish Health Registries.

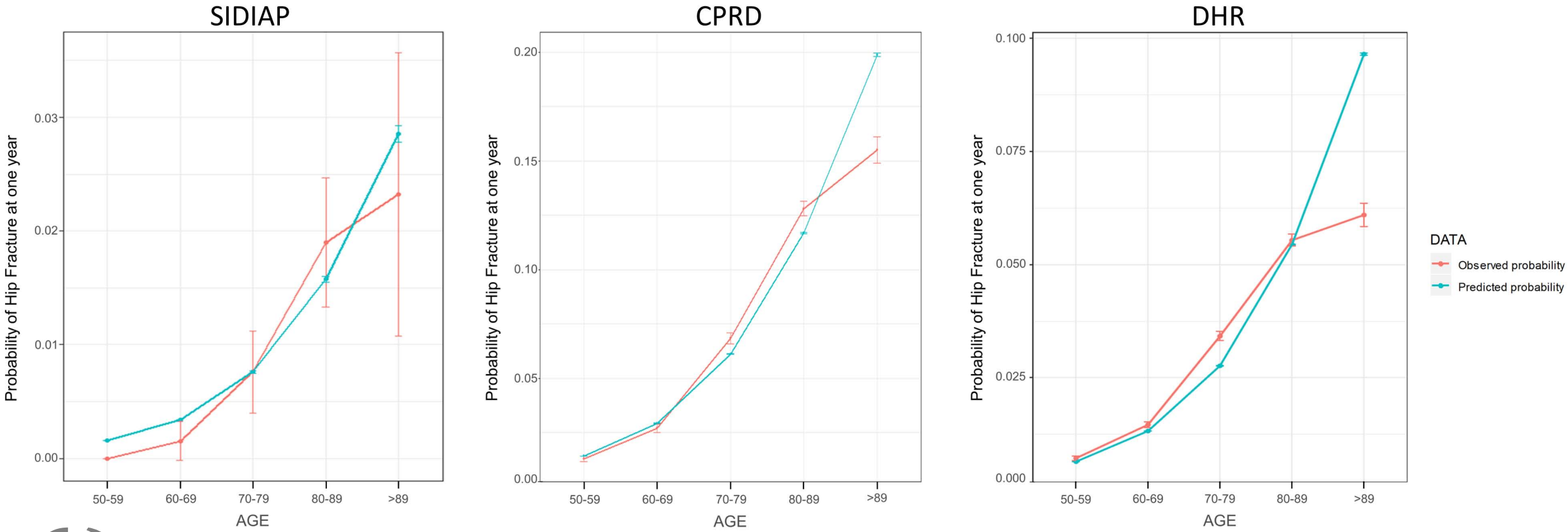
Figure 5. Calibration curve stratified by age and gender. a) One-year hip fracture model for IFx cohort, b) one-year hip fracture model for OBP cohort, c) two-years hip fracture model for IFx cohort, d) two-years hip fracture model for OBP cohort. Models were internally validated using SIDIAP cohort, and externally validated by CPRD and DHR cohorts. Abbreviations: IFx, Incident Fracture cohort; OBP, Oral Bisphosphonates cohort; SIDIAP, Catalan Information System for Research in Primary Care; CPRD, UK Clinical Practice Research Datalink; DHR, Danish Health Registries.



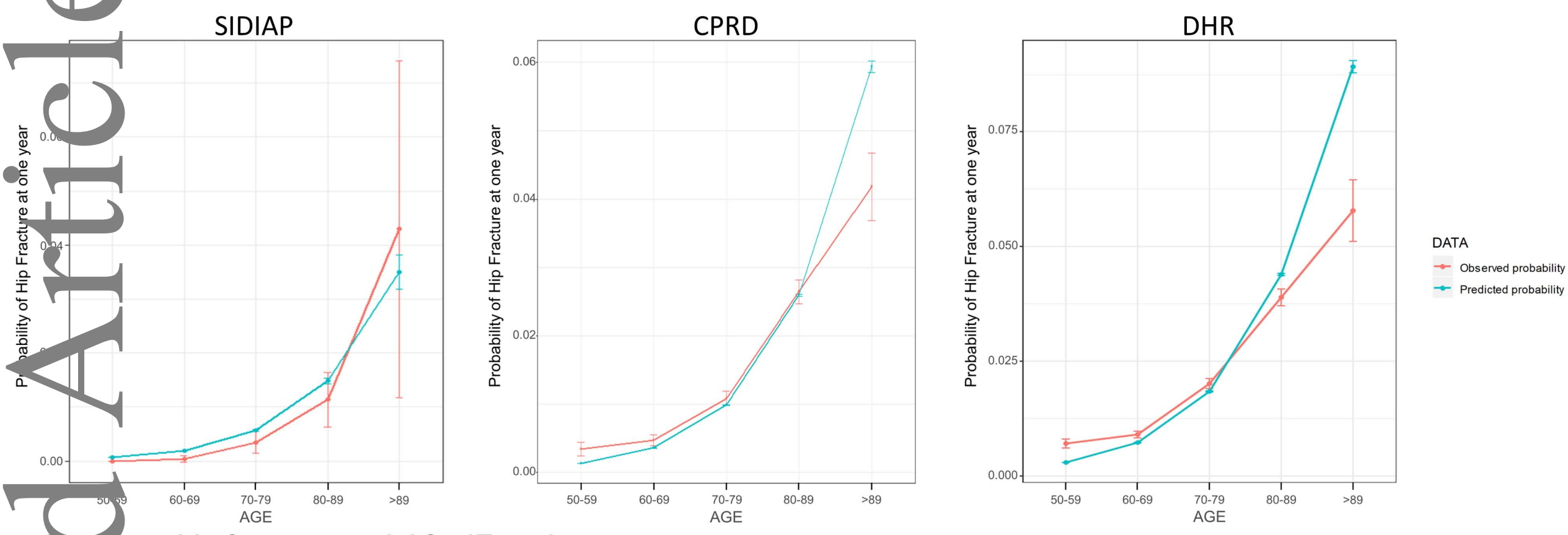




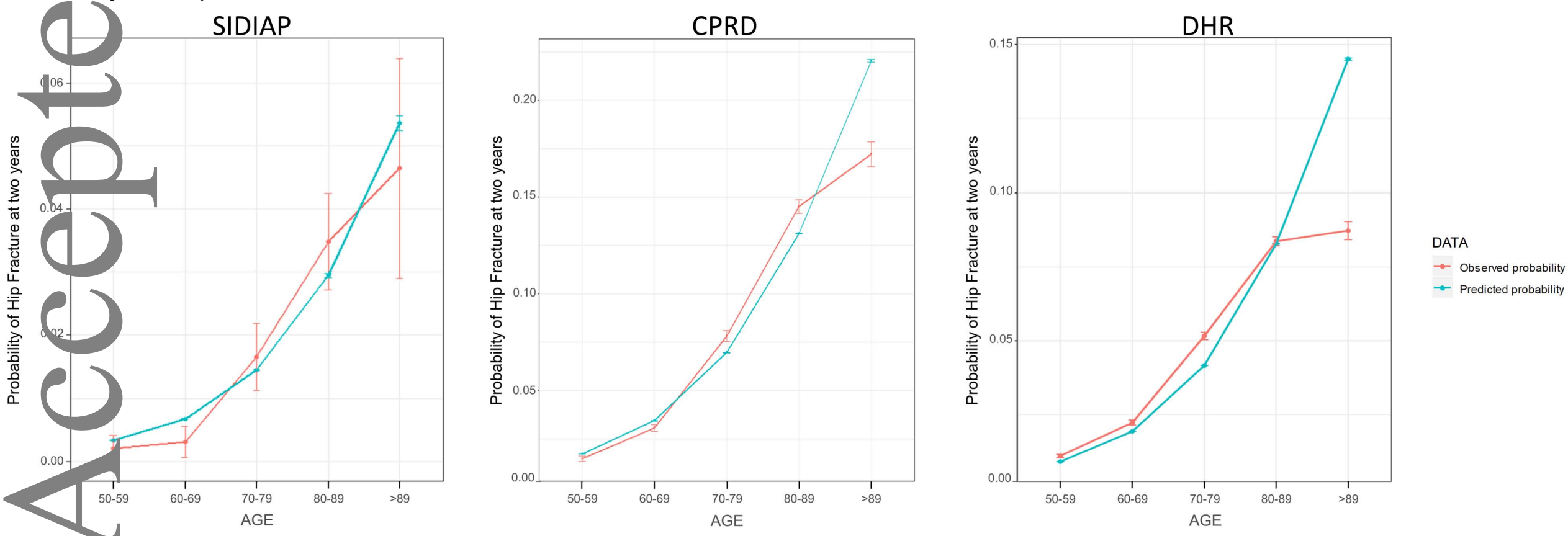
a. One-year hip fracture model for IFx cohort



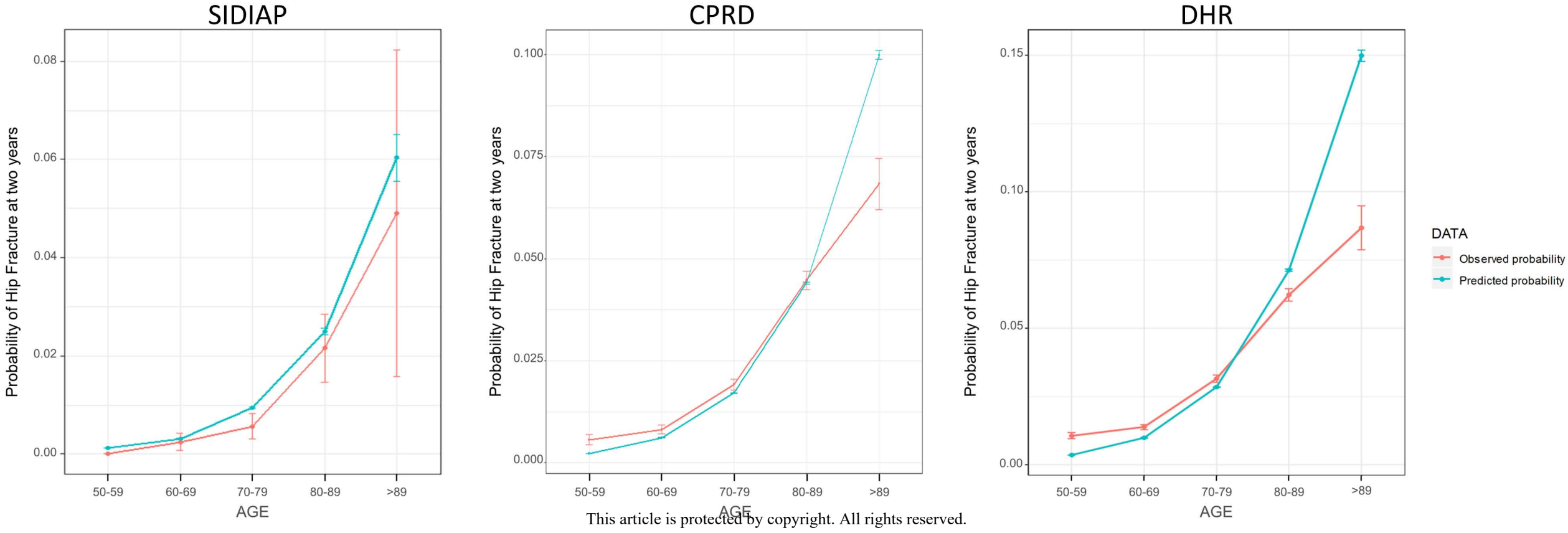
b. One-year hip fracture model for OBP cohort



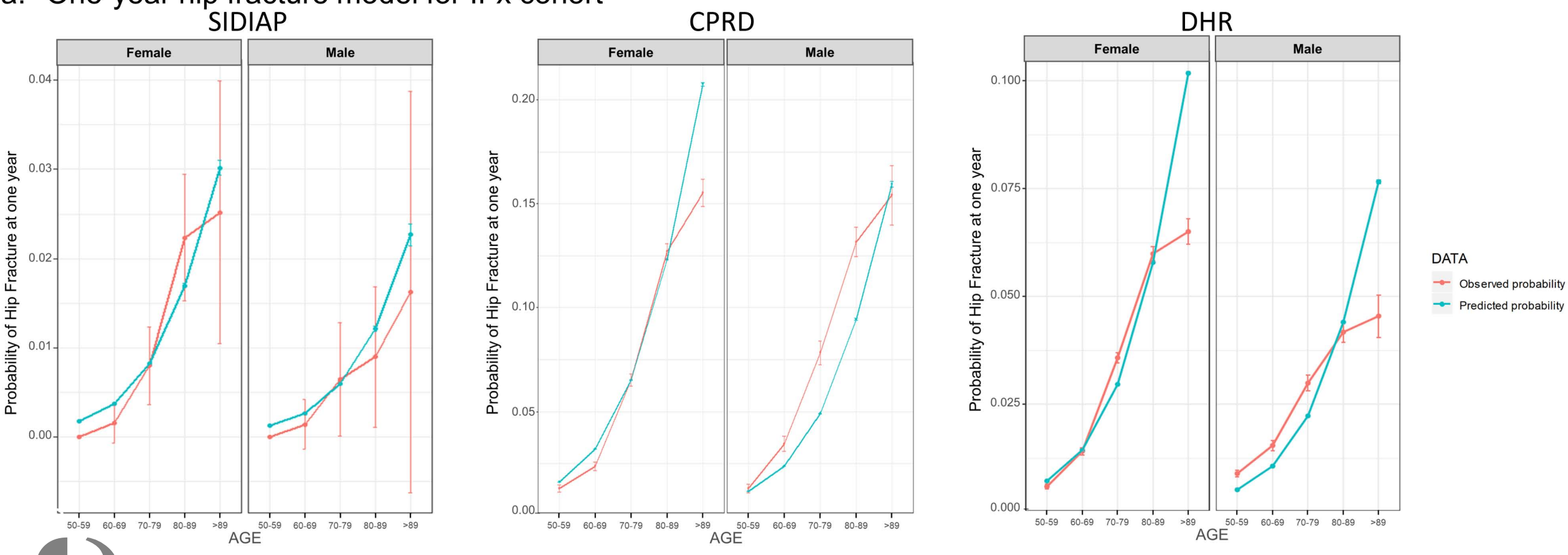
c. Two-year hip fracture model for IFx cohort



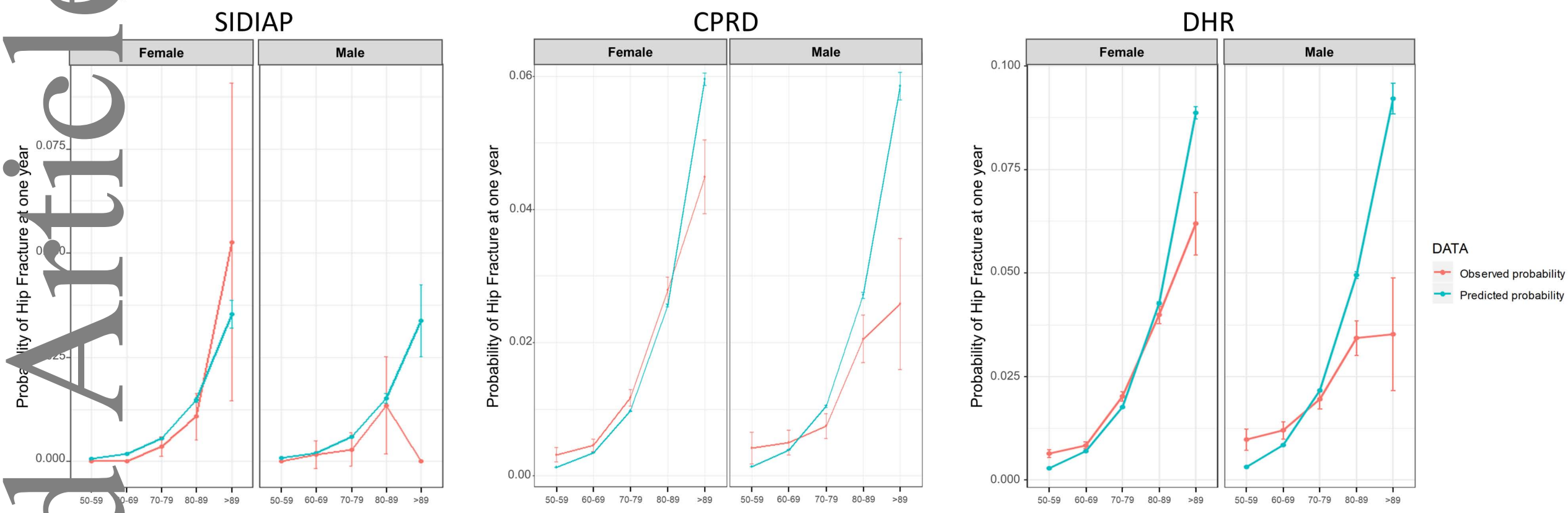
d. Two-year hip fracture model for OBP cohort



a. One-year hip fracture model for IFx cohort



b. One-year hip fracture model for OBP cohort



c. Two-year hip fracture model for IFx cohort

d. Two-year hip fracture model for OBP cohort