

Potential of Health Insurance Claims Data to Predict Fractures in Older Adults: A Prospective Cohort Study

Jonas Reinold ¹, Malte Braitmaier ², Oliver Riedel ¹, Ulrike Haug ^{1,3}

¹Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, 28359, Germany; ²Department of Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, 28359, Germany; ³Faculty of Human and Health Sciences, University of Bremen, Bremen, Germany

Correspondence: Jonas Reinold, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Achterstraße 30, Bremen, 28359, Germany, Tel +49 421 218-56868, Fax +49 421 218-56821, Email reinold@leibniz-bips.de

Purpose: In older adults, fractures are associated with mortality, disability, loss of independence and high costs. Knowledge on their predictors can help to identify persons at high risk who may benefit from measures to prevent fractures. We aimed to assess the potential of German claims data to predict fractures in older adults.

Patients and Methods: Using the German Pharmacoepidemiological Research Database (short GePaRD; claims data from ~20% of the German population), we included persons aged ≥ 65 years with at least one year of continuous insurance coverage and no fractures prior to January 1, 2017 (baseline). We randomly divided the study population into a training (80%) and a test sample (20%) and used logistic regression and random forest models to predict the risk of fractures within one year after baseline based on different combinations of potential predictors.

Results: Among 2,997,872 persons (56% female), the incidence per 10,000 person years of any fracture in women increased from 133 in age group 65–74 years (men: 71) to 583 in age group 85+ (men: 332). The maximum predictive performance as measured by the area under the curve (AUC) across models was 0.63 in men and 0.60 in women and was achieved by combining information on drugs and morbidities. AUCs were lowest in age group 85+.

Conclusion: Our study showed that the performance of models using German claims data to predict the risk of fractures in older adults is moderate. Given that the models used data readily available to health insurance providers in Germany, it may still be worthwhile to explore the cost–benefit ratio of interventions aiming to reduce the risk of fractures based on such prediction models in certain risk groups.

Keywords: fracture, older adults, claims data, prediction

Introduction

Older adults have a high risk of fractures that further increases with advancing age.^{1–4} Fractures can be detrimental for older adults as they are associated with a high risk of death, disability and loss of independence.^{5–7} In addition to age and sex, a number of other factors like prior fractures, chronic morbidities such as osteoporosis, Parkinson's disease, dementia as well as lifestyle-related factors such as alcohol and illicit drug abuse, heavy smoking and low Body Mass Index (BMI) have been shown to be associated with an increased risk of fractures.^{8–15} Moreover, the use of certain medications has been linked to an increased risk of falls and fractures such as those included in the so-called list of fall risk increasing drugs (FRIDs) (loop diuretics, digitalis, antipsychotics, antidepressants, benzodiazepines, opioids and antiepileptics) as well as further drugs such as proton pump inhibitors and glucocorticoids.^{16–20} Additionally, the number of used medications overall, which is associated with multimorbidity, as well as the cumulative effects of medications with anticholinergic activity, known as anticholinergic burden (AB), have been identified as potential risk factors for fractures.^{21,22}

Due to the effects of fractures on morbidity, mortality as well as healthcare costs,²³ risk-based prevention strategies directed at persons with a high risk of fractures are needed. However, in order to implement these strategies detailed knowledge regarding risk factors of fractures and their relevance is required. Information on some of the known predictors of fractures is available in claims data. Prediction of fractures based on claims data would be useful as the data is readily available, includes information from various settings (inpatient, outpatient, pharmacy) and the analysis is fairly cheap and often representative of entire populations. However, it is not clear to what extent the information available in (German) claims data is useful for predicting fractures, which of the available predictors are most useful and whether the predictive power differs by sex and age.

We therefore aimed to assess the potential of German claims data to predict fractures in older adults stratified by age group and sex.

Methods

Data Source

We used the German Pharmacoepidemiological Research Database (GePaRD), which is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented. In Germany, about 90% of the general population is covered by statutory health insurance. The healthcare system is characterized by uniform access to all levels of care and free choice of providers.

In addition to demographic data, GePaRD contains information on outpatient drug dispensations as well as outpatient (ie, from general practitioners and specialists) and inpatient services and diagnoses. Information on medication includes the anatomical-therapeutic-chemical (ATC) code, the prescription and dispensation date, the specialty of the prescriber as well as the number of defined daily doses (DDDs). Diagnoses are coded according to the German modification of the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-GM).

Study Design and Study Population

A cohort was established which included all persons from GePaRD with continuous insurance coverage from January 1, 2016 to January 1, 2017 (inclusion period) without missing information on sex and age. Further inclusion criteria were German residency, age 65 years or older during the inclusion period. Moreover, only persons with no record of a fracture between January 1, 2017 and the beginning of the individual lookback period (as early as January 1, 2004) were included to focus on persons most relevant for primary prevention of fractures. It is already known that persons with prior fractures are at high risk for subsequent fractures,^{24–26} so measures to prevent a second fracture may already have been taken. Time before January 1, 2017 was defined as baseline period where information on potential predictors was assessed. The occurrence of fractures was assessed during the follow-up period from January 1 to December 31, 2017. Persons were followed until the first of the following criteria: death, occurrence of fractures, end of insurance or end of follow-up period.

Potential Predictors of Fractures and Study Outcome

We considered the following potential predictors of fractures, which were identified from literature and are available in claims data: (i) morbidities influencing the risk of fractures and falls: osteoporosis,¹⁰ osteoarthritis,²⁷ rheumatoid arthritis,^{19,28} vitamin D deficiency,^{19,29} Parkinson's disease,¹¹ dementia³⁰ and type 2 diabetes mellitus;^{31–33} (ii) codes for lifestyle-related factors or morbidities relevant to the risk of fractures: alcohol abuse,¹³ heavy smoking¹⁴ and obesity (high BMI associated with lower risk of fractures);^{15,34} (iii) codes indicating frailty;³⁵ nursing home residency; (iv) medications relevant to the risk of fractures: high-ceiling diuretics, cardiac glycosides, antidepressants, antipsychotics, benzodiazepines, opioids, antiepileptics,^{16–18} glucocorticoids,³⁶ proton pump inhibitors,¹⁹ AB²² and polypharmacy²¹ (Table 1). The study outcome fractures, including hip and femur fractures, vertebral fractures, wrist, hand and shoulder

Table 1 Included Models and Predictors

Model	Included Predictor(s)
A	AB
B	FRIDs
D	Polypharmacy
D	AB, FRIDs
E	AB, polypharmacy
F	FRIDs, polypharmacy
G	Glucocorticoids, proton pump inhibitors, osteoporosis medication, osteoporosis, osteoarthritis, rheumatoid arthritis, vitamin D deficiency, obesity, heavy smoking, alcohol abuse, illicit drug abuse, Parkinson's disease, dementia, type 2 diabetes mellitus, nursing home residency
H	AB, FRIDs, glucocorticoids, proton pump inhibitors, osteoporosis medication, osteoporosis, osteoarthritis, rheumatoid arthritis, vitamin D deficiency, obesity, heavy smoking, alcohol abuse, illicit drug abuse, Parkinson's disease, dementia, type 2 diabetes mellitus, nursing home residency, polypharmacy

Abbreviations: AB, anticholinergic burden; FRIDs, fall risk increasing drugs.

fractures, pelvis fractures and other fractures, were assessed based on ICD-10-GM codes recorded as inpatient main discharge diagnoses (see [Appendix 1](#)).

Definition of Study Variables

Information on medication and healthcare utilization was assessed between January 1 and December 31, 2016. We considered a person to be exposed to a medication of interest if the person had ≥ 1 dispensation in the outpatient setting of the respective medication. AB was assessed through the Anticholinergic Cognitive Burden (ACB) scale as described by Kiesel et al.³⁷

Information on morbidities was assessed any time prior to January 1, 2017 (starting from database inception on January 1, 2004). Most morbidities were assessed through the presence of records of ≥ 1 ICD-10-GM inpatient or outpatient diagnoses. For some morbidities, also specific procedure (OPS) or service (EBM) codes relevant in the treatment of these conditions were considered (eg, hemodialysis in the case of renal failure). For type 2 diabetes, dementia and Parkinson's disease specific disease identification algorithms were used to minimize misclassification (see [Appendix 2](#)).

Statistical Analyses

Crude incidence rates were calculated by dividing the number of fractures observed in the study period by the sum of person-time under risk of any fractures. Exact confidence intervals were calculated using the relationship between the chi-squared and the Poisson distribution.³⁸ Univariate odds ratios (OR) were calculated to assess the association between the occurrence of fractures during follow-up (as binary variable) and selected pre-baseline predictor variable (with two or more categories). Estimation of univariate odds ratios and corresponding 95% confidence intervals was done non-parametrically.³⁹

To develop and validate a prediction model, the data was split (8:2) into a training sample ($n = 2,406,861$) and a test sample ($n = 591,011$). The training sample was used to train a range of pre-specified models ([Table 1](#)) using both logistic regression and random forests. We considered models that used only information on medication (FRIDs, AB, polypharmacy), models that used only information on morbidities (including nursing home residency as indicator for frailty) as well as models that considered both. Given that glucocorticoids and proton pump inhibitors are mainly relevant due to their association with osteoporosis, these drugs were considered in the morbidity model rather than in the medication models. For random forests, 10-fold cross-validation was performed on the training sample. Threshold values for

predicting case vs non-case status were set using Youden's J (sensitivity + specificity – 1).⁴⁰ Predictive performance of all models was assessed on the test sample, using receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC). The selected models included combinations of potential predictors of fractures, namely AB, FRIDs, polypharmacy and morbidities, co-medication and nursing home residency in order to assess their usefulness as predictors of fractures alone and in combination with other predictors.

Data preparation, calculation of summary statistics, incidence rates and univariate OR were done in SAS 9.4. Statistical modelling (ie, logistic regression and random forests) was done in R version 4.0.2 (caret package version 6.0–86, ranger package version 0.12.1). No parameter tuning was applied for random forests due to computational limitations, using the default settings in ranger instead.

Ethics and Approvals

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen, studies based on GePaRD are exempt from institutional review board review.

Results

The study population comprised a total of 2,997,872 persons (56% women) with a median age of 74 years at baseline (interquartile range (IQR): 10 years). Crude incidence of any fracture across all age and sex groups was 176.1 per 10,000 person years. The incidence varied by sex and increased with age: While in age group 65–74 years, it was 133.1 in women and 70.6 in men, it was more than four times higher in age group ≥85 years (women: 583.1, men: 332.0). The highest incidence was observed for wrist, hand and shoulder fractures, followed by hip and femur fractures (Table 2). Compared to persons without fractures during follow-up, individuals with fractures had more chronic diseases at baseline (eg, dementia, Parkinson's disease or osteoporosis) and were prescribed more medication for the treatment of chronic diseases as well as FRIDs. Individuals with fractures were also more likely to have high AB (ACB≥3) and polypharmacy (Table 3).

Table 2 Incidence of Fractures (per 10,000 Person Years) in the Study Population by Age and Sex

	Age Groups						
	65–74 Years		75–84 Years		85+ Years		
	Men (N = 669,702)	Women (N = 838,130)	Men (N = 537,772)	Women (N = 656,261)	Men (N = 116,149)	Women (N = 179,858)	
Any fractures	70.6 (68.6–72.6)	133.1 (130.6–135.6)	126.3 (123.3–129.4)	249.9 (246.0–253.8)	332.0 (321.2–343.1)	583.1 (571.5–594.8)	176.1 (174.6–177.6)
Hip fractures/femur fractures	14.2 (13.3–15.1)	19.8 (18.8–20.8)	38.8 (37.1–40.5)	65.9 (63.9–67.9)	155.0 (147.7–162.6)	255.3 (247.7–263.0)	50.5 (49.7–51.3)
Vertebral fractures	10.4 (9.7–11.2)	17.0 (16.1–17.9)	26.2 (24.8–27.6)	48.3 (46.6–50.0)	66.3 (61.6–71.3)	108.4 (103.5–113.5)	31.1 (30.5–31.7)
Wrist, hand and shoulder fractures	20.2 (19.1–21.3)	63.0 (61.3–64.7)	25.0 (23.6–26.3)	88.5 (86.2–90.8)	41.3 (37.5–45.3)	133.3 (127.8–138.9)	55.4 (54.5–56.2)
Pelvis fractures	1.7 (1.4–2.0)	2.2 (1.9–2.6)	4.6 (4.0–5.2)	7.9 (7.2–8.6)	14.5 (12.3–16.9)	25.2 (22.9–27.7)	5.5 (5.3–5.8)
Other fractures	25.1 (23.9–26.4)	32.8 (31.6–34.0)	34.6 (33.1–36.3)	45.5 (43.8–47.1)	61.9 (57.3–66.8)	78.1 (73.9–82.4)	37.9 (37.2–38.6)

Table 3 Description of Study Population by Age, Sex and Fracture Status During Follow-Up

	Age Groups											
	65–74 Years				75–84 Years				85+ Years			
	Men		Women		Men		Women		Men		Women	
	Fracture (N = 4660)	No Fracture (N = 665,042)	Fracture (N = 10,991)	No Fracture (N = 827,139)	Fracture (N = 6622)	No Fracture (N = 531,150)	Fracture (N = 15,974)	No Fracture (N = 640,287)	Fracture (N = 3570)	No Fracture (N = 112,579)	Fracture (N = 9658)	No Fracture (N = 170,200)
AB												
None (ACB=0)	1930 (41.4%)	323,468 (48.6%)	4370 (39.8%)	376,507 (45.5%)	1887 (28.5%)	204,445 (38.5%)	4452 (27.9%)	221,747 (34.6%)	998 (28.0%)	36,055 (32.0%)	2516 (26.1%)	47,632 (28.0%)
Low (ACB=1)	1187 (25.5%)	177,390 (26.7%)	2635 (24.0%)	209,641 (25.3%)	1734 (26.2%)	150,370 (28.3%)	3854 (24.1%)	169,730 (26.5%)	983 (27.5%)	31,940 (28.4%)	2412 (25.0%)	44,450 (26.1%)
Medium (ACB=2)	604 (13.0%)	82,509 (12.4%)	1522 (13.8%)	106,863 (12.9%)	1181 (17.8%)	80,959 (15.2%)	2754 (17.2%)	101,986 (15.9%)	616 (17.3%)	19,229 (17.1%)	1844 (19.1%)	30,598 (18.0%)
High (ACB≥3)	939 (20.2%)	81,675 (12.3%)	2464 (22.4%)	134,128 (16.2%)	1820 (27.5%)	95,376 (18.0%)	4914 (30.8%)	146,824 (22.9%)	973 (27.3%)	25,355 (22.5%)	2886 (29.9%)	47,520 (27.9%)
Mean cumulative AB (SD)	244 (420.0)	161 (300.7)	232 (397.7)	166 (315.7)	303 (429.9)	205 (332.3)	293 (413.4)	222 (350.2)	277 (387.1)	236 (345.7)	290 (374.3)	269 (364.7)
Use of different medication												
0	617 (13.2%)	111,448 (16.8%)	1481 (13.5%)	141,058 (17.1%)	435 (6.6%)	49,117 (9.2%)	1023 (6.4%)	56,775 (8.9%)	172 (4.8%)	7121 (6.3%)	433 (4.5%)	9536 (5.6%)
1 to 4	1909 (41.0%)	316,735 (47.6%)	5127 (46.6%)	422,946 (51.1%)	2092 (31.6%)	217,861 (41.0%)	5707 (35.7%)	272,309 (42.5%)	1080 (30.3%)	37,719 (33.5%)	3061 (31.7%)	56,785 (33.4%)
5 to 9 (polypharmacy)	1472 (31.6%)	186,679 (28.1%)	3176 (28.9%)	209,699 (25.4%)	2720 (41.1%)	198,042 (37.3%)	6342 (39.7%)	232,815 (36.4%)	1645 (46.1%)	50,194 (44.6%)	4379 (45.3%)	75,872 (44.6%)
≥ 10 (hyper-polypharmacy)	662 (14.2%)	50,180 (7.5%)	1207 (11.0%)	53,436 (6.5%)	1375 (20.8%)	66,130 (12.5%)	2902 (18.2%)	78,388 (12.2%)	673 (18.9%)	17,545 (15.6%)	1785 (18.5%)	28,007 (16.5%)
FRIDs	1564 (33.6%)	140,213 (21.1%)	3801 (34.6%)	214,677 (26.0%)	3209 (48.5%)	167,949 (31.6%)	7917 (49.6%)	246,652 (38.5%)	2126 (59.6%)	55,749 (49.5%)	6009 (62.2%)	98,666 (58.0%)
High-ceiling diuretics	677 (14.5%)	54,239 (8.2%)	1101 (10.0%)	52,984 (6.4%)	1769 (26.7%)	86,007 (16.2%)	3140 (19.7%)	95,819 (15.0%)	1406 (39.4%)	36,518 (32.4%)	3447 (35.7%)	57,063 (33.5%)
Cardiac glycosides	81 (1.7%)	8096 (1.2%)	89 (0.8%)	6121 (0.7%)	189 (2.9%)	13,239 (2.5%)	426 (2.7%)	16,755 (2.6%)	153 (4.3%)	4711 (4.2%)	505 (5.2%)	10,318 (6.1%)
Antidepressants	576 (12.4%)	45,764 (6.9%)	1987 (18.1%)	109,522 (13.2%)	925 (14.0%)	42,319 (8.0%)	3583 (22.4%)	99,653 (15.6%)	509 (14.3%)	11,391 (10.1%)	2116 (21.9%)	31,872 (18.7%)
Antipsychotics	576 (12.4%)	45,764 (6.9%)	1987 (18.1%)	109,522 (13.2%)	925 (14.0%)	42,319 (8.0%)	3583 (22.4%)	99,653 (15.6%)	407 (11.4%)	7969 (7.1%)	1266 (13.1%)	17,534 (10.3%)
Benzodiazepines	106 (2.3%)	9915 (1.5%)	372 (3.4%)	20,893 (2.5%)	262 (4.0%)	11,600 (2.2%)	750 (4.7%)	23,689 (3.7%)	155 (4.3%)	3814 (3.4%)	523 (5.4%)	8347 (4.9%)
Opioids	431 (9.2%)	36,273 (5.5%)	1180 (10.7%)	57,826 (7.0%)	800 (12.1%)	40,987 (7.7%)	2561 (16.0%)	74,348 (11.6%)	495 (13.9%)	12,424 (11.0%)	1,893 (19.6%)	30,442 (17.9%)
Antiepileptics	359 (7.7%)	26,781 (4.0%)	780 (7.1%)	34,558 (4.2%)	631 (9.5%)	31,230 (5.9%)	1475 (9.2%)	41,381 (6.5%)	270 (7.6%)	7887 (7.0%)	727 (7.5%)	12,649 (7.4%)
Other medication												
Glucocorticoids	628 (13.5%)	66,424 (10.0%)	1735 (15.8%)	102,501 (12.4%)	949 (14.3%)	62,657 (11.8%)	2659 (16.6%)	87,919 (13.7%)	435 (12.2%)	13,293 (11.8%)	1187 (12.3%)	19,421 (11.4%)
Proton pump inhibitors	1477 (31.7%)	165,777 (24.9%)	3,702 (33.7%)	233,182 (28.2%)	2427 (36.7%)	157,349 (29.6%)	6447 (40.4%)	220,256 (34.4%)	1361 (38.1%)	38,776 (34.4%)	3912 (40.5%)	66,408 (39.0%)
Morbidities												
Osteoporosis	425 (9.1%)	31,390 (4.7%)	3,622 (33.0%)	193,352 (23.4%)	1072 (16.2%)	46,675 (8.8%)	7823 (49.0%)	237,768 (37.1%)	673 (18.9%)	15,087 (13.4%)	5278 (54.6%)	80,721 (47.4%)
Osteoarthritis	2753 (59.1%)	365,400 (54.9%)	7631 (69.4%)	542,637 (65.6%)	4435 (67.0%)	348,606 (65.6%)	12,730 (79.7%)	489,633 (76.5%)	2644 (74.1%)	81,813 (72.7%)	7854 (81.3%)	139,216 (81.8%)
Rheumatoid arthritis	1426 (30.6%)	182,086 (27.4%)	3262 (29.7%)	216,121 (26.1%)	2347 (35.4%)	167,866 (31.6%)	5486 (34.3%)	200,196 (31.3%)	1197 (33.5%)	37,900 (33.7%)	3249 (33.6%)	56,931 (33.4%)
Vitamin D deficiency	227 (4.9%)	26,120 (3.9%)	1049 (9.5%)	68,185 (8.2%)	485 (7.3%)	28,717 (5.4%)	1699 (10.6%)	60,139 (9.4%)	246 (6.9%)	7211 (6.4%)	938 (9.7%)	15,317 (9.0%)
Obesity	1524 (32.7%)	200,040 (30.1%)	3435 (31.3%)	264,319 (32.0%)	2027 (30.6%)	152,403 (28.7%)	5157 (32.3%)	213,926 (33.4%)	778 (21.8%)	26,972 (24.0%)	2442 (25.3%)	49,304 (29.0%)
Heavy smoking	957 (20.5%)	104,173 (15.7%)	1676 (15.2%)	102,782 (12.4%)	861 (13.0%)	46,642 (8.8%)	1279 (8.0%)	38,148 (6.0%)	193 (5.4%)	5403 (4.8%)	273 (2.8%)	4607 (2.7%)
Alcohol abuse	719 (15.4%)	52,633 (7.9%)	726 (6.6%)	29,372 (3.6%)	683 (10.3%)	30,059 (5.7%)	711 (4.5%)	17,291 (2.7%)	163 (4.6%)	3973 (3.5%)	207 (2.1%)	3206 (1.9%)
Parkinson's disease	170 (3.6%)	7705 (1.2%)	213 (1.9%)	6058 (0.7%)	521 (7.9%)	16,525 (3.1%)	674 (4.2%)	13,038 (2.0%)	241 (6.8%)	5375 (4.8%)	391 (4.0%)	5818 (3.4%)
Dementia	264 (5.7%)	13,598 (2.0%)	434 (3.9%)	14,395 (1.7%)	1169 (17.7%)	41,555 (7.8%)	2428 (15.2%)	48,387 (7.6%)	1103 (30.9%)	23,506 (20.9%)	3170 (32.8%)	43,175 (25.4%)
Type 2 diabetes mellitus	1076 (23.1%)	135,608 (20.4%)	1500 (13.6%)	109,770 (13.3%)	1809 (27.3%)	127,709 (24.0%)	3136 (19.6%)	118,810 (18.6%)	804 (22.5%)	25,923 (23.0%)	1835 (19.0%)	32,041 (18.8%)
Nursing home residence	532 (11.4%)	37,392 (5.6%)	903 (8.2%)	42,229 (5.1%)	1266 (19.1%)	56,603 (10.7%)	2728 (17.1%)	71,472 (11.2%)	1043 (29.2%)	24,712 (22.0%)	3077 (31.9%)	48,506 (28.5%)

Abbreviations: AB, anticholinergic burden; ACB, anticholinergic cognitive burden scale; FRIDs, fall risk increasing drugs.

Results of the univariate analysis showed an increased risk of fractures over all age and sex categories for persons with Parkinson's disease, dementia, polypharmacy, FRIDs (particularly antipsychotics and high-ceiling diuretics), alcohol abuse, osteoporosis and high AB. The highest ORs regarding any fractures were observed for persons with Parkinson's disease (age group 65–74 years: 3.2 for men, 2.7 for women; age group 75–84 years: 2.7 for men, 2.1 for women and age group 85+: 1.4 for men, 1.2 for women) and dementia (age group: 65–74 years: 2.9 in men, 2.6 in women; age group 75–84 years: 2.2 in men, 2.3 in women and age group 85+: 1.5 in men, 1.4 in women) (Table 4).

Table 4 Predictors of Any Fractures by Sex and Age (Univariate Model)

Predictors	Age Groups					
	65–74 Years		75–84 Years		85+ Years	
	Men (N = 669,702)	Women (N = 838,130)	Men (N = 537,772)	Women (N = 656,261)	Men (N = 116,149)	Women (N = 179,858)
AB						
None (ACB=0) (ref)	–	–	–	–	–	–
Low (ACB=1)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	1.2 (1.2–1.3)	1.1 (1.1–1.2)	1.1 (1.0–1.2)	1.0 (1.0–1.1)
Medium (ACB=2)	1.2 (1.1–1.3)	1.2 (1.2–1.3)	1.6 (1.5–1.7)	1.3 (1.3–1.4)	1.2 (1.0–1.3)	1.1 (1.1–1.2)
High (ACB≥3)	1.9 (1.8–2.1)	1.6 (1.5–1.7)	2.1 (1.9–2.2)	1.7 (1.6–1.7)	1.4 (1.3–1.5)	1.1 (1.1–1.2)
AB						
0 (ref)	–	–	–	–	–	–
1–25th percentile	1.1 (1.0–1.2)	1.0 (1.0–1.1)	1.3 (1.2–1.4)	1.1 (1.1–1.2)	1.1 (1.0–1.3)	1.1 (1.0–1.1)
26–50th percentile	1.2 (1.1–1.3)	1.2 (1.1–1.2)	1.4 (1.3–1.5)	1.2 (1.2–1.3)	1.1 (1.0–1.3)	1.0 (1.0–1.1)
51–75th percentile	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.5 (1.4–1.6)	1.4 (1.3–1.4)	1.2 (1.0–1.3)	1.1 (1.0–1.2)
76–100th percentile	1.9 (1.7–2.0)	1.7 (1.6–1.8)	2.1 (2.0–2.3)	1.8 (1.7–1.8)	1.4 (1.3–1.6)	1.2 (1.1–1.3)
Use of different medication						
0 (ref)	–	–	–	–	–	–
1 to 4	1.1 (1.0–1.2)	1.2 (1.1–1.2)	1.1 (1.0–1.2)	1.2 (1.1–1.2)	1.2 (1.0–1.4)	1.2 (1.1–1.3)
Polypharmacy (5 to 9 different medications)	1.4 (1.3–1.6)	1.4 (1.4–1.5)	1.6 (1.4–1.7)	1.5 (1.4–1.6)	1.4 (1.2–1.6)	1.3 (1.1–1.4)
Hyper-polypharmacy (≥ 10 different medications)	2.4 (2.1–2.7)	2.2 (2.0–2.3)	2.3 (2.1–2.6)	2.1 (1.9–2.2)	1.6 (1.3–1.9)	1.4 (1.3–1.6)
FRIDs	1.9 (1.8–2.0)	1.5 (1.4–1.6)	2.0 (1.9–2.1)	1.6 (1.5–1.6)	1.5 (1.4–1.6)	1.2 (1.1–1.2)
High-ceiling diuretics	1.9 (1.8–2.1)	1.6 (1.5–1.7)	1.9 (1.8–2.0)	1.4 (1.3–1.4)	1.4 (1.3–1.4)	1.1 (1.1–1.1)
Cardiac glycosides	1.4 (1.2–1.8)	1.1 (0.9–1.4)	1.1 (1.0–1.3)	1.0 (0.9–1.1)	1.0 (0.9–1.2)	0.9 (0.8–0.9)
Antidepressants	1.9 (1.7–2.1)	1.4 (1.4–1.5)	1.9 (1.7–2.0)	1.6 (1.5–1.6)	1.5 (1.3–1.6)	1.2 (1.2–1.3)
Antipsychotics	2.3 (2.0–2.6)	1.7 (1.6–1.9)	2.7 (2.4–2.9)	1.9 (1.8–2.0)	1.7 (1.5–1.9)	1.3 (1.2–1.4)
Benzodiazepines	1.5 (1.3–1.9)	1.4 (1.2–1.5)	1.8 (1.6–2.1)	1.3 (1.2–1.4)	1.3 (1.1–1.5)	1.1 (1.0–1.2)
Opioids	1.8 (1.6–2.0)	1.6 (1.5–1.7)	1.6 (1.5–1.8)	1.5 (1.4–1.5)	1.3 (1.2–1.4)	1.1 (1.1–1.2)
Antiepileptics	2.0 (1.8–2.2)	1.8 (1.6–1.9)	1.7 (1.6–1.8)	1.5 (1.4–1.6)	1.1 (1.0–1.2)	1.0 (0.9–1.1)
Other medication						
Glucocorticoids	1.4 (1.3–1.5)	1.3 (1.3–1.4)	1.3 (1.2–1.3)	1.3 (1.2–1.3)	1.0 (0.9–1.1)	1.1 (1.0–1.2)
Proton pump inhibitors	1.4 (1.3–1.5)	1.3 (1.2–1.3)	1.4 (1.3–1.4)	1.3 (1.2–1.3)	1.2 (1.1–1.3)	1.1 (1.0–1.1)
Morbidities and lifestyle factors						
Osteoporosis	2.0 (1.8–2.2)	1.6 (1.5–1.7)	2.0 (1.8–2.1)	1.6 (1.6–1.7)	1.5 (1.3–1.6)	1.3 (1.3–1.4)
Osteoarthritis	1.2 (1.1–1.3)	1.2 (1.1–1.2)	1.1 (1.0–1.1)	1.2 (1.2–1.3)	1.1 (1.0–1.2)	1.0 (0.9–1.0)
Rheumatoid arthritis	1.2 (1.1–1.2)	1.2 (1.1–1.2)	1.2 (1.1–1.2)	1.1 (1.1–1.2)	1.0 (0.9–1.1)	1.0 (1.0–1.1)
Vitamin D deficiency	1.3 (1.1–1.4)	1.2 (1.1–1.3)	1.4 (1.3–1.5)	1.1 (1.1–1.2)	1.1 (0.9–1.2)	1.1 (1.0–1.2)
Obesity	1.1 (1.1–1.2)	1.0 (0.9–1.0)	1.1 (1.0–1.2)	1.0 (0.9–1.0)	0.9 (0.8–1.0)	0.8 (0.8–0.9)

(Continued)

Table 4 (Continued).

Predictors	Age Groups					
	65–74 Years		75–84 Years		85+ Years	
	Men (N = 669,702)	Women (N = 838,130)	Men (N = 537,772)	Women (N = 656,261)	Men (N = 116,149)	Women (N = 179,858)
Heavy smoking	1.4 (1.3–1.5)	1.3 (1.2–1.3)	1.6 (1.4–1.7)	1.4 (1.3–1.5)	1.1 (1.0–1.3)	1.0 (0.9–1.2)
Alcohol abuse	2.1 (2.0–2.3)	1.9 (1.8–2.1)	1.9 (1.8–2.1)	1.7 (1.6–1.8)	1.3 (1.1–1.5)	1.1 (1.0–1.3)
Parkinson's disease	3.2 (2.8–3.8)	2.7 (2.3–3.1)	2.7 (2.4–2.9)	2.1 (2.0–2.3)	1.4 (1.3–1.7)	1.2 (1.1–1.3)
Dementia	2.9 (2.3–3.6)	2.6 (2.2–3.1)	2.2 (2.0–2.5)	2.3 (2.1–2.5)	1.5 (1.3–1.7)	1.4 (1.3–1.6)
Type 2 diabetes mellitus	1.2 (1.1–1.3)	1.0 (1.0–1.1)	1.2 (1.1–1.3)	1.1 (1.0–1.1)	1.0 (0.9–1.1)	1.0 (1.0–1.1)
Nursing home residence	2.2 (2.0–2.4)	1.7 (1.6–1.8)	2.0 (1.9–2.1)	1.6 (1.6–1.7)	1.5 (1.4–1.6)	1.2 (1.1–1.2)

Abbreviations: AB, anticholinergic burden; ACB, anticholinergic cognitive burden scale; FRIDs, fall risk increasing drugs.

Predictive performance of the models, as measured by the AUC, is shown in [Table 5](#) for men and in [Table 6](#) for women. In models using medication and utilization of medication as predictors (models A–F), the range of AUC was 0.51–0.60 for both the random forest models and the logistic regression models. In model G, which included predictors related to morbidities and lifestyle, the AUC in the age group 65–74 years was 0.60 in men (logistic regression model: 0.60) and 0.59 in women (logistic regression model: 0.59). In the age group 75–84 years, the AUC for the random forest model was 0.61 in men (logistic regression model: 0.61) and 0.60 in women (logistic regression model: 0.60). In the age group ≥85 years, the AUC for the random forest model was 0.57 for men (logistic regression model: 0.57) and 0.54 in women (logistic regression model: 0.55). In model H, which included all predictors used in the previous models, the AUC in the age group 65–74 years, was 0.60 in men (logistic regression model: 0.61) and 0.58 in women (logistic regression model: 0.60). In the age group 75–84 years the AUC for the random forest model was 0.62 in men (logistic regression model: 0.63) and 0.59 in women (logistic regression model: 0.60). In the age group ≥85 years, the AUC for the random forest model was 0.56 for men (logistic regression model: 0.58) and 0.54 in women (logistic regression model: 0.55). Across all sex and age groups, models G and H had the highest AUCs in random forest and logistic regression models.

Discussion

Based on a large and unselected population sample including 2,997,872 persons aged 65 or older, we assessed the usefulness of information available in GePaRD for the prediction of fractures within up to one year after baseline, stratified by age and sex. In the univariate analysis, the predictors Parkinson's disease, dementia, hyper-polypharmacy, FRIDs, alcohol abuse, osteoporosis and AB showed the strongest association with fractures. In the multivariate analysis, models that included medication, morbidities and lifestyle-related factors achieved the highest predictive performance as measured by the AUC. AUCs were lowest in age group 85+. The performance of the random forest models was largely similar to the logistic regression models.

A study (n = 288,086) aiming to predict osteoporotic hip fractures based on German claims data using machine learning reported AUCs ranging from 0.65 to 0.70.⁴¹ However, unlike in our study, this study did not exclude persons with prior fractures, so occurrence of the strong predictor “prior fracture” was included in the models, which likely explains the higher AUC compared to our study. Moreover, the study had information on the level of care (a higher level suggesting a higher frailty and thus a higher risk of falls and fractures) and the study population was based only on statutory health insurance data of persons working in agriculture and their families, ie, a study cohort with higher baseline risk for fractures. Indeed, the authors reported that 3% of the study population experienced a hip fracture during follow-up, which is much higher compared to our study in which 1.7% of the population had any fracture during follow-up. Compared to studies analyzing data with more clinical and laboratory information such as bone mineral density, vitamin D3, T-scores of the hip and lumbar spine as well as biochemical glucose measurements, the predictive performance of our model using only claims data is not as good. A recent study from the Netherlands reported

Table 5 Predictive Performance of All Models (Men)

Model	Age Group																							
	65–74 Years								75–84 Years								85+ Years							
	Random Forest				Logistic Model				Random Forest				Logistic Model				Random Forest				Logistic Model			
	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*
A	0.55	0.007	0.20	0.88	0.55	0.00697	0.20	0.88	0.58	0.0126	0.45	0.67	0.58	0.0126	0.45	0.67	0.53	0.0297	0.73	0.32	0.53	0.0297	0.73	0.32
B	0.57	0.007	0.35	0.79	0.57	0.00697	0.35	0.79	0.58	0.0126	0.48	0.69	0.58	0.0126	0.48	0.69	0.56	0.0296	0.61	0.51	0.56	0.0296	0.61	0.51
C	0.57	0.007	0.39	0.73	0.58	0.00697	0.39	0.73	0.58	0.0126	0.43	0.69	0.58	0.0126	0.43	0.69	0.53	0.0297	0.45	0.62	0.55	0.0296	0.37	0.7
D	0.57	0.007	0.35	0.79	0.57	0.00696	0.35	0.79	0.60	0.0126	0.55	0.63	0.60	0.0126	0.55	0.63	0.56	0.0296	0.61	0.51	0.55	0.0296	0.61	0.51
E	0.57	0.007	0.3	0.81	0.58	0.00697	0.39	0.74	0.59	0.0126	0.45	0.7	0.59	0.0126	0.42	0.72	0.54	0.0297	0.41	0.66	0.54	0.0297	0.41	0.67
F	0.58	0.007	0.4	0.74	0.59	0.00696	0.40	0.74	0.60	0.0126	0.51	0.66	0.60	0.0126	0.49	0.67	0.55	0.0296	0.61	0.5	0.56	0.0296	0.62	0.49
G	0.60	0.007	0.38	0.79	0.60	0.00696	0.37	0.80	0.61	0.0126	0.45	0.72	0.61	0.0126	0.43	0.74	0.57	0.0296	0.55	0.58	0.57	0.0296	0.57	0.57
H	0.60	0.007	0.43	0.75	0.61	0.00696	0.49	0.70	0.62	0.0127	0.62	0.57	0.63	0.0126	0.59	0.62	0.56	0.0297	0.49	0.61	0.58	0.0296	0.42	0.71

Note: *Youden (sensitivity and specificity are given at the optimal Youden value).
Abbreviations: AUC, area under the curve; MSPE, mean squared prediction error; Se, sensitivity; Sp, specificity.

Table 6 Predictive Performance of All Models (Women)

Model	Age Group																							
	65–74 years								75–84 Years								85+ Years							
	Random Forest				Logistic Model				Random Forest				Logistic Model				Random Forest				Logistic Model			
	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*	AUC	MSPE	Se*	Sp*
A	0.54	0.0129	0.36	0.71	0.54	0.01286	0.36	0.71	0.56	0.0233	0.48	0.61	0.56	0.0233	0.48	0.61	0.51	0.051	0.48	0.54	0.51	0.051	0.48	0.54
B	0.54	0.0129	0.34	0.74	0.54	0.01286	0.34	0.74	0.55	0.0233	0.49	0.61	0.55	0.0233	0.49	0.61	0.52	0.051	0.63	0.42	0.52	0.051	0.63	0.42
C	0.56	0.0129	0.32	0.77	0.56	0.01286	0.32	0.77	0.57	0.0233	0.49	0.61	0.57	0.0233	0.49	0.61	0.51	0.051	0.75	0.28	0.52	0.051	0.75	0.28
D	0.55	0.0129	0.39	0.70	0.55	0.01286	0.39	0.70	0.57	0.0233	0.55	0.56	0.57	0.0233	0.55	0.56	0.52	0.051	0.63	0.42	0.53	0.051	0.63	0.42
E	0.56	0.0129	0.65	0.43	0.56	0.01286	0.37	0.72	0.57	0.0233	0.59	0.52	0.57	0.0233	0.53	0.58	0.52	0.051	0.45	0.59	0.52	0.051	0.47	0.57
F	0.56	0.0129	0.44	0.65	0.56	0.01286	0.44	0.65	0.57	0.0233	0.62	0.50	0.57	0.0233	0.57	0.54	0.53	0.051	0.61	0.44	0.53	0.051	0.58	0.47
G	0.59	0.0129	0.48	0.67	0.59	0.01284	0.55	0.6	0.60	0.0233	0.60	0.54	0.60	0.0233	0.51	0.63	0.54	0.0509	0.56	0.52	0.55	0.0509	0.72	0.36
H	0.58	0.0129	0.46	0.67	0.60	0.01284	0.47	0.68	0.59	0.0233	0.54	0.60	0.60	0.0233	0.48	0.68	0.54	0.0511	0.61	0.45	0.55	0.0509	0.68	0.40

Note: *Youden (sensitivity and specificity are given at the optimal Youden value).

Abbreviations: AUC, area under the curve; MSPE, mean squared prediction error; Se, sensitivity; Sp, specificity.

a c-index of 0.70 (CI: 0.66–0.73) for the prediction of subsequent major osteoporotic fractures in patients with prior fractures,⁴² and a Danish study reported an AUC of up to 0.92 (CI: 0.89–0.94) for the prediction of hip fractures in patients who had undergone bone mineral density measurement with dual-energy X-ray absorptiometry.⁴³ Again, however, patients included in both studies might be subject to higher fracture risk. In the Dutch study, 11% of patients sustained a fracture within a median time of 114 weeks, and in the Danish study, approximately 7% of patients sustained a hip fracture within five years.

The various models assessed in our study suggest that combining information on medication and morbidity is important to achieve at least an AUC of ≥ 0.60 . In age group 85+, however, even models combining this information showed hardly any predictive performance. This may reflect the difficulty of capturing frailty in GePaRD, a factor that becomes increasingly important with age. Generally, it seems reasonable to judge the discriminatory power of a model based on the context and its intended use. If a model is intended to be used for diagnostic purposes in oncology, eg, to distinguish between persons with and without preclinical cancer, a model performance of 0.6 would likely be considered as poor because at acceptable levels of specificity a high proportion of cancer patients would remain undetected. The situation is different if a model is intended to predict future occurrence of a disease in order to narrow down, for example, the population at risk that may benefit from preventive measures. In the context of our study, the question is whether the prediction of fractures based on a model with an AUC of ~ 0.6 may still be of some practical use in Germany to screen for persons at high risk of fractures in older adults below the age of 85. Model H may serve as an example (see Table 1). If we select a cutoff level yielding a sensitivity of 0.62 and 0.54 in men and women, respectively, and a specificity of 0.57 and 0.60 and apply this to a theoretical population of 2000 older adults aged 74–85 years (1000 men, 1000 women), the screening tool has a positive predictive value of 2% in men and 3% in women. Among the 432 men and 403 women identified by the model to have a high risk of fractures, 8 men and 13 women would actually have a fracture within one year. Considering the high impact of fractures on health, life expectancy and quality of life in those afflicted and the fact that fall prevention measures have no harm, it seems plausible to assume a net benefit if the measures are effective. Evaluating whether such a program would be affordable requires a systematic assessment of costs saved due to prevented fractures versus costs of the intervention. An advantage regarding the costs of such an intervention is certainly the fact that the data are readily available at the statutory health insurance providers. It could be an option that statutory health insurance providers directly analyze their data in order to identify and inform groups of persons that may particularly benefit from preventive measures. The screening tool itself would thus not cause high additional costs; however, this would constitute only a part of the total costs of such an intervention.

Even though including persons with prior fractures would likely have increased the predictive performance of the models in our study, we consider it a strength that we excluded these persons. It is known that these persons are at high risk of subsequent fractures.^{24–26} However, as they already experienced a fracture they or their caregivers are alerted and may already have taken measures, so this would not be the relevant target group for prevention of a first fracture. Mixing persons with and without prior fractures may thus overrate the value of such models in terms of preventing a first fracture, which is different from the question of preventing subsequent fractures.

Another strength of our study is the population-based setting and the large sample size, which made it possible to conduct analyses specific to sex and age group. Indeed, predictive performance in our model tended to differ by age and sex, therefore it seems logical not to combine these categories. Given the nature of claims data analysis, our study is free of non-responder and recall bias. In order to mitigate outcome misclassification and ensure a high specificity of the outcome definition, fractures were assessed based on ICD-10-GM main hospital discharge diagnoses as these are the most valid diagnoses in German claims data. This also means that we did not capture fractures treated conservatively outside the hospital, but from a public health perspective we think it is more relevant to predict the risk of fractures leading to hospitalization as these are likely the more severe kind.

Our study also has limitations. First, while inpatient diagnosis codes in German claims data have a very high validity, there is often an over-reporting of diagnoses in the outpatient setting. To minimize misclassification, it is therefore often advisable to use algorithms that consider outpatient diagnosis codes only, for example, if there is also a specific treatment for the respective disease. In our study, we used specific algorithms for type 2 diabetes, dementia and Parkinson's disease, which were developed in prior projects,^{44–46} but considered any in- or outpatient diagnosis codes for the other morbidities. This corresponds to a sensitive but less specific definition of these other morbidities; consequently, the

prevalence of some predictors may have been overestimated. Second, information on medication in German claims data is limited to outpatient pharmacy records except for certain expensive medications (eg, monoclonal antibodies). As in most pharmacoepidemiological studies, no information on adherence was available, ie, whether dispensed medication was actually taken by the patient. Moreover, over-the-counter medication is not captured in GePaRD. Third, our findings may not be generalizable to all German claims databases. While we could only use codes indicating nursing home residency to capture “frailty”, there may be databases with information on the level of care, as the study mentioned above,⁴¹ or on the reimbursement of medical devices such as walkers.

In conclusion, our study showed that the performance of models using German claims data to predict the risk of fractures in older adults is moderate. Given that the models used data readily available to health insurance providers in Germany, it may still be worthwhile to explore the cost–benefit ratio of interventions aiming to reduce the risk of fractures based on such prediction models in certain risk groups.

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Disclosure

The authors report no conflicts of interest in this work.

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