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Contribution of an extensive medication-based comorbidity index (Rx-Risk) in explaining the excess mortality after hip fracture in older Norwegians: a NOREPOS cohort study

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ABSTRACT

Objectives Patients with hip fracture are typically characterised by extensive comorbidities and excess mortality. Methods that account for a wide range of comorbidities are needed when attempting to identify causal associations in registry-based studies. We aimed to study the association between the prescription-based Rx-Risk Comorbidity Index (abbreviated Rx-Risk) and mortality by history of hip fracture, and to quantify the contribution of Rx-Risk in explaining the excess mortality after hip fracture.

Setting In this prospective study, we used nationwide registry data from outpatient care. Rx-Risk was based on filled prescriptions recorded in the Norwegian Prescription Database. Medications were mapped to 46 comorbidity categories by Anatomical Therapeutic Chemical code. Information on hip fractures during 1994–2013 was available from the Norwegian Epidemiologic Osteoporosis Studies hip fracture database, and year of death was obtained from Statistics Norway. We estimated 1-year mortality risk (January through December 2014) according to Rx-Risk score based on dispensed prescriptions in 2013, history of hip fracture, age and sex using Poisson regression.

Participants All individuals aged 65 years and older who were alive by the end of 2013 and had filled at least one prescription in an outpatient pharmacy in Norway in 2013 (n=735 968).

Results Mortality increased exponentially with increasing Rx-Risk scores, and it was highest in persons with a history of hip fracture across the major range of Rx-Risk scores. Age- and sex-adjusted mortality risk difference according to history of hip fracture (yes vs no) was 4.4 percentage points (7.8% vs 3.4%). Adjustment for Rx-Risk score further attenuated this risk difference to 3.3 percentage points.

Conclusions History of hip fracture and comorbidity assessed by Rx-Risk are independent risk factors for mortality in the community-dwelling older population in Norway. Comorbidity explained a quarter of the excess mortality in persons with a history of hip fracture.

Strengths and limitations of this study

- ► Population-wide study covering the older population in Norway, using registries to which reporting is mandatory, and thereby not affected by self-selection or recall bias.
- ► Detailed information about all dispensed prescription drugs, with or without reimbursement, in outpatient pharmacies nationwide.
- ► Large sample size ensuring high statistical power and precise estimates.
- ► Filled prescriptions are used as proxies for chronic conditions, involving some degree of misclassification of individual patients.
- ► Drugs used by persons living in institutions are not covered in the Norwegian Prescription Database.

INTRODUCTION

Hip fracture is associated with high excess mortality.[1 2] Identifying the subgroups who have a poorer prognosis in terms of their demographic and clinical characteristics is important for targeting and prioritising care and rehabilitation resources. The availability of nationwide health and population registries, allowing individual-level linkage of data by the unique personal identification number, enables us to identify explanatory factors for disease risk and survival across the whole population, to inform prevention and healthcare planning. Complete population coverage that minimises selection bias is a strength of registry-based research.[3 4] However, the level of details may be limited, and information about individual lifestyle and biological characteristics is often unavailable. Without such information, it can be challenging to achieve comparability between a patient population of interest and the background population of comparison when aiming to

estimate effects of risk factors on health outcomes in observational studies. To overcome such possible shortcomings, various indexes based on available registry data have been developed. In countries where prescription databases are available, indexes of comorbidity based on drug prescriptions have been proposed.[5–12] Prescription drugs are thus applied as proxies for chronic illnesses and conditions, and such indexes have typically been developed for outpatient populations with the goal of predicting mortality, hospitalisations or healthcare costs. As indicators of different chronic diseases, drug classes differ in their associations with mortality, and this can be taken into account by applying severity weights. We may anticipate that such indexes could be used as meaningful indicators of fragility in observational studies where there is a need for information about the comorbidity level of a population. Prescription data are to a lesser extent than hospital discharge diagnosis data subject to variations in coding practices and financial incentives for coding. Yet, the types of medications available, treatment guidelines and practices, and reimbursement schemes vary between countries and over time. A medication-based comorbidity index developed in a certain population at a certain point in time may therefore not necessarily be directly applicable to other populations, but needs to be adapted and validated in a new context.

In the Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) we have available individual-level registry data for the population of Norway, including computerised discharge diagnostic codes for all hip fractures treated in the specialist healthcare service over two decades (1994–2013) as well as all information on dispensed prescription drugs from outpatient pharmacies in Norway to patients in ambulatory care from 2004.[13] It is therefore of interest to investigate the predictive ability of a medication-based comorbidity index in our setting, calculating severity weights for the population. We chose to apply the Anatomical Therapeutic Chemical (ATC)[14] mapped Rx-Risk Comorbidity Index,[11] hereafter abbreviated as Rx-Risk, due to several advantages. It has been developed for an ambulatory older population, it covers an extensive list of drugs grouped into 46 mutually exclusive disease categories, and it has been mapped in detail to the ATC Classification System at the most detailed level (ATC 5). Weights are assigned based on the magnitude of the coefficients from logistic regression analyses of 1-year mortality in users of drugs in each category. The ability of the index to classify patients according to 1-year mortality was found to be high in an Australian population, with a concordance statistic (c statistic) of 0.83 in an external validation study.[11]

We hypothesised that comorbidity partly accounts for the excess mortality after hip fracture, and that this may be captured by a prescription-based comorbidity index. Our main objective was to implement the Rx-Risk Comorbidity Index and assess its performance in the Norwegian population aged 65 years and older. Specifically, we aimed to: (1) apply Rx-Risk with minor adaptations to accommodate national treatment practices where necessary and assign severity weights to each comorbidity category based on 1-year mortality, (2) examine the association of Rx-Risk with 1-year mortality risk in persons with a history of hip fracture and their non-fractured counterparts and (3) quantify the contribution of Rx-Risk to explaining the excess mortality in the subpopulation with a history of hip fracture.

METHODS

Using national registry data, we designed a prospective study to assess 1-year mortality risk according to Rx-Risk, history of hip fracture, sex and age. The study population was defined as individuals aged 65 years and older who were alive on 31 December 2013, and who retrieved at least one prescription drug from an outpatient pharmacy in Norway during 2013 (n=735 968). We chose not to include individuals who did not retrieve any prescribed drugs from outpatient pharmacies in 2013, comprising 9% of the population aged 65+ years, since healthy community-dwelling individuals using no medications could not be distinguished from nursing home residents who receive their medications through the institution and are thus not recorded in the Norwegian Prescription Database (NorPD) (see below). Notably, a higher age distribution and a high 1-year mortality risk suggest a high proportion of nursing home residents in the subgroup of the population who did not fill any prescriptions in 2013.

Prescription data

The NorPD is based on mandatory electronic reports from outpatient pharmacies on dispensed prescriptions, both reimbursed and non-reimbursed, from January 2004 onwards.[15] Drugs administered through hospitals and nursing homes are not included, and over-the-counter drugs are not registered. The drugs are classified according to the ATC Classification System.[14] The patient's sex and year of birth are also recorded.

Dispensed drugs

Rx-Risk, covering drugs grouped into 46 mutually exclusive disease categories, was constructed based on drugs dispensed in 2013 (index year). All individuals who filled at least one prescription within a specific category during the index year were counted in that category. Definitions were based on the ATC-mapped index as published by Pratt *et al*,[11] with only minor modifications to accommodate treatment practices in Norway (table 1). Individual reimbursement codes, dosages and number of filled prescriptions were not taken into account when constructing the index. Our definitions in terms of ATC codes were unique for each comorbidity category, meaning that each active substance could only be assigned to one category. To that end, a simplification was done when allocating ATC codes of dispensed medications to either of the two categories congestive heart failure and hypertension. Drugs in groups like diuretics,

Table 1 Comorbidity categories and their definitions in terms of ATC codes, number of individuals aged 65 years and older in each comorbidity category,* crude 1-year mortality risk, adjusted mortality ORs and assigned weights

	Category	ATC codes†	All	Men	Women	% died in 2014	OR‡	Weight
0	Drugs not mapped to a comorbidity category		37 892	17 046	20 846	1.4	–	–
1	Alcohol dependency	N07BB§	2 909	1 330	1 579	4.1	1.75	4
2	Allergies	R01AC§ R01AD§ R06AD02 R06AD03 R06AE§ R06AX§ R06AB§	107 407	39 982	67 425	2.7	0.81	–1
3	Anticoagulants	B01AA§ B01AB§ B01AE07 B01AF§ B01AX§	97 138	52 098	45 040	6.3	1.31	2
4	Antiplatelets	B01AC§	266 586	139 584	127 002	3.8	1.09	1
5	Anxiety	N05BA§ N05BE§	94 527	26 603	67 924	5.4	1.31	2
6	Arrhythmia	C01AA§ C01B§	25 205	13 225	11 980	7.7	1.36	2
7	Benign prostatic hyperplasia (men)	G04C§	47 685	47 685	–	3.9	0.79	–1
8	Bipolar disorder	N05AN01	1 923	762	1 161	3.8	1.41	3
9	Chronic airways disease	R03§	108 979	46 692	62 287	4.6	1.39	2
10	Congestive heart failure	C03DA§ C07AB07 C07AG02	39 553	20 383	19 170	7.1	1.57	3
11	Dementia	N06DA§ N06DX01	13 871	5 109	8 762	9.9	2.10	6
12	Depression	N06A§	88 075	25 662	62 413	5.2	1.27	2
13	Diabetes	A10§	76 319	41 249	35 070	4.3	1.35	2
14	Epilepsy	N03A§	30 981	12 830	18 151	5.9	1.46	3
15	Glaucoma	S01E§	55 466	22 831	32 635	4.2	0.90	–1
16	Gastro-oesophageal reflux disease	A02B§ except A02BX12	157 384	65 725	91 659	4.8	1.21	2
17	Gout	M04§	29 515	19 808	9 707	6.3	1.15	1
18	Hepatitis B	J05AF08 J05AF10 J05AF11	n/r	n/r	n/r	0	0.00¶	0
19	Hepatitis C	J05AP§ L03AB10 L03AB11 J05AB54 J05AB60 J05AB61 J05AE14 J05AE11 J05AE12 J05AX14 J05AX15 J05AX65 J05AB04	n/r	n/r	n/r	3.6	0.76¶	0
20	HIV	J05AE§ J05AF12 J05AF13 J05AG§ J05AR§ J05AX07 J05AX08 J05AX09 J05AX12 J05AF01 J05AF02 J05AF03 J05AF04 J05AF05 J05AF06 J05AF07 J05AF09	184	n/r	n/r	3.8	2.16	6
21	Hyperkalaemia	V03AE01 V03AE10	305	216	89	16.4	1.72	4
22	Hyperlipidaemia	C10§	297 164	146 741	150 423	2.8	0.74	–1
23	Hypertension	C03A§ C03B§ C03DB§ C03EA§ C09BA§ C09DA§ C02A§ C02DB§ C03C§ C09C§	310 471	134 422	176 049	4.1	1.15	1
24	Hyperthyroidism	H03B§	1 842	333	1 509	4.7	1.22	2
25	Hypothyroidism	H03A§	80 643	16 057	64 586	3.2	0.91	–1
26	Irritable bowel syndrome	A07EA§ A07EC§ L04AA33	6 432	2 891	3 541	2.9	0.83	–1

Continued

Table 1 Continued

	Category	ATC codes†	All	Men	Women	% died in 2014	OR‡	Weight
27	Ischaemic heart disease: angina	C01D§ C08EX02	50 804	25 177	25 627	6.5	1.10	1
28	Ischaemic heart disease: hypertension	C07AA03 C07AA05 C07AA06 C07AA12 C07AB02 C07AB03 C07AG01 C08CA01 C08CA02 C08CA03 C08CA05 C08CA06 C08CA13 C08DA01 C08DB01 C09BB02 C09DB01 C09DB02 C09DX01	301 220	144 844	156 336	4.0	1.05	1
29	Incontinence	G04BD§	32 357	10 595	21 762	3.6	0.95¶	0
30	Inflammation/pain	M01A§	164 036	65 587	98 449	1.9	0.63	–1
31	Liver failure	A06AD11 A07AA11	6 752	3 072	3 500	22.1	3.91	6
32	Malignancies	L01§	3 398	1 656	1 742	25.0	8.06	6
33	Malnutrition	B05BA§	148	65	83	35.1	8.11	6
34	Migraine	N02C§	8 452	1 656	6 796	1.1	0.60	–1
35	Osteoporosis	M05B§ G03XC01 H05AA02 H05BA01	46 086	4 857	41 229	4.3	1.02¶	0
36	Pain	N02A§ N02B§	223 043	79 671	143 372	5.4	1.68	4
37	Pancreatic insufficiency	A09AA02	2 497	1 025	1 472	9.1	2.30	6
38	Parkinson's disease	N04A§ N04B§	11 387	5 529	5 858	5.7	1.38	2
39	Psoriasis	D05§	8 208	4 364	3 844	3.2	1.13	1
40	Psychotic illness	N05A§ except N05AN01	25 515	8 822	16 693	6.4	1.50	3
41	Pulmonary hypertension	C02KX§	46	n/r	n/r	15.2	7.96	6
42	Renal disease	B03X§ A11CC03 A11CC04 V03AE§ except V03AE01 and V03AE10	4 612	2 643	1 969	13.8	2.55	6
43	Smoking cessation	N07BA§	3 356	1 570	1 786	3.5	1.58	3
44	Steroid-responsive disease	H02§	75 191	31 153	44 038	7.3	1.93	5
45	Transplant	L04AA06 L04AA10 L04AA18 L04AD01 L04AD02	1 653	1 040	613	7.4	1.37	2
46	Tuberculosis	J04A§	278	136	142	7.9	1.97	5

The Norwegian Prescription Database population aged 65 years and older in 2013
*Defined by at least one dispensed prescription drug in outpatient pharmacies in Norway in 2013, conditioned on survival through 2013. The same individual may occur in one or more category. Numbers lower than 40 in total or in any sex stratum are not reported and replaced by n/r.
†WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. https://www.whocc.no/atc_ddd_index/.
‡From a logistic regression model including age, sex and all comorbidity categories as indicator (0/1) variables.
§With all subcodes.
¶p>0.10.
ATC, Anatomical Therapeutic Chemical.

beta-blockers, calcium channel blockers and ACE inhibitors/angiotensin II receptor blockers (ARBs), are used to treat different diseases, most commonly hypertension, angina, oedema and heart failure. Others have required concomitant use of high-ceiling diuretics and ARBs or ACE inhibitors to merit inclusion in the congestive heart failure category, while classifying use of only one of these drug types alone as hypertension.[11] To maintain a feasible approach, we classified these drugs into the hypertension category and did not consider concomitant use. Consequently, hypertension may be somewhat overestimated, and congestive heart failure may be correspondingly underestimated in our version.

Construction of the comorbidity scores

Following the procedure described by Pratt *et al*,[11] the unweighted score was defined as the number of different comorbidity categories from which the individual had retrieved one or more drugs during the index year (2013), with a possible range of 0–46. Individuals who only filled prescriptions that did not represent a comorbidity category were assigned the value 0. Examples of

commonly used prescription drugs that were not mapped to a comorbidity category include hypnotics/sedatives, oestrogens, antibiotics/anti-infectives, mineral supplements and cough and cold preparations. A weighted score was obtained by assigning severity weights to each category (1–46) after fitting a binary logistic regression model with death during 2014 (yes/no) as the outcome variable, and age, sex and indicators (0/1) of each comorbidity category as predictors. Depending on the magnitude of the estimated OR, the weight assigned to each comorbidity category took a value between −1 and 6, in accordance with an algorithm previously used by others,[8 11] shown in online supplemental table 1. Finally, each person's weighted Rx-Risk score was calculated as the net sum of weights for all categories from which the individual had filled at least one prescription in 2013. Since a negative severity weight (−1) was assigned to comorbidity categories with an OR below 1, implying a relatively lower mortality in users of those drugs, a negative total Rx-Risk score was also attainable.

Hip fractures

The NOREPOS hip fracture database (NORHip) contains information on all hip fractures treated in Norway from 1994 through 2013, with inpatient data obtained from hospitals' patient administrative systems and the Norwegian Patient Registry.[13 16 17] A detailed description of the data collection, classification, validation and quality assurance of the data is available on the NOREPOS website (http://www.norepos.no/documentation). Information from NORHip was linked to the other data sources at the individual level. For the current purpose, a history of hip fracture was defined as having at least one hip fracture diagnosis registered in NORHip during 1994–2013, regardless of time since the fracture (range 0–19 years).

Deaths

Deaths constituted the outcome in this study. Residence status according to the National Population Register and year of death was provided by Statistics Norway. The study population was followed with regard to death in 2014 (yes/no) by registry linkage. Emigrations in 2014 (0.03% of the study population) were disregarded.

Statistical analyses

Data preparation and statistical analyses were performed in R V.4.0.2 (22 June 2020).[18] Graphics were prepared in R and in Microsoft Excel 2016. For graphical presentation, Rx-Risk was truncated at the values −3 and 25 for all categories to contain at least 400 observations. Deaths in the calendar year following the index year (2014) varied exponentially across age and Rx-Risk scores. To achieve appropriate age adjustment, death in 2014 was therefore regressed on Rx-Risk score, adjusting for age, sex and history of hip fracture, in a Poisson regression model with robust variance estimates.[19] This method produces similar estimates as the log-binomial model and is a widely accepted alternative when the latter does not converge, as was the case in our study. The model was fitted using the 'glm' function with the 'family=poisson' and 'link=log' arguments, available in the package 'stats' in R.[18] Robust variance estimates were obtained by the 'vcovHC' function of the 'sandwich' package.[20] We allowed for any interactions between Rx-Risk scores, sex, age and history of hip fracture. Statistically, non-significant (p>0.05) interaction terms were excluded using the 'dropterm' function in the package 'MASS' in R.[21]

In a sensitivity analysis examining the consistency across elapsed time since an individual's hip fracture, persons with a history of hip fracture were stratified into two categories according to time since their most recent hip fracture, divided at the median (≤4 years vs >4 years).

Validation

To study the consistency across time of the predictive performance of the implemented Rx-Risk index in the Norwegian population aged 65 years and older,[22] we applied the ATC codes and severity weights derived from the 2013 data to the 2005 population (individuals aged 65 years and older who were alive on 31 December 2005). For this analysis, we used 2005 as the index year for dispensed drugs recorded in the NorPD and follow-up with regard to deaths in 2006. The ability of the index to classify individuals according to 1-year mortality risk was examined by the c statistic, using the 'Cstat' function in the R package 'DescTools'.[23] The c statistic is equivalent to the area under the receiver operating characteristics curve. It takes a value between 0 and 1, with 1 indicating perfect discrimination and 0.5 representing the expected variation due to chance alone.[24] We compared the c statistic calculated for 2013/2014 with that of 2005/2006.

Patient and public involvement

No patient involved.

RESULTS

Of all individuals aged 65 years and older who filled at least one prescription in an outpatient pharmacy in Norway in 2013, n=735 968 individuals (97%) were alive by 31 December 2013 and comprise the study population. Among these, 55.2% (n=406 498) were women. The mean age was 74.7 years (SD: 7.7 years) and higher in women (75.4 years in women vs 73.8 years in men, p<0.001). A total of 33 925 individuals (4.6%) had suffered a hip fracture during 1994–2013. Median time since each person's most recent hip fracture was 4 years (IQR: 1–8 years). Persons with a history of hip fracture were older than those with no history of hip fracture, mean 81.6 years vs 74.3 years (p<0.001), and a higher percentage of the former group were women: 74.1% vs 54.3% (p<0.001). A total of 26 266 individuals (3.6%) died in the subsequent calendar year (2014): 13 212 men (4.0% of the male study population) and 13 054 women (3.2% of the female study population).

Table 2 Distribution of unweighted Rx-Risk comorbidity scores* in individuals aged 65 years and older in Norway in 2013† by sex and history of hip fracture.

	Men with no hip fracture N=320 694		Men with hip fracture N=8776		Women with no hip fracture N=381 349		Women with hip fracture N=25 149	
Mean (SD)	3.9 (2.5)		4.6 (2.6)		4.0 (2.5)		4.8 (2.6)	
Range	0–18		0–17		0–20		0–17	
N (%)	n	%	n	%	n	%	n	%
0	16 773	5.2	273	3.1	20 206	5.3	640	2.5
1	42 701	13.3	759	8.6	47 958	12.6	1830	7.3
2	46 238	14.4	956	10.9	55 695	14.6	2519	10.0
3	50 392	15.7	1257	14.3	58 114	15.2	3371	13.4
4	48 686	15.2	1291	14.7	54 950	14.4	3619	14.4
5	40 500	12.6	1199	13.7	46 525	12.2	3638	14.5
6	29 610	9.2	1042	11.9	35 958	9.4	3097	12.3
7	19 598	6.1	793	9.0	25 214	6.6	2446	9.7
8	11 947	3.7	489	5.6	16 425	4.3	1702	6.8
9	6953	2.2	343	3.9	9857	2.6	1046	4.2
10	3842	1.2	209	2.4	5464	1.4	644	2.6
11	1933	0.6	83	0.9	2750	0.7	315	1.3
≥12	1521	0.5	82	0.9	2233	0.6	282	1.1

*Defined as the number of different comorbidity categories from which an individual retrieved one or more drugs in 2013, possible range 0–46.
†Conditioned on survival through 2013.

Level of comorbidity

The number of persons who filled prescriptions within each comorbidity category in 2013 are shown in table 1. While 698 076 individuals (94.9%) filled at least one prescription within one or more of the 46 comorbidity categories, 37 892 individuals (5.1%) retrieved only drugs that were not assigned to any comorbidity (ie, category 0). Table 1 also shows the allocated weights for each category, based on age- and sex adjusted logistic regression with death during 2014 as the outcome.

The distribution of unweighted Rx-Risk scores according to sex and history of hip fracture is shown in table 2. Unweighted scores ranged from 0 through 20, with an overall mean score of 4.0 (SD 2.5). Unweighted scores were slightly higher in women than in men (mean 4.0 vs 3.9, p<0.001) and considerably higher in persons with a history of hip fracture than in those without (4.8 vs 4.0 in women and 4.6 vs 3.9 in men, both p<0.001; table 2).

The weighted Rx-Risk scores in the study population ranged from −5 to 44 with a median score of 3 (IQR 1–7) and a mean score of 4.5 (SD 4.7). Only 900 individuals (0.1%) had scores higher than 25, at which the index value was truncated. The scores were higher in women than in men and substantially higher among those with a history of hip fracture than those with no history of hip fracture; the mean scores ranged from 3.6 in men aged 65–74 years with no history of hip fracture to 7.2 in women aged 75–84 and 85+ years with a history of hip fracture (figure 1).

Mortality risk according to level of comorbidity and history of hip fracture

Figure 2 shows the observed 1-year mortality risk (%) across Rx-Risk scores entered as the midpoints of 5-unit intervals, grouped by history of hip fracture, sex and three age groups, and the predicted mortality risk from the fully adjusted Poisson regression model. Mortality risk increased exponentially across the range of Rx-Risk scores. In all sex and age groups, mortality risk was higher in persons with a history of hip fracture across the major range of Rx-Risk scores. At the upper range of comorbidity scores, this picture was less clear, most likely due to few observations (note that a score of 15 represented the 97th percentile of the Rx-Risk distribution).

Contribution to explaining excess deaths

In men and women combined, the observed crude 1-year mortality risk was 10.4% in those with a history of hip fracture and 3.2% in those with no history of hip fracture, corresponding to a mortality risk difference of 7.2 percentage points. The risk difference was attenuated to 4.4 percentage points (95% CI: 4.2 to 4.6) when adjusting for age and sex, and to 3.3 percentage points (95% CI: 3.1 to 3.5) after further adjustment for Rx-Risk scores (table 3).

Results according to time since hip fracture

In the subgroup of those with a history of hip fracture, time since hip fracture was inversely related to mortality risk in age- and sex adjusted Poisson regression (overall

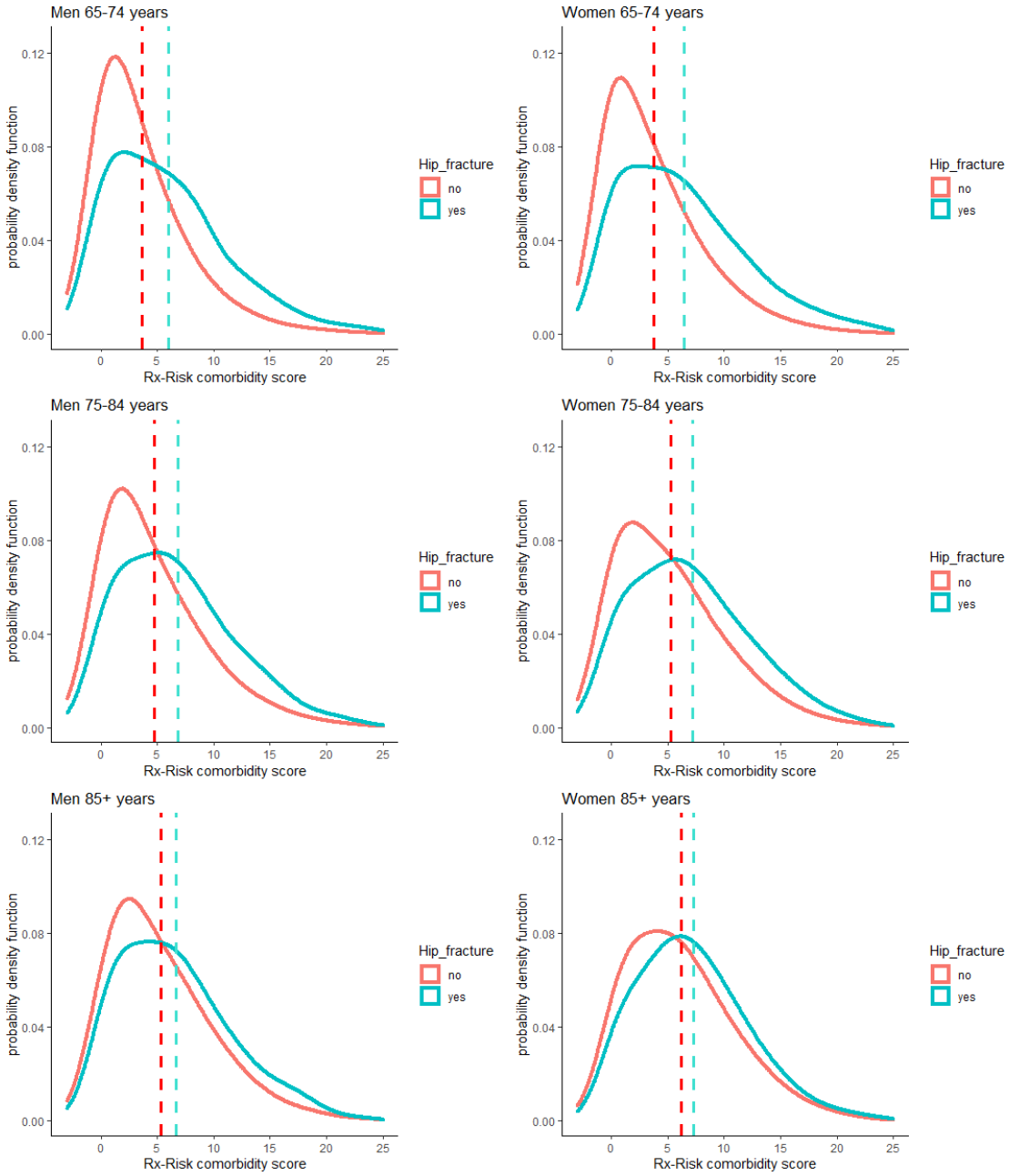

Figure 1 Empirical distribution of individual-weighted Rx-Risk comorbidity scores according to a history of hip fracture, grouped by sex and three age groups in a population study in Norway. Vertical dashed lines represent mean Rx-Risk scores in the two subgroups. The densities are estimated using the R-function 'geom_density' with bw=1.4. The curves are truncated at value 25.

RR 0.97 per year (p<0.001)). As examples, compared with having had a hip fracture in the current year, a hip fracture 4 years ago was associated with RR 0.86, and a hip fracture 15 years ago was associated with RR 0.67.

When separating those with a history of hip fracture according to time since their last fracture (≤4 years vs >4 years) in age-adjusted and sex-adjusted Poisson regression, the same pattern of increasing mortality risk with increasing Rx-Risk scores was seen in all groups (online supplemental figure 1). For both men and women, the estimated mortality risk was highest in the subgroup with a recent hip fracture (≤4 years ago). Across the major range of Rx-Risk scores, the estimated mortality risk was highest in men with a recent (≤4 years) hip fracture, and lowest in women with no history of hip fracture.

Validation by applying the index on prescriptions in 2005

In 2005, a total of 11 950 346 prescriptions were filled by a total of 601 914 community-dwelling men and women aged 65 years and older who were alive by the end of the year. Of these, 25 840 individuals (4.3%) died in 2006. When applying the ATC codes and severity weights derived from the 2013 data to the NorPD 2005 population for validation, Rx-Risk scores ranged from −5 through 40 with a

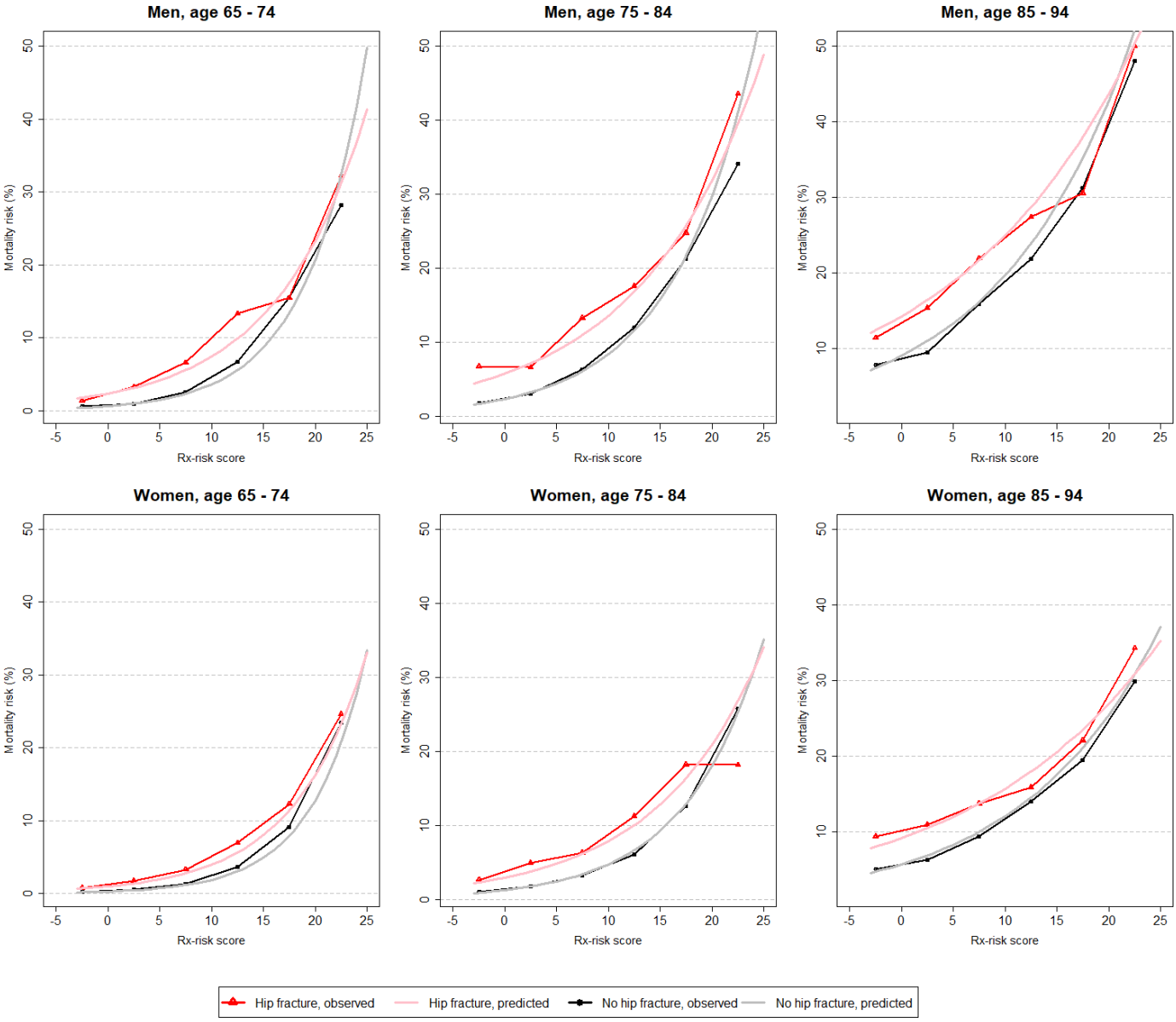

Figure 2 Observed and predicted 1-year mortality risk (%) across Rx-Risk scores, grouped by sex and age in a population study in Norway. Red and black points show observed mortality risks in midpoints of 5-unit intervals of Rx-Risk scores in persons with and without a history of hip fracture. Pink and grey curves show predicted mortality risks in persons with and without a history of hip fracture, from a fully adjusted Poisson regression model allowing for mutual statistical interactions between Rx-Risk score, sex, age and history of hip fracture. Rx-Risk scores are truncated at value 25.

median score of 3 (IQR: 1–6) and a mean score of 4.1 (SD: 4.3). Results were similar when applying separately calculated severity weights for 2005 based on ORs for deaths in 2006. These results were similar to those using the 2013 population, suggesting that patterns of drug prescriptions to the older population in Norway did not change materially over the 8-year period. The c statistic for mortality risk according to Rx-Risk scores in 2005 in Poisson regression with no covariates was 0.70, and 0.79 when including age and sex, regardless of whether severity weights were derived from 2013 or 2005 for calculating the scores. For comparison, the corresponding c statistic for the index year 2013 was 0.73 in the crude model, and 0.82 when adjusting for age and sex.

DISCUSSION

We found that the prescription-based Rx-Risk Comorbidity Index performed well in nationwide registry data in Norway for two separate calendar years, with a c statistic of approximately 0.8 for the ability to classify individuals according to 1-year risk of death. We infer that this index can serve as a useful tool to account for comorbidity in future pharmacoepidemiologic studies. Furthermore, when adjusting for comorbidity expressed by Rx-Risk, the estimated risk difference in 1-year mortality between individuals with or without a history of hip fracture was attenuated from 4.4 to 3.3 percentage points. Thus, a quarter of the excess mortality in those with a history of hip fracture was explained by comorbidity as defined by

Table 3 1-year mortality risk (%) in people with a history of hip fracture and those with no hip fracture, and risk differences with 95% CIs*

	Total study population N=735 968			Men N=329 470			Women N=406 498		
	1-year mortality (%), history of hip fracture	1-year mortality (%), no hip fracture	Risk difference, percentage points (95% CI)	1-year mortality (%), history of hip fracture	1-year mortality (%), no hip fracture	Risk difference, percentage points (95% CI)	1-year mortality (%), history of hip fracture	1-year mortality (%), no hip fracture	Risk difference, percentage points (95% CI)
Observed (crude)	10.4	3.2	7.2 (7.0 to 7.4)	12.5	3.8	8.7 (8.3 to 9.1)	9.7	2.8	6.9 (6.7 to 7.2)
Adjusted for age and sex†	7.8	3.4	4.4 (4.2 to 4.6)	9.8	3.9	6.0 (5.6 to 6.4)	7.0	3.0	4.0 (3.8 to 4.3)
Adjusted for age, sex† and Rx-Risk scores	5.9	2.6	3.3 (3.1 to 3.5)	7.4	2.9	4.5 (4.1 to 4.9)	4.9	1.7	3.2 (3.0 to 3.5)

The Norwegian Prescription Database population aged 65 years and older in 2013.
*Estimated by using linear regression.
†Adjustment for sex applies to the analyses in men and women combined.

Rx-Risk. Most of the observed excess mortality cannot be explained by this measure of comorbidity. This is in line with other studies suggesting that there are important risk factors beyond chronic illnesses that contribute to the poor prognosis in those who have suffered a hip fracture.[25–27] These may involve consequences of the fracture that in turn affect mobility, functional level, activities of daily living, nutritional status, psychosocial well-being and resilience in a broader sense.

In this study, we examined the 1-year mortality risk of the community-dwelling older population in Norway who were alive by the end of 2013, of whom 4.6% had a history of hip fracture during the previous two decades (1994–2013). Time since hip fracture varied from 0 to 19 years, with a median of 4 years. The approximately 34 000 individuals who had suffered a hip fracture during the past two decades comprise one-fifth of the total number of patients who suffered a hip fracture in Norway in this period, as the large majority had died before 2013. Because one might expect that the mortality in this subpopulation of hip fracture survivors had decreased over time towards the level of mortality in the general older population, it is notable that we observed a clear age-adjusted excess mortality in those with a history of hip fracture that was only partly attenuated when accounting for an extensive prescription-based comorbidity index.

Strengths

This is a population study covering the older population of Norway using nationwide registries to which reporting is mandatory and thereby not affected by sampling or self-selection. The study population included those who had retrieved at least one prescription drug, irrespective of reimbursement, from an outpatient pharmacy during 2013. Norway has universal public healthcare coverage and most common drugs for chronic illnesses are reimbursed. The study population comprised 91% of all persons 65 years and older who were alive and residing in Norway on 1 January 2014 according to Statistics Norway (https://www.ssb.no/en/befolkning). The large sample size ensured high statistical power, yielding precise estimates with small standard errors.

Limitations

The NorPD covers only outpatient pharmacies. Drugs provided in hospitals and nursing homes are not recorded, and we did not have information about nursing home admissions. Therefore, we could not know whether individuals who had no dispensed drugs in NorPD were healthy community-dwelling individuals not in need of any prescription medications, or whether they were nursing home residents who received their drugs through the institution. However, a clearly higher age distribution and a higher 1-year mortality risk in this subgroup than in the NorPD population suggest a high proportion of nursing home residents. We therefore decided not to include persons who did not fill a prescription during the index year (comprising 9% of the population) in

the study population. We cannot rule out that we have failed to capture all drugs used during the index year for some individuals if they were admitted to a nursing home during the year.

Using an index based on prescription data as a proxy for comorbidity needs some comments. Information on dispensed drugs will only capture those who sought medical attention and received a prescription for their illness. Furthermore, receiving treatment should be expected to reduce the burden and consequences of the illness and improve prognosis. Naturally, this type of index will cover only conditions that are commonly treated with drugs, and drug treatment may be uncommon or inconsistent for some of the included comorbidities (such as treatment of alcohol dependency).

While an ATC-mapped prescription-based score based on 46 predefined comorbidity categories provides a convenient tool for operationalising data in population-wide research, it is nevertheless imprecise at the individual level. ATC mapping to indicate comorbidity is imperfect because although most drugs are associated with a main indication for prescription, there is often a range of possible indications for which the drug may have been prescribed. Drugs in groups like diuretics, beta-blockers, calcium channel blockers and ACE inhibitors/ARBs, are used to treat a number of conditions that may vary in severity and prognosis, most commonly hypertension, angina, oedema, arrhythmia and heart failure. Conversely, for many conditions, there is a range of possible drugs that may be indicated and prescribed. Consequently, there is often no clear-cut one-to-one relationship between the type of illness and the drug prescribed. Assigning comorbidity categories based on ATC codes of prescribed drugs is therefore associated with a certain degree of misclassification of illness at the individual level, which is expected to apply to several comorbidity categories. While some categories are expected to be highly valid indicators of the underlying condition with low degree of misclassification of illness, such as dementia, diabetes and migraine, categories defining various cardiovascular diseases are expected to have lower validity due to the heterogeneity of symptoms and severity associated with prescription of these ATC codes. The depression category may also have limited sensitivity, since these drugs are also used to treat anxiety, insomnia and pain. Despite these limitations, the comorbidity categories showed plausible associations with mortality risk in our population, as shown in table 1.

Since 2008, reimbursed prescriptions are accompanied by a reimbursement code in the NorPD, that is, the diagnosis code from the primary (International Classification of Primary Care, 2nd Edition) or specialist (International Classification of Diseases, 10th Revision) healthcare service. There is a potential to construct novel comorbidity indexes based on reimbursement codes associated with drug prescriptions. However, their generalisability and potential for transferability and comparison across countries may be more limited than that of the current index, as they will be strongly tied to local practices. While establishing novel comorbidity indexes was not within the scope of the current study, it offers possibilities for future research.

CONCLUSION

The Rx-Risk Comorbidity Index, based on dispensed drugs in outpatient pharmacies, performed well in nationwide registry data in Norway for two separate calendar years, with a c statistic of approximately 0.8 for the ability to classify individuals according to 1-year risk of death. This index can serve as a useful tool to account for comorbidity in future pharmacoepidemiologic studies. History of hip fracture and comorbidity scores were both independent risk factors for mortality in the community-dwelling older population in Norway. Comorbidity explained a quarter of the excess mortality in persons with a history of hip fracture, supporting the existing evidence that both comorbid conditions and other aspects related to follow-up and care after hip fracture contribute to the increased mortality in these patients.

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