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The association of degree of polypharmacy before and after among hospitalised internal medicine patients and clinical outcomes: a retrospective, population-based cohort study

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ABSTRACT

Objectives To determine the prevalence and incidence of polypharmacy/hyperpolypharmacy and which medications are most prescribed to patients with varying burden of polypharmacy.

Design Retrospective, population-based cohort study.

Setting Iceland.

Participants Including patients (≥18 years) admitted to internal medicine services at Landspitali – The National University Hospital of Iceland, between 1 January 2010 with a follow-up of clinical outcomes through 17 March 2022.

Main outcomes measures Participants were categorised into medication use categories of non-polypharmacy (<5), polypharmacy (5–10) and hyperpolypharmacy (>10) based on the number of medications filled in the year predischarge and postdischarge. The primary outcome was prevalence and incidence of new polypharmacy. Secondary outcomes were mortality, length of hospital stay and re-admission.

Results Among 85 942 admissions (51% male), the median (IQR) age was 73 (60–83) years. The prevalence of preadmission non-polypharmacy was 15.1% (95% CI 14.9 to 15.3), polypharmacy was 22.9% (95% CI 22.6 to 23.2) and hyperpolypharmacy was 62.5% (95% CI 62.2 to 62.9). The incidence of new postdischarge polypharmacy was 33.4% (95% CI 32.9 to 33.9), and for hyperpolypharmacy was 28.9% (95% CI 28.3 to 29.5) for patients with preadmission polypharmacy. Patients with a higher level of medication use were more likely to use multidose drug dispensing and have a diagnosis of adverse drug reaction. Other comorbidities, including responsible subspeciality and estimates of comorbidity and frailty burden, were identical between groups of varying polypharmacy. There was no difference in length of stay, re-admission rate and mortality.

Conclusions Preadmission polypharmacy/hyperpolypharmacy and postdischarge new polypharmacy/hyperpolypharmacy is common amongst patients admitted to internal medicine. A higher level of medication use category was not found to be associated with demographic, comorbidity and clinical outcomes. Medications that are frequently inappropriately prescribed were among the most prescribed medications in the group. An increased focus on optimising medication usage is needed after hospital admission.

Trial registration number NCT05756400.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Connection between the nationwide prescription database, which included 95% of prescriptions in Iceland, with clinical data from hospital and primary care settings.
⇒ Comprehensive examination of all tertiary care and most of secondary care of internal medicine patients in Iceland, as Landspitali is the main referral hospital for the country.
⇒ Extended study period allowing many patients in the study cohort.
⇒ Limitations include the absence of information on the patient's medication adherence, which may lead to an overestimation of the prevalence of polypharmacy and hyperpolypharmacy.
⇒ The study does not include over-the-counter medications, which may lead to an underestimation of polypharmacy and hyperpolypharmacy.

INTRODUCTION

Polypharmacy refers to the simultaneous use of multiple medicines.[1] The most widely accepted definition for polypharmacy refers to the use of 5 or more medications, but more recently, hyperpolypharmacy has been defined as the use of 10 or more medications.[2] Polypharmacy has predominantly been studied in older populations,[3–5] and only a minority of studies describe the epidemiology in populations including younger adults.[1 6] The prevalence varies among studies depending on study settings, applied definitions and study period. A recent meta-analysis reported pooled prevalence of polypharmacy was 37% (95% CI 31% to 43%).[7] The Global

Patient Safety Challenge, released by WHO in 2017, highlights high-risk situations, polypharmacy and transitions of care as three key areas to focus on to prevent avoidable medication-related harm.[8]

Improved survival of the population will likely result in increased burden of multimorbidity and, consequently, polypharmacy in the upcoming years.[9–11] Increasing multimorbidity and associated polypharmacy is associated with several adverse health consequences, including increased likelihood of potentially inappropriate prescribing,[12] hospitalisation,[13–15] re-admission[16] and death.[15 17 18] Prescription of multiple medications simultaneously may be appropriate and clinically needed in certain instances. Nevertheless, inappropriate prescribing of multiple medications simultaneously contributes to adverse health outcomes if medications are used when no longer clinically indicated.[19] Polypharmacy is associated with higher age (45% ≥65 years vs 25% <65 years), and management in certain healthcare settings have been identified as patient-related risk factors for developing polypharmacy (community 20% vs outpatients 37% vs inpatients 52%).[7]

Studies have shown that a medication review, where healthcare professionals identify inappropriate prescribing during hospitalisation, is associated with reduced risk of re-admission.[20 21] Deprescribing is 'the withdrawal process of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes, and should be a part of a medication review'.[22–24] Clinical trials on safety aspects of new medicine usually exclude older patients with multiple comorbidities, which may lead to limited knowledge of the potential risk of taking numerous medications.[25] Additionally, there has been a significant increase in clinical guidelines addressing specific conditions that risk shifting the focus on individual conditions rather than how multiple coexisting conditions and their treatments interact.[7 26 27] System-related risk factors for polypharmacy include poorly updated medical records and automated medication re-prescribing.[28]

Polypharmacy in patients admitted to internal medicine is likely prevalent as this population carries a significant burden of comorbidities and frailty. Furthermore, an acute admission to the internal medicine ward may increase the burden of polypharmacy.

The study aimed to determine the prevalence of preadmission polypharmacy and incidence of postdischarge polypharmacy/hyperpolypharmacy and their association with patient factors, admitting subspeciality, and clinical outcomes.

We hypothesised that predischarge and postdischarge polypharmacy is common, especially among: (1) Older patients and (2) Patients with a high comorbidity and frailty burden. We further hypothesised that preadmission polypharmacy and hyperpolypharmacy were associated with: (1) Increased short-term and long-term mortality; (2) A more extended primary hospitalisation; and (3) A higher risk of re-admission.

METHODS

Study population

The study was a retrospective, population-based cohort study that included all patients ≥18 years hospitalised in internal medicine wards at Landspitali – The National University Hospital of Iceland during the study period between 1 January 2010, with a follow-up of clinical outcomes through 17 March 2022. The hospital serves as the primary hospital for approximately 75% of the nation and the tertiary hospital for the whole country. While the hospital has subspeciality-specific wards (eg, haematology, oncology, cardiology, pulmonology), patients with generic admission diagnoses not requiring subspecialty care are often admitted to general internal medicine or any subspeciality wards with bed availability.

All data sources used for research were de-identified before statistical analysis, and all work was compliant with the General Data Protection Regulation of the European Union. The study protocol was published on clinicaltrials.gov before analysis (NCT05756400), and the study reporting adheres to the STROBE guideline reporting of observational studies in epidemiology.[29]

Patient and public involvement

None

Clinical data

The processing of variables for this study from various electronic data sources resulted in the generation of the Icelandic Internal Medicine Database. This retrospective database includes clinical data on all patients admitted to internal medicine services at Landspitali – the National University Hospital of Iceland, between 1 January 2010 and 31 December 2020. The database contains baseline patient characteristics such as gender, age and admitting internal medicine subspecialty. If the patient was transferred between services (1.8% of admissions), the service primarily available for the admission was documented as the admitting service. The database also included information on whether the patient was admitted to the intensive care unit and whether the admission was linked to rehabilitation, geriatric or palliative care services following discharge from the acute service. Information on the date of admission and discharge, as well as the length of acute admission and length of acute and rehabilitation admission, was also registered. An admission to the internal medicine ward was defined as any admission for patients to an inpatient status within internal medicine service regardless of its duration. This excluded patients who solely received care in the acute and emergency departments.

Patient comorbidities were gathered from hospital information and primary care coded with *the* International Statistical Classification of Diseases, and Related Health Problems, tenth revision, (ICD10) classification system, and these diagnoses were also used to estimate the comorbidity and frailty burden using the van Walraven Modified Score,[30] the Elixhauser Comorbidity Index[31]

and the Hospital Frailty Risk Score.[32] Information on the date of death was collected from the Iceland Causes of Death Register. While establishing this Internal Medicine Database, no patients were lost to follow-up for mortality outcomes. Adverse drug reactions were defined as any documentation of ICD10 codes for adverse drug effects (Y40–59, X40–59, T36–59).

Medication data

Information on filled/dispensed medications from the Prescription Medicines Registry of the Directorate of Health database spanning 1 year before admission and 1 year postdischarge was gathered. The Icelandic Prescription Registry provides real-time information about all outpatient drug prescriptions in Iceland. Its accuracy is estimated frequently by comparing prescribed medications against dispensed medications and is estimated to be 95%. The database includes all prescribed regular and as-required drugs but does not include over-the-counter, topical and herbal medications. Medication information was coded based on the Anatomical Therapeutical Chemical (ATC) classification. The database also includes information that can be used to identify whether a multidose drug dispensing service was used.[33]

Exposure variable definition

The primary exposure was the extent of medication use, defined as the number of different medications filled in the year preceding (preadmission) and the year following discharge (postdischarge). Patients were separated into three groups based on these medication use categories of non-polypharmacy (<5), polypharmacy[5–9] and hyperpolypharmacy (≥10) based on their predischarge and postdischarge medication filling. Furthermore, the number of medications within different anatomical/pharmacological groups (ATC first level) and pharmacological/therapeutical subgroups (ATC second level) filled in the year preceding and following admissions were counted. The medication use category was also estimated after eliminating antibiotics from the medication database to estimate the burden of polypharmacy without antibiotics. The additional analysis was done to evaluate for how many patients the inclusion of antibiotics would change the polypharmacy/hyperpolypharmacy classification.

Outcome data

Primary outcomes included prevalence of preadmission and incidence of new postdischarge polypharmacy. Secondary outcomes were mortality (short-term, < 30 days and long-term mortality), length of hospital stay (number of days, ≥10 days) and re-admission (number of days until re-admission, re-admission <30 days).

Statistical analysis

Data analysis was undertaken from December 2022 through March 2023. All statistical analyses for this study were conducted using R V.4.2.2 (The R Foundation for Statistical Computing R, Vienna, Austria), via R studio V.2022.12.0 (RStudio PBC, USA). Descriptive statistics were used to exhibit the number of medications. The distribution of the medication use into categories of varying polypharmacy predischarge and postdischarge was described as a percentage with a 95% CI calculated using the Pearson-Klopper method to obtain binomial probability in the *binom* package in R. Logistic regression was used to compare patient and admission properties between the medication use categories predischarge and postdischarge, mortality within 30 days and re-admission within 30 days. The Kaplan Meier plot was used to plot long-term mortality between different medication use categories. No missing data were identified in the variables used for this study.

Adverse outcomes were compared between categories of medication use using χ^2 tests. Likewise, adverse outcomes were contrasted between patients with and without an increase in polypharmacy from the year preceding admission to the year following discharge (an increase from no polypharmacy to polypharmacy/hyperpolypharmacy or polypharmacy to hyperpolypharmacy).

RESULTS

Clinical characteristics of the patient cohort

The cohort included 85 942 individual admissions to internal medicine at the Landspitali University Hospital for 38 338 patients with a median (IQR) 1 (1–3) admission, ranging from 1 to 40 admissions. Of the cohort, 43 914 were male (51.1%), and the median (IQR) age was 73 (60–82) years. Most of the study population had a high burden of comorbidity (Elixhauser Comorbidity Score (39%>8) and a risk of frailty (medium or high Hospital Frailty Risk Index classification (62.5%)). The most common comorbidity was hypertension (54.1%), chronic obstructive pulmonary disease (32.3%), ischaemic heart disease (30.8), malignant neoplasm (25.0%) and congestive heart failure (20.2%).

Admissions were most common to cardiology (21.7%), general medicine (13.5%) and pulmonology (10.6%). Most patients used a multidose drug dispensing service (54.7%) before admission (online supplemental table S1). Table 1 also compares admitting specialty and medication usage for the patient cohort based on varying degrees of polypharmacy.

Clinical characteristics of the patient cohort by preadmission filling

The prevalence of preadmission non-polypharmacy was 15.1% (95% CI 14.9% to 15.3%), polypharmacy was 22.9% (95% CI 22.6% to 23.2%) and hyperpolypharmacy was 62.5% (95% CI 62.2 to 62.9) (figure 1). Patients with a higher level of medication use category were more likely to be male and have a previous diagnosis of adverse drug reaction. Patients with hyperpolypharmacy were more likely to use multidose drug dispensing services (65.9%) compared with polypharmacy (45.6%) and non-polypharmacy (22.0%). Patients who used multidose

Table 1 Patient characteristics of the patient cohorts are based on the number of medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5–9 medications = polypharmacy and ≥10 medications = hyperpolypharmacy)

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Total number of patients	12926 (15.1)	19554 (22.9)	53462 (62.5)	85942	
Sex (male)	6664 (51.6)	10052 (51.4)	27198 (50.9)	43914 (51.1)	0.250
Age, (median (IQR)), years	72.00 (60.00, 83.00)	73.00 (60.00, 82.00)	73.00 (60.00, 82.00)	73.00 (60.00, 82.00)	0.877
(15, 25)	227 (1.8)	351 (1.8)	960 (1.8)	1538	0.558
(25, 35)	475 (3.7)	708 (3.7)	1875 (3.5)	3058	
(35, 45)	598 (4.7)	936 (4.8)	2501 (4.7)	4035	
(45, 55)	1024 (8.0)	1590 (8.2)	4360 (8.2)	6974	
(55, 65)	1923 (15.0)	2968 (15.3)	7996 (15.1)	12887	
(65, 75)	2838 (22.1)	4067 (21.0)	11534 (21.7)	18439	
(75, 85)	3360 (26.2)	5207 (26.9)	13879 (26.2)	22446	
(85, 95)	2384 (18.6)	3563 (18.4)	9954 (18.8)	15901	
Multidose dispensing services	2838 (22.0)	8919 (45.6)	35235 (65.9)	46992 (54.7)	<0.001
Number of preadmission medications (median (IQR))	2.00 (1.00, 3.00)	7.00 (6.00, 8.00)	16.00 (13.00, 21.00)	12.00 (7.00, 18.00)	<0.001
Number of postdischarge medications (median (IQR))	5.00 (2.00, 8.00)	9.00 (6.00, 12.00)	15.00 (10.00, 20.00)	12.00 (7.00, 17.00)	<0.001
Number of preadmission medications without antibiotics (median (IQR))	2.00 (0.00, 3.00)	6.00 (5.00, 8.00)	14.00 (11.00, 19.00)	11.00 (6.00, 16.00)	<0.001
Elixhauser Comorbidity Index (IQR))	6.00 (0.00, 12.00)	6.00 (0.00, 13.00)	6.00 (0.00, 12.00)	6.00 (0.00, 12.00)	0.804
(<1)	3492 (27.0)	5245 (26.8)	14523 (27.2)	23260 (27.1)	0.791
(1–4)	1911 (14.8)	2963 (15.2)	8039 (15.0)	12913 (15.0)	
(4–5)	860 (6.7)	1355 (6.9)	3608 (6.7)	5823 (6.8)	
(5–8)	1618 (12.5)	2351 (12.0)	6421 (12.0)	10390 (12.1)	
(>8)	5045 (39.0)	7640 (39.1)	20871 (39.0)	33556 (39.0)	
Hospital Frailty Risk Score class					0.976
Low (< 5)	4823 (37.3)	7334 (37.5)	20111 (37.6)	32268 (37.5)	
Medium (5–15)	5844 (45.2)	8828 (45.1)	24070 (45.0)	38742 (45.1)	
High (> 15)	2259 (17.5)	3392 (17.3)	9281 (17.4)	14932 (17.4)	
Comorbidities					
Ischaemic heart disease	4017 (31.1)	5967 (30.5)	16477 (30.8)	26461 (30.8)	0.545
Congestive heart failure	2644 (20.5)	3952 (20.2)	10734 (20.1)	17330 (20.2)	0.621

Continued

Table 1 Continued

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Hypertension	7081 (54.8)	10 554 (54.0)	28 855 (54.0)	46 490 (54.1)	0.236
Diabetes mellitus	2108 (16.3)	3143 (16.1)	8804 (16.5)	14 055 (16.4)	0.438
Chronic obstructive pulmonary disease	4118 (31.9)	6379 (32.6)	17 288 (32.3)	27 785 (32.3)	0.353
Liver disease	405 (3.1)	658 (3.4)	1635 (3.1)	2698 (3.1)	0.109
Chronic kidney disease	1311 (10.1)	2054 (10.5)	5268 (9.9)	8633 (10.0)	0.032
Malignant neoplasm	3265 (25.3)	4821 (24.7)	13 376 (25.0)	21 462 (25.0)	0.431
Psychiatric	2094 (16.2)	3284 (16.8)	8812 (16.5)	14 190 (16.5)	0.354
Dementia	253 (2.0)	402 (2.1)	1139 (2.1)	1794 (2.1)	0.438
Delerium	1183 (9.2)	1715 (8.8)	4800 (9.0)	7698 (9.0)	0.480
Internal medicine speciality					0.129
General internal medicine	1741 (13.5)	2671 (13.7)	7205 (13.5)	11 617 (13.5)	
Geriatrics	1072 (8.3)	1611 (8.2)	4602 (8.6)	7285 (8.5)	
Cardiology	2746 (21.2)	4269 (21.8)	11 646 (21.8)	18 661 (21.7)	
Endocrine	198 (1.5)	315 (1.6)	864 (1.6)	1377 (1.6)	
Gastroenterology	1112 (8.6)	1598 (8.2)	4293 (8.0)	7003 (8.1)	
Infectious diseases	733 (5.7)	1111 (5.7)	2901 (5.4)	4745 (5.5)	
Haematology	665 (5.1)	958 (4.9)	2783 (5.2)	4406 (5.1)	
Nephrology	302 (2.3)	479 (2.4)	1299 (2.4)	2080 (2.4)	
Neurology	1107 (8.6)	1699 (8.7)	4316 (8.1)	7122 (8.3)	
Oncology	853 (6.6)	1218 (6.2)	3391 (6.3)	5462 (6.4)	
Dermatology	79 (0.6)	106 (0.5)	257 (0.5)	442 (0.5)	
Pulmonology	1352 (10.5)	2054 (10.5)	5674 (10.6)	9080 (10.6)	
Rheumatology	588 (4.5)	923 (4.7)	2699 (5.0)	4210 (4.9)	
Rehabilitation	144 (1.1)	207 (1.1)	597 (1.1)	948 (1.1)	
Palliative care	234 (1.8)	335 (1.7)	935 (1.7)	1504 (1.8)	
Linked admissions					
Geriatrics	467 (3.6)	687 (3.5)	2007 (3.8)	3161 (3.7)	0.283
Palliative care	127 (1.0)	173 (0.9)	534 (1.0)	834 (1.0)	0.375
Rehabilitation	125 (1.0)	215 (1.1)	530 (1.0)	870 (1.0)	0.371
Intensive care unit admission	715 (5.5)	1127 (5.8)	2937 (5.5)	4779 (5.6)	0.366
Outcomes					

Continued

Table 1 Continued

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Number of preadmission medications (median (IQR))	2.00 (1.00, 3.00)	7.00 (6.00, 8.00)	16.00 (13.00, 21.00)	12.00 (7.00, 18.00)	<0.001
Number of postdischarge medications (median (IQR))	5.00 (2.00, 8.00)	9.00 (6.00, 12.00)	15.00 (10.00, 20.00)	12.00 (7.00, 17.00)	<0.001
Number of preadmission medications without antibiotics (median (IQR))	2.00 (0.00, 3.00)	6.00 (5.00, 8.00)	14.00 (11.00, 19.00)	11.00 (6.00, 16.00)	<0.001
Diagnosis of adverse drug reaction preadmission (%)	506 (3.9)	1436 (7.3)	7393 (13.8)	9335 (10.9)	<0.001
Diagnosis of adverse drug reaction postdischarge (%)	388 (3.0)	946 (4.8)	3793 (7.1)	5127 (6.0)	<0.001
Next admission (median (IQR))	118.00 (26.00, 438.00)	124.00 (26.00, 463.25)	128.00 (27.00, 468.00)	125.00 (27.00, 462.00)	0.031
Mortality <30 days (%)	853 (6.6)	1266 (6.5)	3519 (6.6)	5638 (6.6)	0.857
Re-admission within 30 days (%)	1961 (15.2)	2946 (15.1)	7973 (14.9)	12 880 (15.0)	0.717
Length of stay (median (IQR))	6.00 (3.00, 12.00)	6.00 (3.00, 12.00)	6.00 (3.00, 12.00)	6.00 (3.00, 12.00)	0.630

Values are presented as count (%) or median (IQR) unless specified otherwise. Linked admissions refers to whether the admission was linked to rehabilitation, geriatric or palliative care services following discharge from the acute service.

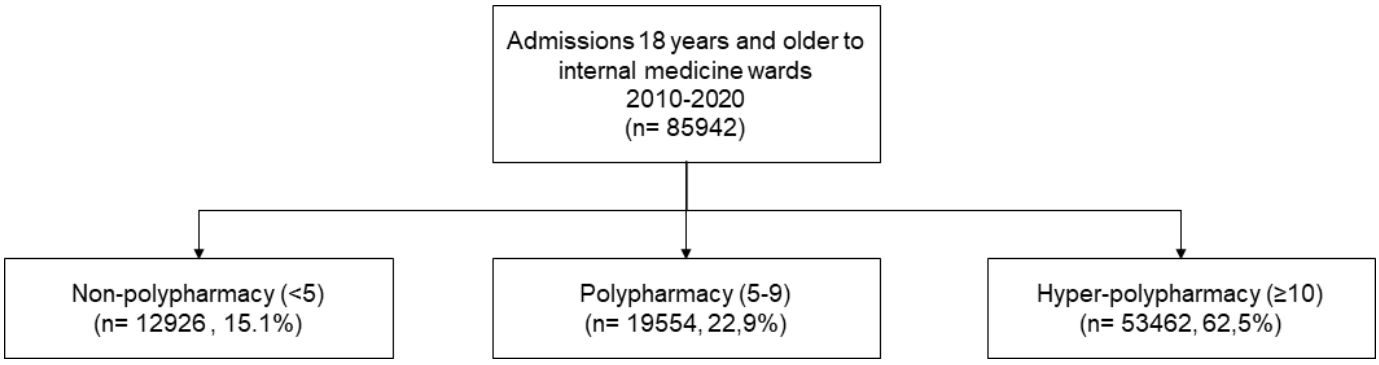

Figure 1 A consort diagram of participant inclusion based on the number of different medications filled in the year preceding admission by internal medicine (<5 medications = non-polypharmacy, 5–9 medications = polypharmacy and ≥10 medications = hyperpolypharmacy).

drug dispensing services before admission were more likely to have a previous diagnosis of an adverse drug reaction. Figure 2 shows a comparison of the medication use categories separated into three groups based on the medication use categories of non-polypharmacy (<5), polypharmacy[5–9] and hyperpolypharmacy (≥10) and over the observation period 2010–2020. If antibiotics were excluded from the medication list the patients, 87.9% of patients with polypharmacy and 90.8% with hyperpolypharmacy would have remained within their medication use category. There was no change in the prevalence of polypharmacy/hyperpolypharmacy over the study period.

Types of medications used and multidose dispensing

The most common classes of medications filled in the year preceding preadmission are medications acting on the central nervous system. A total of 80.6% of the group filled prescriptions within this category, including opioids (51.0%), Z-drugs (43%), antidepressants (37.9%) and benzodiazepines (29.0%). The second most filled medication class was cardiac medications (74.5%) (table 2).

For the group with preadmission hyperpolypharmacy, the most filled medication class was medications acting on the nervous system (94.4%), including opioids (65.7.0%), antidepressants (50.2%) and benzodiazepines (40.2%). The second most filled medication class was cardiac medications (87.4%). Similarly, in patients with polypharmacy, the most filled medications class was medications acting on the nervous system (74.1%), including opioids (34.6%), antidepressants (24.6%) and benzodiazepines (14.9%). The second most filled medication class was cardiac medications (69.9%). In patients with non-polypharmacy, the most filled medication class was medications acting on the nervous system (33.5%), including opioids (14.8%), antidepressants (7.2%) and benzodiazepines (4.0%); the second most filled medication class was cardiac medications (27.7%).

Incidence of new postdischarge polypharmacy/hyperpolypharmacy

Of 85942 admissions, 18.4% (95% CI 18.2% to 18.7%) had an increase in the medication use category, moving

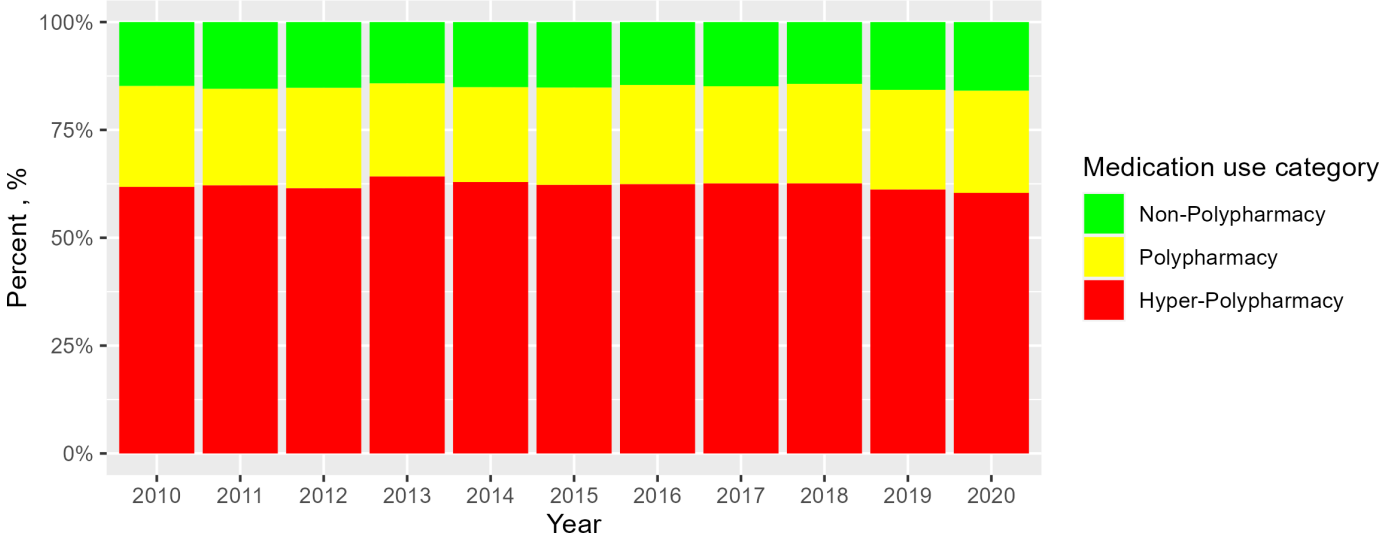

Figure 2 The annual prevalence of the medication use categories over the study period 2010–2020. Colours indicate the medication use categories (green <5 medications = non-polypharmacy, yellow 5–9 medications = polypharmacy and red ≥10 medications = hyperpolypharmacy) filled in the year preceding admission by internal medicine.

Table 2 The table shows the patients' patterns of preadmission prescribed medications

	Non-polypharmacy	Polypharmacy	Hyperpolypharmacy	All patients	P value
Total number of patients	12926 (15.1)	19554 (22.9)	53462 (62.5)	85942	
Preadmission medication					<0.001
Proton pump inhibitors	1163 (9.0)	5352 (27.4)	33063 (61.8)	39578 (46.1)	
Antidiabetics	281 (2.2)	1632 (8.3)	10481 (19.6)	12394 (14.4)	
Anticoagulants	729 (5.6)	5303 (27.1)	27087 (50.7)	33119 (38.5)	
Antiplatelets	365 (2.8)	3023 (15.5)	16125 (30.2)	19513 (22.7)	
Cardiovascular	3578 (27.7)	13660 (69.9)	46748 (87.4)	63986 (74.5)	
Beta-blockers	1434 (11.1)	7386 (37.8)	29415 (55.0)	38235 (44.5)	
Calcium channel blockers	550 (4.3)	3198 (16.4)	15536 (29.1)	19284 (22.4)	
ACE inhibitors and angiotensin II receptor blockers	1582 (12.2)	7057 (36.1)	27140 (50.7)	35779 (41.6)	
Statins	997 (7.7)	5660 (28.9)	24057 (45.0)	30714 (35.7)	
Urinary	1241 (9.6)	4399 (22.5)	20449 (38.2)	26089 (30.4)	
Hormones	874 (6.8)	4464 (22.8)	29318 (54.8)	34656 (40.3)	
Corticosteroids	461 (3.6)	2896 (14.8)	23863 (44.6)	27220 (31.7)	
Medication acting on the nervous system	4330 (33.5)	14485 (74.1)	50477 (94.4)	69292 (80.6)	
Antibiotics	2906 (22.5)	9120 (46.6)	40158 (75.1)	52184 (60.7)	
Opioids	1911 (14.8)	6766 (34.6)	35120 (65.7)	43797 (51.0)	
Paracetamol/orphenadrine combinations	1524 (11.8)	4188 (21.4)	16400 (30.7)	22112 (25.7)	
Non-steroidal anti-inflammatory drugs	1352 (10.5)	3389 (17.3)	11921 (22.3)	16662 (19.4)	
Selective COX-2 inhibitors	200 (1.5)	940 (4.8)	6236 (11.7)	7376 (8.6)	
Antipsychotics	362 (2.8)	1815 (9.3)	10011 (18.7)	12188 (14.2)	
Z-drugs	9281 (19.0)	11613 (23.7)	28060 (57.3)	48954 (57.0)	
Benzodiazepines	522 (4.0)	2914 (14.9)	21473 (40.2)	24909 (29.0)	
Antidepressants	935 (7.2)	4804 (24.6)	26832 (50.2)	32571 (37.9)	
Antidementia	147 (1.1)	902 (4.6)	2269 (4.2)	3318 (3.9)	
Respiratory	1229 (9.5)	5147 (26.3)	27612 (51.6)	33988 (39.5)	
Antihistamin	281 (2.2)	1180 (6.0)	7725 (14.4)	9186 (10.7)	

The number of medications preadmission (<5 medications = non-polypharmacy, 5–9 medications = polypharmacy and ≥10 medications = hyperpolypharmacy). Values are presented as count (%) or median (IQR) unless specified otherwise.

either from non-polypharmacy to polypharmacy/hyperpolypharmacy or polypharmacy to hyperpolypharmacy (online supplemental table S2). The incidence of new postdischarge polypharmacy/hyperpolypharmacy was 55.5% (95% CI 54.7% to 56.4%). For patients with polypharmacy, the incidence of new postdischarge hyperpolypharmacy was 44.3% (95% CI 43.6% to 45.0%). The patient characteristics were comparable between the group of patients who had an increase in the polypharmacy burden and those who did not, apart from the fact that patients with increased polypharmacy burden after discharge were less likely to use multidose dispensing services at the time of admission (40.6% vs 57.9%). They were also less likely to have been diagnosed with adverse drug reactions before admission (12.0% vs 5.8%) or after discharge (6.2% vs 15.0%) than those with no change (online supplemental table S2). The most frequently added medications were anticoagulants (15.6%), antibiotics (14.9%), opioids (14.2%), proton pump inhibitors (13.2%), antiplatelets (12.0%), corticosteroids (10.3%), respiratory medications (9.6%) and medication acting on the central nervous system (8.9%), with Z-drugs (8.4%).

Clinical outcomes of patients with varying preadmission medication use

An unadjusted restricted cubic spline analysis revealed no relationship between the absolute number of different medications filled in the year preceding admission and the incidence of 30-day mortality (online supplemental figure S1), the risk of re-admission within 30 days (online supplemental figure S2), and with a prolonged length of primary hospital stay (>10 days) (online supplemental figure S3). Online supplemental figure S4 compares the long-term survival between the medication use categories, and there was no survival difference. Among the total cohort, 30-day mortality was 6.6%. The incidence of prolonged admission was 10.2%, and the 30-day re-admission rate was 15.0%.

DISCUSSION

This current study identified that preadmission polypharmacy/hyperpolypharmacy and postdischarge new polypharmacy/hyperpolypharmacy were common among internal medicine patients, which aligns with the previously stated primary hypothesis. However, no association was found between the category of medication use (non-polypharmacy <5, polypharmacy 5–9 and hyperpolypharmacy ≥10) and the patient characteristics, admitting internal subspecialities and clinical outcomes. This contradicts the secondary hypothesis that a higher category of medication use is associated with adverse clinical outcomes and increased comorbidity burden in this patient cohort. However, there is obviously an immense difference in the amount and different types of medication patients use depending on their medication use category (non-polypharmacy <5, polypharmacy 5–9 and hyperpolypharmacy ≥10).

Prevalence and incidence

Although this study aligns with previous studies claiming that preadmission polypharmacy/hyperpolypharmacy (22.9% and 62.5%) and postdischarge new polypharmacy/hyperpolypharmacy is common (55.5%), the prevalence is significantly higher in this cohort deriving from an inpatient hospital setting. A recent systematic review determined that the pooled estimated prevalence was 37%; however, the prevalence was higher among inpatients at 52%, like our study.[7] The prevalence of polypharmacy in the community setting was 20% and 37% in a cohort derived from an outpatient setting.[7] Similarly, a study focusing on surgical inpatients reported a prevalence of polypharmacy at 32.2% and hyperpolypharmacy at 23.5%.[34] This was anticipated as the internal medicine patients have higher comorbidity and frailty indices compared with the surgical population, which contains a substantial number of patients undergoing elective surgery.[34] The internal medicine patients were also older (73 vs 55 years).[34] Additionally, the results reveal that in the cohort, patients with a higher level of polypharmacy burden were more likely to be male. Previous evidence has been conflicting. A recent meta-analysis reported that there were no differences in polypharmacy prevalence in subgroup analyses based on sex.[7] In our entire cohort, the proportion of men, 43 914 (51.1%) vs 42 028 (48.9%) women, reflects the general population in Iceland (51.3% were male).[35] It is unclear why the level of polypharmacy is higher for this group but it is possible that a burden of frailty or disease is higher for men in this subgroup of society exposed to internal medicine admission.

The only patient characteristics differentiating patients with different levels of polypharmacy burden were the likelihood of using multidose dispensing services, which was higher with more polypharmacy burden, similar to a study on older adults.[36] Secondarily, patients with polypharmacy/hyperpolypharmacy were more likely to have been diagnosed with adverse drug reactions, which aligns with previous studies.[37] However, studies have reported that adverse drug reactions are under-reported and therefore it is likely that the prevalence is higher in real life. Therefore, the findings of our study raise various intriguing questions regarding the appropriateness of medication use among internal medicine patients with polypharmacy and hyperpolypharmacy, as they are unlikely to be explained solely by a higher comorbidity burden.

Potentially inappropriate prescribing

One interpretation of these findings is that a higher medication use category is due to potentially inappropriate prescribing. Polypharmacy has been identified as the leading risk for potentially inappropriate prescribing.[12] Potentially inappropriate medication is associated with adverse health and economic outcomes.[38 39] Among the medicines that are common in our patient cohort, in particular within the groups of patients with polypharmacy, are sedatives (43%) or benzodiazepines (29%). Polypharmacy, therefore, can be a helpful indicator of prescribing practice and medicine safety. However, healthcare professionals must identify when polypharmacy is inappropriate, as it can lead to adverse effects and poorer patient health outcomes.[38 40] Several criteria-based methods to identify inappropriate prescribing have been published; examples are the Beers criteria, the most widely used and recently updated.[41] Another widely used tool is a Screening Tool for Older Persons' potentially inappropriate Prescriptions (START (Screening Tool to Alert to Right Treatment) and STOPP (Screening Tool of Older Persons' Prescriptions)) criteria.[42] These tools are all only for older adults. There is a lack of tools to identify potentially inappropriate prescribing among all adults and studies focusing on polypharmacy among all adults and not solely older patients. Studies have shown that frailty is increasing among younger adults,[43] which emphasises the need for tools to address medication appropriateness regularly across the life course to hinder and prevent problematic polypharmacy through the life course.

Medications

Medications that are often predicted to be inappropriate[41 42] were more frequently used by patients with higher polypharmacy burden preceding the admission, including opioids (14.8% non-polypharmacy vs 34.6% polypharmacy vs 65.7% hyperpolypharmacy), benzodiazepines (4.0% vs 14.9% vs 40.2%) and proton pump inhibitors (7.3% vs 24.3% vs 51.5%). Our findings of high prevalence prescribing of those medication classes among internal medicines reveal the lack of solutions to tackle health problems like anxiety and mood disorder by other means than medication use and also challenges in the process of deprescribing.[44 45] It could also be linked to a lack of follow-up after hospital admission or new prescription that should be a short-term relief rather than long-term management, like benzodiazepines,[46] sedatives,[46] opioids[47] and proton pump inhibitors.[48]

Clinical outcomes

Contrary to the findings of numerous studies,[34 49–51] we did not find a link between the polypharmacy burden and clinical outcomes like mortality, longer hospital stay and re-admission rate. This may be because patients in all three medication use categories have similar burden of comorbidity (Elixhauser Comorbidity Score (39%>8) and risk of frailty (medium or high hospital frailty risk index classification)), which likely drives the observed difference in these outcomes in studies where there is a good correlation between comorbidity burden and polypharmacy. This study implies that the increased polypharmacy burden, like polypharmacy and hyperpolypharmacy, might be driven by potentially inappropriate medication use.

Strength and limitations

A key strength of the present research is the ability to link the nationwide prescription database, which included 95% of prescriptions in Iceland, with clinical data from hospital and primary care settings. One of the strengths of this study is that it represents a comprehensive examination of all tertiary care and most of secondary care of internal medicine patients in Iceland, as Landspitali is the main referral hospital for the country. The extended study period also allows for many patients in the study cohort. Finally, another strength is that there is no loss of follow-up of patients.

Among the limitations is a retrospective design that relies on the data collected and documented in the healthcare system for clinical purposes. The study is limited by the absence of information on the patient's medication adherence, which may, on the one hand, lead to an overestimation of the prevalence of polypharmacy and hyperpolypharmacy. We are also unable to determine if a medication was prescribed for short-term use only, which could overestimate the burden of polypharmacy. However, it must be noted that over-the-counter medications were not included in the study, which may, on the other hand, lead to an underestimation of polypharmacy and hyperpolypharmacy. Additionally, combination therapies frequently used in cardiology like thiazide and angiotensin receptor blockers are counted as one medication in this study, which may lead to underestimation in some patients using this methodology.

CONCLUSION

Preadmission polypharmacy and hyperpolypharmacy, new polypharmacy, and hyperpolypharmacy postdischarge are common among internal medicine patients. There appears to be no association between the level of medication use category and comorbidities and admitting specialty clinical outcomes in this selected population. It is, therefore, likely that the underlying disease does not explain polypharmacy in this population and serves as an indicator of potentially inappropriate prescribing. Recognition of polypharmacy and hyperpolypharmacy is significant, and increased emphasis is needed to review patients' medications regularly and after a hospitalisation.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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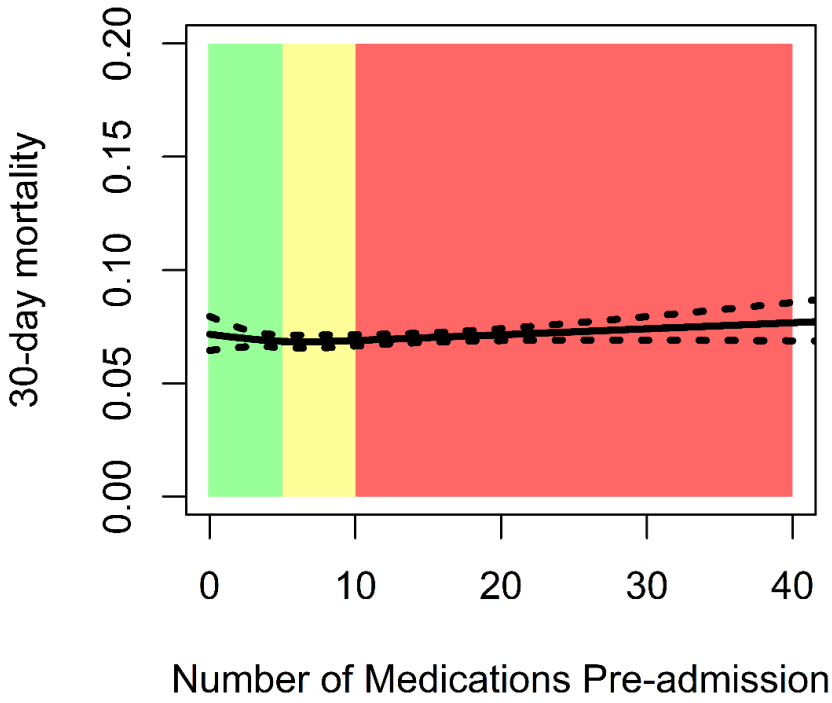
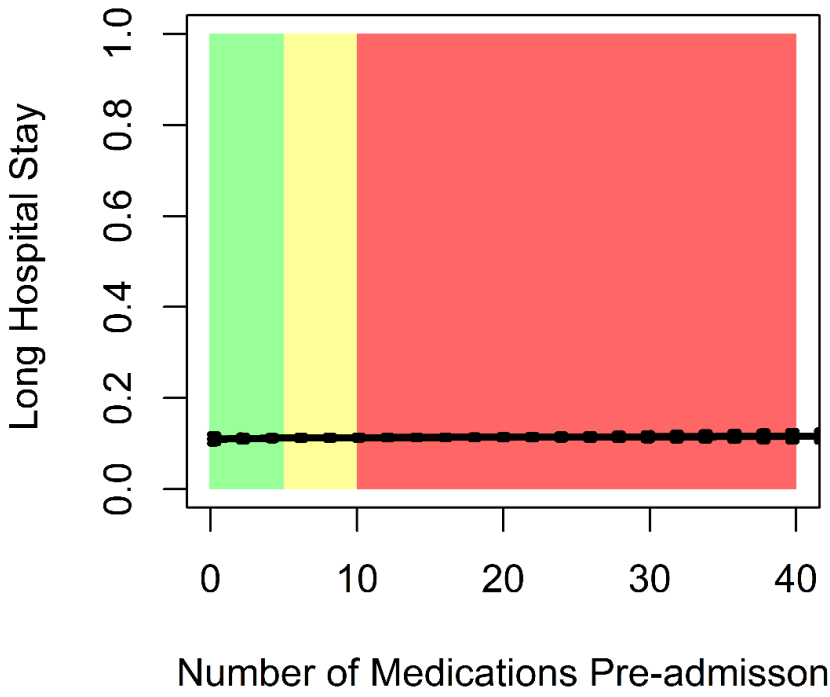
Appendix A. Supplementary data



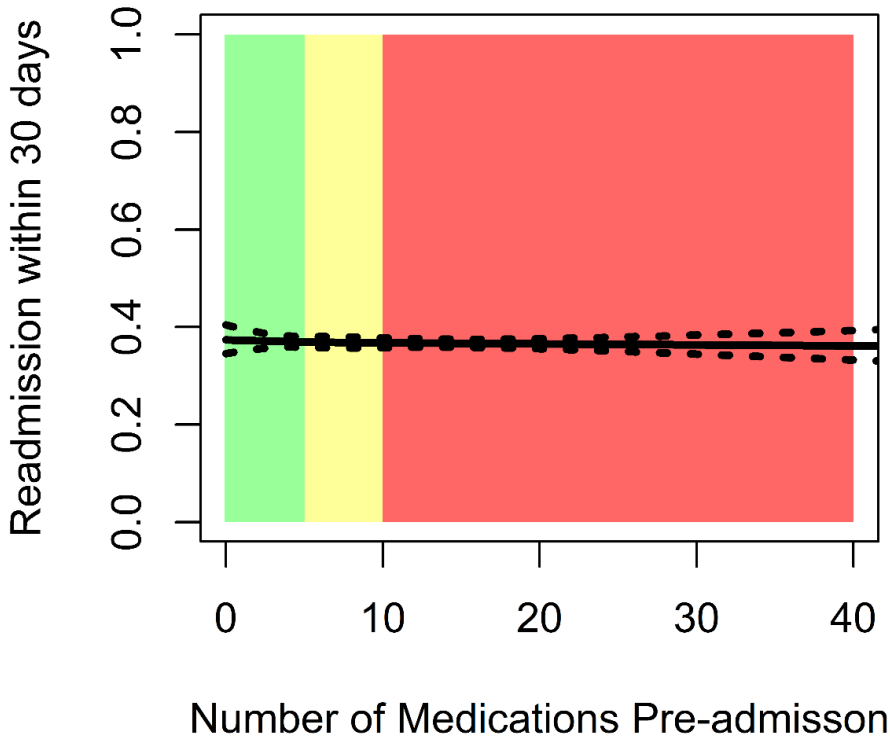
Supplementary Figure 1

Prevalence of polypharmacy among patients admitted to internal medicine ward (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy, and ≥ 10 medications = hyper-polypharmacy)and 30-day mortality. The figure shows the result of restricted cubic spline analysis of proportion of patients with the three outcomes. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine.



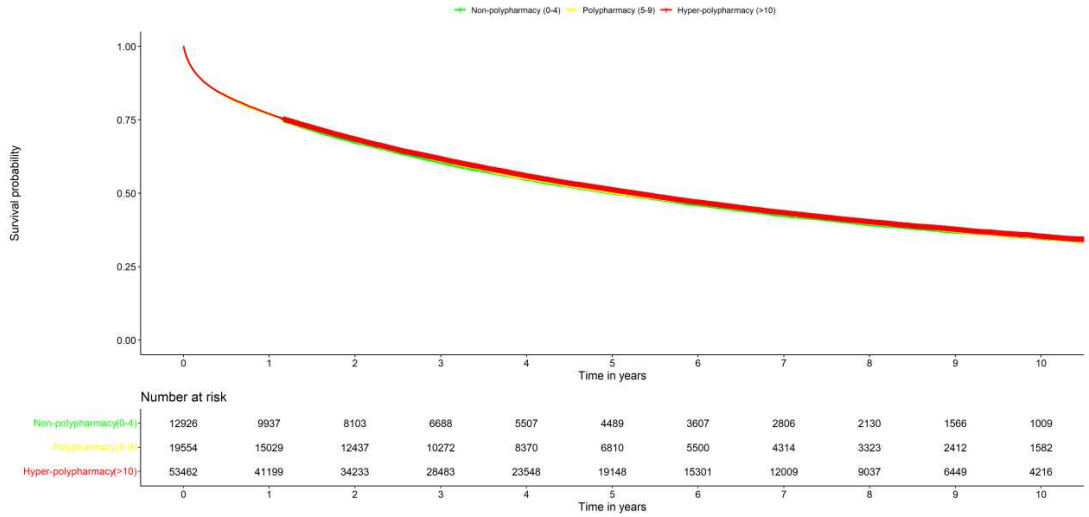
Supplementary Figure 2

The association between the number of medications pre-admission and a long hospital stay (> 10 days). The figure shows the result of restricted cubic spline analysis of proportion of patients with the three outcomes. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine.



Supplementary Figure 3

The association between the number of medications pre-admission and risk of readmission within 30 days. The figure shows the result of restricted cubic spline analysis of proportion of patients with the three outcomes. Colours indicate the number of different medications (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy) filled in the year preceding admission by internal medicine.



Supplementary Figure 4

A Kaplan-Meier survival curve of long-term survival of patients compared based on the number of medications pre-admission (green <5 medications = non-polypharmacy, yellow 5-9 medications = polypharmacy, and red ≥ 10 medications = hyper-polypharmacy).). Bolder lines indicate patients censored at end of follow-up.

Supplementary Table 1

Patient characteristics of cohorts (<5 medications = non-polypharmacy, 5-9 medications = polypharmacy and ≥ 10 medications = hyper-polypharmacy) based on the number of medications filled in the year preceding admission by internal medicine and whether they used multidose dispensing services. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No multidose dispensing	**Multidose dispensing**	p
Total number of patients	38950	46992	
Sex (male)	19876 (51.0)	24038 (51.2)	0.786
Age (median [IQR]), years	72.00 [69.00, 77.00]	78.00 [73.00, 84.00]	<0.001
Number of pre-admission medications (median [IQR])	9.00 [6.00, 13.00]	13.00 [9.00, 18.00]	<0.001
Number of pre-admission medications (median [IQR])	9.00 [5.00, 13.00]	14.00 [9.00, 18.00]	<0.001
Elixhauser Comorbidity Index [IQR])			0.503
(<1]	10578 (27.2)	12682 (27.0)	
(1-4]	5932 (15.2)	6981 (14.9)	
(4-5]	2632 (6.8)	3191 (6.8)	
(5-8]	4685 (12.0)	5705 (12.1)	
(>8]	15123 (38.8)	18433 (39.2)	
Internal Medicine Sepciality			0.710
Cardiology	8405 (21.6)	10256 (21.8)	
Dermatology	200 (0.5)	242 (0.5)	
Endocrinology	613 (1.6)	764 (1.6)	
Gastroenterology	3215 (8.3)	3788 (8.1)	
General Medicine	5255 (13.5)	6362 (13.5)	
Geriatrics	3353 (8.6)	3932 (8.4)	
Haematology	2015 (5.2)	2391 (5.1)	
Infectious Disease	2203 (5.7)	2542 (5.4)	
Nephrology	920 (2.4)	1160 (2.5)	
Neurology	3230 (8.3)	3892 (8.3)	
Oncology	2484 (6.4)	2978 (6.3)	
Palliative Care	679 (1.7)	825 (1.8)	
Pulmonology	4099 (10.5)	4981 (10.6)	
Rehabilitation	407 (1.0)	541 (1.2)	
Rheumatology	1872 (4.8)	2338 (5.0)	
Linked admissions			
Geriatrics	1447 (3.7)	1714 (3.6)	0.613
Palliative care	378 (1.0)	456 (1.0)	1.000
Rehabilitation	407 (1.0)	463 (1.0)	0.403
General internal medicine	820 (2.1)	994 (2.1)	0.938
Intensive care unit admission	2181 (5.6)	2598 (5.5)	0.662
Charlson (mean (SD))	2.95 (3.18)	2.95 (3.17)	0.805

Hospital Frailty Risk Score Class			0.384
Low (< 5)	14533 (37.3)	17735 (37.7)	
Med (5-15)	17650 (45.3)	21092 (44.9)	
High (> 15)	6767 (17.4)	8165 (17.4)	
Comorbidities			
Hypertension	21093 (54.2)	25397 (54.0)	0.756
Diabetes Mellitus	6275 (16.1)	7780 (16.6)	0.080
Chronic obstructive pulmonary disease	12596 (32.3)	15189 (32.3)	0.965
Ischemic heart disease	11898 (30.5)	14563 (31.0)	0.163
Liver disease	1281 (3.3)	1417 (3.0)	0.023
Chronic kidney disease	3874 (9.9)	4759 (10.1)	0.385
Malignant neoplasm	9668 (24.8)	11794 (25.1)	0.356
Benign neoplasm	15442 (39.6)	18678 (39.7)	0.767
Delerium	3568 (9.2)	4130 (8.8)	0.059
Dementia	834 (2.1)	960 (2.0)	0.327
Psychiatric	6503 (16.7)	7687 (16.4)	0.188
Diagnosis of adverse drug reaction pre-admission(%)	2713 (7.0)	6622 (14.1)	<0.001
Diagnosis of adverse drug reaction post admission(%)	1847 (4.7)	3280 (7.0)	<0.001

Supplementary Table 2

Patient characteristics of cohorts based on whether they changed to a higher polypharmacy category. Values are presented as count (%) or median (IQR) unless specified otherwise.

	No shift to higher polypharmacy category	**Shift to higher polypharmacy category**	**P-value**
Total number of patients	70095	15847	
Sex (male)	35816 (51.1)	8098 (51.1)	0.642
Age (median [IQR]), years	73.00 [60.00, 82.00]	73.00 [60.00, 83.00]	0.622
Number of pre-admission medications (median [IQR])	14.00 [10.00, 19.00]	5.00 [3.00, 8.00]	<0.001
Number of post-admission medications (median [IQR])	12.00 [6.00, 18.00]	11.00 [8.00, 13.00]	<0.001
Multidose dispensing services	40559 (57.9)	6433 (40.6)	<0.001
Internal Medicine Sepciality			0.425
Cardiology	15175 (21.6)	3486 (22.0)	
Dermatology	350 (0.5)	92 (0.6)	
Endocrinology	1124 (1.6)	253 (1.6)	
Gastroenterology	5687 (8.1)	1316 (8.3)	
General internal medicine	9518 (13.6)	2099 (13.2)	
Geriatrics	5944 (8.5)	1341 (8.5)	
Haematology	3617 (5.2)	789 (5.0)	
Infectious_Disease	3846 (5.5)	899 (5.7)	
Nephrology	1726 (2.5)	354 (2.2)	
Neurology	5772 (8.2)	1350 (8.5)	
Oncology	4449 (6.3)	1013 (6.4)	
Palliative_Care	1229 (1.8)	275 (1.7)	
Pulmonology	7397 (10.6)	1683 (10.6)	
Rehabilitation	774 (1.1)	174 (1.1)	
Rheumatology	3487 (5.0)	723 (4.6)	
Linked admissions			
Geriatrics	2621 (3.7)	540 (3.4)	0.048
Palliative care	681 (1.0)	153 (1.0)	0.980
Rehabilitation	706 (1.0)	164 (1.0)	0.787
Intensive care unit admission	3899 (5.6)	880 (5.6)	0.978
Elixhauser Comorbidity Index [IQR])			0.599
(<1]	18967 (27.1)	4293 (27.1)	
(1-4]	10527 (15.0)	2386 (15.1)	
(4-5]	4770 (6.8)	1053 (6.6)	
(5-8]	8523 (12.2)	1867 (11.8)	
(>8]	27308 (39.0)	6248 (39.4)	
Hospital Frailty Risk Score Class			0.138
Low (< 5)	26264 (37.5)	6004 (37.9)	
Med (5-15)	31707 (45.2)	7035 (44.4)	
High (> 15)	12124 (17.3)	2808 (17.7)	

Comorbidities			
Congestive heart failure	14078 (20.1)	3252 (20.5)	0.220
Diabetes Mellitus	11469 (16.4)	2586 (16.3)	0.903
Hypertension			
Chronic obstructive pulmonary disease	22701 (32.4)	5084 (32.1)	0.465
Ischemic heart disease	21610 (30.8)	4851 (30.6)	0.598
Liver disease	2185 (3.1)	513 (3.2)	0.449
Chronic kidney disease	7006 (10.0)	1627 (10.3)	0.311
Malignant neoplasm	17520 (25.0)	3942 (24.9)	0.762
Benign neoplasm	27819 (39.7)	6301 (39.8)	0.871
Delirium	6239 (8.9)	1459 (9.2)	0.229
Dementia	1462 (2.1)	332 (2.1)	0.966
Psychiatric	11536 (16.5)	2654 (16.7)	0.381
Fall pre-admission	201 (0.3)	18 (0.1)	<0.001
Fall post admission	71 (0.1)	21 (0.1)	0.342
Diagnosis of adverse drug reaction pre-admission (%)	8423 (12.0)	912 (5.8)	<0.001
Diagnosis of adverse drug reaction post admission(%)	4332 (6.2)	795 (5.0)	<0.001

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.