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ORIGINAL RESEARCH ARTICLE

Implied ADR-Admissions: A Cohort Study Introducing a Novel Administrative Data Approach for Identifying Drug-Related Hospitalisations

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Abstract

Background Adverse drug reactions (ADRs) are a key contributor to unplanned hospitalisations, particularly in patients with polypharmacy. Traditional detection methods, such as expert reviews or diagnostic coding, are limited in scalability and sensitivity.

Objective This study introduces and evaluates a novel scalable method, *implied ADR-admissions*, that links drug exposures to adverse events using administrative data to improve the detection of plausible drug-related hospitalisations.

Methods A retrospective cohort study was conducted using linked health data from 123,662 individuals aged ≥ 40 years with polypharmacy in two Scottish health boards. *Implied ADR-admissions* were defined as emergency hospitalisations with one of 15 adverse events plausibly linked to drug exposure (based on a structured consensus process) within the prior 90 days. Incidence was compared with three existing approaches: *adverse event-admissions* (regardless of drug exposure), *explicit ADR-admissions* (explicitly coded as ADRs) and *preventable ADR-admissions* (with prior medication error). Multivariate logistic regression was used to identify predictors of *implied ADR-admissions*.

Results Over 1 year, 2.6% experienced an *implied ADR-admission*, compared with 5.7% with *adverse event-admissions*, and 0.4% with *explicit ADR-admissions*. For gastrointestinal bleeding, the *implied ADR-admission* incidence was 20 times higher than the *preventable ADR-admission* incidence. Key predictors for *implied ADR-admissions* included prior hypokalaemia-related hospitalisation and use of potentially inappropriate medications.

Conclusions The *implied ADR-admission* approach has improved specificity relative to broad adverse event definitions while enhancing sensitivity beyond methods that rely solely on explicit ADR codes or pre-specified medication errors. It offers a scalable automated tool for pharmacovigilance, though further validation is needed prior to routine use in medication safety monitoring.

Plain Language Summary

Taking many medications (called polypharmacy) can increase the risk of harmful side effects, which sometimes lead to emergency hospital visits. However, these drug-related hospitalisations are often missed because they are difficult to detect with current methods. This study tested a new way to spot these cases using healthcare records. It looked at over 120,000 people aged 40 years or older in Scotland who were taking multiple medications. The method linked medications to hospital events and found that one in seven first emergency admissions of the year in these patients were likely caused by medicines—much more than what is usually reported. The most common problems were falls and bleeding, especially in those taking blood

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thinners. This new approach could help healthcare providers better track and prevent harm from medicines by focusing on risky drugs and vulnerable patients.

Key Points

The implied adverse drug reaction-admission approach identified more drug-related hospitalisations than both explicitly coded adverse drug reactions and admissions preceded by medication errors, but it identified fewer such admissions than broader definitions, indicating improved balance between sensitivity and specificity.

The novel approach identified a similar frequency but a broadened spectrum of drug-related admissions compared with previous studies with primary data collection.

Prior hypokalaemia and use of potentially inappropriate medications were key predictors of implied adverse drug reaction-admissions, supporting better pharmacovigilance and targeted interventions.

1 Introduction

Reducing harm from polypharmacy, commonly defined as the simultaneous use of five or more medicines, is a World Health Organization priority [1]. Polypharmacy substantially increases the risk of adverse drug reactions (ADRs), which are among the leading causes of unplanned hospital admissions [2–8]. However, accurately detecting drug-related hospitalisations remains challenging because of under-reporting, limitations of traditional diagnostic coding systems and the reliance on expert judgement to identify ADRs in clinical settings. In research studies aiming to quantify drug-related admissions, expert judgement (e.g. via World Health Organization [9] or Naranjo [10] algorithms) is often used to manually review hospital records and assign ADR causality [3]. While this approach is valuable, it is time consuming, resource intensive and not scalable to large populations.

Existing methods to measure drug-related hospitalisations in administrative data can be broadly categorised into three approaches (see Table 1): (1) *'AE-admissions'*, which identify hospitalisations for certain adverse events (AEs) relevant to medication safety, regardless of drug exposure at the time of admission [11]; (2) *'explicit ADR-admissions'*, which rely on AEs explicitly coded as ADRs in hospital records [11, 12]; and (3) *'preventable ADR-admissions'*, which focus on admissions with AEs preceded by a pre-specified medication error [13–15]. While each of these approaches has strengths, they also have limitations that hinder comprehensive ADR detection.

The *AE-admissions* approach, for instance, identifies hospitalisations for AEs that may be highly relevant to medication safety, but it does so without requiring evidence of drug exposure. This broad approach may capture many unrelated

Table 1 Approaches of measuring drug-related hospitalisations in administrative data sources

Approach	Example	Strengths and limitations
(1) **AE-admission** Hospitalisation with an AE with high relevance to medication safety	GI bleeding	High sensitivity and low specificity
(2) **Explicit ADR-admission** Hospitalisation with an AE with high relevance to medication safety and is explicitly coded as an ADR	GI bleeding, which is coded as being drug induced	Low sensitivity and high specificity
(3) **Preventable ADR-admission** Hospitalisation with an AE with high relevance to medication safety and was preceded by a causally linked medication error	GI bleeding preceded by the use of NSAIDs without gastroprotection in high-risk patients	Low sensitivity and high specificity
(4) **Implied ADR-admission** Hospitalisation with an AE with high relevance to medication safety and was preceded by a medication known to cause that AE	GI bleeding preceded by the use of NSAIDs	Potentially higher sensitivity (than approaches 2 and 3) and higher specificity (than approach 1)

ADR adverse drug reaction, *AE* adverse event, *GI* gastrointestinal, *NSAIDs* non-steroidal anti-inflammatory drugs

cases where the AE is not caused by a drug, thus reducing specificity. *Explicit ADR-admissions*, in contrast, rely on ADR codes explicitly documented in hospital records, but these codes are often under-reported or missing, leading to a significant underestimation of drug-related hospitalisations. Similarly, *preventable ADR-admissions* focus on cases where a medication error has preceded the AE (e.g. prescribing non-steroidal anti-inflammatory drugs without a proton pump inhibitor for gastrointestinal [GI] bleeding), but this approach misses ADRs caused by drugs in the absence of a pre-specified error. For example, non-steroidal anti-inflammatory drugs may cause GI bleeding even when a proton pump inhibitor is co-prescribed, highlighting the limitations of this approach in fully capturing drug-related harm.

In response to these limitations, we propose a fourth approach—*implied ADR-admissions*—which combines evidence of relevant drug exposure with a specific AE to enhance sensitivity compared to approach 2 and 3 while improving specificity relative to approach 1. Specifically, we define *implied ADR-admissions* as hospitalisations involving AEs that are associated with recent exposure to medications known to precipitate those events. This method does not require explicit ADR coding or pre-specified medication errors, addressing the under-reporting issue seen with traditional methods and providing a more scalable solution for identifying drug-related hospitalisations.

This study introduces the *implied ADR-admission* approach using administrative health data to enhance ADR detection at the population level, which is critical for scalable medication safety research and public health surveillance. The specific objectives are (a) to demonstrate the *implied ADR-admission* approach, linking drug exposure data to 15 relevant AEs, (b) to explore the potential utility of this approach for public health surveillance by comparing its ability to measure drug-related hospitalisations at the population level against the three existing approaches, and (c) to identify predictors of *implied ADR-admissions* among polypharmacy patients, supporting risk stratification for targeted interventions.

2 Methods

2.1 Study Design

We conducted a retrospective population-based cohort study using administrative health data from two Scottish health boards, Tayside and Fife. The study focused on people with an elevated baseline risk of drug-related harm, namely individuals aged 40 years or older with polypharmacy [1], defined as the concurrent use of five or more medications at baseline (1 January, 2019). We developed indicators for *implied ADR-admissions* by linking drug exposure data to AEs known to be caused by specific medications. Over a 12-month follow-up period, we compared the incidence of *implied ADR-admissions* with *all-cause admissions*, *AE-admissions* (approach 1), *explicit ADR-admissions* (approach 2) and *preventable ADR-admissions* (approach 3). Only hospital admissions via the emergency department were considered; elective admissions were excluded. We also conducted multivariate logistic regression to identify and compare key predictors of *all-cause admissions*, *AE-admissions* and *implied ADR-admissions*. The focus of the regression models was on informing risk stratification for medication safety interventions, rather than estimating causal relationships.

2.2 Data Source and Setting

The study utilised data from the National Health Service (NHS) Tayside/University of Dundee Health Informatics Centre (HIC). The database links healthcare data for all residents registered with a general practice under NHS contracts in the two health boards of Tayside and Fife—geographic regions, where all NHS health services are managed by a central statutory body—which together represent a population of ~900,000. The HIC collects data on all prescriptions dispensed to all Tayside and Fife residents by community pharmacies, and these can be linked to each other using the NHS Scotland unique identifiers (the Community Health Index number) and to other datasets held by the HIC, including sociodemographic information, all hospital admissions, as well as all inpatient and outpatient laboratory test results. Registration with a single general practice is required to obtain UK NHS care, and with the exception of a few highly specialised drugs, general practitioners are responsible for all community prescribing to patients. In contrast, non-prescription ("over-the-counter") medicines purchased by patients without a prescription are not captured by the data set. Only non-identifiable data were provided in the HIC secure safe haven (ISO27001 and Scottish Government accredited), and individual study ethical review was therefore not required (www.hic.dundee.ac.uk).

2.3 Study Population

The study included individuals aged 40 years or older, registered with NHS Tayside or NHS Fife general practices on 1 January, 2019 (cohort entry), and with at least 12 months of prior registration. We focused on patients with polypharmacy, defined as having dispensed drugs from five or more distinct British National Formulary (BNF) drug classes, which typically contain a single class of agent with similar mechanisms of action (as described in reference [16]), in the 90 days before cohort entry. These individuals were followed

up until deregistration, death or the end of the study period (31 December, 2019), whichever occurred first.

2.4 Definitions and Measurements

We defined *AE-admissions* and *implied ADR-admissions* based on 38 AEs identified as being of "high" or "very high" importance for drug-related harm in primary care, as determined through a formal consensus process involving a panel of 13 experts [17]. Of these, we excluded AEs that were judged to be very rare (e.g. rhabdomyolysis) or insufficiently serious to lead to hospital admission (e.g. dizziness). The following 15 AEs were included: acute kidney injury, anaemia, bleeding outside the gastrointestinal tract (GIT), dehydration, delirium, fall or fall injury, GI bleeding, heart failure, hyperkalaemia, hypoglycaemia, hypokalaemia, hyponatraemia, hypotension, respiratory depression and syncope. The detection of these AEs was based on *International Classification of Diseases, Tenth Revision* (ICD-10) codes documented as the "main condition", along with laboratory tests. Where laboratory test results were used to detect AEs, we considered those reported on the day or the day after hospital admission.

For *implied ADR-admissions*, we linked these AEs to drug exposure within a 90-day window before the admission. This window reflects standard prescription refill intervals in Scotland (typically 2 months) and an additional 1-month grace period to accommodate delays (e.g. because of holidays). This approach aimed to ensure that recent drug exposure was relevant to the AE, balancing sensitivity and specificity. The selection of drugs linked to each AE was based on a structured consensus process within the research team, and involved: (a) a structured literature review (systematic reviews and meta-analyses, supplemented by narrative reviews or individual studies where review articles were not available) to generate a list of candidate drugs with potential causal links to each AE; (b) a summary of this evidence for each event supplemented by information from the summary of product characteristics on specific drugs; (c) based on the evidence summaries, independent voting by two researchers on each candidate drug (on whether an ADR could be assumed in a patient presenting with a respective drug-event combination on admission); and (d) consensus discussion involving a third researcher to resolve any disagreements, when required. When selecting relevant drugs, we aimed to strike a balance between sensitivity (i.e. capturing all drugs with a relevant risk of the event) and specificity (i.e. avoiding identification of situations where the AE and the drug exposure merely coincide without a causal link).

For *explicit ADR-admissions*, we identified cases using ICD-10 codes that indicate drug- or substance-related causation or poisoning by drugs or other substances based on previous work [11]. Only emergency admissions with these diagnoses recorded as the "main condition" were considered.

To compare the *implied ADR-admission* approach with the *preventable ADR-admission* approach, we identified hospital admissions for GI bleeding that were preceded, within 90 days, by any of six high-risk prescribing patterns (based on age, comedication or comorbidity) [14], representing the medication error component of this approach. We then compared the incidence of such admissions under this approach to the incidence of GI bleeding admissions with exposure to causally linked drugs under the *implied ADR-admission* approach. Detailed information on the 15 AEs, linked drugs, associated BNF codes, and mapping of *explicit ADR-admissions* and the six indicators of *preventable ADR-admissions* is provided in Tables S1–S8 of the Electronic Supplementary Material (ESM).

2.5 Statistical Methods

2.5.1 Descriptive Statistics

All metric variables are reported as median [first quartile–third quartile], and categorical variables are reported as frequency (percentage). *P*-values of <0.05 were considered statistically significant.

2.5.2 Cumulative Incidence of Admissions Under Different Approaches

We calculated the cumulative incidence per 10,000 residents with polypharmacy aged 40 years or older for *all-cause admissions*, *AE-admissions*, *explicit ADR-admissions*, *preventable ADR-admissions* and *implied ADR-admissions*. We considered both the first occurrence of each of the 15 AEs individually, and the first occurrence of any of the 15 AEs as a composite endpoint. We also calculated the total number of such admissions. Finally, we computed the ratio of incidence rates for *implied ADR-admissions* and *AE-admissions* to quantify the relative burden of drug-related versus non-drug-related AEs.

2.5.3 Prediction of All-Cause, AE-Admissions, and Implied ADR-Admissions

We identified predictors of *all-cause*, *AE-admissions* and *implied ADR-admissions* using group lasso regression for variable selection [18]. The Schwarz Bayesian Information Criterion was employed as the selection criterion to generate a sparse model. This method was chosen to prevent overfitting and ensure that the selected predictors were the most relevant for predicting these admissions. A multivariate logistic regression model was then used to assess the

relationships between selected predictors and the outcomes of interest.

The focus of the analysis was on predictive modelling for risk stratification, rather than causal inference. Consequently, the analysis does not attempt to control for all potential confounders, and we accepted that some predictors may be proxies for unmeasured variables. The goal was to identify key predictors of *implied ADR-admissions* to inform more targeted interventions to improve medication safety.

2.5.4 Candidate Predictors

A total of 71 candidate predictors were considered in the analysis, including sociodemographics, frailty markers (e.g. hospitalisations in the prior year and a medication-based comorbidity score [19]), renal and liver function, number of drugs dispensed from different BNF chapters [16], potentially inappropriate medication (PIM) use according to EU(7)-PIM [20], and other drugs taken at cohort entry that are known to cause ADRs. These predictors were selected based on clinical relevance and their potential to identify high-risk individuals for *implied ADR-admissions*. Detailed information on the 71 candidate predictors and their mappings to BNF codes is provided in Tables S9–S14 of the ESM. All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA), R (version 4.1.3; http://www.R-project.org) or SPSS Statistics (Version 28, 2021; IBM Corporation, Armonk, NY, USA).

3 Results

3.1 Study Population

Table 2 presents the baseline characteristics of the study cohort, which included 123,662 individuals aged 40 years or older with polypharmacy registered with a general practice in NHS Fife or NHS Tayside on 1 January, 2019. The median age was 70 years (interquartile range [IQR] 59–79) with a slightly higher proportion of women than men (57.0% vs 43.0%). Among the cohort, 26.8% were dispensed ten or more drugs and 5.2% were dispensed 15 or more drugs. Notably, 21.0% were aged 65 years or older and received one or more PIM.

3.2 Cumulative Incidence of Admissions Under Different Approaches

The 123,662 cohort was followed for a median of 365 days with a total follow-up time of 109,064 person-years. During the 1-year follow-up period, a total of 5864 (4.7%) cohort members either died or deregistered.

Table 2 Baseline characteristics of the study population

Characteristics	No. of patients (%)
Total	123,662 (100.0)
Sex	
Female	70,513 (57.0)
Male	53,149 (43.0)
Age, years	Median 70 [IQR 59–79]
40–64	44,467 (36.0)
65–79	50,021 (40.4)
≥ 80	29,174 (23.6)
Deprivation quintile[a]	
1 (most deprived)	22,701 (18.4)
2	24,185 (19.6)
3	23,610 (19.1)
4	29,046 (23.5)
5 (least deprived)	19,696 (15.9)
Residence[a,b]	
Large urban area	25,058 (20.3)
Urban area	54,766 (44.3)
Accessible rural area	34,553 (27.9)
Remote rural area	4861 (3.9)
Hospital days in year before cohort entry	Median 0 [IQR 0–0]
0	102,212 (82.6)
1–7	12,995 (10.5)
8–30	6150 (5.0)
> 30	2305 (1.9)
medCDS	Median 3 [IQR 2–4]
Low risk (≤ 5 points)	101,748 (82.3)
Medium risk (6 points)	7916 (6.4)
High risk (≥ 7 points)	13,998 (11.3)
Number of drugs in 90 days before cohort entry[c]	Median 7 [IQR 6–10]
5–9	90,530 (73.2)
10–14	26,756 (21.6)
≥ 15	6376 (5.2)
Number of PIMs in 90 days before cohort entry[d]	Median 0 [IQR 0–1]
0	85,999 (69.5)
1	25,994 (21.0)
≥ 2	11,629 (9.5)

IQR interquartile range, *medCDS* medication-based chronic disease score (for prediction of all-cause mortality), *PIMs* potentially inappropriate medications

[a]Deprivation and residence missing for 4424 (3.6%) residents

[b]Scottish Executive Urban-Rural Classification

[c]Dispensed drugs from five or more distinct British National Formulary drug classes in the 90 days before cohort entry

[d]According to the EU(7)-PIM list

In total, 38,606 emergency admissions occurred among cohort members. Overall, 19.0% (n = 23,551) experienced at least one *all-cause admission*, with a median of

Table 3 Absolute and relative incidence of AE-related and implied ADR-related hospitalisations per 10,000 residents in 2019

Emergency hospital admission because of (linked drugs considered in implied ADR-admission detection)	Absolute incidence (95% CI) of[a]		Relative incidence (implied ADR-/AE-admission incidence ratio)
	AE-admission	Implied ADR-admission	
Any of the below[b]	574.9 (561.5–588.2)	260.4 (251.4–269.4)	0.45
Fall or fall injury (≥ 1 of: benzodiazepines, drug(s) with ACB ≥ 3, glucocorticoids)	209.6 (201.5–217.7)	91.1 (85.8–96.5)	0.43
Acute kidney injury (≥ 1 of: aminoglycosides, methotrexate, NSAIDs)	85.4 (80.2–90.5)	7.4 (5.9–9.0)	0.09
Heart failure (≥ 1 of: diltiazem, dronedarone, glitazones, NSAIDs, sotalol, verapamil)	57.7 (53.5–62.0)	4.4 (3.3–5.6)	0.08
Delirium (≥ 1 of: baclofen, barbiturates, benzodiazepines, drugs with ACB ≥ 3, Z-drugs)	49.7 (45.7–53.6)	21.5 (18.9–24.1)	0.43
Syncope (≥ 1 of: clozapine, diuretics, opioids, quetiapine)	46.4 (42.6–50.2)	25.7 (22.9–28.5)	0.55
Bleeding outside the GIT (≥ 1 of: antiplatelet drugs, DOACs, heparins, vitamin K antagonists)	40.0 (36.5–43.6)	27.8 (24.9–30.8)	0.70
Hyponatremia (≥ 1 of: certain antiepileptics, desmopressin, diuretics, SNRIs, SSRIs)	33.4 (30.2–36.6)	19.7 (17.2–22.1)	0.59
GI bleeding (≥ 1 of: antiplatelets, DOACs, NSAIDs [excluding coxibs], vitamin K antagonists)	28.8 (25.8–31.8)	17.8 (15.4–20.1)	0.62
Hypokalaemia (≥ 1 of: diuretics [excluding potassium-sparing diuretics], laxatives)	28.6 (25.6–31.6)	20.2 (17.7–22.7)	0.70
Hypotension (≥ 1 of: antihypertensive drugs, antipsychotics [second generation], TCAs)	23.9 (21.1–26.6)	20.7 (18.2–23.2)	0.87
Anaemia (≥ 1 of: metformin, methotrexate, methyldopa)	21.7 (19.1–24.3)	3.3 (2.3–4.3)	0.15
Hyperkalaemia (≥ 1 of: potassium-containing agents, potassium-sparing diuretics, RAS drugs)	17.5 (15.1–19.8)	9.3 (7.6–11.0)	0.53
Hypoglycaemia (≥ 1 of: insulinotropic antidiabetic drugs, insulins)	7.0 (5.5–8.4)	0.2 (0.0–0.5)	0.03
Respiratory depression (≥ 1 of: baclofen, barbiturates, benzodiazepines, opioids)	6.5 (5.1–7.9)	3.9 (2.8–5.0)	0.60
Dehydration (≥ 1 of: diuretics, laxatives, SGLT-2 inhibitors)	6.2 (4.8–7.6)	4.2 (3.1–5.3)	0.68

ACB anticholinergic burden, *ADR* adverse drug reaction, *AE* adverse event, *AE-admission* adverse event-related hospital admission, *CI* confidence interval, *coxibs* cyclo-oxygenase inhibitors, *DOACs* direct oral anticoagulants, *GI* gastrointestinal, *GIT* gastrointestinal tract, *implied ADR-admission* hospitalisation implied to be because of an adverse drug reaction, *NSAIDs* non-steroidal anti-inflammatory drugs, *RAS* renin-angiotensin system, *SGLT-2* sodium-dependent glucose cotransporter 2, *SNRIs* serotonin noradrenaline re-uptake inhibitors, *SSRIs* selective serotonin re-uptake inhibitors, *TCAs* tricyclic antidepressants

[a]Absolute incidence of emergency: all-cause admissions: 1904.5 (1880.1–1928.8), explicit ADR-admissions: 44.1 (40.4–47.8), preventable ADR-admissions (for GI bleeding): 309.0 (126.4–491.6)

[b]Event definitions are shown in Tables S1 and S2 of the ESM

one admission (IQR 1–2; range 1–25). *AE–admissions* (approach 1) occurred in 5.7% ($n = 7109$), with a median of one admission (IQR 1–1; range 1–11). *Explicit ADR-admissions* (approach 2) were observed in 0.4% ($n = 545$), with a median of one admission (IQR 1–1; range 1–5), while *implied ADR-admissions* were recorded in 2.6% ($n = 3220$), also with a median of one admission (IQR 1–1; range 1–7). Among patients admitted for GI bleeding, 3.1% ($n = 11$) met criteria for a *preventable ADR-admissions* (approach 3), based on evidence of a preceding medication error. These patients had a median of one admission (IQR 1–1; range 1–2). In contrast, 61.8% ($n = 220$) had prior exposure to drugs linked to GI bleeding, consistent with the *implied ADR-admission* approach. The cumulative incidence of *implied ADR-admissions* was thus about one seventh that of *all-cause admissions*, half that of *AE-admissions*, six times higher than *explicit ADR-admissions* and (for GI bleeding) 20 times higher than for *preventable ADR-admissions*.

Table 3 displays the cumulative incidence per 10,000 residents of individual *AE-admissions* and *implied ADR-admissions.* For *AE-admissions*, the cumulative incidence ranged from 6.2 per 10,000 residents for dehydration to 209.6 for fall or fall injury. For *implied ADR-admissions*, the cumulative incidence ranged from 0.2 per 10,000 residents for hypoglycaemia to 91.1 for fall or fall injury. The corresponding numbers of events are provided in Table S15 of the ESM.

Implied ADR-/AE-admission incidence ratios varied from 0.03 (for hypoglycaemia) to 0.87 (for hypotension).

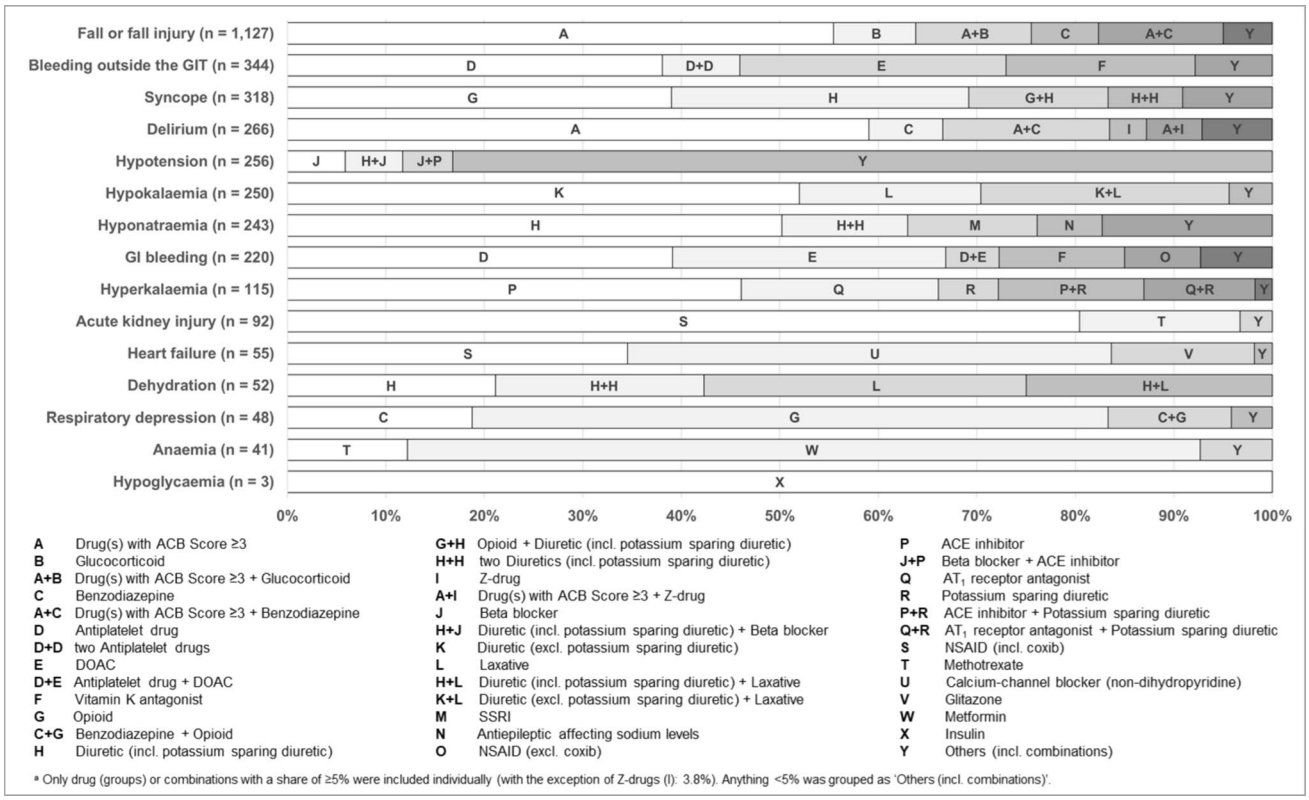

Fig. 1 Drug-event combinations. Proportion of implied adverse drug reaction-related hospitalisations associated with different pre-admission drug exposures. *ACB* anticholinergic burden, *ACE* angiotensin converting enzyme, *AT* angiotensin, *DOAC* direct oral anticoagulant, *excl.* excluding, *GI* gastrointestinal, *GIT* gastrointestinal tract, *incl.* including, *NSAID* non-steroidal anti-inflammatory drug, *SSRI* selective serotonin re-uptake inhibitors

These ratios do not reflect a simple proportion of *implied ADR-admissions* among all *AE-admissions*, as each outcome was calculated independently based on the first qualifying event per patient. Nine events (hypotension, bleeding outside the GIT, hypokalaemia, dehydration, GI bleeding, respiratory depression, hyponatraemia, syncope, hyperkalaemia) had higher implied ADR-/AE-admission incidence ratios (>0.5), two (delirium, fall or fall injury) had intermediate incidence ratios (0.2–0.5), and four events (anaemia, acute kidney injury, heart failure, hypoglycaemia) had lower (<0.2) implied ADR-/AE-admission incidence ratios.

3.3 Common Drug-Event Combinations

The most common drug-event combinations (accounting for > 10% of all *implied ADR-admissions*) were fall or fall injury with exposure to anticholinergic drugs (anticholinergic drug burden of ≥ 3) and/or benzodiazepines ($n = 956$, 27.9%), and bleeding events (GI or non-GI bleeding) with exposure to antiplatelet drugs and/or oral anticoagulant drugs ($n = 541$, 15.8%) (see Fig. 1). Other common drug-event combinations (accounting for > 5% of all *implied ADR-admissions*) were syncope with exposure to opioids and/or diuretics ($n = 315$, 9.2%), delirium with exposure to anticholinergic drugs (anticholinergic drug burden ≥ 3) and/or benzodiazepines ($n = 255$, 7.4%), and hypokalaemia with exposure to diuretics and/or laxatives ($n = 250$, 7.3%).

3.4 Relative Contributions of AEs and ADRs

Figure 2 shows Pareto charts presenting the cumulative contribution of individual AEs and ADRs to the total of all incident *AE-admissions* [panel (a)] and *implied ADR-admissions* [panel (b)], respectively. Among *AE-admissions*, the most common causes were fall or fall injury (34.7%), acute kidney injury (11.8%) and heart failure (8.9%). Among *implied ADR-admissions*, fall or fall injury also accounted for just over one third (34.3%) of all *implied ADR-admissions*, but apart from this, showed a distinct profile: the next two most common events were bleeding outside the GIT (10.4%) and syncope (9.3%), with acute kidney injury (2.7%) and heart failure (1.6%) accounting for much lower proportions of *implied ADR-admissions* than for *AE-admissions*. Other notable differences in contributions included hypoglycaemia (0.9% vs 0.1%), anaemia (3.3% vs 1.1%) and hypotension (3.7% vs 7.5%).

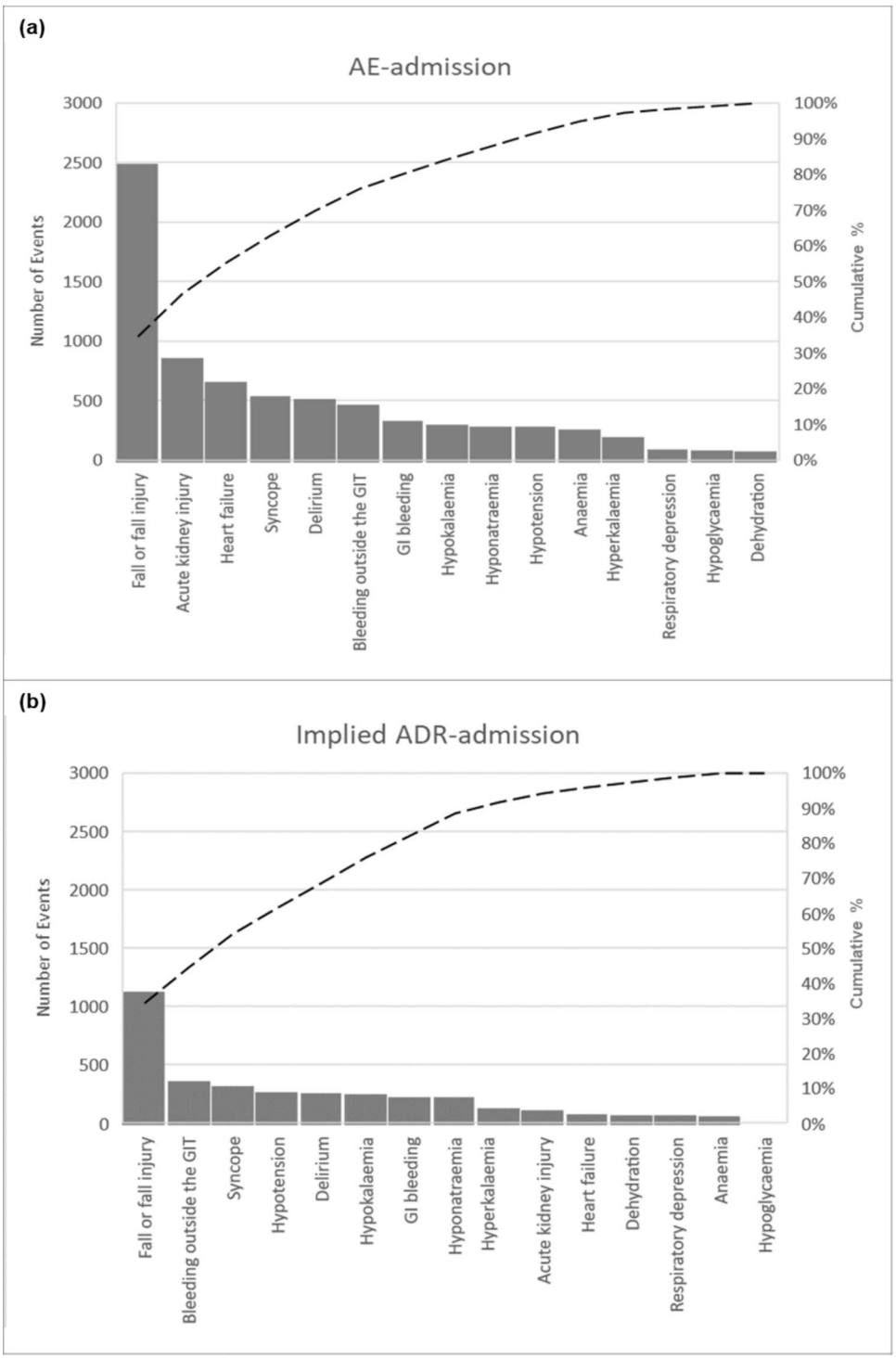

Fig. 2 Pareto charts of **a** all 7109 adverse event (AE)-related hospitalisations and **b** all 3220 implied adverse drug reaction (ADR)-related hospitalisations. *GI* gastrointestinal, *GIT* gastrointestinal tract

3.5 Predictors Associated with All-Cause, AE-Admissions, and Implied ADR-Admissions

From the 71 candidate predictors, lasso regression selected 33 for *all-cause admissions*, 20 for *AE-admissions* and 28 for *implied ADR-admissions* (see Table S16 of the ESM). These predictors explained 10.6% in the variance of *all-cause admissions*, 11.1% in *AE-admissions* and 10.5% in *implied ADR-admissions*.

Table 4 presents the results of the binomial multivariate logistic regression. Age was a common predictor for all three types of admissions, with individuals aged ≥ 80 years being more likely to experience *implied ADR-admissions* (odds ratio [OR] 2.79, 95% CI 2.41–3.22).

Impaired renal function, a higher number of hospital days in the prior year and more severe comorbidity (measured by the medication-based chronic disease score) were also associated with all three outcomes. However, there were notable differences between the predictors for the three types of admissions: prior heart failure-related hospitalisation was linked to *AE-admissions*, but was not a significant predictor of *implied ADR-admissions*. In contrast, prior hypokalaemia-related hospitalisation was a particularly strong predictor for *implied ADR-admissions* (OR 6.25, 95% CI 2.46–14.70), but not for *all-cause admissions*. Potentially inappropriate medication use was uniquely associated with *implied ADR-admissions*, reflecting its drug specificity compared with broader *AE-* or *all-cause admission* models. Key drug-related predictors for *implied ADR-admissions* included: antiepileptic drugs (OR 1.87, 95% CI 1.52–2.27); anticholinergic drugs (OR 1.68, 95% CI 1.53–1.84); benzodiazepines (OR 1.43, 95% CI 1.28–1.61).

4 Discussion

4.1 Summary of Findings

In this population-based cohort of 123,662 patients with polypharmacy, 2.6% experienced an *implied ADR-admission* within 1 year. This compares with 5.7% with *AE-admissions* (approach 1), 0.4% with *explicit ADR-admissions* (approach 2) and 19.0% with *all-cause admissions* (i.e. any emergency admission). Among those hospitalised for GI bleeding specifically, *preventable ADR-admissions* (approach 3) were observed in 3.1% of cases compared with 61.8% under the *implied ADR-admission* approach. These findings highlight the *implied ADR-admission* approach as a method that captures more drug-related cases than coding- or preventability-based definitions, while remaining more specific than AE-based definitions. The *implied ADR-admissions* accounted for 13.7% of *all-cause admissions*—consistent with previous estimates from studies using expert review as a gold standard [3].

Fall or fall injury had the highest incidence of both *AE-* and *implied ADR-admissions*, accounting for about one third of cases in each group when measured by incidence rates. However, the distribution of other event types differed notably. Acute kidney injury and heart failure were less common in *implied ADR-admissions*, suggesting these may occur without a high-risk medication trigger. In contrast, bleeding events were more prominent among *implied ADR-admissions*, often linked to antithrombotic medications. Two drug-event combinations— fall or fall injury with anticholinergic drugs and/or benzodiazepines and bleeding outside the GIT with antithrombotic medications—accounted for nearly half of all *implied ADR-admission* incidence. Findings based on patients' first admissions closely reflected those from analyses including all admissions, underscoring the robustness of the results across different analytical perspectives.

In a secondary analysis, we examined baseline predictors for *all-cause, AE-admissions* and *implied ADR-admissions* to explore distinct risk profiles. Older age, polypharmacy, multimorbidity and prior healthcare use were common predictors across all admission types, highlighting the vulnerability of high-risk patients. Some differences emerged: sex was associated only with *all-cause admissions*, and prior heart failure-related hospitalisations predicted *AE-admissions* but not *implied ADR-admissions*. Notably, exposure to PIMs was uniquely associated with *implied ADR-admissions*, suggesting it as a key marker of drug-related harm. Prior hypokalaemia-related hospitalisation (OR > 6) and elevated liver enzymes (gamma-glutamyl transferase) were also strongly linked to *implied ADR-admissions*, pointing to risks related to diuretic and alcohol use. These findings indicate that, while *implied ADR-admissions* share general risk factors with other admissions, certain characteristics—especially PIM exposure and specific prior AEs—disproportionately increase ADR risk. This supports the utility of the *implied ADR-admission* approach in identifying high-risk patients and guiding preventive strategies.

4.2 Comparison to Literature

4.2.1 Incidence of Drug-Related Admissions

Our study introduces the concept of *implied ADR-admissions*, defined as hospitalisations for specific AEs in patients recently exposed to medications known to cause those events, without requiring explicit ADR codes or pre-specified medication errors. Using this approach, we found that roughly one in seven *all-cause admissions* in polypharmacy patients were drug-related. This compares to two major bodies of literature: studies using explicit ADR codes and those using primary data collection (e.g. chart review or prospective observation).

Studies relying on explicit ADR coding have consistently reported very low rates of drug-related admissions because of under-reporting, with figures as low as 0.7% in a German study [11, 12]. Even when broader algorithms are applied (e.g. including "likely" or "possible" ADRs), the incidence only rises slightly. Our findings (the *explicit ADR-admission* incidence was 2.3% of that of *all-cause admissions*) are consistent with these low estimates. Even the *preventable ADR-admission* approach (i.e. identifying cases linked to prior medication errors) captures

Table 4 Predictors associated with all-cause, AE-related and implied ADR-related hospitalisations

Variable	Multivariate odds ratio (95% CI)		
	All-cause admission	AE-admission	Implied ADR-admission
Sex			
Female	Reference	-	-
Male	1.14 (1.11–1.18)	-	-
Age, years			
40–64	Reference	Reference	Reference
65–79	1.24 (1.19–1.29)	1.65 (1.53–1.78)	1.63 (1.44–1.86)
≥ 80	1.95 (1.85–2.06)	2.91 (2.66–3.18)	2.79 (2.41–3.22)
Deprivation quintile			
1 (most deprived)	Reference	-	-
2	0.93 (0.89–0.98)	-	-
3	0.90 (0.86–0.94)	-	-
4	0.84 (0.80–0.88)	-	-
5 (least deprived)	0.81 (0.77–0.86)	-	-
Hospital days in year before cohort entry			
0	Reference	Reference	Reference
1–7	1.95 (1.81–2.10)	1.65 (1.53–1.77)	1.57 (1.41–1.74)
8–30	2.85 (2.63–3.08)	2.24 (2.05–2.44)	1.87 (1.65–2.12)
> 30	3.21 (2.91–3.55)	2.59 (2.30–2.92)	2.04 (1.72–2.42)
medCDS			
Low risk (≤ 5 points)	Reference	Reference	Reference
Medium risk (6 points)	1.25 (1.17–1.33)	1.33 (1.22–1.46)	1.23 (1.08–1.40)
High risk (≥ 7 points)	1.28 (1.20–1.36)	1.34 (1.23–1.47)	1.19 (1.05–1.35)
Diseases included in medCDS			
Cancer	1.31 (1.19–1.44)	-	-
Cardiac arrhythmias	1.29 (1.22–1.37)	1.41 (1.29–1.54)	1.63 (1.44–1.84)
Chronic gastritis, gastroesophageal reflux disease	1.06 (1.03–1.10)	-	-
Heart failure	1.29 (1.22–1.37)	1.22 (1.13–1.31)	1.04 (0.91–1.20)
Psychiatric diseases	1.09 (1.05–1.13)	-	-
Stages of chronic kidney disease			
Normal	Reference	Reference	Reference
Mild	0.96 (0.92–1.00)	0.95 (0.89–1.02)	1.17 (1.06–1.29)
Moderate	1.16 (1.11–1.21)	1.19 (1.11–1.27)	1.19 (1.08–1.31)
Severe	1.69 (1.51–1.90)	1.94 (1.67–2.23)	1.47 (1.17–1.82)
End-stage	2.83 (2.27–3.52)	4.01 (3.13–5.09)	2.47 (1.69–3.51)
Liver enzymes			
Normal GGT	Reference	Reference	Reference
Elevated GGT[a]	1.57 (1.42–1.73)	1.69 (1.47–1.95)	1.81 (1.49–2.18)
Number of drugs in 90 days before cohort entry			
5–9	Reference	Reference	Reference
10–14	1.38 (1.32–1.43)	1.40 (1.32–1.49)	1.36 (1.25–1.49)
≥ 15	1.77 (1.65–1.90)	1.56 (1.42–1.72)	1.37 (1.18–1.57)
Number of PIMs in 90 days before cohort entry			
0	-	-	Reference
1	-	-	1.08 (0.98–1.18)
≥ 2	-	-	1.11 (0.98–1.25)
Any of the 15 AE-admissions in year before cohort entry	-	1.39 (1.26–1.53)	1.18 (1.02–1.36)
Bleeding outside the GIT	-	1.38 (1.07–1.77)	1.44 (1.01–2.01)

Table 4 (continued)

Variable	Multivariate odds ratio (95% CI)		
	All-cause admission	AE-admission	Implied ADR-admission
Heart failure	-	1.22 (0.98–1.51)	-
Hypokalaemia	-	6.01 (2.65–13.62)	6.25 (2.46–14.70)
Hypotension	1.54 (1.17–2.03)	-	1.52 (0.98–2.29)
Syncope	1.36 (1.11–1.65)	-	1.63 (1.16–2.24)
Non-AE-admission in year before cohort entry	1.17 (1.09–1.26)	-	-
Any linked drugs in 90 days before cohort entry			
Antidiabetic drugs affecting insulin levels (insulinotropic antidiabetic agents, insulins)	1.20 (1.14–1.26)	1.27 (1.17–1.38)	1.25 (1.11–1.39)
Antiepileptic drugs affecting sodium levels (carbamazepine, oxcarbazepine, eslicarbazepine, valproic acid)	1.38 (1.25–1.53)	1.65 (1.40–1.92)	1.87 (1.52–2.27)
Antiplatelet drugs	1.19 (1.15–1.24)	1.16 (1.10–1.23)	1.33 (1.22–1.44)
Antipsychotics (second generation) (excluding clozapine and quetiapine)	-	-	1.41 (1.14–1.74)
Benzodiazepines	1.12 (1.06–1.19)	-	1.43 (1.28–1.61)
Calcium-channel blockers (dihydropyridines)	0.92 (0.89–0.96)	-	-
Calcium-channel blockers (non-dihydropyridines)	-	-	1.31 (1.09–1.57)
Diuretics (excluding potassium-sparing diuretics)	0.84 (0.80–0.88)	-	1.30 (1.17–1.45)
Drug(s) with ACB score ≥ 3[b]	1.13 (1.08–1.18)	-	1.68 (1.53–1.84)
Glucocorticoids	1.36 (1.29–1.43)	-	1.26 (1.13–1.41)
Heparins	1.85 (1.42–2.40)	-	-
Laxatives	1.15 (1.11–1.20)	1.13 (1.06–1.20)	1.12 (1.02–1.23)
NSAIDs (excluding coxibs)	0.84 (0.79–0.89)	0.76 (0.67–0.86)	-
Opioids	1.08 (1.04–1.12)	-	-
Oral anticoagulants (DOACs, vitamin K antagonists)	1.21 (1.12–1.31)	1.11 (0.99–1.23)	1.16 (1.00–1.34)
Potassium-sparing diuretics	-	-	1.31 (1.13–1.51)
Renin-angiotensin system drugs (ACE inhibitors, AT_1 receptor antagonists, renin inhibitors)	0.84 (0.81–0.86)	0.87 (0.82–0.91)	0.85 (0.79–0.92)
Serotonin re-uptake inhibitors (SSRIs, SNRIs)	-	-	1.19 (1.08–1.30)
SGLT-2 inhibitors	0.78 (0.69–0.87)	0.47 (0.36–0.61)	-
Tricyclic antidepressants	0.87 (0.83–0.92)	-	-
Z-drugs	1.13 (1.06–1.21)	-	-

ACB anticholinergic burden, *ACE* angiotensin converting enzyme, *AE-admission* adverse event-related hospital admission, *AT* angiotensin, *CI* confidence interval, *coxibs* cyclo-oxygenase inhibitors, *DOACs* direct oral anticoagulants, *GGT* gamma-glutamyl transferase, *GIT* gastrointestinal tract, *implied ADR-admission* hospitalisation implied to be because of an adverse drug reaction, *medCDS* medication-based chronic disease score, *non-AE-admission* hospitalisation because of other cause than an adverse event, *NSAIDs* non-steroidal anti-inflammatory drugs, *PIMs* potentially inappropriate medications, *SGLT-2* sodium-dependent glucose cotransporter 2, *SNRIs* serotonin noradrenaline re-uptake inhibitors, *SSRIs* selective serotonin re-uptake inhibitors

[a]Common Terminology Criteria for Adverse Events (CTCAE) grade 1 [21]

[b]ACB Score calculation is shown in Table S5 of the ESM

drug-related hospitalisations only to a small extent, as we demonstrated using GI bleeding as an example. In contrast, studies using primary data collection have reported up to 14% of hospital admissions as drug-related [3, 4, 6, 8]. Our *implied ADR-admission* rate (approximately 13.7% of *all-cause admissions*) falls within this range, far exceeding the rates captured by reliance on ADR coding alone or prior medication errors. This suggests that the *implied ADR-admission* approach markedly improves sensitivity in identifying drug-related hospitalisations, capturing cases that may otherwise remain undetected. In sum, the observed incidence of *implied ADR-admissions* confirms that a substantial portion of acute hospitalisations in polypharmacy patients is likely drug-related, and that our administrative data-based approach can effectively capture this burden with reasonable fidelity to the "true" rates found in observational studies with primary data collection and expert judgement.

4.2.2 Causes of Drug-Related Admissions

Our study's findings on *implied ADR-admissions* align with key patterns from studies with primary data collection, such as the frequent involvement of antithrombotic medications (bleeding complications) and diuretics (electrolyte disturbances) [3, 4]. However, our results also highlight a prominent role of falls and fall-related injuries, particularly associated with anticholinergic drugs and benzodiazepines—a key finding not typically emphasised in such studies [3, 4]. The likely explanation is that many of these prior studies have focused on internal medicine wards (presumably because of resource constraints) while under-representing patients in surgical or orthopaedic wards, where fall injuries are predominantly treated [3]. In contrast, our scalable administrative data-based methodology captures ADRs across all emergency admissions (irrespective of the ward patients were admitted to), offering a broader view of drug-related harm. Our findings thus show that when a broad range of events is considered across all hospital wards—including those often seen in surgical contexts—falls (often medication-induced) emerge as equally or more important than those highlighted by studies with primary data collection, such as bleeding or renal events, which aligns with the central focus of falls prevention in geriatric pharmacotherapy [22].

In contrast to our findings here and those of investigations with primary data collection, studies applying the *explicit ADR-admission* approach [11], like the German claims data analysis, have identified *Clostridium difficile* colitis linked to antibiotics as a key driver of drug-related hospital admissions. This discrepancy partly reflects that our predefined set of AEs did not include infection-related complications, but also highlights the documentation bias inherent in the *explicit ADR-admission* approach. *Clostridium difficile* colitis may be more readily captured by specific drug-related ICD codes in administrative data, whereas other AEs with a broader range of possible causes (e.g. fall injuries or GI bleeding), may be under-reported. In contrast, our *implied ADR-admission* approach avoids this documentation bias, providing a more comprehensive detection of drug-related hospitalisations.

4.2.3 Predictors for Drug-Related Admissions

Several studies have identified various predictors for drug-related hospitalisations, including sociodemographic factors, medication use, behavioural characteristics, healthcare utilisation patterns and comorbidities [6, 7, 23–26]. Research using explicit ADR coding has highlighted predictors such as older age, male sex, residence in long-term care facilities, polypharmacy, newly prescribed medications, multiple pharmacies, recent hospitalisations and a higher comorbidity burden [12]. In contrast, studies employing primary data collection methods—like chart review or prospective observation—have identified additional predictors not consistently captured by the *explicit ADR-admission* approach, including impaired cognition [6, 24], renal impairment [6, 24], medication non-adherence [6], alcohol use [23] and specific drug classes, including antihypertensive drugs and anticholinergic drugs [24]. Administrative data-based studies have captured a subset of these predictors, notably comorbidity burden and male sex, and have also identified the use of PIMs as a predictor of drug-related hospitalisations [25, 26].

Our study, using the novel *implied ADR-admission* approach, identified a set of predictors that largely aligns with findings from both primary data collection and administrative data studies. These include prior hospitalisations, multimorbidity, renal impairment, polypharmacy, PIM use and anticholinergic exposure. Older age emerged as a significant predictor in our analysis, consistent with studies using explicit ADR coding, though not with those based on primary data collection. In contrast to some previous findings, we did not observe a significant association with sex. The observed association between elevated liver enzymes (gamma-glutamyl transferase) and *implied ADR-admissions* may reflect alcohol use as a known risk factor [23], while the strong association with prior hypokalaemia-related admissions likely points to complications associated with diuretic therapy or the underlying conditions they treat. Our findings therefore demonstrate that the *implied ADR-admission* approach effectively identifies key predictors of drug-related hospitalisations, aligning closely with results from both primary data collection studies and administrative data analyses. The consistency of these findings validates our approach and highlights its robustness and potential for broader application in pharmacovigilance research.

4.3 Strengths and Limitations

Key strengths of the study are its population-based design and large sample size, as well as the availability of laboratory data to measure renal impairment and elevated liver enzymes as predictors, and acute kidney injury and electrolyte disturbances as endpoints. A further methodological strength is the use of group lasso regression for variable selection prior to multivariate logistic regression to prevent overfitting in the presence of multicollinearity of predictors or high-dimensional data.

However, a key limitation of this study is the lack of direct validation of the *implied ADR-admission* approach against clinical hospital records. While our method uses linked administrative data to infer likely drug-related admissions, we were unable to validate its classification through detailed case note reviews, which would have allowed for a formal assessment of its sensitivity and specificity. As such, although the method shows promise as a tool for identifying

drug-related hospitalisations at scale, its diagnostic performance remains uncertain. Any incidence estimates presented should therefore be interpreted cautiously until further validation studies—ideally involving expert adjudication—are conducted. Moreover, our approach of measuring *implied ADR-admissions* using administrative data relies on prespecified drug-event combinations, without assessment of causality for individual cases. Instead, it focuses on hospitalisations where the drug exposure could have plausibly contributed to the ADR known to be associated with the drug. Not all such admissions will therefore actually be caused by the drug exposure alone. As such, commonly used causality assessment algorithms [9, 10] would classify these admissions as "possibly" drug-related. Nevertheless, it is worth noting that "possible" causality is also the most frequent classification in studies with primary data collection. For example, a multi-centre prospective observational study in Germany found that 87.6% of drug-related emergency admissions were rated as "possibly" drug-related, compared with 10.7% as "probably" and 1.7% as "certainly" drug-related [27]. In addition, even with access to more detailed health records, distinguishing between drug-related and alternative causes for hospitalisation therefore often remains challenging, as data typically requested by causality assessment algorithms [9, 10, 28] (e.g. drug concentrations, and de-challenge/rechallenge) are rarely available. The limitations of our *implied ADR-admission* approach are therefore largely shared by the current reference standard of an expert-based causality assessment. Another limitation of the study is that, although drug selection for each AE was based on a structured literature review and internal consensus within the research team, the inclusion of a larger expert panel might have improved face validity. Nonetheless, further refinement of drug-event linkages is likely best guided by empirical validation studies using hospital records. Additional limitations of our approach include reliance on ICD-10 codes for detecting most AEs, which may result in some AEs being missed. Furthermore, the absence of data on over-the-counter drug use and the use of a 90-day exposure window for dispensed prescriptions could, in some cases, lead to misclassification of drug exposure at the time of admission. The absence of data on certain predictors, such as nursing home residence and cognitive impairment, may have contributed to the relatively low proportion of variance explained by the multivariate models (10.6%, 11.1% and 10.5% for *all-cause*, *AE-admissions* and *implied ADR-admissions*, respectively).

4.4 Implications for Clinical Practice and Research

Our findings have important implications for clinical practice and future research. First, the *implied ADR-admission* approach offers a useful balance of specificity and sensitivity for identifying drug-related hospitalisations. By linking drug exposure to outcomes, it improves specificity compared to *all-cause* or *AE-admissions*, which may include non-drug-related events. We found that the incidence of *implied ADR-admissions* was about half of that of *AE-admissions*, suggesting our approach filters out admissions unlikely to be drug-related, while improving sensitivity over methods relying solely on ADR codes or prior medication errors. The proportion of admissions flagged by our method (roughly one in seven *all-cause admissions* in polypharmacy patients) aligns with observational studies with primary data collection, showing that many drug-related hospitalisations are missed in routine coding.

Second, the *implied ADR-admission* approach can immediately guide medication safety interventions, offering an automated, clinically relevant endpoint that tracks drug-related hospitalisations more accurately than *all-cause admissions*. It is a promising candidate for integration into healthcare analytics and pharmacovigilance systems, helping track drug-related harm and evaluate policy impacts. Our findings reinforce current safety efforts around antithrombotic medications, diuretics and psychotropic medications, emphasising the need for careful prescribing and monitoring of these drug classes, especially to minimise fall risks associated with central nervous system-active medications.

Finally, this study opens avenues for further ADR detection and prevention research. Future studies should validate the implied ADR detection algorithm against expert case reviews to quantify its accuracy. Our findings indicate that predicting the combined endpoint of *implied ADR-admissions* using administrative data sources is challenging, as demonstrated by the relatively low proportion of variance explained by the multivariate models (10.6%, 11.1% and 10.5% for *all-cause, AE-admissions* and *implied ADR-admissions*, respectively). Incorporating additional patient factor data may enhance prediction to some degree. However, because of the heterogeneity of ADRs within the combined *implied ADR-admission* endpoint, focusing on predicting individual ADRs or clusters of ADRs with shared predictors may represent a more effective strategy. Further research could explore machine learning approaches to improve risk prediction and expand the list of drug-event combinations. We also see potential in applying this approach to other populations and healthcare settings to compare ADR patterns internationally.

5 Conclusions

We introduced a novel administrative data approach to measure drug-related hospitalisations, linking specific drug exposures with AEs to infer likely drug-induced hospitalisations. This method improves specificity compared with broad AE criteria and enhances sensitivity

over relying solely on explicit ADR codes or pre-specified medication errors. In a large cohort of older polypharmacy patients, we found that roughly one in seven *all-cause admissions* were drug-related, a proportion consistent with intensive observational studies and far higher than routine coding alone.

The *implied ADR-admission* measure shows potential as a tool for evaluating quality improvement interventions in polypharmacy by providing an automated yet clinically meaningful outcome. Our findings also highlight certain drug classes, such as anticholinergic drugs, benzodiazepines, antithrombotic medications and diuretics, as major contributors to drug-related harm, suggesting that optimising their use could help reduce hospital admissions.

However, we acknowledge that this study is exploratory in nature and that our approach has, so far, only been validated indirectly. Further research, including validation against expert adjudication and pilot implementation, is necessary to confirm its clinical utility and refine its performance. Until then, this method should be considered a promising, but preliminary, tool for supporting pharmacovigilance and healthcare quality improvement efforts, particularly in managing medication risks among older adults with polypharmacy.

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Ethics Approval All research procedures adhered to HIC policies and standard operating procedures (Data Access Approvals-HIC Policies and Standard Operating Procedures-Confluence [atlassian.net]). These are approved by the East of Scotland Research Ethics Service and the NHS Tayside Caldicott Guardian, with agreement that studies adhering to the standard operating procedures do not require individual ethical review. Non-identifiable data were used for data linkage and analysis, and all data were analysed in an ISO27001 and Scottish Government accredited Data Safe Haven.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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