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Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study

Min Zhang, senior research fellow, C D’Arcy J Holman, professor of public health, Sylvie D Price, research associate, Frank M Sanfilippo, research fellow, David B Preen, senior research fellow, Max K Bulsara, associate professor of biostatistics

ABSTRACT

Objectives To identify factors that predict repeat admission to hospital for adverse drug reactions (ADRs) in older adults.

Design Population based retrospective cohort study.

Setting All public and private hospitals in Western Australia.

Participants 28 548 patients aged ≥60 years with an admission for an ADR during 1980-2000 followed for three years using the Western Australian data linkage system.

Results 5056 (17.7%) patients had a repeat admission for an ADR. Repeat ADRs were associated with sex (hazard ratio 1.08, 95% confidence interval 1.02 to 1.15, for men), first admission in 1995-9 (2.34, 2.00 to 2.73), length of hospital stay (1.11, 1.05 to 1.18, for stays ≥14 days), and Charlson comorbidity index (1.71, 1.46 to 1.99, for score ≥7); 60% of comorbidities were recorded and taken into account in analysis. In contrast, advancing age had no effect on repeat ADRs. Comorbid congestive cardiac failure (1.56, 1.43 to 1.71), peripheral vascular disease (1.27, 1.09 to 1.48), chronic pulmonary disease (1.61, 1.45 to 1.79), rheumatological disease (1.65, 1.43 to 1.92), mild liver disease (1.48, 1.05 to 2.07), moderate to severe liver disease (1.85, 1.18 to 2.92), diabetes (1.18, 1.07 to 1.30), diabetes with chronic complications (1.91, 1.65 to 2.22), renal disease (1.93, 1.71 to 2.17), any malignancy including lymphoma and leukaemia (1.87, 1.68 to 2.09), and metastatic solid tumours (2.25, 1.92 to 2.64) were strong predictive factors. Comorbidities requiring continuing care predicted a reduced likelihood of repeat hospital admissions for ADRs (cerebrovascular disease 0.85, 0.73 to 0.98; dementia 0.62, 0.49 to 0.78; paraplegia 0.73, 0.59 to 0.89).

Conclusions Comorbidity, but not advancing age, predicts repeat admission for ADRs in older adults, especially those with comorbidities often managed in the community. Awareness of these predictors can help clinicians to identify which older adults are at greater risk of admission for ADRs and, therefore, who might benefit from closer monitoring.

INTRODUCTION

Adverse drug reactions (ADRs) are a major public health problem in older populations. In Western countries, ADRs cause 3-6% of all hospital admissions and are responsible for about 5-10% of inpatient costs. We have previously reported that repeat ADRs resulting in either hospital admission or extended hospital stay increased at a greater rate than first time ADRs in older adults from 1980-2003. Furthermore, in Western Australia by 2003 over 30% of all ADRs were repeat ADRs.
changes in pharmacokinetics and pharmacodynamics. Risk factors reported to be independently associated with ADRs have included advancing age, sex, comorbidity, multiple drug regimens, inappropriate use of medication, alcohol intake, poor cognitive function, and depression. There is currently no consensus on which factors have the greatest impact.

We conducted a retrospective cohort study based on a state-wide population of patients to investigate whether or not comorbid conditions, age and other demographic factors, and drug category are associated with a repeat admission for ADRs in people aged ≥60.

**METHODS**

**Study setting and population**

We used administrative data from all public and private hospitals in Western Australia, a state with a population of 2.09 million in 2007. The study population consisted of all residents aged ≥60 with a hospital admission related to an ADR identified through the data linkage system. This system links state-wide administrative health data at the individual level using probabilistic matching of patients’ names and other identifiers with clerical review of doubtful matches. It includes links between seven core databases, of which the statutory death registry from 1969 and the hospital morbidity data system (HMDS) from 1970 form the main parts. We used extracts of linked hospital morbidity records and death records, with encryption to protect the identity of individual patients. The data were extracted in February 2005.

The hospital morbidity data system contained information on encrypted patient identification and episode number; age, sex, indigenous status, and postcode; date of admission and date of separation (that is, transfer, discharge, or inpatient death); international classification of diseases (ICD) codes for the main diagnosis and up to 19 additional diagnoses for up to four external causes (E codes), and for the main procedure and up to 10 additional procedures; type of hospital attended (public, private, other), admission type (emergency or elective), and payment classification. We used ICD-9 for 1980-7, ICD-9-CM for 1988-June 1999, and ICD-10-AM from July 1999 onwards. Data from the death records included encrypted patient identification, age, sex, indigenous status, primary cause of death, date of death, and postcode. We extracted linked hospital and death records for all patients aged ≥60 with an admission for ADR in 1980-2003 in Western Australia. In an assessment of the technical performance of the linkage system in finding true matches between records, both the proportion of invalid links (false positives) and of missed links (false negatives) was estimated to be 0.11%.

**Definition of ADR and identification of patients**

We included all ADRs that resulted in hospital admission or that occurred while patients were in hospital and extended the length of hospital stay. An ADR event was defined as any hospital separation with an ICD E code indicating that either the admission or extended hospital stay was because of the adverse effect caused by correct use of drugs, medicines, or biological substances properly administered in therapeutic or prophylactic doses, excluding errors in the technique of administration of drugs, intentional and unintentional overdose, and abuse of a drug. Thus, our definition of ADRs was consistent with the more recent and clearer version: “An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”

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**Table 1 | Drug categories (from ICD external cause codes) responsible for admission for first time adverse drug reaction (ADR) in patients aged ≥60, Western Australia, 1980-2000**

| Drug category (as defined in ICD-10-AM) | ICD-9/ICD-9-CM | ICD-10-AM | No (%) of patients |
|----------------------------------------|----------------|-----------|-------------------|
| Systemic antibiotics*                  | E930 Y40       | E937      | 2672 (9.4)        |
| Other systemic anti-infectives/antiparasitics | E931 Y41   | E932      | 430 (1.5)         |
| Hormones (including synthetics and antagonists) | E932 Y42   | E933      | 2174 (7.6)        |
| Primarily systemic agents               | E934 Y44       | E935      | 2122 (7.4)        |
| Agents primarily affecting blood constituents | E936 Y45   | E937      | 2432 (8.5)        |
| Analgesics/antipyretics/anti-inflammatory drugs | E938 Y46   | E939      | 4694 (16.4)       |
| Antiepileptics/antiparkinsonian drugs   | E940 Y50       | E941      | 1121 (3.9)        |
| Sedatives, hypnotics, antianxiety drugs | E942 Y51       | E943      | 406 (1.4)         |
| Anaesthetics and therapeutic gases      | E944 Y52       | E945      | 414 (1.5)         |
| Psychotropic drugs†                    | E946 Y53       | E947      | 1534 (5.4)        |
| Central nervous system stimulants      | E948 Y54       | E949      | 18 (0.1)          |
| Drugs primarily affecting autonomic nervous system‡ | E950 Y55   | E951      | 476 (1.7)         |
| Agents primarily affecting cardiovascular system | E952 Y56   | E953      | 5576 (19.5)       |
| Agents primarily affecting gastrointestinal system | E954 Y57   | E955      | 252 (0.9)         |
| Agents affecting water balance/minerals/uric acid§ | E956 Y58   | E957      | 2024 (7.1)        |
| Agents affecting muscles/respiratory system | E958 Y59   | E959      | 563 (2.0)         |
| Topical agents affecting skin, eyes, ENT, dental | E960 Y60   | E961      | 577 (2.0)         |
| Other and unspecified drugs and medicines | E962 Y61   | E963      | 982 (3.4)         |
| Bacterial vaccines                     | E964 Y62       | E965      | 16 (0.1)          |
| Other and unspecified vaccines/biologicals | E966 Y63   | E967      | 65 (0.2)          |
| Total                                  |                |           | 28 548 (100.0)    |

ADR=adverse drug reaction; ICD=international Classification of Diseases; ENT=ear, nose, throat.
*Excludes antineoplastic antibiotics (E939.7) from ICD-9/ICD-9-CM (were added to primarily systemic agents, which include antineoplastics).
†Excludes benzodiazepines (E939.4) from ICD-9/ICD-9-CM (were added to group sedatives, hypnotics, antianxiety drugs, which includes benzodiazepines in ICD-10).
‡Excludes sympatholytics (E941.3) from ICD-9/ICD-9-CM (were added to agents primarily affecting cardiovascular system, which include these in ICD-10).
§Excludes theophylline (E944.2) from ICD-9/ICD-9-CM (was added to agents affecting muscles/respiratory system, which includes antiallergics).
An ADR hospital episode was defined as a period of continuous treatment for an ADR in one or more hospitals, as a person might have been transferred from one hospital to another before they were discharged. We checked all records for transfers between hospitals and, where they existed, combined the admissions into a single “episode” for analysis.

To ensure correct identification of first time ADRs, we initially examined all admissions of the patients dating back to 1970. We included 803,732 hospital separations and audited these records to ensure that each patient met the selection criteria. We excluded people who were not residents of Western Australia and those with hospital episodes unrelated to ADRs. There were 37,296 patients who lived and were treated in Western Australia and had at least one admission episode for an ADR. Each patient’s first ADR record was identified, thereby distinguishing first time from repeat episodes. We included 28,548 patients with a first time ADR in 1980–2000 as a cohort and followed them up for three years. The figure shows the process of selecting patients for the study.

### Table 2 | Top 30 drug groups (ICD E codes) most often implicated in admission for first time adverse drug reaction (ADR) in 28,548 patients aged ≥60, Western Australia, 1980–2000

| Drug groups (as defined in ICD-10-AM) | ICD-9/ICD-9-CM | ICD-10-AM | No (%) of patients |
|---------------------------------------|----------------|-----------|-------------------|
| **Systemic antibiotics:**             |                |           |                   |
| Penicillins                           | E930.1         | Y40.0     | 881 (3.1)         |
| Unspecified systemic antibiotics      | E930.9         | Y40.9     | 569 (2.0)         |
| Other systemic antibiotics            | E930.8         | Y40.8     | 505 (1.8)         |
| Cephalosporins and other β lactams    | E930.5         | Y40.1     | 353 (1.2)         |
| **Hormones (including synthetics and antagonists):** | | | |
| Glucocorticoids and synthetics        | E932.0         | Y42.0     | 1328 (4.7)        |
| Insulins and oral anti-diabetic drugs | E932.3         | Y42.3     | 416 (1.5)         |
| **Topically affecting skin, eyes, ENT, dental:** | | | |
| Local anti-infectives/anti-inflammatory drugs | E946.0 | Y56.0 | 435 (1.5) |
| Other unspecified drugs and medicines | | | |
| Unspecified drug or medicines         | E947.9         | Y57.9     | 555 (1.9)         |
| Other drugs or medicines              | E947.8         | Y57.8     | 354 (1.2)         |
| **Primary systemic agents:**          |                |           |                   |
| Antineoplastic/immunosuppressive drugs| E933.1/E930.7  | Y43.1-4   | 1980 (6.9)        |
| Agents primarily affecting blood constituents: | | | |
| Anticoagulants                        | E934.2         | Y44.2     | 1964 (6.9)        |
| Thrombolytic drugs                    | E934.4         | Y44.5     | 247 (0.9)         |
| Analgesics/antiinflammatory drugs:    |                |           |                   |
| NSAIDs and antiinflammatics           | E935.6         | Y45.2-4   | 2026 (7.1)        |
| Opioids and related analgesics        | E935.2         | Y45.0     | 1388 (4.9)        |
| Salicylates                           | E935.3         | Y45.1     | 442 (1.5)         |
| 4-aminophenol derivatives (such as paracetamol) | E935.4 | Y45.5 | 361 (1.3) |
| **Other systemic agents:**            |                |           |                   |
| Antiepileptics and antiparkinsonian drugs: | | | |
| Hydantoin derivatives                 | E936.1         | Y46.2     | 408 (1.4)         |
| Antiparkinsonian drugs                | E936.4         | Y46.7     | 359 (1.3)         |
| Other and unspecified antiepileptics  | E936.3         | Y46.6     | 302 (1.1)         |
| **Psychotropic drugs:**               |                |           |                   |
| Antidepressants                       | E939.0         | Y49.0-2   | 596 (2.1)         |
| Phenothiazine antipsychotics/neuroleptics | E939.1 | Y49.3 | 365 (1.3) |
| Agents primarily affecting cardiovascular system: | | | |
| Cardiac stimulant glycosides/similar drugs | E942.1 | Y52.0 | 1702 (6.0) |
| Other antihypertensive drugs          | E942.6         | Y52.5     | 1708 (6.0)        |
| Other antidyssrhythmic drugs          | E942.0         | Y52.2     | 786 (2.8)         |
| Coronary vasodilators                 | E942.4         | Y52.3     | 662 (2.3)         |
| Peripheral vasodilators (ICD-9 sympatholytics) | E941.3 | Y52.7 | 269 (0.9) |
| **Agents affecting water balance, mineral/uric acid metabolism:** | | | |
| Loop and other diuretics              | E944.4         | Y54.4-5   | 1257 (4.4)        |
| Benzothiadiazine derivatives          | E944.3         | Y54.3     | 322 (1.1)         |
| Uric acid metabolism drugs (such as colchicine) | E944.7 | Y54.8 | 242 (0.8) |
| **Agents affecting muscles/respiratory system:** | | | |
| Antiallergics (including theophylline) | E944.1/E945.7  | Y55.6     | 472 (1.7)         |
| **Topical agents affecting skin, eyes, ENT, dental:** | | | |
| Local anti-infectives/anti-inflammatory drugs | E946.0 | Y56.0 | 435 (1.5) |
| Other unspecified drugs and medicines: | | | |
| Unspecified drug or medicines         | E947.9         | Y57.9     | 555 (1.9)         |
| Other drugs or medicines              | E947.8         | Y57.8     | 354 (1.2)         |
| **Total**                             |                |           | 23,254 (81.5)     |

ADR=adverse drug reaction; ICD=International Classification of Diseases; NSAIDs=non-steroidal anti-inflammatory drugs; ENT=ear, nose, throat.
Table 3 | Charlson comorbidity conditions (with weights) present at admission for first time adverse drug reaction (ADR) in 28,548 patients aged ≥60, Western Australia, 1980-2000

| Charlson comorbid conditions | Weight | No (%) of patients |
|-------------------------------|--------|--------------------|
| Myocardial infarction         | 1      | 1,556 (5.5)        |
| Congestive cardiac failure    | 1      | 4,745 (16.6)       |
| Peripheral vascular disease   | 1      | 1,174 (4.1)        |
| Cerebrovascular disease       | 1      | 1,827 (6.4)        |
| Dementia                      | 1      | 868 (3.0)          |
| Chronic pulmonary disease     | 1      | 2,034 (7.1)        |
| Rheumatological disease      | 1      | 832 (2.9)          |
| Peptic ulcer disease          | 1      | 2,145 (7.5)        |
| Mild liver disease            | 1      | 199 (0.7)          |
| Diabetes (mild to moderate)   | 2      | 2,807 (9.8)        |
| Diabetes with complications   | 2      | 755 (2.6)          |
| Hemiplegia or paraplegia      | 2      | 864 (3.0)          |
| Renal disease                 | 2      | 1,418 (5.0)        |
| Any malignancy, including lymphoma/leukaemia | 2 | 3,349 (11.7) |
| Moderate or severe liver disease | 3 | 108 (0.4) |
| Metastatic solid tumour       | 6      | 1,518 (5.3)        |
| AIDS                          | 6      | 5 (0.0)            |

Table 3 presents the Charlson comorbidity conditions (with weights) present at admission for first time adverse drug reactions (ADRs) in 28,548 patients aged ≥60, Western Australia, 1980-2000. The table shows the weight and the number (%) of patients with each comorbidity condition.

Australian Bureau of Statistics and consists of four variables that reflect or measure relative disadvantage, including low income, low educational attainment, high unemployment, and low skilled occupation; it has been used extensively in public health research.27 The continuous values of the indexes were then partitioned into fifths.

Statistical analysis

Statistical analysis was performed with SPSS version 12.0.1 (SPSS, Chicago, IL). We used the independent samples t test for continuous variables and a χ² test for categorical variables to compare characteristics between patients with first time only and repeat ADR episodes. Variables associated with first time admissions for an ADR were used for univariate and multivariate analysis. Univariate analysis was undertaken to screen for potentially important variables to be used in the subsequent multivariate analysis. Multivariate Cox proportional hazards regression models were fitted by using all variables included as main effects terms, and we performed corresponding linear trend tests. When assessing each drug category, we fitted the Cox regression models using deviation coding, which compared the effect on repeat ADRs of each first time drug category with the average risk of all 20 drug categories. We obtained hazard ratios and associated 95% confidence intervals after adjusting for age, sex, indigenous status, residential locality, socioeconomic disadvantage, admission type, hospital type, length of hospital stay, calendar period of ADR, Charlson comorbidity index, and drug categories. Other studies have identified these variables as those influencing the risk of first time ADRs,10-15 and they were significant predictors of repeat ADRs based on the preceding univariate analysis. To assess potential for survival bias, we separately analysed data from all patients and from a subset that excluded those who died in the three year follow-up period.

RESULTS

Results using data from all patients were similar to those obtained when we excluded patients who died in the follow-up period. We have therefore reported only the results from analyses that included all patients. Within the first three years of follow-up, 5056 patients (17.7%) experienced a repeat admission for an ADR. Table 4 presents unadjusted and adjusted hazard ratios for repeat ADRs for selected characteristics in the participants. The adjusted hazard ratios for repeat ADRs were 1.08 (95% confidence interval 1.02 to 1.15) for men, 0.87 (0.80 to 0.93) for private hospital admissions, 1.11 (1.05 to 1.18) for length of hospital stay ≥14 days, 2.34 (2.00 to 2.73) for admission in 1995-9 compared with the earliest time period, and 1.71 (1.46 to 1.99) for a Charlson comorbidity index score ≥7, with a significant linear trend across quantitative or ordinal quantitative variables. Residential location in the metropolitan area (1.10, 1.01 to 1.19) was marginally significant (P=0.03). There was no significant effect on repeat ADRs for age, indigenous status, type of admission, and socioeconomic disadvantage.

Table 5 shows the effects of individual Charlson comorbid conditions on repeat ADRs. Compared with patients who had no recorded comorbidity, the analysis identified sizeable adjusted hazard ratios for congestive cardiac failure (1.56, 1.43 to 1.71), peripheral vascular disease (1.27, 1.09 to 1.48), chronic pulmonary disease (1.61, 1.45 to 1.79), rheumatological disease (1.65, 1.41 to 1.92), mild liver disease (1.48, 1.05 to 2.07), mild to moderate diabetes (1.18, 1.07 to 1.30), diabetes with chronic complications (1.91, 1.65 to 2.22), renal disease (1.93, 1.71 to 2.17), any malignancy including lymphoma and leukaemia (1.87, 1.68 to 2.09), moderate to severe liver disease (1.85, 1.18 to 2.92), and metastatic solid tumour (2.25, 1.92 to 2.64). Cerebrovascular disease (0.85, 0.73 to 0.98), dementia (0.62, 0.49 to 0.78), and hemiplegia or paraplegia (0.73, 0.59 to 0.89) were apparently preventive for repeat ADRs. There was no significant relation for myocardial infarction, peptic ulcer disease, or AIDS, although people with AIDS had only two repeat ADRs.

Table 6 shows the effect of each drug category (as defined in ICD-10-AM) responsible for first time ADRs. Three drug categories were associated with a greater than average risk of repeat ADRs, with adjusted hazard ratios of 1.51 (1.34 to 1.69) for hormones, 2.12 (1.89 to 2.38) for primarily systemic agents (including antineoplastics, immunosuppressives, and anti-neoplastic antibiotics), and 4.06 (2.00 to 8.26) for bacterial vaccines. The latter category, however, had low counts for first time and repeat ADRs.

DISCUSSION

Predictive factors for repeat ADR admission

In this population based cohort study of factors that predict repeat admission for ADRs in older adults we...
found strong evidence that comorbidity from chronic disease rather than advancing age increases their rate of repeat ADRs. Comorbid congestive cardiac failure, diabetes, and peripheral vascular, chronic pulmonary, rheumatological, hepatic, renal, and malignant diseases were all strong predictors of readmissions for ADRs. Our results were consistent with those of earlier studies that a higher Charlson comorbidity index score, renal insufficiency, and diabetes were all risk factors for first time ADRs. We also found that comorbid cerebrovascular disease, dementia, and hemiplegia or paraplegia were associated with a

| Characteristics at first admission for ADR | First time ADR only (n=23,492) | Repeat ADR (n=5,056) | Unadjusted HR (95% CI) | P value* | Adjusted HR (95% CI)† | P value* |
|-------------------------------------------|---------------------------------|----------------------|------------------------|----------|-----------------------|----------|
| Age at admission (years):                 |                                 |                      |                        |          |                       |          |
| 60-64                                     | 3226                            | 790                  | 1.00‡                  | 0.18     | 1.00‡                 | 0.19     |
| 65-69                                     | 3830                            | 870                  | 0.96 (0.87 to 1.05)    |          | 0.97 (0.88 to 1.07)   |          |
| 70-74                                     | 4697                            | 982                  | 0.90 (0.82 to 0.99)    |          | 0.93 (0.84 to 1.02)   |          |
| 75-79                                     | 4647                            | 1009                 | 0.95 (0.86 to 1.04)    |          | 0.99 (0.91 to 1.10)   |          |
| ≥80                                       | 7092                            | 1405                 | 0.92 (0.84 to 1.00)    |          | 0.96 (0.87 to 1.05)   |          |
| Sex:                                      |                                 |                      |                        |          |                       |          |
| Female                                    | 13,264                          | 2810                 | 1.00‡                  |          | 1.00‡                 |          |
| Male                                      | 10,228                          | 2246                 | 1.13 (1.07 to 1.19)    | <0.001   | 1.08 (1.02 to 1.15)   | <0.01    |
| Indigenous status:                        |                                 |                      |                        |          |                       |          |
| Non-Aboriginal/TSI                        | 23,288                          | 5006                 | 1.00‡                  |          | 1.00                  |          |
| Aboriginal/TSI                            | 204                             | 50                   | 1.15 (0.87 to 1.52)    | 0.34     | 1.03 (0.77 to 1.37)   | 0.85     |
| Residential locality:                    |                                 |                      |                        |          |                       |          |
| Regional/rural area                       | 3936                            | 847                  | 1.00‡                  |          | 1.00                  |          |
| Metropolitan Perth                       | 19,556                          | 4209                 | 1.02 (0.95 to 1.10)    | 0.53     | 1.10 (1.01 to 1.19)   | 0.03     |
| Admission type:                           |                                 |                      |                        |          |                       |          |
| Elective                                  | 6469                            | 1405                 | 1.00‡                  |          | 1.00                  |          |
| Emergency                                 | 17,007                          | 3648                 | 1.01 (0.95 to 1.07)    | 0.75     | 1.05 (0.99 to 1.12)   | 0.13     |
| Type of hospital attended:               |                                 |                      |                        |          |                       |          |
| Public                                    | 19,542                          | 4063                 | 1.00‡                  |          | 1.00                  |          |
| Private                                   | 3275                            | 930                  | 1.32 (1.23 to 1.42)    | <0.001   | 0.87 (0.80 to 0.93)   | <0.001   |
| Other                                     | 675                             | 63                   | 0.41 (0.32 to 0.53)    |          | 0.80 (0.61 to 1.04)   |          |
| Length of hospital stay (days):           |                                 |                      |                        |          |                       |          |
| <14                                       | 15,803                          | 3408                 | 1.00‡                  | <0.001   | 1.00                  | <0.001   |
| ≥14                                       | 7689                            | 1648                 | 1.14 (1.08 to 1.21)    |          | 1.11 (1.05 to 1.18)   | 0.001    |
| Socioeconomic disadvantage (fifths):      |                                 |                      |                        |          |                       |          |
| 1 (most)                                  | 4671                            | 982                  | 1.00‡                  |          | 1.00                  |          |
| 2                                         | 5495                            | 1055                 | 0.92 (0.85 to 1.01)    | <0.001   | 0.90 (0.83 to 0.99)   | 0.15     |
| 3                                         | 3184                            | 710                  | 1.05 (0.96 to 1.16)    |          | 0.99 (0.90 to 1.09)   |          |
| 4                                         | 3365                            | 733                  | 1.04 (0.95 to 1.15)    | <0.001   | 0.95 (0.86 to 1.04)   |          |
| 5 (least)                                 | 6752                            | 1575                 | 1.11 (1.02 to 1.20)    | <0.001   | 0.94 (0.87 to 1.02)   |          |
| Calendar period of ADR:                  |                                 |                      |                        |          |                       |          |
| 1980-4                                    | 2097                            | 183                  | 1.00‡                  | <0.001   | 1.00                  | <0.001   |
| 1985-9                                    | 3540                            | 459                  | 1.48 (1.25 to 1.76)    |          | 1.44 (1.21 to 1.72)   |          |
| 1990-4                                    | 5915                            | 780                  | 1.53 (1.31 to 1.80)    |          | 1.52 (1.29 to 1.79)   |          |
| 1995-9                                    | 9409                            | 1946                 | 2.37 (2.03 to 2.75)    | <0.001   | 2.34 (2.00 to 2.73)   | <0.001   |
| Charlson comorbidity index score:         |                                 |                      |                        |          |                       |          |
| 0                                         | 9511                            | 1719                 | 1.00‡                  | <0.001   | 1.00                  | <0.001   |
| 1-2                                       | 10,220                          | 2396                 | 1.46 (1.38 to 1.56)    |          | 1.30 (1.22 to 1.38)   |          |
| 3-4                                       | 2262                            | 579                  | 1.86 (1.69 to 2.04)    |          | 1.42 (1.29 to 1.57)   |          |
| 5-6                                       | 563                             | 151                  | 2.82 (2.38 to 3.33)    |          | 2.04 (1.72 to 2.42)   |          |
| ≥7                                        | 936                             | 211                  | 3.10 (2.68 to 3.58)    | <0.001   | 1.71 (1.46 to 1.99)   |          |

TSI=Torres Strait Islander.
*Test for trend or standard P value across quantitative or ordinal quantitative variables.
†Estimates from Cox regression model included terms for age (continuous), sex (female, male), indigenous status (non-Aboriginal, Aboriginal), residence (regional/rural area, metropolitan), admission type (elective, emergency), type of hospital attended (public, private, other), length of stay (continuous), socioeconomic disadvantage (fifths), calendar period of ADR (continuous), Charlson comorbidity index score (continuous), and drug categories responsible for first time ADR.
‡Reference category.
Table 5 | Adjusted hazard ratios (HR) with 95% confidence intervals for repeat adverse drug reactions (ADRs) for Charlson comorbidity at first admission to hospital for ADR in older adults

| Comorbid conditions                 | No (%) with first time ADR only | No (%) with repeat ADR | Adjusted HR (95% CI)* | P value† |
|-------------------------------------|---------------------------------|------------------------|------------------------|----------|
| Congestive cardiac failure          | 3858 (16.4)                     | 889 (17.6)             | 1.56 (1.43 to 1.71)    | <0.001   |
| Peripheral vascular disease         | 978 (4.2)                       | 196 (3.9)              | 1.27 (1.09 to 1.48)    | <0.01    |
| Chronic pulmonary disease           | 1537 (6.5)                      | 497 (9.8)              | 1.61 (1.45 to 1.79)    | <0.001   |
| Rheumatological disease             | 622 (2.6)                       | 210 (4.2)              | 1.65 (1.41 to 1.92)    | <0.001   |
| Mild liver disease                  | 164 (0.7)                       | 35 (0.7)               | 1.48 (1.05 to 2.07)    | 0.03     |
| Diabetes (mild to moderate)         | 2276 (9.7)                      | 531 (10.5)             | 1.18 (1.07 to 1.30)    | <0.01    |
| Diabetes with chronic complications | 507 (2.2)                       | 248 (4.9)              | 1.91 (1.65 to 2.22)    | <0.001   |
| Renal disease                       | 1045 (4.4)                      | 373 (7.4)              | 1.93 (1.71 to 2.17)    | <0.001   |
| Any malignancy including lymphoma and leukaemia | 2538 (10.8)                  | 811 (16.0)             | 1.87 (1.68 to 2.09)    | <0.001   |
| Moderate or severe liver disease    | 89 (0.4)                        | 19 (0.4)               | 1.85 (1.18 to 2.92)    | <0.01    |
| Metastatic solid tumour             | 1245 (5.3)                      | 273 (5.4)              | 2.25 (1.92 to 2.64)    | <0.001   |
| Cerebrovascular disease             | 1601 (6.8)                      | 226 (4.5)              | 0.85 (0.73 to 0.98)    | 0.02     |
| Dementia                            | 791 (3.4)                       | 77 (1.5)               | 0.62 (0.49 to 0.78)    | <0.001   |
| Hemiplegia or paraplegia            | 762 (3.2)                       | 102 (2.0)              | 0.73 (0.59 to 0.89)    | <0.01    |
| Myocardial infarction               | 1332 (5.7)                      | 224 (4.4)              | 0.98 (0.84 to 1.13)    | 0.73     |
| Peptic ulcer disease                | 1847 (7.9)                      | 298 (5.9)              | 1.09 (0.95 to 1.25)    | 0.24     |
| AIDS                                | 3 (0.1)                         | 2 (0.1)                | 1.65 (0.41 to 6.71)    | 0.48     |

*Estimates from Cox regression models included terms for age (continuous), sex (female, male), Indigenous status (non-Aboriginal, Aboriginal), residence (regional/rural area, metropolitan), admission type (elective, emergency), type of hospital attended (public, private, other), length of stay (continuous), socioeconomic disadvantage (fifths), calendar period of ADR (continuous), and drug categories responsible for first-time ADR. †For hazard ratio (HR), using patients with absent comorbidity as reference category.

Strengths and limitations

There are several potential explanations for the observed importance of comorbidity. Comorbidity might increase vulnerability to ADRs by impairing body systems—for example, cardiovascular, pulmonary, renal, and hepatic insufficiency can cause changes in pharmacokinetics and pharmacodynamics. There might be increased opportunity for drug interactions because of polypharmacy for multiple morbidities. Finally, Berkson’s bias—that is, ADRs are more likely to be identified and diagnosed because of comorbid conditions increasing a person’s contact with the health system. A reduced risk of repeat ADRs associated with admission to private hospital might be explained by private patients having generally better health or being socioeconomically advantaged and having stronger social supports. This latter theory, however, is inconsistent with the direct measure of least socioeconomic disadvantage used in this study, which had no effect (hazard ratio 0.94, 0.87 to 1.02).

An important limitation of the study was the absence of data in the hospital morbidity data system on specific drug doses and multiple drug regimens. Nevertheless, we did have information on the drug category primarily responsible for ADRs. We assessed the effect of each drug category by comparing it with the average risk of a repeat ADR from the 20 drug categories responsible for first time ADRs. Hormones, primarily systemic agents, and bacterial vaccines were associated with higher than average risks of repeat ADR, although the numbers in the bacterial vaccines group was small. The higher risk of repeat ADRs from hormones and primarily systemic agents (which include anti-neoplastic drugs) was expected as severe side effects of these drugs are well known. We examined the diagnoses in patients who had first time ADRs caused by bacterial vaccines and found that nearly 38% of these patients had malignant diseases treated with bacillus Calmette-Guerin (BCG) vaccine or other vaccine based immunotherapy. Hence, the increased effect on repeat ADRs observed in the category of bacterial vaccines was probably caused by the concomitant use of antineoplastic agents (part of “primarily systemic agents”). The age standardised rates of all cancers for males and females in 2005 were 356.1 and 260.9 per 100 000 person years, based on a publication from the Western Australia cancer registry. Hence, men have a higher incidence of cancer than women in Western Australia, which might explain the observed higher risk of repeat ADRs in men.

The risk of adverse drug effects might increase with increasing drug dose. Although we did not have specific data on drug dose for individuals in our population dataset, we investigated the extent to which doses were prescribed within the normal limits set by the manufacturers as documented in the Monthly Index of Medical Specialties (MIMS-Australia), a database containing approved product information from manufacturers for medicines used in Australia. We obtained data on pharmacy dispensing of drugs for discharge and outpatients for the year 2000 from the...
The strengths of our study include the cohort design with population based and audited data of high quality,\textsuperscript{17} thus overcoming issues related to selection and recall biases as well as loss to follow-up. Loss to follow-up would have been small as interstate migration occurred in only 3.5% of residents in Western Australia. Analysis of prescribed doses for these drugs showed that nearly all (99.6%) were within the range recommended by the manufacturer as recorded in MIMS Australia.\textsuperscript{34}

The diagnosis of an ADR was made by senior hospital doctors (consultants and registrars) and junior doctors recorded them in text on a structured hospital separation abstract. This step in the process was subject to diagnostic error at a level that is usual in clinical practice. The second step in the process involved clinical coders who are trained in the use of the ICD AM coding manuals (for different time periods). This coding the text, including external causes or contributing factors, using the ICD-9, ICD-9-CM, or ICD-10-AM coding manuals (for different time periods). This was performed in each of the hospitals by qualified clinical coders who are trained in the use of the ICD codes and were able to obtain additional information from the medical notes as required. The accuracy of

## Table 6 | Adjusted hazard ratios (with 95% confidence intervals) of repeat adverse drug reactions (ADRs) for primary drug category responsible for first time ADRs in older adults

| Drug category* | No (%) with first time ADR only | No (%) with repeat ADR | Adjusted HR (95% CI)‡ | P value‡ |
|---------------|-------------------------------|------------------------|-----------------------|---------|
| E930/Y40 Systemic antibiotics§ | 2249 (9.6) | 423 (8.4) | 0.81 (0.45 to 1.50) | 0.53 |
| E931/Y41 Other systemic anti-infectives/antiparasitics | 365 (1.6) | 65 (1.3) | 1.02 (0.80 to 1.30) | 0.89 |
| E932/Y42 Hormones (including synthetic and antagonists) | 1649 (7.0) | 525 (10.4) | 1.51 (1.34 to 1.69) | <0.001 |
| E933/Y43 Primarily systemic agents | 1456 (6.2) | 666 (13.2) | 2.12 (1.89 to 2.38) | <0.001 |
| E934/Y44 Agents primarily affecting blood constituents | 1980 (8.4) | 452 (8.9) | 0.93 (0.82 to 1.05) | 0.23 |
| E935/Y45 Analgesics/antipyretics/anti-inflammatory drugs | 4006 (17.1) | 688 (13.6) | 0.76 (0.68 to 0.84) | <0.001 |
| E936/Y46 Antiepileptics/antiparkinsonian drugs | 903 (3.8) | 218 (4.3) | 1.13 (0.97 to 1.32) | 0.12 |
| E937/Y47 Sedatives, hypnotics, anxiolytic drugs | 356 (1.5) | 50 (1.0) | 0.74 (0.56 to 0.97) | 0.03 |
| E938/Y48 Anaesthetics, therapeutic gases | 372 (1.6) | 42 (0.8) | 0.52 (0.39 to 0.71) | <0.001 |
| E939/Y49 Psychotropic drugs§ | 1266 (5.4) | 268 (5.3) | 0.96 (0.83 to 1.11) | 0.56 |
| E940/Y50 Central nervous system stimulants | 15 (0.1) | 3 (0.1) | 0.76 (0.26 to 2.22) | 0.61 |
| E941/Y51 Drugs primarily affecting autonomic nervous system§ | 377 (1.6) | 99 (2.0) | 0.87 (0.71 to 1.07) | 0.18 |
| E942/Y52 Agents primarily affecting cardiovascular system | 4702 (20.0) | 874 (17.3) | 0.93 (0.84 to 1.04) | 0.21 |
| E943/Y53 Agents primarily affecting gastrointestinal system | 220 (0.9) | 32 (0.6) | 0.64 (0.46 to 0.90) | 0.01 |
| E944/Y54 Agents affecting water balance/minerals/uric acid metabolism§ | 1703 (7.2) | 321 (6.4) | 0.99 (0.86 to 1.13) | 0.96 |
| E945/Y55 Agents affecting muscle/respiratory system | 490 (2.1) | 73 (1.4) | 1.01 (0.80 to 1.27) | 0.96 |
| E946/Y56 Topical agents affecting skin, ENT, dental | 496 (2.1) | 81 (1.6) | 0.86 (0.69 to 1.07) | 0.18 |
| E947/Y57 Other and unspecified drugs and medicines | 824 (3.5) | 158 (3.1) | 1.02 (0.86 to 1.21) | 0.80 |
| E948/Y58 Bacterial vaccines | 9 (<0.1) | 7 (0.1) | 4.06 (2.00 to 8.26) | <0.001 |
| E949/Y59 Other and unspecified vaccines/biologicals | 54 (0.2) | 11 (0.2) | 0.96 (0.54 to 1.69) | 0.88 |

*See table 1 for more explicit specifications of ICD-9/ICD-9-CM and ICD-10-CM code definitions.

†P value for each drug category responsible for first time ADR compared with overall effect of drug categories.

§See table 1 for details of modification in drug category between coding systems.
Adverse drug reactions (ADRs) are a major public health problem in older populations. Repeat ADRs leading to hospital admission have increased at a greater rate than first time ADRs in older adults and by 2003 in Western Australia they had reached 30% of all ADRs. Little information is available on risk factors that predict repeat ADRs.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Comorbid congestive cardiac failure, diabetes, peripheral vascular, chronic pulmonary, hepatic, renal, rheumatological, and malignant diseases predict readmission for ADRs. Comorbid cerebrovascular disease, dementia, and paraplegia seem to protect against repeat ADRs, possibly because such patients are under closer healthcare supervision.

**WHAT THIS STUDY ADDS**

Clinical coding (including E codes) is routinely checked by coding supervisors as well as by random internal audits.

We found that older adults who experienced an ADR during the most recent study period, 1995-9, had a 2.4-fold greater risk of recurrence than their counterparts in 1980-4. As the study was longitudinal, we need to consider the influence of factors that changed with time. The results are consistent with national drug consumption data that showed an increase in drug exposure in older Australians of 4.7% during 2000-1 alone. This increase greatly exceeded population growth, suggesting either a larger population at risk or a higher average level of drug exposure per patient. Our results, derived from population level data, suggest that there exists a strong temporal correlation between repeat ADRs in older adults and greater use of drugs in the community generally. While efforts to improve the coding of ADRs in hospital morbidity data systems during the observation period might have contributed to some of the observed rise in admissions for ADRs, an earlier validation study in Western Australia, involving a review of hospital charts, found a real increase in hospital morbidity caused by ADRs from 1980 to 1991.

**Conclusions**

This population based cohort study found that comorbidity and not advancing age predicted repeat admission for ADRs in patients aged over 60. Comorbid congestive cardiac failure, peripheral vascular, chronic pulmonary, rheumatological, hepatic, renal, and malignant diseases, and diabetes were the comorbid conditions most likely to predict readmission for ADRs from the therapeutic use of drugs. An apparent preventive effect was observed with comorbid cerebrovascular disease, dementia, and hemiplegia or paraplegia, possibly because such patients are under more consistent healthcare supervision. Careful and frequent monitoring of prescribed drugs in older adults with at risk comorbidities might prevent readmissions for ADRs. Evaluation of monitoring programmes delivered by local pharmacists, community nurses, and general practitioners might be the next step towards prevention.

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