Use of case-time-control design in pharmacovigilance applications: exploration with high risk medications and unplanned hospital admissions in the Western Australian elderly

Running head: High risk drugs and hospital admissions in elderly

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Key points:

- The linkage of pharmaceutical claims with inpatient and other health records has allowed this study to assess the strength of association between exposure to high risk medications and unplanned hospitalisations using a case-time-control design and to derive preliminary estimates of hospitalisations attributable to this exposure.
- Previous studies using ICD external cause codes on inpatient summaries appear to have underestimated hospitalisations due to adverse drug effects when compared with results based on our methodological approach, especially for opioids and corticosteroids.
- Although our method also has its limitations, in combination with other established mechanisms, it shows great potential in helping to identify individual 'problem' drugs as part of a post-marketing pharmacovigilance monitoring system in Australia and elsewhere.

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SUMMARY

Purpose: To use a case-time-control design to derive preliminary estimates of unplanned hospitalisations attributable to suspected high risk medications in elderly Western Australians.

Methods: Using pharmaceutical claims linked to inpatient and other health records, the study applied a case-time-control design and conditional logistic regression to estimate odds ratios (ORs) for unplanned hospital admissions associated with anticoagulants, antirheumatics, opioids, corticosteroids and four major groups of cardiovascular drugs. Attributable fractions (AFs) were derived from the ORs to estimate the number and proportion of admissions associated with drug exposure. Results were compared with those obtained from a more conventional method using International Classification of Diseases (ICD) external cause codes to identify admissions related to adverse drug events.

Results: The study involved 1,899,699 index hospital admissions. Six of the eight drug groups were associated with an increased risk of unplanned hospitalisation, opioids (adjusted OR=1.81, 95% CI 1.75-1.88; AF=44.9%) and corticosteroids (1.48, 1.42-1.54; 32.2%) linked with the highest risks. For all six, the estimated number of hospitalisations attributed to the medication in the exposed was higher (two to 31-fold) when derived from the case-time-control design compared with identification from ICD codes.

Conclusions: This study provides an alternative approach for identifying potentially harmful medications and suggests that the use of ICD external causes may underestimate adverse drug events. It takes drug exposure into account, can be applied to individual medications and may overcome under-reporting issues associated with conventional methods. The approach shows great potential as part of a post-marketing pharmacovigilance monitoring system in Australia and elsewhere.

INTRODUCTION

Adverse drug events (ADEs) are a major cause of hospitalisation, especially in the elderly.[1-3] In Australia, some 15-22% of unplanned hospital admissions in people aged ≥65 years are drug-related.[4] In the United States, ADEs account for nearly 100,000 emergency hospitalisations each year in this age group.[5]

Different approaches exist for estimating medication harm resulting in hospitalisation, such as medical record reviews,[6-12] analysis of spontaneous reporting data,[13-19] and identification of ADE-related codes from the International Classification of Diseases (ICD) on inpatient records.[20-26] Some of these methods are labour-intensive while others are subject to under-reporting and selection bias.[6,20,26-31]

Ideally, assessment of ADE-related hospitalisation needs to consider drug exposure upon admission and the likelihood that exposure effects may have contributed to the cause of hospitalisation. Until recent years, it has been difficult to achieve this in Australia at a population level due to the segregation of pharmaceutical claims data from hospital inpatient records. Linkage of records from these and other sources through the Western Australian Data Linkage System (WADLS)[32,33] has facilitated this process, permitting the development of an alternative approach for obtaining preliminary estimates of unplanned hospitalisations attributable to drug exposure.

This paper describes the use of this approach applied to medication groups previously reported to be associated with a high rate of ADE-related hospitalisations in Western Australian (WA) elderly people.[21,34,35] The results are compared with those obtained from the identification of ADE-related ICD codes on inpatient summary records.

METHODS

Data linkage and study cohort selection

This study linked Australian Pharmaceutical Benefits Scheme (PBS),[36,37] Medicare Benefits Scheme (MBS)[38,39] and System for Payment of Aged Residential Care (SPARC)[40] data with inpatient, death and electoral roll records from the WADLS[32,33] through probabilistic linkage. The research protocol was approved by the University of Western Australia's Human Research Ethics Committee.

The selection of participants is outlined in Figure 1. The cohort was restricted to people who were ≥65 years old by the end of 2004, continuously lived in WA during 1993-2005 (until death) and had at least one PBS prescription dispensed during that time. These criteria ensured that those included in the study had ascertainable drug exposures. People with problem data (e.g. records post-death, no gender on any record) were excluded, following an extensive cross-validation process. The final study group comprised 74.3% of the source population.

INSERT FIGURE 1 HERE

Establishment of drug reference database

Details of all PBS items were assembled into a reference database from schedules published between August 1991 and June 2007.[41] Relevant prescription information was extracted from the last published entry for each item. Anatomical Therapeutic Chemical (ATC) codes were reconciled with the 2007 World Health Organization (WHO) ATC classification.[42,43]

Because PBS claims did not include the prescribed dose, average daily doses for each item were determined from comparisons between average prescribed daily doses obtained from the Australian Bettering the Evaluation and Care of Health (BEACH)[44-46] data, the Australian MIMS[47-49] registered drug information and the 2008 WHO ATC Defined Daily Doses (DDDs)[50,51] corresponding to the drug form and route. Precedence was given to the most appropriate information applicable to older Australians. Furthermore, each drug's elimination half-life was obtained (predominantly from MIMS),[47-49] from which the period of drug effect, defined as five times the drug's half-life,[52,53] was estimated.

Once finalised, drug reference variables were merged to PBS records to facilitate data analysis.

Definition of high risk drug groups and domains

Previous studies of the WA elderly,[21,34,35] which used ICD external cause codes (ecodes) from inpatient records, associated the following drugs with a high rate of ADE-related hospitalisation: anticoagulants, cytotoxics, antirheumatics, corticosteroids, opioids and cardiovascular agents. All were included in this study except cytotoxics, which are predominantly administered in WA public hospitals for

which prescriptions were not recorded in the PBS data. Cardiovascular agents were further expanded to include hypertension drugs, cardiac rhythm regulators, beta-blockers and serum lipid reducing agents.

ATC code definitions for each of these high risk medication groups are presented in Table 1. The table also includes ATC definitions for associated study domains, which consisted of broad classes of medications used to treat similar conditions to those treated by each high risk drug group.

INSERT TABLE 1 HERE

Case-time-control design

Associations between high risk medications and unplanned hospitalisations were expressed as odds ratios (ORs) estimated from a case-time-control design.[54,55] This approach involved case distribution analysis in which index subjects acted both as cases and as their own historical controls, while background time trends in predisposition to exposure due to ageing, natural disease progression and treatment patterns were adjusted using similarly constructed case and control observation windows in a reference group drawn from the same general domain of patients as the index subjects. The reference subjects essentially played the role of 'negative controls' in this design. In this instance, the patient domain for each drug group included everyone in the study cohort who had ever been prescribed a medication from the associated list under "ATC Domain Definition" in Table 1 during 1993-2005.

Index subjects were patients within the drug domain who had experienced an unplanned hospital admission between 1 July 1994 and 31 December 2005 whilst aged ≥67 years, thus ensuring sufficient lead-up time for the control observation period. Many individuals were included in the analysis as multiple index subjects, although those with >50 index admissions were excluded due to concerns about representativeness. Two records were created for each index subject, one representing the 'case time' (i.e. the admission date) and the other the 'control time' (usually 365 days prior). In 2-3% of subjects, where the patient was in hospital at this preferred control time, the admission date of that earlier hospitalisation was used as control time instead.

Each index subject was matched by gender, general practitioner (GP) coverage category (based on the proportion of days with GP coverage over the entire study

period), and year of birth to a randomly selected reference subject from the sub-study's domain. Each GP visit identified in the MBS dataset was allocated a 'coverage' period of 61 days, overlapping and adjacent periods for each patient being merged together. Subjects born prior to 1900 were allocated a notional year of birth of 1900 for matching purposes only. 'Case time' and 'control time' records were created for each reference subject as per the index subjects, matching the case and control dates of corresponding index subjects as closely as possible.

Once created, the case and control time records for index and reference subjects were populated with the variables required for analysis, including nursing home status at the time specified on the record (i.e. case or control time); number of hospital days, overall Charlson comorbidity index[56] and GP coverage percentage, all based on the one-year period prior to the specified time; and a drug consumption profile for the period covering the 90 days preceding the specified time (plus the specified date itself), which included the number of broad medication categories involved, the overall number of daily doses consumed (for any drug) and a count of daily doses for each broad drug category. For the Charlson index and GP coverage percentage, the one-year period included the case or control date, but that day was excluded from calculations of hospital days.

Additionally, PBS records were checked to ascertain exposure status at each case and control date. If a prescription was found for a relevant high risk drug and if the time period bound by its supply date and exposure effect end date overlapped with the case or control time, the exposure status was set to 'exposed'. The end date was calculated by adding the number of drug consumption days associated with the script to the supply date (-1) plus the period of drug effect (up to seven days) and a seven-day latency period. Thus, the exposure status indicated the potential for a hospital admission at the case or control time to have resulted from the effects of high risk drug exposure.

For each high risk drug sub-study, conditional logistic regression models with robust analysis of variance were applied using the SAS PHREG procedure (i.e. stratified Cox proportional hazard regression), with the COVS option and stratification based on a unique identifier for each subject.[57] The baseline model included the binary exposure variable and the cross-product between exposure and the binary index/reference indicator. The OR of primary interest was derived from the

coefficient of this interaction term, which represented the association between exposure and unplanned hospitalisation in the index subjects, over and above apparent time-trend effects that applied to both index and reference subjects.[54] The adjusted model controlled for all health and drug consumption indicators mentioned earlier, except for the three-month count of daily doses for the drug group of interest.

Estimation of unplanned hospitalisations related to drug group

Using the OR derived from the interaction term in the adjusted model described above, it was possible to calculate the attributable fraction (AF) of unplanned hospitalisations associated with each high risk drug group within the exposed, where AF=(OR-1)/OR. The estimate of unplanned hospital admissions attributed to each drug group was then derived as AF times the number of exposed index subjects.[58-60]

Identification of ADE-related hospitalisations from ICD ecodes

For comparison, the count of ADE-related unplanned hospitalisations in cohort members considered exposed to each high risk drug group was determined based on relevant ICD ecodes for accidental drug poisoning and adverse drug reactions[61,62] recorded on inpatient summaries, as per Table 2. These derivations more closely reflected the conventional approach for identifying ADE-related hospitalisations using inpatient data. However, other studies would not usually restrict their admission counts to exposed patients as most often exposure status is not readily available.

INSERT TABLE 2 HERE

RESULTS

Table 3 presents results for each high risk drug group under investigation. The number of people involved from each sub-study domain ranged between 39,596 (cardiac rhythm regulators) and 193,196 (opioids). Overall, 1,899,699 unplanned admissions ('index subjects') were included, each sub-study yielding 128,241-358,570 admissions, which were associated with 29,919-108,513 patients. Around 45-46% of index subjects were male and the mean age was 78-79 years. The proportion of index subjects considered exposed to a medication of interest at the time of admission ranged from 12-13% (anticoagulants and opioids) to 57% (hypertension drugs).

INSERT TABLE 3 HERE

Both the unadjusted and adjusted ORs were below one for hypertension and serum lipid reducing medications, suggesting that these drugs may have had an overall protective effect against unplanned hospitalisations. The corresponding ORs for the other high risk drug groups (after adjustment for health indicators and medication use) ranged between 1.08 (95% CI 1.05-1.11) for beta-blockers and 1.81 (1.75-1.88) for opioids. Most adjusted ORs were lower than the corresponding unadjusted ORs.

For high risk drug groups with OR>1, the proportion of unplanned admissions attributed to the medication in exposed subjects ranged from 7.4% (beta-blockers) to 32.2% (corticosteroids) and 44.9% (opioids). This represented 20,539 (19,572-21,477) unplanned admissions associated with opioids alone, an average of 1,786 per year.

By contrast, for drug groups with OR>1, the number and proportion of unplanned ADE-related hospitalisations in exposed index subjects were lower when determined from ICD ecodes than corresponding values derived using the OR/AF approach (Figure 2). For corticosteroids and opioids they were 19- and 31-fold lower, respectively. Obviously, this did not apply to the two medication groups that appeared to have an overall protective effect against unplanned hospitalisations.

INSERT FIGURE 2 HERE

Given the magnitude of our ORs for opioids and corticosteroids, we sought to investigate further whether residual confounding effects might partially explain our results for these two drug groups. This involved the decomposition of our case-time-control design into its various components; inclusion of more explicit Charlson index covariates in our models; stratification by cancer status; and sensitivity analysis using other medications. The decomposition process showed the independent effects on our results of each confounding control measure already included in our adjusted models, whereas model variations attempted to isolate potential confounding effects due to drug indication (e.g. reverse causation bias). Results of our investigations (Table 4) were unable to demonstrate any substantial residual confounding due to indication.

INSERT TABLE 4 HERE

DISCUSSION

This study applied an alternative approach for deriving estimates of unplanned hospital admissions attributable to medication exposure, using existing methodologies and linked health data. Unlike the more conventional method, which relies on the presence of ICD ecodes on inpatient summaries, this approach took patients' drug exposure status upon admission into account. Although applied to broad ICD categories in this instance for comparative purposes, the methods presented are intended for use with individual medications.

A strength of the study is its large sample sizes and thus narrow confidence intervals. Nearly two million index admissions were included, each sub-study comprising well over 100,000. This is considerably more than is generally reported from ADE studies involving medical record reviews, for instance.[6-12]

Most ORs derived from the case-time-control models without adjustment for health indicators were higher than corresponding adjusted ORs. Furthermore, adjusted ORs obtained from the equivalent case-crossover design[63] involving only the index subjects (not shown) were also generally higher than those from the case-time-control design. This was expected, as both the health status adjustments and the use of case-time-control reference subjects sought to adjust for increasing disease severity and other sources of time trend bias, which became associated with drug exposure whilst independently predicting the effect (i.e. unplanned hospitalisation).[54]

The attributable fractions in the exposed (7.4%-44.9%) from our analysis of high risk drug groups seem plausible given that several previous studies based on medical record reviews have produced overall estimates of 15-22% for the proportion of unplanned hospitalisations that were drug-related in Australians aged ≥65 years.[4] Similarly, a meta-analysis involving 17 studies of elderly patients from various countries (all but two involving people aged ≥65 years) estimated that 16.6% were hospitalised due to adverse drug reactions.[2]

We expected that, in general, results based on the OR/AF method would yield higher estimates than corresponding statistics derived from ICD ecodes, mainly because ADEs may not always be recorded on inpatient summaries.[20,21,34] This may occur because presenting symptoms are not readily linked to harmful drug effects or, even

when identified as ADEs by clinicians, due to incomplete patient notes or omissions by clinical coders. Our results support this hypothesis.

However, in some instances, the difference between the two methods was not as pronounced as anticipated. The likely explanations are two-fold. Firstly, the ADE counts obtained from ICD ecodes included ADEs that occurred during the hospital stay. Restriction of index admissions to unplanned hospitalisations minimised this to some extent but not entirely. Consequently, despite the likely under-reporting of ADEs through ecodes, our ICD results were inflated by a number of hospitalisations for which the ADE was not the actual cause of admission. Although recent clinical coding amendments in WA now distinguish between pre- and post-admission ADEs,[64] these were not in place during the study period.

Conversely, the figures obtained using the OR/AF method were net estimates of unplanned hospitalisations attributable to ADEs, over and above beneficial therapeutic effects that may have prevented some hospitalisations. In other words, for drugs that also have preventive effects, the OR/AF approach may yield lower counts than the true number of ADE-caused hospitalisations. In fact, for hypertension and lipid reducing medications, it appears that, for the study period at least, the prevention of unplanned hospital admissions may possibly have outweighed the corresponding harm associated with ADEs, highlighting the likely strong preventive value of these drugs. However, it is possible that, in some instances, these medications were purposely discontinued with the development of a serious illness that eventually resulted in an unplanned hospitalisation, giving the false impression that the withdrawn medication was the cause of the subsequent hospital stay. Study limitations prevented us from examining this issue in any more detail.

Our findings also indicate that corticosteroids and opioids are associated with a particularly high risk of unplanned hospitalisations in the WA elderly. We sought to identify whether our estimates for these two drug groups might be affected by unadjusted confounding (especially in relation to reverse causation bias), but were unable to find any strong evidence in support of this premise. However, we acknowledge that our investigations were constrained by study limitations, and suspect that some of the apparent hospitalisation burden attributed to opioid and

corticosteroid exposure was likely due to the condition being treated rather than the drug itself.

For these two drug groups, the risk derived from our OR/AF approach appears substantially (19- and 31-fold) higher than that suggested by the identification of ADE-related hospitalisations from ICD ecodes. Corticosteroids and opioids have a wide range of side effects with multiple causes, making it difficult to establish a connection between drug use and presenting symptoms. Consequently, ADEs are less likely to be recorded for resulting hospitalisations. Corticosteroid ADEs may manifest as mental disturbances, infections, hypertension-related conditions and endocrine disorders (potentially leading to fractures and diabetes), whereas common opioid side effects include dizziness and drowsiness (which may cause falls and injuries), as well as nausea, constipation and other gastrointestinal complaints.[48] Our results suggest that clinicians need to be more aware of the potential for these drugs to increase unplanned hospital admissions for a range of seemingly obtuse reasons.

In comparison, the gap between corresponding ADE hospitalisation estimates for anticoagulants was considerably smaller (only two-fold). This is possibly due to the more conspicuous nature of ADE symptoms for this drug group (e.g. bleeding) or to clinicians' greater awareness of associated risks, not least because anticoagulant activity has been routinely monitored and 'overdose' readily confirmed from laboratory tests.[65,66]

The adopted case-time-control design seems appropriate for our study in which drug exposures varied over time and related outcomes (i.e. unplanned hospitalisations) were acute in nature. However, one should be mindful of the inherent assumptions and conditions associated with this design,[54,55,67] especially in relation to potential time trend bias. To minimise this source of error, we adjusted for each subject's health status and overall drug consumption over time using a number of relevant variables. This was facilitated by the availability of a fairly comprehensive health profile for each individual, made possible through record linkage. The reference subjects' inclusion further controlled for time-dependent confounders for which adequate measures were unavailable. These measures are not perfect though. In particular, they are unable to fully control for reverse causation bias, which may have affected our results. Additionally, for drugs recently introduced on the market, it may be more difficult to control for exposure trends using reference subjects, as uptake

may be faster in patients with more severe conditions (i.e. index subjects who are hospitalised) than in a general reference group.

The study results were also constrained by limitations of the administrative health data. Difficulties in the ascertainment of drug exposure at the specific times of interest were of particular concern. No data were available on the daily dose prescribed for each dispensed drug or on patient compliance. Much attention was devoted to the derivation of exposure status from average recommended daily doses but this could not have been completely accurate for every subject. Nonetheless, given the study size, we expect that sufficient numbers abided by average drug consumption patterns to yield adequate results. In any event, since there is no reason to suspect that exposure misclassification would have been different at 'case time' compared with 'control time' for a given subject (i.e. non-differential measurement error), estimated ORs would likely have been attenuated (i.e. pushed towards null) should exposure measurement issues have affected the outcome.[68]

Additionally, results may have been affected by the accuracy, completeness and coverage of the data from each source, the quality of the record linkage, and the availability of relevant data items. Every effort was made to improve data quality through extensive cross-validations between sources, to exclude subjects for whom information appeared problematic and to obtain appropriate proxy measures where necessary for data items of particular interest. The WADLS is a well-established record linkage facility.[32,33] Thus, the quality of the record links was likely very good. Nonetheless, our findings should be considered suggestive rather than conclusive until supported by other high-quality studies, especially ones that can more adequately control for potential confounding associated with reverse causation bias.

The prototype developed through this research, assisted by continued improvements in the quality, coverage and linkage of related data sources, should help guide the development of ongoing pharmacovigilance initiatives in Australia and potentially elsewhere. Such a system on its own may not provide full details of medication harm, but should be a valuable tool for monitoring potentially serious ADEs, in combination with other existing mechanisms. In particular, the demonstrated approach could help identify ADE 'hot spots', ensuring that more extensive post-marketing investigations are better targeted towards medications of greatest concern.

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Table 1 Definition of high risk drug groups and associated domains based on the 2007 WHO ATC classification[#]

High Risk Drug Group	ATC Drug Group Definition		ATC Domain Definition[†]	
Anticoagulants	B01AA	Vitamin K antagonists (including warfarin)	B01	Antithrombotic agents
	B01AB	Heparin group		
Antirheumatic/antiinflammatory drugs (excluding corticosteroids and salicylates)	M01	Antiinflammatory and antirheumatic products	M01	Antiinflammatory and antirheumatic products
Opioids and related narcotics (excluding methadone and heroin)	N02A	Opioids (excluding methadone; including therapeutic heroin (i.e. diamorphine), but drug is not available in Australia)	N02	Analgesics
Corticosteroids (systemic)	H02A	Corticosteroids for systemic use, plain	H02A	Corticosteroids for systemic use, plain
	M01BA	Antirheumatics with corticosteroids	M01BA	Antirheumatics with corticosteroids
Hypertension medications (excluding diuretics other than low-ceiling, beta-blocking agents and peripheral vasodilators)	C01D	Vasodilators used in cardiac diseases	C01D	Vasodilators used in cardiac diseases
	C02	Antihypertensives	C02	Antihypertensives
	C03A/B/EA	Low-ceiling diuretics, including thiazides	C03A/B/EA	Low-ceiling diuretics, including thiazides
	C08	Calcium channel blockers	C08	Calcium channel blockers
	C09	Agents acting on the renin-angiotensin system	C09	Agents acting on the renin-angiotensin system
			C07B-E	Beta-blocking agents with antihypertensives
Cardiac rhythm regulators (including cardiac glycosides, excluding beta-blockers)	C01A	Cardiac glycosides	C01A	Cardiac glycosides
	C01B	Antiarrhythmics, Class I & III	C01B	Antiarrhythmics, Class I & III
Beta-blockers	C07	Beta-blocking agents	C07	Beta-blocking agents
Serum lipid reducing agents	C10	Lipid modifying agents	C10	Lipid modifying agents

 # Code definitions are based on the World Health Organization's Anatomical Therapeutic Chemical classification of therapeutic drugs (2007 edition)[42,43]

† Drugs within each domain definition are those used to treat similar conditions to those included in the definition for the corresponding high risk drug group; individuals from the study cohort who were prescribed medications from a given domain definition were considered part of the 'domain' (sub-study cohort) for the related high risk drug sub-study (i.e. they were considered to be part of the sub-study's population at risk).

Table 2 International Classification of Diseases codes (Australian ICD-9-CM[61] and ICD-10-AM[62] editions) for all causes that could potentially identify accidental poisoning or ADR due to medications within each high risk drug group

High Risk Drug Group	ICD-9-CM External Cause (Accidental Poisoning or ADR)		ICD-10-AM External Cause (Accidental Poisoning or ADR)	
Anticoagulants	E858.2	Poisoning - Agents primarily affecting blood	X44	Poisoning - Other and unspecified drugs/medicaments
	E934.2	ADR - Anticoagulants	Y44.2	ADR - Anticoagulants
Antirheumatic/antiinflammatory drugs (excluding cortico-steroids and salicylates)	E850.6	Poisoning - Antirheumatics	X40	Poisoning - Nonopioid analgesics, antipyretics, antirheumatics
	E935.6	ADR - Antirheumatics	Y45.2	ADR - Propionic acid derivatives
			Y45.3	ADR - Other nonsteroidal antiinflammatory drugs
			Y45.4	ADR - Antirheumatics
Opioids and related narcotics (excluding methadone and heroin)	E850.2	Poisoning - Other opiates and related narcotics	X42	Poisoning - Narcotics and psychodysleptics, NEC
	E935.2	ADR - Other opiates and related narcotics (both codes exclude methadone and heroin)	Y45.0	ADR - Opioids and related analgesics (both codes include methadone and heroin)
Corticosteroids (systemic)	E858.0	Poisoning - Hormones and synthetic substitutes	X44	Poisoning - Other and unspecified drugs/medicaments
	E932.0	ADR - Adrenal cortical steroids	Y42.0	ADR - Glucocorticoids and synthetic analogues
			Y54.0	ADR - Mineralocorticoids
Hypertension medications (excluding diuretics other than low-ceiling, beta-blockers and peripheral vasodilators)	E858.3	Poisoning - Agents affecting cardiovascular system	X43	Poisoning - Other autonomic nervous system drugs
	E858.5	Poisoning - Water, mineral, uric acid metabolism drugs	X44	Poisoning - Other and unspecified drugs/medicaments
	E942.0	ADR - Cardiac rhythm regulators	Y51.2	ADR - Ganglionic blocking drugs, NEC
	E942.3	ADR - Ganglion-blocking agents	Y52.1	ADR - Calcium channel blockers
	E942.4	ADR - Coronary vasodilators	Y52.2	ADR - Other antidysrhythmic drugs, NEC
	E942.6	ADR - Other antihypertensive agents	Y52.3	ADR - Coronary vasodilators, NEC
	E944.3	ADR - Saluretics	Y52.4	ADR - Angiotensin-converting enzyme (ACE) inhibitors
	E944.4	ADR - Other diuretics	Y52.5	ADR - Other antihypertensive drugs, NEC
			Y54.3	ADR - Benzothiadiazine derivatives
			Y54.5	ADR - Other diuretics
Cardiac rhythm regulators (including cardiac glycosides, excluding beta-blockers)	E858.3	Poisoning - Agents affecting cardiovascular system	X44	Poisoning - Other and unspecified drugs/medicaments
	E942.0	ADR - Cardiac rhythm regulators	Y52.0	ADR - Cardiac-stimulant glycosides (and similar)
	E942.1	ADR - Cardiac glycosides (and similar)	Y52.2	ADR - Other antidysrhythmic drugs, NEC
Beta-blockers	E855.6	Poisoning - Sympatholytics [antiadrenergics]	X43	Poisoning - Other autonomic nervous system drugs
	E855.8	Poisoning - Other autonomic nervous system drugs	X44	Poisoning - Other and unspecified drugs/medicaments
	E855.9	Poisoning - Unspecified drug affecting nervous system	Y51.7	ADR - Beta-adrenoreceptor antagonists, NEC
	E858.3	Poisoning - Agents affecting cardiovascular system	Y52.2	ADR - Other antidysrhythmic drugs, NEC
	E941.3	ADR - Sympatholytics [antiadrenergics]	Y52.3	ADR - Coronary vasodilators, NEC
	E941.9	ADR - Unspecified autonomic nervous system drug	Y52.5	ADR - Other antihypertensive drugs, NEC
	E942.0	ADR - Cardiac rhythm regulators		
	E942.4	ADR - Coronary vasodilators		
	E942.6	ADR - Other antihypertensive agents		
Serum lipid reducing agents	E858.3	Poisoning - Agents affecting cardiovascular system	X44	Poisoning - Other and unspecified drugs/medicaments
	E942.2	ADR - Antilipemic and antiarteriosclerotic drugs	Y52.6	ADE - Antihyperlipidaemic and antiarteriosclerotic drugs

ADR - Adverse drug reaction; NEC - Not elsewhere classified

Table 3 Associations and preliminary attribution estimates in relation to high risk medications and unplanned hospital admissions in Western Australian elderly, 1993-2005 - summary results

Statistics	Anticoa-gulants	Anti-rheumatic Drugs	Opioids	Cortico-steroids	Hyper-tension Drugs	Cardiac Rhythm Regulators	Beta-Blockers	Serum Lipid Reducing Agents
Domain (number of people in sub-study cohort)	90,124	174,585	193,196	84,960	180,539	39,596	89,017	100,787
Index subjects - number of people involved	57,609	92,903	108,513	53,369	99,635	29,919	55,179	50,295
Index subjects - number of index admissions	212,187	307,276	358,570	197,385	335,259	128,241	195,311	165,470
Index subjects - gender distribution (% males)	47.1%	45.0%	44.9%	45.7%	45.3%	45.5%	45.3%	49.8%
Index subjects - mean age at admission (years)	78.1	78.3	78.5	78.0	78.5	79.5	78.2	76.4
Exposed index subjects (Exp Idx)	26,088	61,595	45,772	30,740	192,674	44,730	60,755	69,286
% exposed index subjects	12.3%	20.0%	12.8%	15.6%	57.5%	34.9%	31.1%	41.9%
Unadjusted odds ratio (Unadj OR)	1.19	1.08	2.01	1.68	0.95	1.17	1.13	0.88
Unadjusted OR 95% confidence interval	1.14-1.25	1.06-1.11	1.94-2.08	1.62-1.75	0.93-0.97	1.13-1.21	1.10-1.16	0.86-0.91
Unadjusted OR p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Adjusted odds ratio (OR)	1.13	1.09	1.81	1.48	0.92	1.11	1.08	0.85
Adjusted OR 95% confidence interval	1.07-1.19	1.06-1.12	1.75-1.88	1.42-1.54	0.90-0.94	1.07-1.15	1.05-1.11	0.82-0.88
Adjusted OR p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Attributable fraction: AF = (OR-1) / OR (%)	11.3%	8.3%	44.9%	32.2%	-9.2%	9.7%	7.4%	-17.8%
AF 95% confidence interval (%)	6.5-15.9%	6.0-10.6%	42.8-46.9%	29.3-35.1%	-11.7--6.7%	6.3-13.0%	4.6-10.2%	-22.0--13.9%
Estimate of index admissions related to drug (AFxExp Idx)[#]	2,960	5,138	20,539	9,913	-17,669	4,360	4,500	-12,323
Exposed index subjects with relevant drug ecode[†]	1,514	793	658	524	2,987	1,051	1,175	147
% exposed index subjects with relevant drug ecode	5.8%	1.3%	1.4%	1.7%	1.6%	2.3%	1.9%	0.2%

 # Estimates were derived from more precise AF figures than those displayed in this table.

† Exposed index subjects with relevant drug ecode refers to hospitalisations among index subjects who were exposed to a high risk drug of interest at the time of admission and for which an ICD external cause code related to accidental poisoning or adverse drug reaction potentially from a medication in this high risk drug group (i.e. codes listed in Table 2 for the drug group) was recorded on the corresponding inpatient summary.

Table 4 Associations between opioid and corticosteroid exposure and unplanned hospital admissions in Western Australian elderly, 1993-2005 - odds ratios and 95% confidence intervals resulting from logistic regression model variations

Regression model variations	Opioids	Corticosteroids
Decomposed case-time-control model[#]		
Case-crossover - index subjects only (unadjusted)	2.57 (2.52-2.62)	2.03 (1.98-2.08)
Case-crossover - reference subjects (i.e. negative controls) only (unadjusted)	1.28 (1.25-1.31)	1.21 (1.17-1.24)
Case-time-control (unadjusted)	2.01 (1.94-2.08)	1.68 (1.62-1.75)
Case-time-control (adjusted with health status and drug consumption covariates)	1.81 (1.75-1.88)	1.48 (1.42-1.54)
Case-time-control models with more explicit adjustment for indications[†]		
Case-time-control (+ Charlson index covariates re cancer)	1.85 (1.78-1.92)	1.49 (1.42-1.55)
Case-time-control (+ Charlson index re rheumatic/connective tissue disease)	No effect on model	No effect on model
Case-time-control (+ Charlson index re chronic pulmonary disease)	Not applicable	1.46 (1.40-1.52)
Case-time-control models with cancer status matching and stratification[‡]		
Case-time-control (cancer instead of GP status matching) - all	1.80 (1.73-1.87)	1.46 (1.40-1.52)
Case-time-control (cancer instead of GP status matching) - non-cancer group	1.81 (1.72-1.89)	1.45 (1.38-1.52)
Case-time-control (cancer instead of GP status matching) - cancer group	1.88 (1.75-2.02)	1.50 (1.38-1.62)
Case-time-control models using other drugs for sensitivity analysis[§]		
Case-time-control (adjusted - with hypertension medications as main exposure)	0.93 (0.91-0.96)	0.90 (0.87-0.93)
Case-time-control (adjusted - with serum lipid reducing agents as main exposure)	0.86 (0.83-0.89)	0.83 (0.79-0.86)

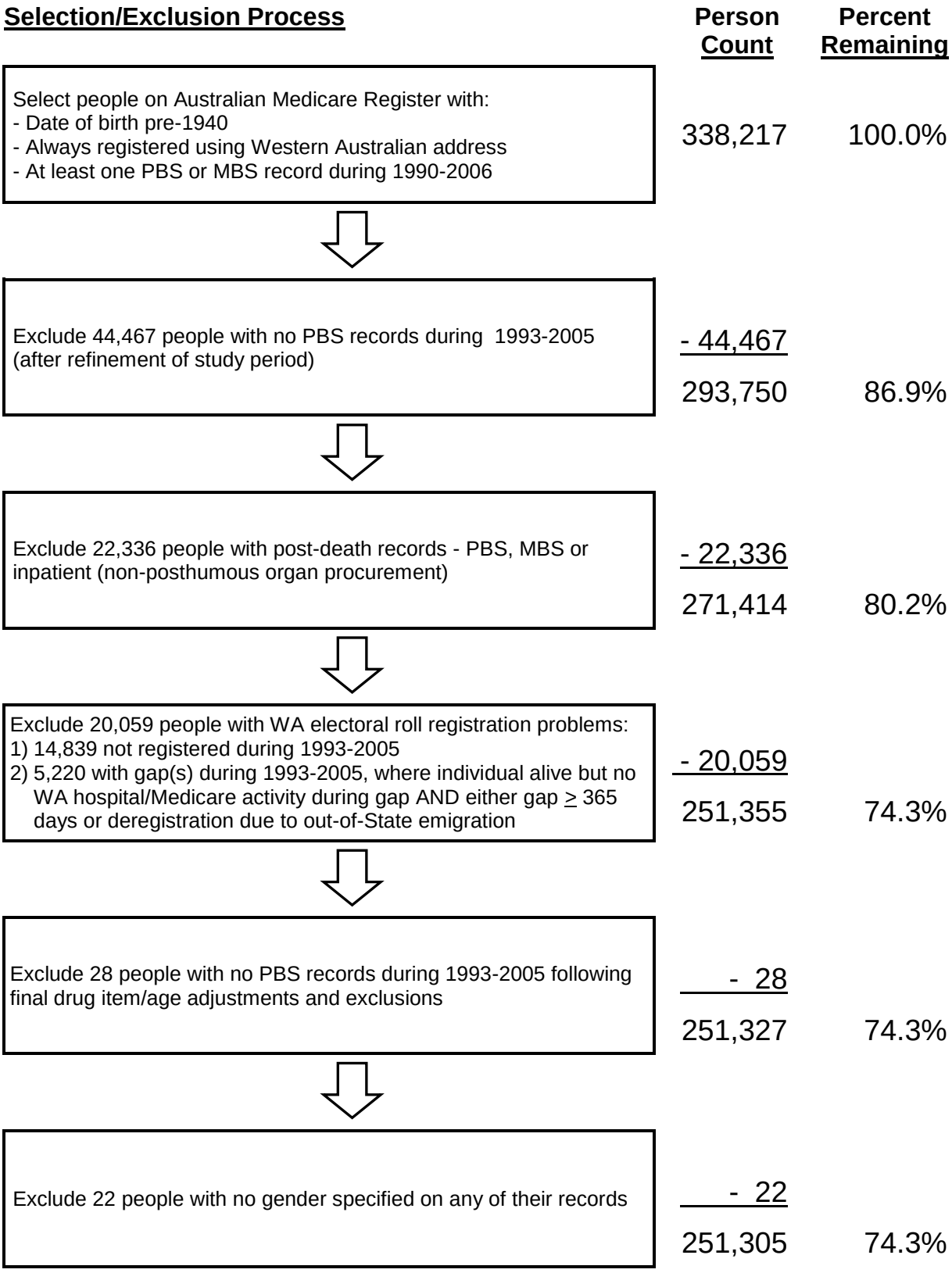
 # Models in the first section show the independent effects on our results of each confounding control measure integrated into our adjusted case-time-control model, including the elimination of unmeasured time trends through the use of reference subjects (i.e. negative controls) and further adjustments through the inclusion of measurable time-varying factors as model covariates. Results from the adjusted case-time-control model shown above correspond with the 'adjusted odds ratios' reported in Table 3.

†Models in the second section included all covariates from our adjusted case-time-control model (including an overall Charlson comorbidity score), with the addition of the specified Charlson index variable(s) to adjust more explicitly for potential confounding due to drug indication. "No effect on model" indicates that, although listed as a covariate in the regression analysis, the specified Charlson index was not included in the final model in a stepwise selection process.

‡ Results shown in the third section were generated from models in which index and reference subjects were matched according to cancer status instead of General Practitioner (GP) coverage (as well as year of birth and gender). The regression analysis was first performed on the entire group to examine the effects of this different matching process, but then applied to the cancer and non-cancer groups independently in an attempt to isolate the effects of cancer (as a drug indication) on the results.

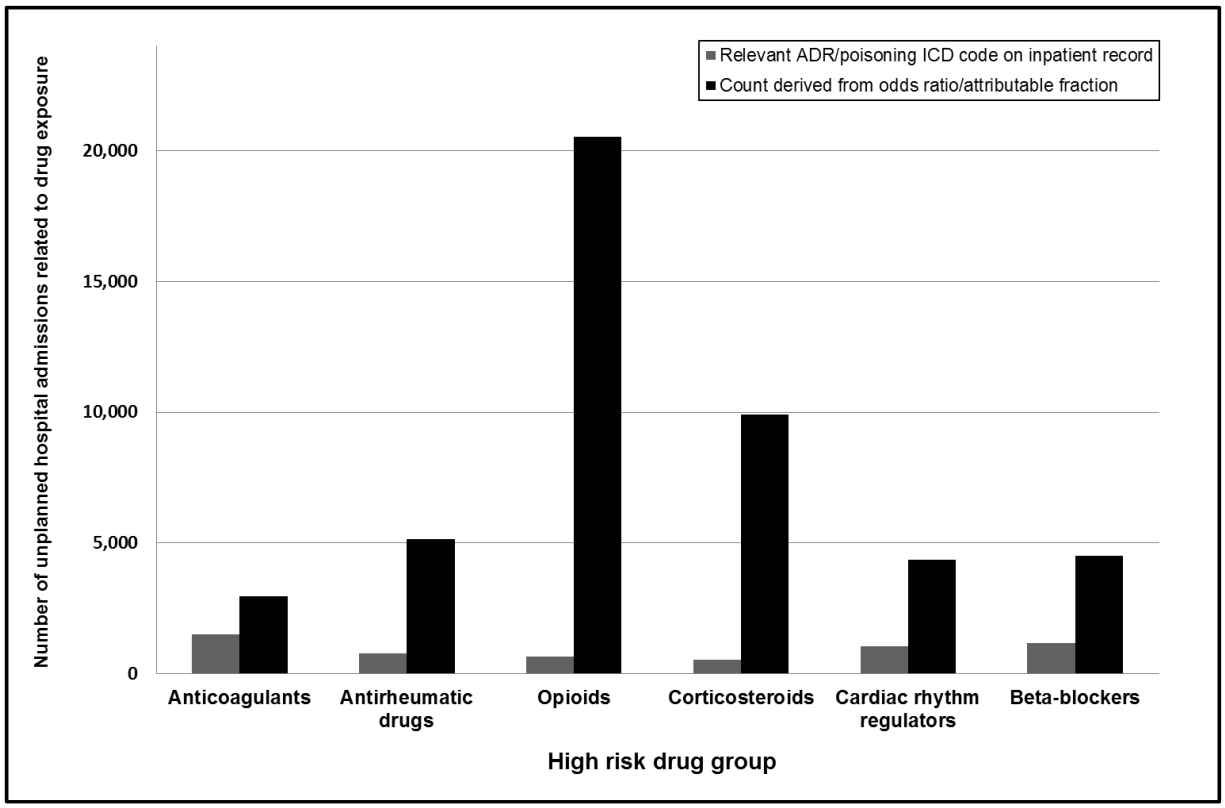
§ Models from the last section included hypertension and serum lipid reducing drugs as primary exposure (instead of opioids or corticosteroids). These medications appeared to have a protective effect against unplanned hospitalisations in our sub-studies involving cardiovascular patients. Similar results to those obtained with opioids and corticosteroids as primary exposure would have suggested that the indications for opioids and corticosteroids might account for most of the apparent associations rather than drug exposure itself. As shown above, our results provide no evidence that this is the case.

Figure 1 Selection of study cohort



PBS - Pharmaceutical Benefits Scheme; MBS - Medicare Benefits Scheme; WA - Western Australian

Figure 2 Estimates of unplanned hospital admissions associated with exposure to medications in high risk drug groups for which the odds ratio suggests an increased risk of hospitalisation



The counts associated with the two columns for each high risk drug group presented in this chart were derived as follows from hospitalisations for index subjects who were considered exposed to a medication in the specified high risk drug group at the time of admission:

1) *Number of these hospitalisations for which an ICD external cause code related to accidental poisoning or adverse drug reaction potentially from a medication within the specified high risk drug group (i.e. codes listed in Table 2 for this drug group) was found on the inpatient summary record.*

2) *Number of these hospitalisations considered to be attributable to the exposure drug, calculated as count = AF x number of exposed index subjects, where AF = (OR-1)/OR and is the attributable fraction derived from the primary adjusted OR in the corresponding regression analysis.*