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Prevalence, nature and potential preventability of adverse drug events – a population-based medical record study of 4970 adults

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Adverse drug events (ADEs) are common and often preventable among hospitalized patients, but evidence outside hospitals and in the general population is lacking.
- Previous studies have focused on all ADEs combined or on adverse drug reactions (ADRs), a category of ADEs, potentially limiting the understanding of ADEs.

WHAT THIS STUDY ADDS

- During 3 months, 12% of adults across care settings experienced ADEs, over one-third of which were potentially preventable, warranting further efforts in healthcare to tackle the problem, also in primary and other outpatient care.
- Associated drugs, affected organs, preventability, and seriousness differ by ADE category, such as ADRs and sub-therapeutic effects, which should be considered in future research and in clinical practice.

AIMS

To estimate the 3 month prevalence of adverse drug events (ADEs), categories of ADEs and preventable ADEs, and the preventability of ADEs among adults in Sweden. Further, to identify drug classes and organ systems associated with ADEs and estimate their seriousness.

METHODS

A random sample of 5025 adults in a Swedish county council in 2008 was drawn from the Total Population Register. All their medical records in 29 inpatient care departments in three hospitals, 110 specialized outpatient clinics and 51 primary care units were reviewed retrospectively in a stepwise manner, and complemented with register data on dispensed drugs. ADEs, including adverse drug reactions (ADRs), sub-therapeutic effects of drug therapy (STEs), drug dependence and abuse, drug intoxications from overdose, and morbidities due to drug-related untreated indication, were detected during a 3 month study period, and assessed for preventability.

RESULTS

Among 4970 included individuals, the prevalence of ADEs was 12.0% (95% confidence interval (CI) 11.1, 12.9%), and preventable ADEs 5.6% (95% CI 5.0, 6.2%). ADRs (6.9%; 95% CI 6.2, 7.6%) and STEs (6.4%; 95% CI 5.8, 7.1%) were more prevalent than the other ADEs. Of the ADEs, 38.8% (95% CI 35.8–41.9%) was preventable, varying by ADE category and seriousness. ADEs were frequently associated with nervous system and cardiovascular drugs, but the associated drugs and affected organs varied by ADE category.

CONCLUSIONS

The considerable burden of ADEs and preventable ADEs from commonly used drugs across care settings warrants large-scale efforts to redesign safer, higher quality healthcare systems. The heterogeneous nature of the ADE categories should be considered in research and clinical practice for preventing, detecting and mitigating ADEs.

Introduction

Improving patient safety and reducing preventable patient harm, including adverse drug events (ADEs), are emphasized by national, regional and global health authorities [1–4]. An ADE is commonly defined as '*an injury resulting from medical intervention related to a drug*' [5], although definitions vary [6, 7]. Approximately 5% of patients at or during hospitalization [6, 8–10], and a median of 13% of ambulatory care patients [9] are reported to experience ADEs, and 11–90% of the ADEs are estimated preventable [8–14]. The few previous studies including outpatients without a hospitalization are commonly small, or limited to certain sub-populations or exclusively self-reports [15–26]. Even though ADEs are commonly described to include not only adverse drug reactions (ADRs), but also intoxications from overdoses, sub-therapeutic effects for example due to patient non-adherence, and events due to lack of therapy [6, 8–12, 25–32], these diverse event categories are rarely reported separately, possibly limiting the characterization of ADEs. Therefore, the burden of ADEs and categories of ADEs across care settings is largely unknown, in particular outside hospitals. The primary objective of this study was to estimate the 3 month prevalence of ADEs, categories of ADEs, and preventable ADEs, and the preventability of ADEs using medical records of a random sample of the adult general public in Sweden. Secondary objectives were to identify drug classes and organ systems associated with ADEs, to assess the seriousness of ADEs, and to estimate the prevalence of serious ADEs and preventable serious ADEs.

Methods

Setting and participants

A random sample of 5025 adult residents (≥18 years on 31 December 2007) in the county council of Östergötland, Sweden, was drawn from the Total Population Register of Statistics Sweden. The sample included all adults with a registered address in the county, including people living in nursing homes etc. We calculated the sample size based on a conservative 8% expected prevalence and for estimating a 50% proportion among individuals with ADEs, with a maximum width of ±5% for the 95% confidence interval (CI), requiring a minimum of 384 individuals with ADEs. Medical care in all care units of the study population was reviewed retrospectively for 3 months in 2008. To account for seasonal variation, the study population was randomly divided into four groups for each quarter of the year.

Outcome measures

The primary outcome measure was an ADE, defined as '*an injury resulting from medical intervention related to a drug*' [5], which could be associated with prescribed, non-prescribed or complementary, but not illicit drugs. Some consider ADEs to consist of non-preventable ADRs, and medication errors that are by definition preventable [33], while others consider also part of ADRs preventable [34, 35]. In our study, an ADR could be preventable and was defined according to the World Health Organization [36] as '*a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function*'. We excluded drug dependence (DD) from ADRs, as DD could occur in higher doses than normally used. Apart from ADRs, medication errors such as omission of a dose [37] may result in other types of injury, which could be included in the broad definition for ADEs [5], but are not detailed in most studies on ADEs. Thus, we identified additional, mutually exclusive ADE categories from the literature [6, 8–12, 25–32, 38–40]. To differentiate from ADRs, we defined drug intoxications from overdose (DIs) as '*a noxious, intended or unintended drug reaction that occurs at higher doses than normally used in man for prophylaxis, diagnosis or treatment. The intention for administrating the drug(s) may or may not be therapeutic*'. DD and drug abuse (DA) were defined according to the American Psychiatric Association as '*a maladaptive pattern of substance use leading to clinically significant impairment or distress*', which had to be manifested according to specific criteria [41]. Sub-therapeutic effects of drug therapy (STEs) included absence of therapeutic response that could be linked causally either to dose that was too low, drug non-compliance, recent dose reduction/discontinuation or inadequate monitoring [40]. We also included STEs due to improper drug selection or when treatment had been rational (e.g. first line treatment not effective). Morbidity due to drug-related untreated indication (UTI) occurred when a person had a clinical condition that under normal circumstances would have required pharmacological therapy but none was received. Secondary outcome measures were preventable [42] and serious [34] ADEs.

Data sources and case assessment

Data from multiple sources were linked using the personal identity number (Figure 1). Data on all individuals' dispensed drugs were retrieved from the Swedish Prescribed Drug Register (SPDR) [43], which covers all prescribed drugs dispensed in pharmacies (also, for example, low dose acetylic salicylic acid and small benzodiazepine packages), including prescription drugs for residential care. The SPDR excludes non-prescription and complementary drugs bought without a prescription, drugs administered in hospitals and emergency drugs administered in residential care. Data on healthcare encounters were retrieved from the regional patient register, Care Data Warehouse of Östergötland [44], including administrative data on all inpatient and outpatient care provided in the county in all

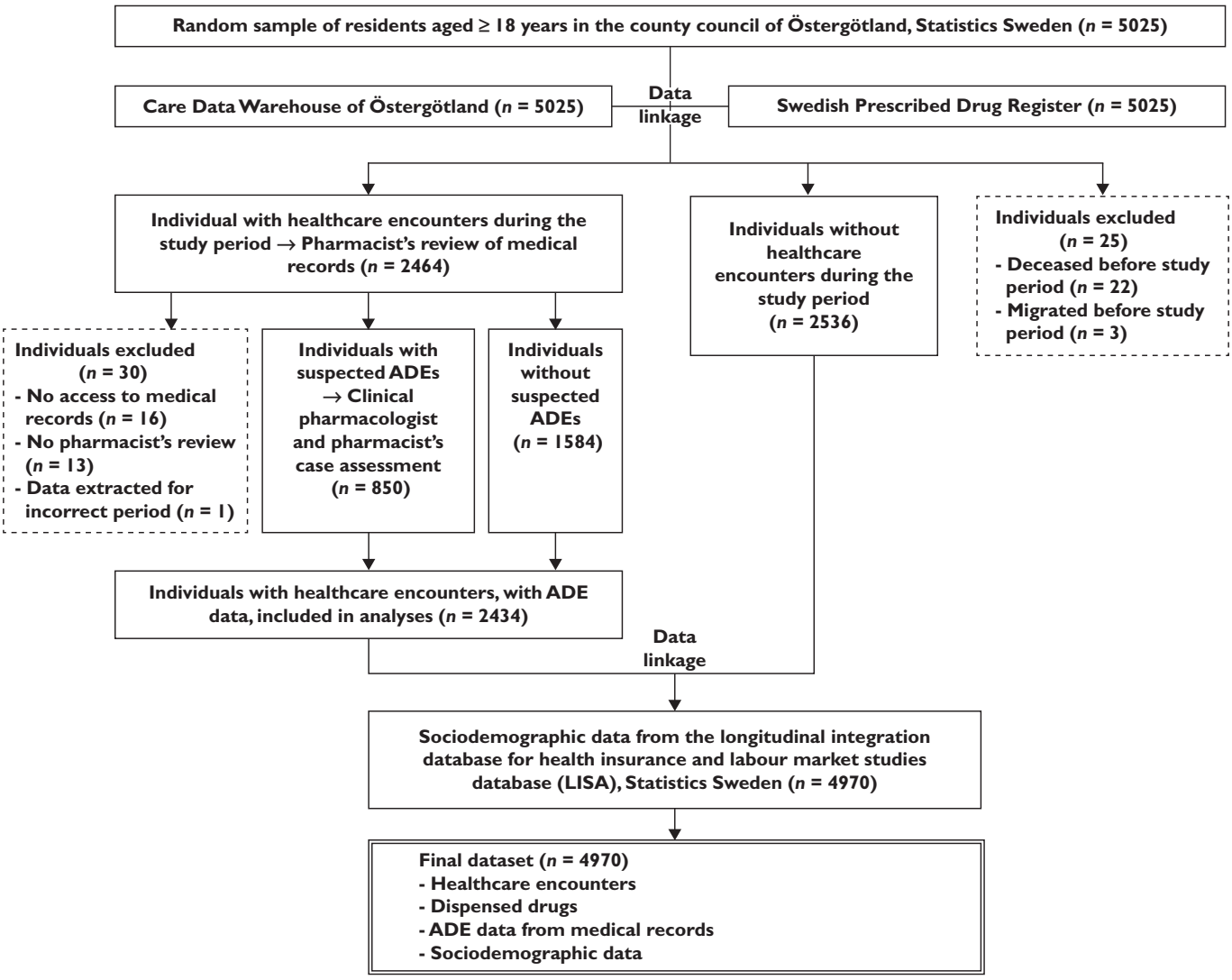

Figure 1

Study flow diagram. ADE, adverse drug event. Data sources were linked using the unique personal identity number

medical specialities. In the study area, private outpatient care (including dental care) constituted 3% of all healthcare expenditure in 2008 [45], practically all of which is recorded (personal communication from Lars Svensson, Östergötland County Council). Thus, the coverage of the care data is considered full. Based on the administrative care data, electronic medical records in all care units were retrieved for individuals with one or more healthcare encounters (nurse or physician, visit or telephone contact, outpatient or inpatient, specialized or not, excluding dental and paramedical care) during the 3 month study period. Healthcare providers were contacted for paper copies when electronic records were missing, including private outpatient care providers (Östergötland had no private inpatient care providers in 2008).

ADEs were detected in the medical records in a stepwise manner similar to previous studies [5, 17], using manuals and standardized, pilot-tested data extraction tools. Pharmacists extracted information on suspected ADEs from the medical records for the 3 month study period, and 9 months before and 3 months after it. For prescribed drugs, data were extracted both from the SPDR and from the medical record, as medical records include drug use in inpatient care and emergency drug use in residential care, which are excluded from the SPDR. Information on non-prescribed and complementary drugs was extracted exclusively from the medical records. Used triggers included diagnoses (e.g. urticaria) [33], drugs (e.g. warfarin) [33] and drug–drug interactions [46]. A clinical pharmacologist and another pharmacist independently assessed the causality [47] between the suspected ADEs and drug therapies, detected possible additional ADEs, and assessed preventability [42], contribution to hospitalization [42] and seriousness [34]. Conflicting assessments

were solved by consensus. Suspected ADEs with at least possible causality [47] were considered ADEs, and ADEs with at least possible preventability [42] preventable ADEs. An ADE was considered to contribute to a hospitalization if its significance for the admission was 'dominant', 'partially contributing', or 'less important' [42]. This assessment was also used for determining seriousness, among other seriousness criteria [34]. All assessors were trained in the process. Data from the medical records were combined with register data for all individuals (Figure 1).

Aggregated data

The individuals' sociodemographic characteristics were compared with the adult general population in Sweden by retrieving aggregated data on age, gender, marital status, area of residence, country of birth, education and income from Statistics Sweden.

Data analysis

In the main analyses, the 3 month prevalences and 95% confidence intervals were calculated for different categories of ADEs and preventable ADEs. Individuals with at least one ADE were used in the numerator in the prevalence calculations. All individuals in the study population were chosen as the denominator in the prevalence calculations, because ADEs could occur without dispensed drugs (non-prescription drugs or stockpile), and UTIs, STEs and prolonged ADEs do not require current drug use. The ADE prevalences were compared by age group using χ^2 or Fisher's exact test, choosing cut-off ages based on changing patterns in morbidity and mortality: 18–44, 45–64 and ≥65 years [48]. The prevalences of serious ADEs, and preventable serious ADEs were also calculated. For the prevalence of hospitalizations contributed by ADEs, individuals with hospitalizations during the study period were used in the denominator. For preventability and seriousness, the number of preventable and/or serious ADEs was divided by the number of all ADEs. STATA software version 11.2 was used.

Drugs associated with each ADE category were classified according to the Anatomical Therapeutic Chemical (ATC) Classification [49], including main groups (first level) and pharmacological subgroups (third level) representing >1% of the ADE category, and chemical substances (fifth level) representing ≥20% of the given pharmacological subgroups. Psycholeptics (N05) and psychoanaleptics (N06) were also classified into the fourth level drug classes. For comparison, the most common drugs dispensed to all individuals were described, from 6 months before the study period until the last day before the study period.

According to the Medical Dictionary for Regulatory Activities (MedDRA) [50], organ systems (System Organ Classes [50]) and symptoms (Preferred Terms [50]) representing >1% of all or preventable ADEs were presented. For ADRs and STEs, chemical substances [49] associated with the Preferred Terms at least twice were reported.

As sensitivity analyses, the ADE prevalences were calculated varying the denominator: individuals with dispensed drugs during 6 months before the study period, and individuals with ≥1 healthcare encounters during the study period. In further sensitivity analyses, the ADE prevalence was calculated without UTIs and non-preventable STEs, to mimic previous ADE definitions. This was done using different denominators: all individuals, individuals with dispensed drugs and individuals with healthcare encounters.

Ethical considerations

An ethical approval was received from the Regional Ethical Review Board in Gothenburg (644-08). According to Swedish legislation, no informed consents from the participants were required, because participation could not change the participants' healthcare or health status and the results were expected to improve care for future patients.

Results

Study population

After excluding 55 individuals (Figure 1), the study population consisted of 4970 individuals, of which 2434 (49.0%) had healthcare encounters, in 29 departments of inpatient care in three hospitals, 110 specialized outpatient clinics, and 51 primary care units. The sociodemographic characteristics of the study population and the general population were similar (Table 1), although a larger proportion of the study population was born in Sweden.

Prevalences of persons with ADEs

ADEs were detected in 596 of the 4970 individuals, resulting in a total prevalence of 12.0% (95% CI 11.1, 12.9%) in the total general population (Table 2). As described in Table 2, ADRs and STEs were more prevalent than the other ADE categories. The prevalences differed by age group for all ADEs, ADRs and STEs, being higher in older age groups. The prevalence of preventable ADEs was 5.6% (95% CI 5.0, 6.2%), also differing by age group. The 3 month prevalence of serious ADEs in the general population was 1.2% (95% CI 0.9, 1.6%), and preventable serious ADEs 0.7% (95% CI 0.5, 1.0%). ADEs contributed to admissions for 0.6% (95% CI 0.4, 0.8%) of the general population, and for 22.1% (95% CI 15.1, 29.1%) of 136 individuals with hospitalizations during the 3 month study period. When only preventable ADEs were analyzed, they contributed to admissions for 0.4% (95% CI 0.2, 0.6%) of the general population, and for 14.0% (95% CI 8.1, 19.8%) of individuals with hospitalizations.

Numbers of events

Of all 981 ADEs, 52.4% were ADRs, 38.8% STEs, 5.3% UTIs, 2.6% DD and DA cases and 0.8% DIs. Of the 596 individuals

Table 1

Characteristics of the study population ($n = 4970$) compared with the adult general population in Sweden ($n = 7\,251\,275$)

Variable	Study population *n* (%)	General population *n* (%)
Age*		
Mean (SD)	48.9 (19.0)	48.9 (18.9)
18–47 years	2359 (47.5)	3 605 647 (49.7)
48–67 years	1693 (34.1)	2 322 001 (32.0)
≥68 years	918 (18.5)	1 323 627 (18.3)
Missing	0 (0.0)	0 (0.0)
Gender		
Male	2427 (48.8)	3 572 603 (49.3)
Missing	0 (0.0)	0 (0.0)
Marital status*		
Single	1914 (38.5)	2 762 464 (38.1)
Married or registered partnership	2203 (44.2)	3 134 181 (43.2)
Separated	526 (10.6)	859 956 (11.9)
Widowed	327 (6.6)	494 674 (6.8)
Missing	0 (0.0)	0 (0.0)
Area of residence*		
Cities and commuting municipalities	3336 (67.1)	4 820 495 (66.5)
Others	1634 (32.9)	2 430 780 (33.5)
Missing	0 (0.0)	0 (0.0)
Country of birth		
Sweden	4437 (89.3)	6 135 688 (84.6)
OECD country, including Sweden	4648 (93.5)	6 677 580 (92.1)
Missing	1 (0.0)	1525 (0.0)
Highest level of education†		
Mandatory school	1264 (25.4)	1 614 887 (22.3)
Secondary/high school	2147 (43.2)	3 250 209 (44.8)
High education	1456 (29.3)	2 198 568 (30.3)
Missing	103 (2.1)	187 611 (2.6)
Disposable monthly income‡		
Median	1817	1905
0–1351 USD	1268 (25.5)	1 797 882 (24.8)
1352–1903 USD	1354 (27.2)	1 800 638 (24.8)
1904–2757 USD	1237 (24.9)	1 799 378 (24.8)
>2858 USD	1111 (22.4)	1 800 562 (24.8)
Missing	0 (0.0)	52 815 (0.7)

OECD, Organization for Economic Co-operation and Development; NA, not applicable; SD, standard deviation; USD, United States dollar. *On 31 December 2007, apart from age for the study individuals in the beginning of the study period. †In 2008. ‡Average in 2008, weighted for number of children. Yearly average exchange rate in 2008 from Swedish krona to United States dollar 6.5808.

with ADEs, 30.4% had two to three, and 6.5% four or more ADEs. Among individuals with ADRs, 30.7% had two or more ADRs, while 15.3% of individuals with STEs had two or more STEs. Of individuals with ADEs, 78.5% experienced exclusively one ADE category.

Preventability and seriousness of events

The preventability of all ADEs was 38.8% (95% CI 35.8, 41.9%), varying by ADE category (Table 3). Serious ADEs represented 9.5% (95% CI 7.6, 11.3%) of all ADEs, of which DIs were the most and ADRs the least serious. Of all serious ADEs, 55.9% (95% CI 45.8, 66.0%) were preventable. By ADE category, the preventability of serious ADEs was similar to all ADEs, apart from the 54.8% (95% CI 36.3, 73.4%) preventability of serious ADRs. Of the ADEs contributing to hospitalizations, 62.8% (95% CI 48.3, 77.2%) were judged preventable.

Drugs associated with events

Drugs for the nervous system were associated with 39.3% of ADRs, 30.4% of STEs, all DD and DA cases and 62.5% of DIs (Table 4). Also cardiovascular drugs attributed to 29.6% of ADRs and 28.3% of STEs. Among nervous system drugs, psychoanaleptics were the most common (19.8%) among ADRs and analgesics (12.1%) among STEs (Table S1).

By and large, the main drug classes associated with all and preventable ADRs and STEs were similar. Drugs for the nervous system contributed to 43.7% of preventable ADRs (psychoanaleptics 17.8%, psycholeptics 15.6%, analgesics 14.1%), and drugs for the cardiovascular system to 37.8% (β-adrenoceptor blocking agents 15.6%, diuretics 14.1%,

Table 2

Three month prevalence of persons with ADEs and preventable ADEs, by ADE category and age group

	Age 18–44 years (n = 2217)		Age 45–64 years (n = 1600)		Age ≥65 years (n = 1153)			All ages (n = 4970)	
	n	Prevalence % (95% CI)	n	Prevalence % (95% CI)	n	Prevalence % (95% CI)	P Value†	n	Prevalence % (95% CI)
Any ADE*	130	5.9 (4.9, 6.8)	210	13.1 (11.5, 14.8)	256	22.2 (19.8, 24.6)	<0.001	596	12.0 (11.1, 12.9)
ADRs	76	3.4 (2.7, 4.2)	107	6.7 (5.5, 7.9)	159	13.8 (11.8, 15.8)	<0.001	342	6.9 (6.2, 7.6)
DIs	3	0.1 (0.0, 0.3)	0	0 (–)	4	0.3 (0.0, 0.7)	0.04	7	0.1 (0.0, 0.2)
DD or DA	7	0.3 (0.1, 0.5)	9	0.6 (0.2, 0.9)	4	0.3 (0.0, 0.7)	0.46	20	0.4 (0.2, 0.6)
STEs	67	3.0 (2.3, 3.7)	121	7.6 (6.3, 8.9)	132	11.4 (9.6, 13.3)	<0.001	320	6.4 (5.8, 7.1)
UTIs	14	0.6 (0.3, 1.0)	17	1.1 (0.6, 1.6)	16	1.4 (0.7, 2.1)	0.08	47	0.9 (0.7, 1.2)
Any preventable ADE*	58	2.6 (2.0, 3.3)	88	5.6 (4.4, 6.6)	132	11.4 (9.6, 13.3)	<0.001	278	5.6 (5.0, 6.2)
Preventable ADRs	16	0.7 (0.4, 1.1)	24	1.5 (0.9, 2.1)	66	5.7 (4.4, 7.1)	<0.001	106	2.1 (1.7, 2.5)
Preventable DIs	3	0.1 (0.0, 0.3)	0	0 (–)	4	0.3 (0.0, 0.7)	0.04	7	0.1 (0.0, 0.2)
Preventable DD or DA	6	0.3 (0.1, 0.5)	9	0.6 (0.2, 0.9)	3	0.3 (0.0, 0.6)	0.27	18	0.4 (0.2, 0.5)
Preventable STEs	31	1.4 (0.9, 1.9)	57	3.6 (2.7, 4.5)	64	5.6 (4.2, 6.9)	<0.001	152	3.1 (2.6, 3.5)
Preventable UTIs	9	0.4 (0.1, 0.7)	12	0.8 (0.3, 1.2)	14	1.2 (0.6, 1.8)	0.03	35	0.7 (0.5, 0.9)

ADE, adverse drug event; ADR, adverse drug reaction; CI, confidence interval; DA, drug abuse; DD, drug dependence; DI, drug intoxication from overdose; STE, sub-therapeutic effect of drug therapy; UTI, morbidity due to drug-related untreated indication. *As one person could have multiple ADEs, the combined prevalence is lower than the sum of the prevalences of the ADE categories. †For testing the statistical significance between all three age groups using χ^2 test, with the exception of using Fisher's exact test for DIs due to low number of cases.

Table 3

Preventability and seriousness of events and the preventability of serious events, by ADE category

	Preventability		Seriousness		Preventability of serious ADEs	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Any ADE (n = 981)	379	38.8 (35.8, 41.9)	93	9.5 (7.6, 11.3)	52	55.9 (45.8, 66.0)
ADRs (n = 514)	135	26.3 (22.4, 30.1)	31	6.0 (4.0, 8.1)	17	54.8 (36.3, 73.4)
DIs (n = 8)	8	100.0 (67.6, 100.0)	5	62.5 (29.0, 96.0)	5	100.0 (56.6, 100.0)
DD or DA (n = 26)	24	92.3 (75.9, 97.9)	8	30.8 (13.0, 48.5)	7	87.5 (52.9, 97.8)
STEs (n = 381)	172	45.1 (40.1, 50.2)	44	11.5 (8.3, 14.8)	19	43.2 (27.9, 58.4)
UTIs (n = 52)	40	76.9 (65.1, 88.8)	5	9.6 (1.6, 17.6)	4	80.0 (37.6, 96.4)

ADE, adverse drug event; ADR, adverse drug reaction; CI, confidence interval; DA, drug abuse; DD, drug dependence; DI, drug intoxication from overdose; STE, sub-therapeutic effect of drug therapy; UTI, morbidity due to drug-related untreated indication.

agents acting on the renin-angiotensin system 11.9%). Drugs for blood and blood forming organs composed 9.6% (antithrombotic agents 8.1%) of preventable ADRs, and drugs for the musculoskeletal system 8.2% (anti-inflammatory and anti-rheumatic products 7.4%). Of preventable STEs, cardiovascular drugs represented 31.4% (β-adrenoceptor blocking agents 16.9%, agents acting on the renin-angiotensin system 15.1%, diuretics 11.1%), nervous system drugs 21.5% (analgesics 8.1%, psychoanaleptics 8.1%, psycholeptics 4.1%), alimentary tract and metabolism drugs 20.4% (drugs used in diabetes 18.0%), and drugs for the musculoskeletal system 9.3% (anti-inflammatory and anti-rheumatic products 9.3%).

Organs affected by events

ADRs were most frequently gastrointestinal (21.6%) or general disorders (12.3%) (Table 5, Table S2), the most frequent ADR symptoms being fatigue, nausea, dizziness and increased weight. Analogously to all ADRs, preventable ADRs were the most frequently gastrointestinal (20.7%) or general disorders (13.3%).

STEs were most frequently vascular (18.9%), dominated by hypertension (Table 6, Table S3). Preventable STEs were frequently vascular (23.8%), psychiatric (12.2%), or musculoskeletal (9.9%), as for all STEs, but endocrine disorders were more common among preventable (14.5%) than all STEs (8.7%).

UTIs were the most commonly psychiatric (17.3%) or vascular (13.5%), hypertension being the most common individual symptom (12.5%). All DD and DA cases were psychiatric (100%), while DIs were distributed in different organ classes.

Sensitivity analyses for total prevalence of persons with ADEs

The prevalences of ADEs and their categories were higher compared with the main analysis when alternative

Table 4

Drug classes associated with ADE categories*, ordered according to the most commonly dispensed drugs to all individuals

Drug class† (ATC code)	Dispensed to all individuals‡ (*n* = 4970) *n* (%)§	ADRs (*n* = 514) *n* (%)¶	STEs (*n* = 381) *n* (%)¶	DD or DA (*n* = 26) *n* (%)¶	DIs (*n* = 8) *n* (%)¶
Cardiovascular system (C)	1242 (25.0)	152 (29.6)	108 (28.3)	–	1 (12.5)
Nervous system (N)	1136 (22.9)	202 (39.3)	116 (30.4)	26 (100.0)	5 (62.5)
Alimentary tract and metabolism (A)	867 (17.4)	37 (7.2)	54 (14.2)	–	2 (25.0)
Blood and blood forming organs (B)	728 (14.6)	38 (7.4)	7 (1.8)	–	–
Anti-infectives for systemic use (J)	697 (14.0)	18 (3.5)	24 (6.3)	–	–
Genitourinary system and sex hormones (G)	651 (13.1)	28 (5.4)	6 (1.6)	–	–
Respiratory system (R)	640 (12.9)	24 (4.7)	27 (7.1)	–	2 (25.0)
Musculoskeletal system (M)	548 (11.0)	29 (5.6)	37 (9.7)	1 (3.9)	–
Systemic hormonal preparations** (H)	349 (7.0)	20 (3.9)	14 (3.7)	–	–
Dermatologicals (D)	325 (6.5)	–	8 (2.1)	–	–
Sensory organs (S)	276 (5.6)	–	5 (1.3)	–	–
Antineoplastic and immunomodulating agents (L)	73 (1.5)	26 (5.1)	–	–	–
No dispensed drugs during the past 6 months	1965 (39.5)	NA	NA	NA	NA

ADE, adverse drug event; ADR, adverse drug reaction; ATC, Anatomical Therapeutic Chemical; DA, drug abuse; DD, drug dependence; DI, drug intoxication from overdose; NA, not applicable; STE, sub-therapeutic effect of drug therapy; –, ≤1% of the ADE category. *Excluding morbidities due to drug-related untreated indication. †Categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System [49] main groups (1st level). ‡Dispensed drugs from the Swedish Prescribed Drug Register, for all study individuals from 6 months before the study period until the last day before the study period. §Representing >1% of the dispensed drugs. ¶Representing >1% of the ADE category. **Excluding sex hormones and insulins.

denominators were used (Table 7), with 18.3% (95% CI 16.9, 19.7%) total ADE prevalence for individuals with dispensed drugs, and 24.5% (95% CI 22.8, 26.2%) for individuals with healthcare encounters. The prevalence of all ADEs remained similar to the main analysis when UTIs were omitted from ADEs: 11.4% (95% CI 10.5, 12.3%) for all individuals, 17.6% (95% CI 16.2, 19.0%) for individuals with dispensed drugs, and 23.2% (95% CI 21.5, 24.9%) for individuals with healthcare encounters. When both UTIs and non-preventable STEs were omitted from ADEs, the prevalence was lower: 9.2% (95% CI 8.4, 10.0%) for all individuals, 14.3% (95% CI 13.1, 15.5%) for individuals with dispensed drugs, and 18.9% (95% CI 17.3, 20.4%) for individuals with healthcare encounters.

Discussion

Our study demonstrates that the prevalence of ADEs is considerable in the entire healthcare, with more than one-third of ADEs potentially preventable. By large, commonly dispensed drugs were commonly associated with ADEs and preventable ADEs, but the associated drugs and affected organs differed by ADE category.

Strengths and weaknesses

This is the first study investigating ADEs in both inpatient and outpatient settings of a random population sample, making our results generalizable to the county and by and large the entire nation. However, the under-representation of persons born outside Sweden in our study population somewhat limits generalizability to the entire nation. We chose a retrospective study design, because recruiting a representative population prospectively for detecting their ADEs in healthcare units would have been practically infeasible and resulted in drop-outs, limiting generalizability. As the retrospective data collection enabled assessing symptoms of ADEs based only on the medical records, symptoms of ADEs that patients had not communicated to care providers or care providers had not recorded are underestimated in our study. To minimize the underestimation, our comprehensive case assessment with clinical experts' causality assessment was designed to detect ADEs that were not recognized, diagnosed, or reported as ADEs, but were otherwise detectable, for example, based on free text or diagnostic tests in the medical records. ADEs from prescribed drugs were probably detected to a greater extent than ADEs from other drugs, because non-prescribed and complementary drugs bought without a prescription are excluded from the SPDR and also less commonly recorded in medical records.

Our study benefited from a thorough ADE definition with categories, enabling the investigation of all adverse events related to drugs combined or divided into categories. However, differing definitions in other studies hindered direct comparisons. We applied established methods for case detection and assessing causality, preventability and seriousness, but the varying reliability and the lack of validation of the current methods [51–54] warrant cautious interpretation of the results.

Comparison to prior research

Our finding that 12% of the adult general population experienced ADEs during a 3 month period was, considering our methods, of similar magnitude with most

Table 5

Organs affected by ADRs and preventable ADRs, with ADR symptoms

Organ system* and symptom†	ADRs (n = 514) n (%)‡	Preventable ADRs (n = 135) n (%)‡
Gastrointestinal disorders	111 (21.6)	28 (20.7)
Nausea	32 (6.2)	4 (3.0)
Dry mouth	12 (2.3)	6 (4.4)
Constipation	12 (2.3)	6 (4.4)
Diarrhoea	11 (2.1)	–
Dyspepsia	9 (1.8)	3 (2.2)
Abdominal pain upper	8 (1.6)	2 (1.5)
General disorders and administration site conditions	63 (12.3)	18 (13.3)
Fatigue	38 (7.4)	9 (6.7)
Hyperhidrosis	8 (1.6)	2 (1.5)
Asthenia	–	2 (1.5)
Withdrawal syndrome	–	2 (1.5)
Cardiac disorders	46 (8.9)	12 (8.9)
Dizziness	22 (4.3)	4 (3.0)
Oedema peripheral	9 (1.8)	4 (3.0)
Palpitations	8 (1.6)	–
Bradycardia	–	2 (1.5)
Nervous system disorders	45 (8.8)	14 (10.4)
Tremor	9 (1.8)	3 (2.2)
Headache	8 (1.6)	3 (2.2)
Dizziness	7 (1.4)	–
Depressed level of consciousness	–	2 (1.5)
Vascular disorders	45 (8.8)	12 (8.9)
Hypotension	10 (1.9)	7 (5.2)
Psychiatric disorders	40 (7.8)	4 (3.0)
Sleep disorder	9 (1.8)	–
Anxiety	8 (1.6)	–
Investigations	30 (5.8)	8 (5.9)
Weight increased	17 (3.3)	2 (1.5)
International normalized ratio increase	8 (1.6)	5 (3.7)
Respiratory, thoracic and mediastinal disorders	24 (4.7)	6 (4.4)
Cough	12 (2.3)	4 (3.0)
Skin and subcutaneous tissue disorders	23 (4.5)	3 (2.2)
Rash	7 (1.4)	–
Renal and urinary disorders	16 (3.1)	6 (4.4)
Renal failure	6 (1.2)	2 (1.5)
Urinary retention	–	2 (1.5)
Reproductive system and breast disorders	14 (2.7)	–
Musculoskeletal and connective tissue disorders	13 (2.5)	5 (3.7)
Myalgia	6 (1.2)	4 (3.0)
Metabolism and nutrition disorders	13 (2.5)	5 (3.7)
Hyperkalaemia	–	2 (1.5)
Injury, poisoning and procedural complications	10 (1.9)	7 (5.2)
Fall	10 (1.9)	7 (5.2)
Endocrine disorders	8 (1.6)	4 (3.0)
Hypoglycaemia	–	3 (2.2)
Blood and lymphatic system disorders	6 (1.2)	3 (2.2)
Anaemia	–	3 (2.2)

ADR, adverse drug reaction; –, ≤1% of ADRs. *System Organ Classes according to the Medical Dictionary for Regulatory Activities (MedDRA) [50]. †According to the Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA) [50]. ‡Representing >1% of all or preventable ADRs.

previous studies [9, 17, 20–26, 55], demonstrating that ADEs are a significant burden in the entire healthcare setting. Our lower prevalence than the recently reported 19% 1 month prevalence of self-reported ADEs among Swedish adults [25] may be explained by our retrospective study design [9], the incompleteness of medical records, and patients' unique ability to report events [21, 56]. In particular, the higher prevalence of UTIs in self-reports [25] implies their insufficient detection from medical records exclusively. Our inclusive ADE definition and thorough case detection facilitated by access to all medical records, including before and after the study period, probably contributed in our reasonably high 25% ADE prevalence among individuals with healthcare

Table 6

Organs affected by STEs and preventable STEs, with STE symptoms

Organ system* and symptom†	STEs (*n* = 381) *n* (%)‡	Preventable STEs (*n* = 172) *n* (%)‡
Vascular disorders	72 (18.9)	41 (23.8)
Hypertension	71 (18.6)	41 (23.8)
Psychiatric disorders	59 (15.5)	21 (12.2)
Depression	15 (3.9)	7 (4.1)
Anxiety	11 (2.9)	4 (2.3)
Sleep disorder	9 (2.4)	–
Depressed mood	5 (1.3)	2 (1.2)
Panic disorder	5 (1.3)	–
Insomnia	4 (1.0)	2 (1.2)
Musculoskeletal and connective tissue disorders	48 (12.6)	17 (9.9)
Back pain	14 (3.7)	3 (1.7)
Arthralgia	11 (2.9)	4 (2.3)
Pain in extremity	5 (1.3)	3 (1.7)
Endocrine disorders	33 (8.7)	25 (14.5)
Hyperglycaemia	31 (8.1)	24 (14.0)
Cardiac disorders	29 (7.6)	8 (4.7)
Oedema peripheral	11 (2.9)	2 (1.2)
Cardiac failure	6 (1.6)	2 (1.2)
Angina pectoris	4 (1.0)	–
Respiratory, thoracic and mediastinal disorders	27 (7.1)	9 (5.2)
Asthma	10 (2.6)	5 (2.9)
Sinusitis	5 (1.3)	2 (1.2)
Gastrointestinal disorders	20 (5.3)	5 (2.9)
Abdominal pain upper	4 (1.0)	–
Constipation	–	2 (1.2)
Skin and subcutaneous tissue disorders	18 (4.7)	11 (6.4)
Eczema	–	3 (1.7)
Nervous system disorders	14 (3.7)	5 (2.9)
Migraine	5 (1.3)	2 (1.2)
Headache	–	2 (1.2)
General disorders and administration site conditions	12 (3.2)	4 (2.3)
Pain	11 (2.9)	3 (1.7)
Renal and urinary disorders	11 (2.9)	7 (4.1)
Urinary tract infection	7 (1.8)	5 (2.9)
Ureteritis	–	2 (1.2)
Metabolism and nutrition disorders	10 (2.6)	8 (4.7)
Hyperlipidaemia	4 (1.0)	4 (2.3)
Investigations	8 (2.1)	5 (2.9)
Reproductive system and breast disorders	7 (1.8)	–
Eye disorders	5 (1.3)	–
Blood and lymphatic system disorders	–	2 (1.2)
Anaemia	–	2 (1.2)

STE, sub-therapeutic effect of drug therapy; –, ≤1% of STEs. *System Organ Classes according to the Medical Dictionary for Regulatory Activities (MedDRA) [50]. †According to the Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA) [50]. ‡Representing >1% of all or preventable STEs.

encounters, compared with studies on outpatients [9, 17, 20–24, 26, 55]. The higher proportion of admissions contributed by ADEs in our study, 22%, compared with prior studies [6, 9, 10], may in addition be explained by the ambition in Sweden to hospitalize only the most severely ill, at high risk of ADEs. Despite our relatively high ADE prevalences compared with previous observational studies, expert panels have estimated ADEs even more common [57–59], indicating that our prevalences are not overestimations.

Drug classes and organ systems associated with ADEs among the general public varied between the ADE categories, but were by and large similar to previous descriptions for ambulatory care patients [9, 12, 15, 17, 25, 26] and different from hospitalized patients [60–62]. As reported previously [9, 17, 25, 26], the most commonly dispensed drugs, nervous system and cardiovascular drugs, contributed to ADEs the most frequently. Within the nervous system drugs, antidepressants dominated ADRs and analgesics STEs, as found before for self-reports [25], while analgesics, hypnotics and sedatives, and anxiolytics caused DD and DA. Although gastrointestinal ADRs have been described as common [12, 15, 25], we found them the most common among ADRs. However, if nervous

Table 7

Sensitivity analyses, by varying the denominator, for the 3 month prevalence of persons with ADEs and preventable ADEs

	Main analysis		Sensitivity analyses			
	Denominator all individuals ($n = 4970$)		Denominator individuals with dispensed drugs† ($n = 3005$)		Denominator individuals with healthcare encounters ($n = 2434$)	
	n	Prevalence % (95% CI)	*n*	Prevalence % (95% CI)	*n*	Prevalence % (95% CI)
Any ADE*	596	12.0 (11.1, 12.9)	550	18.3 (16.9, 19.7)	596	24.5 (22.8, 26.2)
ADRs	342	6.9 (6.2, 7.6)	323	10.7 (9.6, 11.9)	342	14.1 (12.7, 15.4)
DIs	7	0.1 (0.0, 0.2)	6	0.2 (0.0, 0.4)	7	0.3 (0.1, 0.5)
DD or DA	20	0.4 (0.2, 0.6)	20	0.7 (0.4, 1.0)	20	0.8 (0.5, 1.2)
STEs	320	6.4 (5.8, 7.1)	301	10.0 (8.9, 11.1)	320	13.1 (11.8, 14.5)
UTIs	47	0.9 (0.7, 1.2)	36	1.2 (0.8, 1.6)	47	1.9 (1.4, 2.5)
Any preventable ADE*	278	5.6 (5.0, 6.2)	256	8.5 (7.5, 9.5)	278	11.4 (10.2, 12.7)
Preventable ADRs	106	2.1 (1.7, 2.5)	101	3.4 (2.7, 4.0)	106	4.4 (3.5, 5.2)
Preventable DIs	7	0.1 (0.0, 0.2)	6	0.2 (0.0, 0.4)	7	0.3 (0.1, 0.5)
Preventable DD or DA	18	0.4 (0.2, 0.5)	18	0.6 (0.3, 0.9)	18	0.7 (0.4, 1.1)
Preventable STEs	152	3.1 (2.6, 3.5)	141	4.7 (3.9, 5.4)	152	6.2 (5.3, 7.2)
Preventable UTIs	35	0.7 (0.5, 0.9)	28	0.9 (0.6, 1.3)	35	1.4 (1.0, 1.9)

ADE, adverse drug event; ADR, adverse drug reaction; CI, confidence interval; DA, drug abuse; DD, drug dependence; DI, drug intoxication from overdose; STE, sub-therapeutic effect of drug therapy; UTI, morbidity due to drug-related untreated indication. *As one person could have multiple ADEs, the combined prevalence is lower than the sum of the prevalences of the ADE categories. †Dispensed drugs from the Swedish Prescribed Drug Register, for all study individuals from 6 months before the study period until the last day before the study period.

system and psychiatric ADRs and fatigue were combined in our study, ADRs affecting the 'central nervous system' would become the most common, in line with others' findings [12, 15]. ADRs or ADEs related to electrolyte, renal, hepatic, and haematologic functions are reported more common among hospitalized patients [60–62] than in our and others' general population samples [15, 25], probably due to the differing nature of outpatient care, patients' age, and possibly overseeing such events in retrospective studies or studies using patient reports. Similarly to disease specific studies [63, 64], but unlike in studies on all ADEs [12], we found hypertension and hyperglycaemia as STEs of antihypertensives and antidiabetics, and psychiatric and musculoskeletal STEs common in the general population. ADEs have previously been described to constitute of heterogeneous events [6, 8–12, 25–32], but our results illustrate that also reporting the associated drugs and affected organs by ADE category further contributes in understanding their nature.

Our 39% preventability of ADEs in the general population is comparable with previous estimates [8–12, 14], as is the similarity of all and preventable ADEs [25, 26]. As for all ADEs, nervous system and cardiovascular drugs were the most commonly associated with preventable ADEs, in line with the findings of others [12, 25, 26, 65]. Complementary findings to previous research were our high frequencies of preventable STEs of antihypertensives (resulting in hypertension) and antidiabetics (resulting in hyperglycaemia), which in most studies have not been separated from all preventable ADEs from antidiabetics and antihypertensives [12]. These results reveal the usefulness of categorizing ADEs also for investigating preventability and developing preventive strategies.

Implications and future research

The heterogeneous nature of ADEs in our study reinforces the demand for improving and harmonizing definitions and classifications for ADEs and preventable ADEs, and methods for assessing them [7, 51, 52, 66, 67]. Apart from the traditionally emphasized ADRs, the other categories of ADEs combined caused harm more frequently, and differed in their nature from each other and from ADRs in terms of associated drugs, affected organs, preventability and seriousness. The ADE categories should therefore be considered in research and clinical practice for preventing, detecting and mitigating ADEs. Considering the reduction of ADEs more strongly as part of patient safety and quality of care would probably also benefit conceptualizing ADEs.

Although the results of this study reflect the Swedish healthcare system and the prevalence and pattern of ADEs vary depending on the patient population, settings, ADE definitions and methods [6], ADEs are most likely a significant health concern also in other countries and regions. Our results are the most generalizable to other countries with a similar disease burden dominated by non-communicable diseases [68], a similar pattern of drug use with a high annual prevalence of anti-infective, anti-inflammatory, cardiovascular and nervous system drug use [69], and a similarly structured publicly funded healthcare system [70]. Further, ADEs are unlikely to be exceptionally common in Sweden, considering the high

quality of the Swedish healthcare system concerning patient safety indicators, compared with other high-income countries [71].

Despite the higher preventability of serious ADEs and ADEs in hospitals, also described by others [9, 26], ADEs should be prevented, detected and mitigated in the entire healthcare system, because a large quantity of non-serious events combined may result in considerable direct resource consumption [72], and indirect costs [73]. Further, the high burden of ADEs and preventable ADEs from widely used drugs warrants large scale efforts to redesign safer, higher quality healthcare systems, as urged previously [74–76]. Significant improvements in quality and safety require the commitment of clinicians and care units, collaboration with patients, researchers and safety experts, and strong political will and leadership. As framed by Charles Vincent on improving patient safety: '*Only very few systems have probably understood the nature and scale of capacity development that is actually needed; most have relied on enthusiasm, culture change and people doing quality improvement work in their non-existent spare time*' [74].

In conclusion, the considerable burden of ADEs and preventable ADEs from commonly used drugs in the adult general public warrants large-scale efforts to redesign safer, higher quality healthcare systems, across care settings. The heterogeneous nature of the ADE categories should be considered in research and clinical practice for preventing, detecting and mitigating ADEs.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1
Pharmacological sub-groups and drugs associated with ADE categories, ordered according to the most commonly dispensed drugs to all study individuals

Table S2
Drugs associated with symptoms of ADRs or preventable ADRs ≥2 times

Table S3
Drugs associated with symptoms of STEs and preventable STEs ≥2 times