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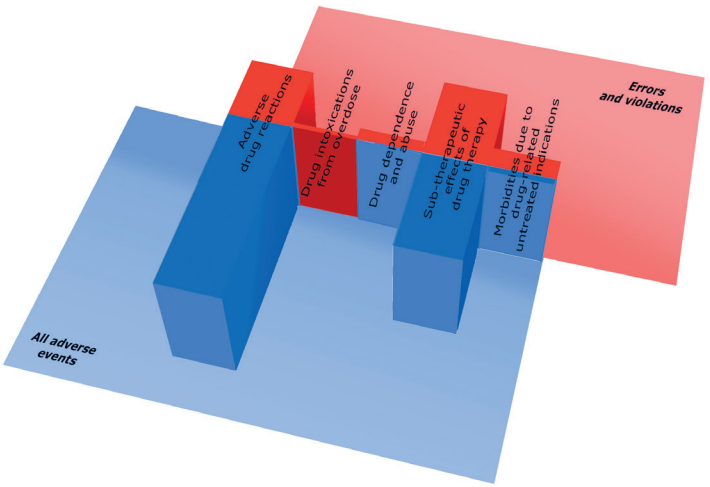
Prevalence and nature of adverse drug events and the potential for their prevention

Population-based studies among adults



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ABSTRACT

Background: Adverse drug events (ADEs) are common and often preventable in hospitals, but few studies have investigated ADEs in outpatient care and none addressed this issue in the general population.

Aim: The aim of this thesis is to estimate the prevalence of ADEs in the general population, to investigate the nature of ADEs, including categories of ADEs, and to evaluate the potential for preventing ADEs.

Methods: An expert panel of Swedish physicians in 2010 (n=19), a population-based survey to Swedish adults in 2010 (n=7099), medical records of adult residents of a county council in Sweden in 2008 (n=4970), and citations of bibliographic databases until 2010 (n=5770) were used as data sources, in addition to regional and national registers. ADEs were categorised into adverse drug reactions (ADRs), drug intoxications from overdose, drug dependence and abuse, sub-therapeutic effects of drug therapy (STEs), and morbidities due to drug-related untreated indications. The physicians estimated the proportions of their current patients with ADEs and preventable ADEs. The survey respondents reported experienced ADEs and their perceived preventability of ADRs and STEs. From the medical records, ADEs and their preventability were assessed manually by pharmacists and physicians, in a stepwise manner. A meta-analysis and a systematic literature review were conducted to summarise previous literature on preventable ADRs and methods to assess the preventability of ADEs.

Results: Swedish physicians estimated that half of their current outpatients and inpatients experienced ADEs. The one-month prevalence of self-reported ADEs in the adult general public was 19%, and the three-month prevalence of ADEs from medical records 12%. In the survey and medical record studies, ADRs and STEs constituted most ADEs and were equally prevalent. ADEs were frequently associated with nervous system and cardiovascular drugs, but the associated drugs, affected organs and seriousness varied by ADE category. The physicians estimated 24-31% of all ADEs preventable, while 39% of ADEs in the medical records were judged preventable. Of the ADE categories, a larger proportion of STEs than

ADRs was perceived preventable by the survey respondents or judged preventable from the medical records. Based on the medical records, 56% of serious ADEs and 55% of serious ADRs were preventable, more than for non-serious ADEs and ADRs. Also based on the meta-analysis, half of ADRs among hospitalised and emergency patients were preventable. By large the associated drugs and affected organs for preventable ADEs were similar to all ADEs. Methods for assessing the preventability of ADEs were diverse, with unknown validity and scattered reliability.

Conclusions: The burden of ADEs in the adult general population, across care settings, demonstrates that ADEs are a considerable public health concern in the entire health system. The heterogeneous nature and varying potential preventability of the ADE categories indicate that categorising ADEs enhances the understanding of their nature and preventability. The diverse and limited methods for assessing the preventability of ADEs, however, enforce improving the assessment. Nonetheless, the high frequency of potentially preventable ADEs from commonly used drugs reinforces large-scale efforts to redesign safer, higher quality healthcare systems to adequately tackle the problem.

Keywords: adverse drug event, prevalence, preventability, medication error, patient safety, pharmacoepidemiology

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Sammanfattning på svenska

Bakgrund: Utifrån studier utförda på sjukhus förefaller läkemedelsrelaterad sjuklighet ("adverse drug events"; ADE) vara vanligt förekommande och ofta möjliga att förebygga. Få tidigare studier har emellertid undersökt ADE utanför sjukhusen eller i hela befolkningen.

Syfte: Detta avhandlingsprojekt syftar till att uppskatta förekomsten av ADE i hela befolkningen och att beskriva karakteristika och typer av ADE samt möjligheten att förebygga dessa.

Metoder: I avhandlingsprojektet användes följande datakällor: en expertpanel som bestod av 19 svenska läkare, en enkät som skickades ut till ett representativt urval av en svensk vuxen befolkning (totalt 14 000 personer varav 7099 svarade), journaldata från 4970 vuxna personer i Östergötland samt 5770 citeringar i bibliografiska databaser. De typer av ADE som undersöktes i projektet var: biverkningar, läkemedelsförgiftningar, läkemedelsberoende och läkemedelsmissbruk, otillräckliga effekter och sjuklighet p.g.a. obehandlade besvär. Läkarna uppskattade hur stor andel av deras nuvarande patienter som drabbades av ADE och förebyggbara ADE. De individer som svarade på enkäten rapporterade upplevda ADE och uppskattade förebyggbarheten för biverkningar och otillräckliga effekter. Farmaceuter och läkare granskade ADE och dess förebyggbarhet utifrån journaluppgifter och andra registerdata. Tidigare forskning om förebyggbara biverkningar samt metoder för att bedöma förebyggbarhet av ADE sammanfattades i en metaanalys och i en systematisk litteraturstudie.

Resultat: Läkarna uppskattade att hälften av deras patienter i öppen- och slutenvård drabbades av ADE. Förekomsten av självrapporterade ADE bland vuxna var 19 % under en månad. Enligt journalstudien förekom ADE hos 12 % av vuxna individer under en tremånaders period. Enligt enkät- och journalstudierna var biverkningar och otillräckliga effekter de vanligaste kategorierna av ADE. De två vanligaste läkemedelsgrupperna som var relaterade till ADE var läkemedel som påverkar nervsystemet och läkemedel mot hjärt- och kärlsjukdomar. Allvarlighetsgraden, relaterade läkemedel och efterföljande symptom varierade mellan ADE-typerna. Läkarna uppskattade att 24-31 % av ADE var förebyggbara, medan 39 % av ADE i journalerna bedömdes som förebyggbara. En större andel av otillräckliga effekter än biverkningar uppskattades som förebyggbara enligt enkätstudien och journalstudien. Baserat på journaluppgifter var 56 % av allvarliga ADE och 55 % av allvarliga biverkningar förebyggbara, vilket var en större andel än icke-allvarliga ADE och biverkningar. Enligt metaanalysen var hälften av

biverkningar hos patienter som sökte sjukvård akut eller som vårdades på sjukhus förebyggbara. För såväl förebyggbara ADE som för samtliga ADE var läkemedlen som orsakade ADE och de organ som ADE påverkade väsentligen lika. Från litteraturen identifierades ett antal olika metoder för att bedöma förebyggbarheten av ADE. Dessa metoder hade okänd validitet samt varierande reliabilitet.

Slutsats: Den utbredda förekomsten av ADE hos den vuxna befolkningen på olika vårdnivåer visar att ADE är ett betydande folkhälsoproblem. Karaktäristika och förebyggbarhet varierar mellan olika typer av ADE. Att närmare beskriva ADE i olika typer av analyser bidrar till en ökad förståelse av ADE och torde i förlängningen kunna öka möjligheten att kunna förhindra dessa. De metoder som används för att bedöma förebyggbarhet av ADE behöver vidare utvecklas. Sammantaget pekar avhandlingsprojektet på ett behov av att förbättra sjukvårdssystemet med avseende på läkemedelsanvändning.

Nyckelord: läkemedelsrelaterad sjuklighet, förekomst, förebyggbarhet, läkemedelsfel, patientsäkerhet, läkemedelsepidemiologi

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List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals. The Papers have been reprinted with the permission of the publishers.

I. Hakkarainen KM, Alström D, Hägg S, Carlsten A, Gyllensten H. Modelling drug-related morbidity in Sweden using an expert panel of physicians. Eur J Clin Pharmacol 2012;68(9):1309-1319

II. Hakkarainen KM, Andersson Sundell K, Petzold M, Hägg S. Prevalence and perceived preventability of self-reported adverse drug events – A population-based survey of 7099 adults. PLoS ONE 2013;8(9):e73166

III. Hakkarainen KM, Gyllensten H, Jönsson AK, Andersson Sundell K, Petzold M, Hägg S. Prevalence, nature and potential preventability of adverse drug events – A population-based medical record study of 4970 adults. Br J Clin Pharmacol 2013 [Epub ahead of print] doi: 10.1111/bcp.12314

IV. Hakkarainen KM, Hedna K, Petzold M, Hägg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – A meta-analysis. PLoS ONE 2012;7(3):e33236

Appendix Paper:

Hakkarainen KM, Andersson Sundell K, Petzold M, Hägg S. Methods for assessing the preventability of adverse drug events: A systematic review. Drug Saf 2012;35(2):105-126

Content

Electronic supplements

eSupplement 1	Conceptual model on drug-related morbidity (Paper I) [in Swedish]
eSupplement 2.1	Questions on self-reported adverse drug events (Paper II) [in Swedish]
eSupplement 2.2	Introductory letter of the survey (Paper II) [in Swedish]
eSupplement 3.1	Medical record review template for primary review (Paper III) [in Swedish]
eSupplement 3.2	Medical record review template for secondary review (Paper III) [in Swedish]
eSupplement 4	Meta-analysis data extraction form (Paper IV) [in English]
eSupplement 5	Literature review data extraction form (Appendix Paper) [in English]

The eSupplements, together with this thesis, are available at:
http://hdl.handle.net/2077/34825.

Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical Classification System
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DA	Drug abuse
DD	Drug dependence
DI	Drug intoxication from overdose
DRM	Drug-related morbidity
DRP	Drug-related problem
EMBASE	Excerpta Medica Database
EUR	Euro
ICD	International Classification of Diseases
IPA	International Pharmaceutical Abstract
LISA	Longitudinal integration database for health insurance and labour market studies
MedDRA	Medical Dictionary for Regulatory Activities
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Heading
NMP	New medical problem
NSAID	Non-steroidal anti-inflammatory drug
OECD	Organisation for Economic Co-operation and Development
PADR	Preventable adverse drug reaction
PIN	Personal identity number
PsycINFO	Abstract database of psychological literature
SCB	Statistics Sweden
SD	Standard deviation
SPDR	Swedish Prescribed Drug Register
STE	Sub-therapeutic effect of drug therapy
TF	Therapeutic failure
UTI	Morbidity due to drug-related untreated indication
VDL	Care Data Warehouse of Östergötland
WHO	World Health Organization

1 Introduction

Over the past 100 years, the discovery of drugs, such as aspirin, smallpox vaccine, penicillin, antipsychotics, insulin, and antiretrovirals, has contributed in the prevention and care of diseases. Today, drugs remain a cornerstone in healthcare, and are among the most common interventions in fostering good health. In Sweden, approximately two-thirds of the population purchase at least one prescribed drug annually (1).

The possible occurrence of unexpected, hazardous effects of drugs gained increased awareness in the early 1960's, starting from the global thalidomide scandal (2). The use of a then new drug, thalidomide, as a sedative and antiemetic among pregnant women was linked with limb malformations among their newborns, effecting at least 10 000 children born worldwide (3,4). To prevent similar public health disasters, many countries developed national centralised systems for collecting reports of suspected adverse drug reactions (ADRs) (2). In an effort to also identify rare ADRs, national ADR reports have been pooled since 1970 by a World Health Organization (WHO) Collaboration Centre, today known as the Uppsala Monitoring Center. In 2010, 136 countries participated in the scheme of centralising ADR reports to the Uppsala Monitoring Center, including Sweden (5). Over the decades, the aims of the reporting scheme have broadened from the original aim of detecting unknown ADRs, and now also include improving drug use when ADRs are known. Other schemes developed or used for detecting ADRs include cohort-event monitoring systems and medical birth registers (6,7).

Patient safety is considered a key element of overall quality of healthcare (8,9). In the early 1990's, a study in the United States demonstrated that one-third of adverse patient outcomes in hospitals occur due to errors and thus, could be prevented (10). This was a turning point in the recognition of errors that occur in the healthcare system. Adverse events resulting from drug therapy, adverse drug events (ADEs), were reported to be the most common types of adverse events in hospitals (10). Another landmark publication in 1999, entitled *To err is human: building a safer health system*, reported that medical errors cause up to 100 000 preventable deaths in American hospitals annually (11). The report advocated improving patient safety, because despite previous evidence on errors, few responsive actions had been taken to address the problem. Today, preventable adverse patient outcomes are widely recognised as a public health concern and improving patient safety is top on the agendas of the WHO (12), the Council of Europe (13), and national health authorities, including those in Sweden (14,15).

In the 21st century, ADEs are still estimated among the most common adverse outcomes in healthcare (16,17). In review studies, at mean or median 13% of

ambulatory care patients (18), 5% of outpatients being hospitalised (19), and 4% of inpatients are reported to experience ADEs (20). The ADEs are associated with increased direct costs for healthcare and the society (21-24), including costs from hospitalisations, control visits and rehabilitation. Indirect costs, such as lost productivity, also result in increased burden to society. In addition, patients describe ADEs to worsen their health status and cause worry and discomfort in their daily lives (25-28).

However, approximately 20-60% of ADEs are potentially preventable, although estimates vary from 11% to 90% (18,20,29-32). Due to the considerable yet avoidable burden of ADEs, associated research is considered a priority area for patient safety research in Western countries (12). The first step in patient safety research is measuring the magnitude and type of adverse events (33,34), as the events do not occur randomly but in identifiable patterns (35). The identification of preventable events enables further studying of the underlying causes leading to preventable harm. Once the underlying causes are understood, solutions for safer healthcare may be developed and implemented, and the impact of the solutions evaluated. Information gained through these steps is used for developing procedures, systems and policies for improving patient safety internationally, national, regionally and in individual organisations.

One definition for public health is *the science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals* (36). An important part of public health is epidemiology, as epidemiological knowledge on the distribution, determinants and causes of health-related states and events enables the development of initiatives for improving health (37). Within patient safety, epidemiological research on the distribution and nature of adverse events and those of which are preventable is required for investigating the causes of preventable events (33).

1.1 Definitions and classifications

Patient safety

The World Health Organization (WHO) defines patient safety as *the reduction of risk of unnecessary harm associated with healthcare to an acceptable minimum* (38). As a fairly young field, however, concepts in patient safety are not harmonised (39,40), hindering the comparison between studies and improving safety practices. To facilitate describing, comparing, measuring, monitoring, analysing and interpreting patient safety information, the WHO recently published a conceptual framework for the International Classification for Patient Safety (Figure 1) (38). The framework is anticipated to assist health professionals, researchers, policy-makers and others working in the field in conducting research and planning health policies.

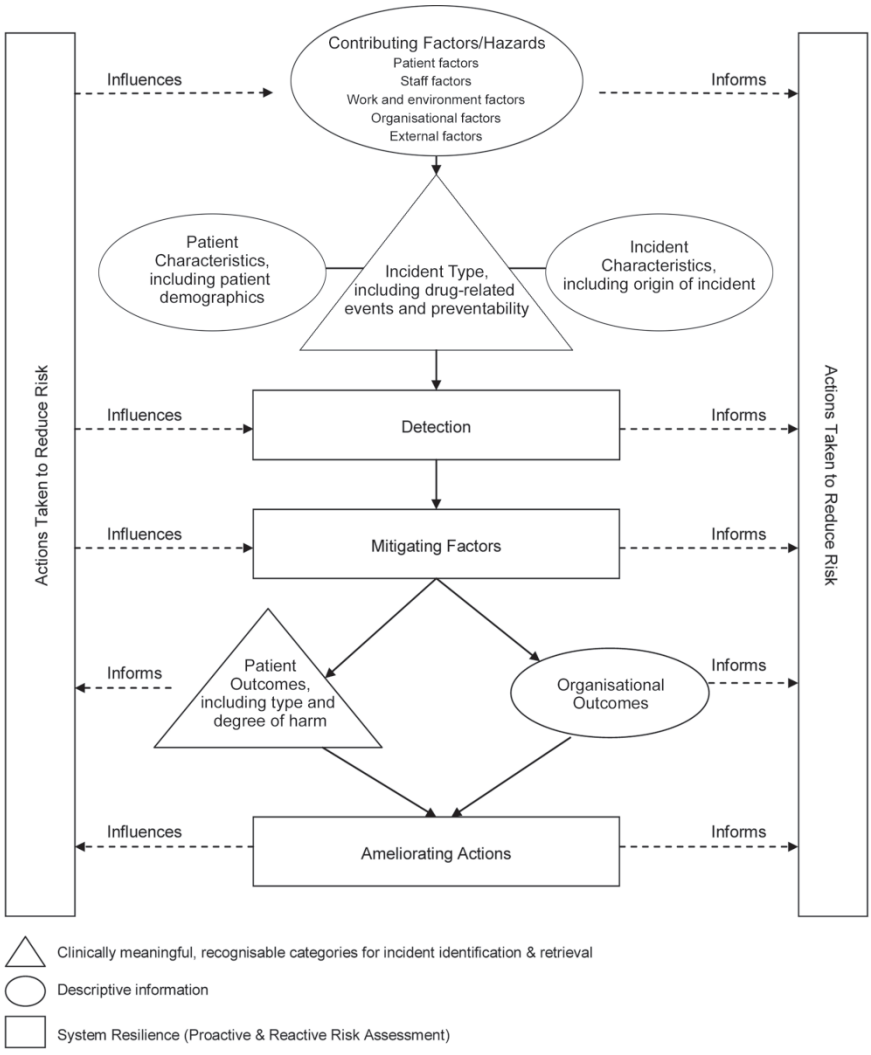


Figure 1. Conceptual Framework for the International Classification for Patient Safety (38). ©WHO, 2009. All rights reserved. WHO/IER/PSP/2010.2. Permission obtained for reproduction.

The WHO's framework conceptualises patient safety through ten domains which are related to each other (Figure 1) (38), each of which is hierarchically arranged into sub-divisions. Collective information from all of the domains is required for improving safety. Two of the main domains, *incident type* and *patient outcomes*, group patient safety incidents into clinically meaningful, recognisable categories. An incident refers to an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient. *Incident type* groups incidents with the same nature, such as drug or nutrition-related incidents. Drug-related incidents may be further classified according to a possible problem behind the incident, such as a contraindication for the drug or a wrong dose, or where in the process of drug therapy they occur, such as prescribing or administering. The domain *patient outcomes* describes the impact that an incident had on a patient, for example the type of harm according to affected organs or the degree of harm from no harm to death. An incident that leads to patient harm is an adverse event. Descriptive information on the context of incidents is captured by the main domains *patient characteristics*, *incident characteristics*, *contributing factors/hazards*, and *organisational outcomes*. The remaining four main domains provide information on how the system proactively and reactively manages incidents.

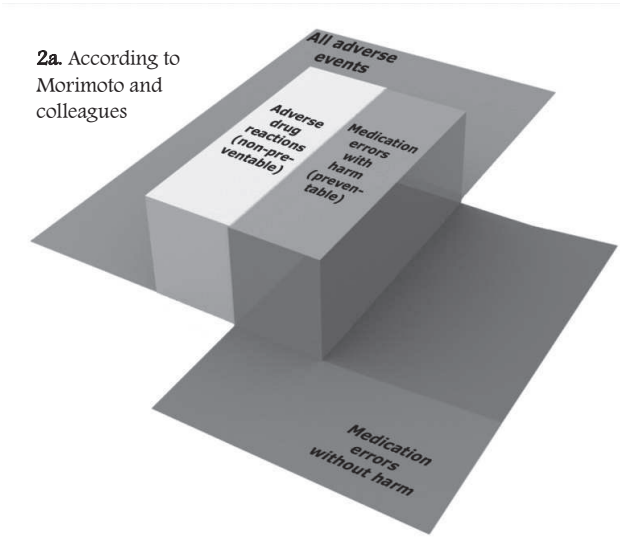
The WHO (38) considers an adverse event preventable when it is accepted by the community as avoidable in the particular set of circumstances. The WHO does not link preventable events to errors, but defines an error as *a failure to carry out a planned action as intended or application of an incorrect plan* (41,42). Errors may occur in planning or execution and include doing the wrong thing (commission) or failing to do the right thing (omission). The WHO differentiates errors, which are unintentional, from violations that are usually deliberate. In other literature, adverse events due to errors and violations are traditionally considered preventable (10).

Adverse drug events and their preventability

In the WHO's classification for patient safety (Figure 1) (38), ADEs represent drug-related incidents (incident type) which lead to patient harm (patient outcome). A common definition for an ADE is *an injury resulting from medical intervention related to a drug* (43). In the literature, ADEs are commonly considered preventable when they occur as a result of a medication error (43), one definition of which is *a failure in the [drug] treatment process that leads to, or has the potential to lead to, harm to the patient* (44). Medication errors may occur at any stage of the drug treatment or use process, including prescribing, dispensing, monitoring or administrating (43). Most medication errors do not result in ADEs, by coincidence or because they were interrupted (43,45). In the literature, the term ADR is also frequent and often defined as *a response to a drug which is noxious and unintended, and which occurs at doses normally used in man* (46). Thus, ADEs include ADRs (47). Even though the terms ADE, ADR, preventable ADE, preventable ADR, and medication error are widely used, there is no consensus on their definitions and classifications (43,47-50).

There are, however, two main approaches to conceptualise ADEs, ADRs and medication errors. According to Morimoto and colleagues (43), ADEs consist of

medication errors that lead to harm, which are by definition preventable, and ADRs (Figure 2a). ADRs and medication errors are considered mutually exclusive, and thus ADRs are never preventable. In the WHO's framework (38), ADEs (drug-related incidents leading to patient harm) are categorised similarly to Morimoto and colleagues' approach (43). Others have defined ADRs differently (51), elaborated on their preventability (49), and found part of them preventable (52). Along these lines, Aronson and Ferner (44,47) categorise medication-related adverse events into medication errors that lead to harm and ADRs, but these two are not mutually exclusive (Figure 2b). Although Aronson and Ferner do not discuss preventability nor the use the term ADE, medication-related adverse events could be considered as ADEs and the ones caused by medication errors as preventable ADEs, based on other literature. Thus, some ADRs are preventable, according Aronson and Ferner.



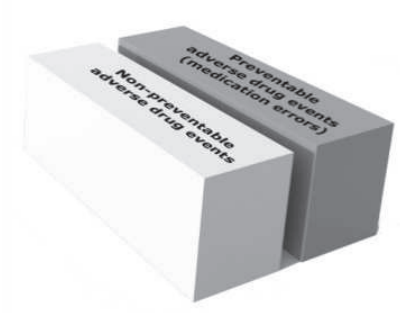
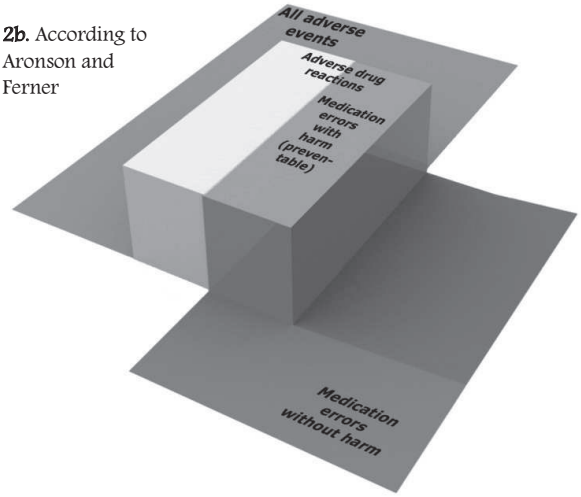
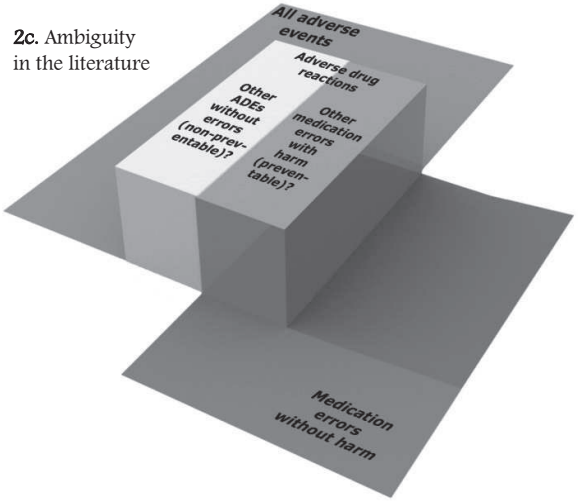


Figure 2. Relationships between all adverse drug events (ADEs), preventable ADEs, adverse drug reactions (ADRs), and medication errors, interpreted from classifications by **2a)** Morimoto and colleagues (43) and **2b)** Aronson and Ferner (44,47). The classification **2c)** illustrates ambiguity in the literature, and **2d)** ADE categorisation in this thesis.

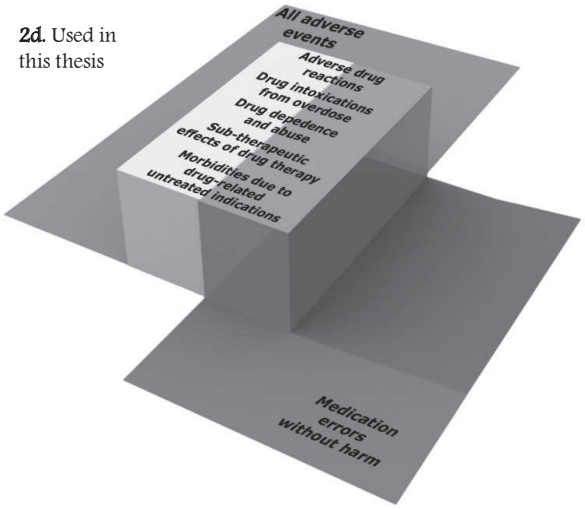
2b. According to Aronson and Ferner



2c. Ambiguity in the literature



2d. Used in this thesis



Even though common definitions for ADEs are broad (43,50), including wording such as *any injury related to drug*, the specific types of events included in ADEs are ambiguous in the literature, apart from ADRs (Figure 2c). The clause *at doses normally used* for defining ADRs (46) implies that intoxications from overdoses are excluded from ADRs, and could thus be another category of ADEs. Others have found drug dependence and abuse frequent (53). Sub-therapeutic effects have also been identified as a category of ADEs (54,55), and are generally considered a public health concern (56). Another introduced ADE category is *adverse events due to failure to receive a drug that the patient has an indication for* (57), which has also been described in disease specific studies (58-60). Because the broad definition for ADEs (43) was interpreted to include this range of events, ADEs in this thesis include (Figure 2d): ADRs, drug intoxications from overdose (DIs), drug dependence (DD), drug abuse (DA), sub-therapeutic effects of drug therapy (STEs), and morbidities due to drug-related untreated indications (UTIs). In this thesis, each of these ADE categories may be associated with a medication error, i.e. may or may not be preventable. This deviates from the classifications by Morimoto and colleagues (43) and Aronson and Ferner (44,47), which do not recognise non-preventable ADEs, apart from ADRs.

ADEs have also been investigated using drug-related visits to healthcare units as outcome measures, such as drug-related admissions or emergency department visits (61-64). In these studies, drug-related visits are commonly divided into subgroups according drug-related problems, for example by Hepler and Strand (65): untreated indication, improper drug selection, sub-therapeutic dosage, failure to receive drugs, overdosage, ADR, drug interaction, and drug use without indication. However, the drug-related problems categories are criticised for mixing morbidity (e.g. ADR) and problems related to it (e.g. drug-drug interaction or inappropriate dose) (66). Thus, the categories are not mutually exclusive. Although efforts have been made to improve the categorisation of drug-related problems (67), categories that are not mutually exclusive hinder using drug-related problems for comparing the frequency of the ADE categories.

Definitions for preventable ADEs (49) and medication errors (48,50) also vary in the literature. Furthermore, a recent narrative review found the current approaches for assessing preventability of ADEs limited (49). It remains unclear also in the WHO's framework (38), whether ADEs related to errors, such as a wrong or omitted dose, are automatically preventable. Further, the definitions of and discussion on preventability of ADEs are focused on medication errors by healthcare providers and patients, but violations are rarely mentioned, even though both errors and violations can be considered preventable in patient safety literature (41,68,69).

1.2 Prevalence of all adverse drug events

Regardless of the heterogeneity of definitions, ADEs are common in both outpatient (18,21,24,70,71) and inpatient care (18-20,24,29,31,32). Of ambulatory

patients, 13% have been estimated to experience ADEs, according to a review study (18). Other review studies have reported that 5% of patients at the time of admission (19) and 4% of patients during hospitalisation experience ADEs (20). In primary care exclusively, 10-12% of patients to have been reported to experience ADEs (70,71). However, the estimates in individual observational studies range from 0.1% to 61% of patients experiencing ADEs (18-20,29,31,32,70,71), probably due to differing settings, patient populations, and used definitions for ADEs (19). As observational studies have mainly investigated ADEs among hospitalised patients, evidence of the proportion of persons with ADEs in the entire healthcare system and among the general public relies on modelling studies. In an American modelling study from 1995, an expert panel of pharmacists estimated that 40% of ambulatory patients receiving drugs experiences ADEs (21). According to Swedish pharmacists' more recent estimation (24), 61% of all patients visiting healthcare experience ADEs. These estimates on the proportion of patients with ADEs are higher than in most observational studies, suggesting that ADEs may be more common in the entire healthcare system than observational studies in specific care settings report, although pharmacists' perception may be subjective.

1.3 Nature of adverse drug events

In this thesis, the nature of ADEs refers to three of the ten main domains of patient safety in the WHO's framework for patient safety (38) (Figure 1): incident types, patient outcomes, and patient characteristics. *Incident type* in this thesis refers to the occurring ADE categories and drugs associated with them. Information on the types of the occurring events is required for further investigating their context, such as their contributing factors, and developing systems for their detection and management during the care process and for their prevention in the future. *Patient outcomes* investigated in this thesis include organ systems in which ADEs manifest, such as the cardiovascular system, and the clinical seriousness of the harm. Understanding such patient outcomes facilitates allocating resources for the prevention of adverse events (72). Other patient outcomes, excluded from this thesis, include the social or economic impact of ADEs on individuals (38). *Patient characteristics* provide information on the context in which the events occurred, and include patient demographics, the original reason for seeking care and the primary diagnosis, of which person demographics are investigated in this thesis. Collective knowledge on these aspects of the nature of ADEs, ADE categories, associated drugs, affected organs, seriousness, and person demographics, enables further investigating possibilities for preventing ADEs. Although the preventability of ADEs is classified under incident types according to the WHO (38), the potential for preventing ADEs is presented and discussed under separate headings in this thesis.

Categories of adverse drug events

Based on the few existing studies dividing ADEs into categories (54,55,57,73-78), most ADEs appear ADRs or STEs in emergency and inpatient care. At the time of an admission or emergency care visit, ADRs have been found to constitute 19-64% and STEs 26-81% of all ADEs (54,55,57,73-75). UTIs were in one study described the most common ADE among elderly admitted patients (76), while another study found untreated indications to account for much fewer, 4% of ADEs at admission (57). DIs have represented 6-12% of all ADEs in emergency care or at admission (57,73,74,77,78). DD and DA have been excluded from some studies on ADEs (79), but most have not mentioned them (80,81), leaving their inclusion unclear.

Based on the studies dividing ADEs into categories, ADRs and STEs also appear to concern more inpatients and emergency care patients, compared to the other ADE categories. ADRs are estimated to be present at mean or median among 3-6% of patients at the time of hospitalisation (19,82-86), with a range of 0.1-54% in individual studies, and among 7-11% of inpatients during hospitalisation (20,85), ranging from 0.3% to 61% across studies. STEs are reported to occur in 1-9% of admissions or emergency visits (54,55,57,73-75,87), and UTIs have been related to 5% of admission among the elderly (76), and 0.4% of admissions among adults (57). DIs are reported to occur in 0.3-2% of admissions or emergency visits (57,73,74,77,78). The 12-month prevalence of DD and DA are separately reported to be 0.3% for sedatives, anxiolytics or opioids (53), and 1.1% for any non-illicit drugs (88).

Despite the large number of observational studies on all ADEs, the distribution of the ADE categories is largely unknown in primary care, the entire healthcare system or the general population.

Drugs associated with events

Drugs associated with ADEs have mainly been studied in hospital settings and are usually reported either for all ADEs as one group or for exclusively ADRs (18,20,29,31,86). In reviews summarising studies in outpatient clinics and hospitals, drug classes associated with at least 10% of ADEs or those preventable include cardiovascular drugs, nervous system drugs, antithrombotic agents, antibacterials for systemic use, nonsteroidal anti-inflammatory drugs (NSAIDs), and drugs for blood and blood forming agents (18,29,89). The same drug classes have been found common for ADRs exclusively (82,84,86), with the addition of corticosteroids for systemic use, antineoplastic agents, and drugs used in diabetes (82,84). Drugs for the nervous system are known to dominate among DD and DA cases (53), while drugs causing intoxications are diverse (90). STEs of cardiovascular drugs have been described the most common among emergency patients with STEs (87), and STEs of antiepileptics and diuretics among patients with preventable STE-related admissions (89). In previous research, drug classes associated with preventable ADEs have by large been similar to drug classes associated with all ADEs, although some have suggested that cardiovascular drugs, analgesics and hypoglycaemic

agents are more frequently associated with preventable than all ADEs in ambulatory care (31). However, as few studies have reported the associated drugs by ADE category, little is known about them, in particular in primary care, the entire healthcare system and the general population.

Organs affected by events

ADEs and preventable ADEs in primarily outpatient settings have most frequently been found to affect the gastrointestinal, cardiovascular or central nervous systems (18,31,80,91). In emergency care, ADEs affecting skin have been described the most common, followed by gastrointestinal and neurological ADEs (79). In hospitals, frequent preventable and non-preventable ADEs included gastrointestinal disorders (such as constipation, nausea, and diarrhoea), allergic reactions, increased international normalised ratio (INR) and bleedings, dizziness and falls, and ADEs related to neurologic, cardiac, electrolyte, renal, endocrine and hematologic functions (29,92-94). However, as organ systems where ADEs manifest have mainly been investigated in specific outpatient populations, emergency care and hospitals and ADE categories are infrequently distinguished (55,63,74,75), evidence on organs affected by ADEs in the community is limited.

Seriousness

In previous studies in hospitals, approximately half of ADEs have been reported as serious (81,95), while fewer ADEs have been described as serious in outpatient settings (80,96). Even though each serious ADE is likely to consume more resources than a non-serious ADE, such as dry mouth or tremor, clinically non-serious ADEs may collectively require more healthcare resources if they are significantly more frequent (72). Furthermore, clinically non-serious ADEs burden individuals and the society through negatively influencing patients' wellbeing and daily lives (25-28). As the burden of serious and non-serious ADEs, by ADE category, is unknown in the general population, such evidence is required for prioritising resources on prevention in a population level.

Person demographics

The demographics of persons experiencing or reporting ADEs, contributing to the context in which ADEs occur (38), influence the occurrence of ADEs (53,63,75,76,92,97-103). ADEs or preventable ADEs, detected primarily from hospital medical records, have been more common among the elderly (63,75,76,92,97,98). When self-reports have been exclusively used, however, the elderly have not reported ADEs more frequently (102), or have reported fewer ADRs (103). Many have also found ADEs more common among females than males (63,75,92,97-101). However, as these studies include selected groups of patient (97,100-103), the characteristics of persons with ADEs probably reflects the patient population, leaving the demographic characteristics in the general population unknown.

1.4 Potential for preventing adverse drug events

Occurrence of preventable adverse drug events

For developing preventive strategies for ADEs, the occurrence of preventable ADEs is particularly interesting. Even though a large proportion of ADEs have been estimated potentially preventable, estimates vary in the literature. In review studies on hospitalised patients, at median or mean 20-60% ADEs are estimated preventable, with a range of 11-90% in individual studies (20,29,30,32). In observational studies conducted in outpatient clinics, 11-28% of ADEs have been judged preventable with a median of 17% (18). In one study in primary care, 23% of ADEs were judged preventable (70). For both outpatients and inpatients, an expert panel of Swedish pharmacists recently estimated that among patients with ADEs 45% of suffered from preventable ADEs (24). However, the preventability of ADEs in the entire healthcare system and the general population has not been investigated in observational studies.

Estimates on the percentage of patients experiencing preventable ADEs also differ between studies (18,20,32,89). Approximately 2% of ambulatory patients may be considered to suffer from preventable ADEs, because at median 13% ambulatory patients experienced ADEs, 17% of which were preventable (18). Approximately 3-4% of all admissions are estimated preventable drug-related admissions (32,89), but the estimates range from 1% to 15% in individual studies. During hospitalisation, at median 2% of inpatients are estimated to experience a preventable ADEs (20), with a wide range of 0.3-60% between studies. Even though preventable ADEs in the entire healthcare system have not been investigated in observational studies, a pharmacist expert panel recently estimated that 27% of all patients in Sweden experience preventable ADEs (24). Despite pharmacists' possibly subjective view, their high estimates indicate that preventable ADEs may be more common in the entire healthcare system than studies in outpatient clinics and hospitals suggest.

Nature of preventable adverse drug events

Few previous studies have compared the preventability of the ADE categories or the nature of preventable ADEs, by ADE category. In review studies exclusively exploring ADRs among hospitalised patients, approximately 30% of ADRs have been found preventable (52,84). In two Spanish studies focused on emergency care, STEs and UTIs were judged preventable more commonly than ADRs (63,104). In a population-based study exclusively on fatal DIs (105), all cases were considered possibly preventable. Even though literature on ADEs rarely separately reports the preventability of DD, DA, STEs and UTIs, they are commonly considered preventable in other literature (56,57,73-75,88). In previous literature on all ADEs, without separating categories, the preventability of ADEs has been described higher for serious ADEs compared to other ADEs (96). Drugs associated with

preventable ADEs and the affected organs, have been found similar for preventable ADEs and all ADEs (96). Nonetheless, research on the nature of preventable ADEs by ADE category, in the general population, is scarce.

Prevention in public health

Public health aims at increasing health, prolonging life and improving the quality of life at a population level through health promotion, disease prevention and other health interventions (106). Preventive interventions may be targeted to individuals or populations (107-109). The individual approach focuses on persons at the greatest risk, while the population approach seeks to control the causes of disease or ill-health at population level, attempting to shift the distribution of risks in populations. The population approach is advocated in public health, because the high number of people at lower risk causes more ill-health than the few people at higher risk (107-110). The challenge of achieving and sustaining behavioural change among risk persons has also been described to limit the individual approach.

Improving patient safety

In preventing harm in patient safety, the systemic approach and organisations' responsibility are emphasised rather than focusing on individuals (41,68,69). Thus, prevention in patient safety (41,68,69) shares a similar principal with prevention in public health with the population approach (107-109): identifying and addressing causes at system or population level, rather than targeting individual persons or events. Even though patient safety is described as part of public health services (111), the two concepts of prevention have not been incorporated.

For improving patient safety, learning from errors is emphasised (11), and collective information from multiple domains is required (38) (Figure 1). Firstly, incidents must be identified and classified into clinically meaningful categories (38), which is the focus of this thesis. Identifying incidents and describing their nature enables further investigating the context in which they occur, including factors that contribute in their origin and development or increase their risk. Because of the complex nature of healthcare, reasons for incidents are multi-factorial (39). The WHO's framework divides contributing factors into six categories (Table 1) (38): staff factors; patient factors; work and environment; organisational and service factors; external factors; and other factors. As described in Table 1, examples of staff and patient factors include cognitive factors such as knowledge base, and examples of organisational and service factors include organisation of teams. In addition to contributing factors described Table 1, improving patient safety also requires other information on the context and the system, including the characteristics of persons experiencing incidents and existing actions to reduce risk (38).

Table 1. Contributing factors of patient safety incidents, according to the Conceptual Framework for the International Classification for Patient Safety (38).

Staff[a] and patient[a] factors	Work/ environment factors	Organisational/ service factors	External factors	Other
Cognitive: perception/ understanding, knowledge based/ problem solving, illusory correlation, halo effects	Physical environment/ infrastructure	Protocols/ policies/ procedures/ processes	Natural environment	
Performance: technical error in execution (physical – skill based), rule based, selectivity, bias	Remote/long distance from service	Organizational decisions/ culture	Products, technology and infrastructure	
Behaviour: attention issues, fatigue/ exhaustion, overconfidence, noncompliance, routine violation, risky behaviour, reckless behaviour, sabotage/ criminal act	Environmental risk assessment/ safety evaluation	Organisation of teams	Services, systems and policies	
Communication: communication method, language difficulties, health literacy, with whom	Current code/ specifications/ regulations	Resources/ workload		
Pathophysiologic/disease related: classification of diseases[b], problems with substance abuse/ use				
Emotional				
Social				

[a]Staff and patient factors are separate categories but have the same sub-categories.
[b]According to the International Classification of Diseases (112) or the International Classification of Primary Care (113).

The systemic approach for improving patient safety is illustrated in the Organisational Accident Causation Model, first introduced by Reason (41,68) and later modified by others (69) (Figure 3). In the model, active failures represent unsafe acts committed by individuals, whose actions can immediately reach patients, possibly causing adverse events. These unsafe acts may be errors (omissions and commissions) or violations (deliberate deviations from safe operating practices). Such errors and violations are classified under incident type in the WHO's framework (38) (Figure 1). According to the Organisational Accident Causation Model (41,68,69) (Figure 3), unsafe acts originate from latent failures in the system, such as organisational processes, which cause triggering factors in the local working conditions. The triggering factors, such as high workload, poor communication or inadequate training of staff, cause the unsafe acts. The latent failures and the triggering factors can be considered to correspond to the contributing factors described in the WHO's framework (Table 1) (38). Thus, the unsafe acts committed by individuals are viewed as consequences of failures in the system, instead of causes for possible adverse events (41,68,69). The systemic approach emphasises that human conditions of the working individuals cannot be affected, but the systems in which they perform can. Since the Organisational

Accident Causation Model (41,68,69) was released in 1990, the responsibility of health systems in improving safety, instead of blaming individuals in the "sharp end" (114), has been advocated by others, including Leape (115), Vincent (116), Cook and colleagues, and Pronovost and Bo-Linn (117). Despite emphasising the responsibility of the system, however, individuals may be held accountable for acts against well-established, reasonable rules (118).

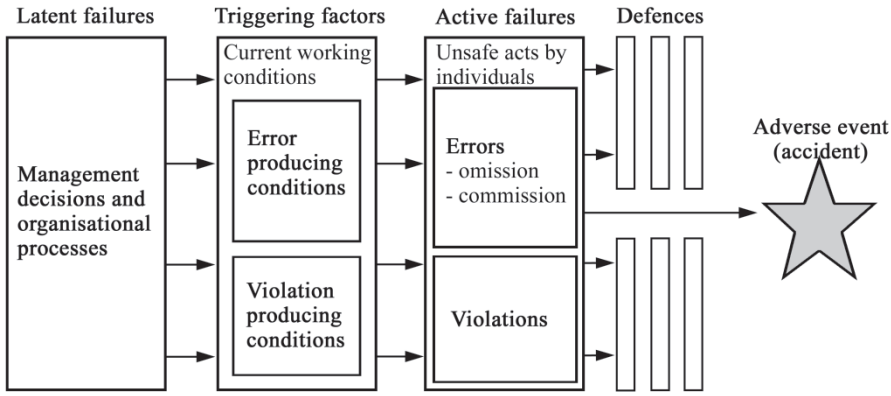


Figure 3. Organisational Accident Causation Model, modified from Reason and Taylor-Adams and colleagues (41,68,69).

According to the systemic approach, adverse events must be prevented by preventing active failures through minimising latent failures, and by building defences for active failures (41,68,69) (Figure 3). For preventing active failures, the corresponding latent failures and the triggering factors must be identified and addressed. However, even the best organisations cannot become free from all active failures, because of inherent human error and unknown or ignored latent failures. Therefore, the system must also build multiple defences for active failures to prevent them from reaching the patient, such as automated alarms and controls by health professionals. Strategies for preventing adverse events should not, however, exclusively focus on building defences, because they alone are unlikely to prevent all preventable adverse events. Unnecessary defences may also alter the pattern of errors without decreasing them (119,120).

As safety can be improved at organisational levels, as described above, the structure and functioning of the healthcare system are crucial in improving patient safety. According to American patient safety experts (121), advancing patient safety in the future requires improving transition of care, information flow, physical environments, health information technology and electronic medical records, patient centeredness, safety climate and learning from errors, and education to health professionals. The European Council and Swedish health authorities

emphasise similar aspects of patient safety, including improving education (122), creating a safety climate (15) and sharing medical records (15). Because patient safety is part of the overall quality of healthcare (8,9), improving patient safety and other aspects of quality of care partially overlap.

However, the progress in improving safety in healthcare has been slow compared to other high-risk industries, such as aviation (8,34). Improving safety in healthcare differs from the other high-risk organisations, because of the diverse and multi-contextual nature of the healthcare, fewer regulations and built-in uncertainty (39). In addition, decision-making on patients' care relies largely on humans: staff, patients and others are involved. Although priorities and required research in patient safety are continuously debated (34,123-128), the need for improving patient safety is indisputable. Thus, improved understanding of the nature of occurring preventable adverse events and the context in which they occur, including their modifiable contributing factors, is urged for improving safety (39), both for minimising latent failures in the organisation and for building defences.

Preventing adverse drug events

Preventing ADEs requires advances in the healthcare system, as described above, for improving patient safety as a whole. In addition to developing the healthcare system for improving patient safety and the overall quality of care, developing specific practices to prevent ADEs are recommended by the European Council (122), and emphasised by Swedish health authorities (129). In Sweden, developed and implemented medication specific practices include integrated medication management services to elderly inpatients (130-134), medication reconciliation at hospital discharge (135-137), improved multidisciplinary collaboration in nursing homes (138), and medication review for the elderly in primary care (139).

Numerous interventions for preventing ADEs have been introduced and studied, but evidence on their effect is scattered. Proposed preventive strategies in the scientific literature include computerised prescribing and dispensing aids (140-142), medication review by health professionals (143-152), automated medication dispensing (123), improved communication in transitions of care (153-156), patient education and counselling (157-160), improved labelling of drugs (161), education of health professionals (145,159,160,162), and monitoring and medication management for patients with specific conditions (148,158,163,164). Numerous individual interventions have shown reduced occurrence of errors or drug-related problems, but by large review studies pooling or summarising the results of individual studies have found no or weak improvement in actual patient outcomes, such as ADEs or mortality (140,144-146,148,150-152,155,156,159,160,163-165).

Despite the numerous interventions for preventing ADEs, research on their contributing factors, described in Table 1, is limited, in particular in primary care. Of potentially modifiable patient-level contributing factors, experiencing ADEs has, in quantitative studies, been associated with an increased number of drugs (61,63,75,76,80,92,94,97-99,102,103,166-174), worsening health status

(61,76,92,98,100,101,103,168,172,173,175), and impaired cognition or renal function (61). Patients' concerns about medicines (101,175) or non-adherence to drug therapy have also been found to be associated with ADEs (61). Apart from patient-level contributing factors, other contributing factors described in patient safety literature (Table 1) are less commonly studied for ADEs. Of staff factors, one quantitative study has shown that increasing the number of prescribers (172) is associated with experiencing ADEs. In qualitative studies on medication errors, without the assessment of actual health outcomes, common contributing factors include physicians' lack of knowledge about patient history (176,177), poor communication between health professionals and with the patient (176,177) and high workload (176).

Considering that developing preventive measures requires information on contributing factors (178), and investigating contributing factors requires knowledge on the occurrence of preventable events, the insufficient understanding of the burden of ADEs, their nature and preventability in the entire healthcare system may have influenced the scattered effect of the developed preventive interventions (140,144-146,148,165). Thus, research describing the prevalence, nature, and preventability of ADEs is required in the entire healthcare system. Such knowledge facilitates allocating resources to tackling ADEs, enables further analysing factors contributing to the development of ADEs, and thus contributes to developing solutions for the prevention, detection, and mitigation of ADEs.

2 Aim

The aim of this thesis is to estimate the prevalence of ADEs in the general population, to investigate the nature of ADEs, including categories of ADEs, and to evaluate the potential for preventing ADEs. The objectives of the conducted studies are described in Table 2.

Table 2. Objectives of the Papers in this thesis.

Paper	Objective
I	To estimate the proportion of patients with ADEs and preventable ADEs in Sweden based on physicians' expert opinion.
II	To estimate the one-month prevalence of self-reported ADEs, categories of ADEs, and two categories of preventable ADEs (ADRs and STEs) among the adult general public in Sweden. To estimate the self-reported preventability of ADRs and STEs. To identify drug classes and organ systems associated with self-reported ADEs.
III	To estimate the three-month prevalence of ADEs, categories of ADEs, and preventable ADEs using medical records of a random sample of the adult general public in Sweden. To estimate the preventability of ADEs. To identify drug classes and organ systems associated with ADEs. To estimate the three-month prevalence of serious ADEs and preventable serious ADEs.
IV	To estimate the percentage of adult outpatients and inpatients with preventable ADRs, and the preventability of ADRs.
Appendix Paper	To identify and systematically evaluate different methods for assessing the preventability of ADEs.

ADE Adverse drug event; *ADR* Adverse drug reaction; *STE* Sub-therapeutic effect of drug therapy.

The domains of patient safety investigated in the Papers are illustrated as part of the framework for the International Classification for Patient Safety (38) in Figure 4.

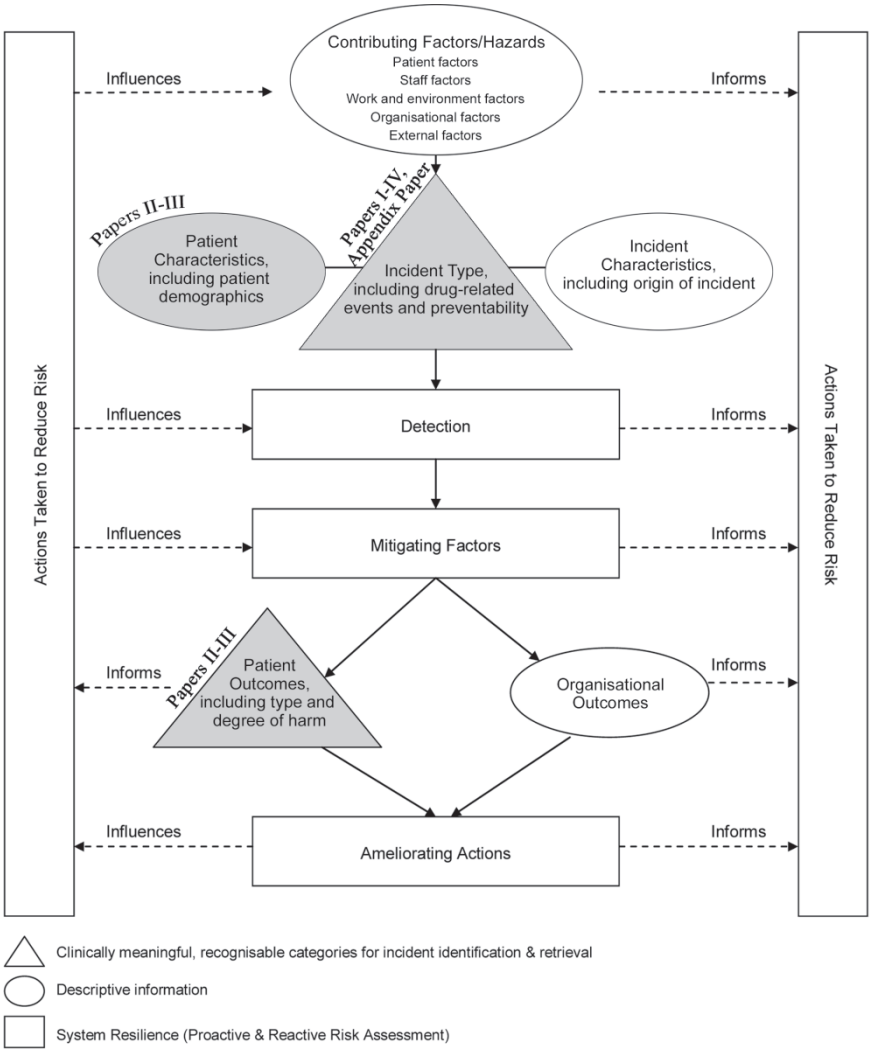


Figure 4. Domains of patient safety studied in Papers I–IV and the Appendix Paper (grey background), in the framework for the International Classification for Patient Safety (38). ©WHO, 2009. All rights reserved. WHO/IER/PSP/2010.2. Permission obtained for reproduction.

3 Methods

3.1 Terminology and definitions

Adverse drug events and their categories

In this thesis, ADEs are defined as *injuries resulting from medical interventions related to drugs* (81), and drug-related morbidity (DRM) is synonymous to ADEs. ADEs are part of all adverse events (Figure 2), and can also represent another type of an adverse event, such as one related to wrong diagnosis. In all Papers, ADEs could be associated with prescribed or non-prescribed, but not illicit drugs. ADEs associated with complementary medicines were included in Papers I-III, but excluded from Paper IV and the Appendix Paper.

ADEs in this thesis are divided into mutually exclusive categories: ADRs, DIs, DD, DA, STEs, and UTIs (Figure 2). The applied definitions for the categories are presented in Table 3. In Paper I, ADEs are further divided into (i) new medical problems (NMPs), which include ADRs, DIs, DD; and (ii) therapeutic failure (TF) which includes STEs and UTIs. However, the definition for DD was not given for the physician participants in Paper I, as physicians are expected to comprehend the concept. In Paper II, the definitions for the event categories were used in formulating questions for the general public, instead of providing the definition. DA was excluded from all ADEs in Papers I-II.

Table 3. Categories of adverse drug events (ADEs) and their definitions in this thesis.

Adverse drug event category	Definition
Adverse drug reaction (ADR)	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 (46).[a]
Drug intoxication from overdose (DI)	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.[b]
Drug dependence (DD)	A maladaptive pattern of substance[c] use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period: 1. Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect; or (b) Markedly diminished effect with continued use of the same amount of the substance. 2. Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance; or (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms. 3. The substance is often taken in larger amounts or over a longer period than intended. 4. There is a persistent desire or unsuccessful efforts to cut down or control substance use. 5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects. 6. Important social, occupational, or recreational activities are given up or reduced because of substance use. 7. The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance. (179)
Drug abuse[d] (DA)	A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period: 1. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household). 2. Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use) 3. Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct) 4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights). (179)
Sub-therapeutic effect of drug therapy (STE)	Include dose-related therapeutic failure, defined as an absence of therapeutic response that could be linked causally either to (prescribed) dose that was too low, to drug non-compliance, recent dose reduction/ discontinuation or inadequate monitoring. STEs also include sub-optimal therapeutic effect due to improper drug selection or sub-optimal therapeutic effect when treatment has been rational (e.g. first line treatment or best available medicines were not effective enough). (Modified from 62)
Morbidity due to drug-related untreated indication (UTI)	Occurs when a person has a clinical condition that under normal circumstances requires pharmacological therapy but the person is not receiving any drug therapy for the condition[b].

[a]Excluding drug dependence in Paper III.
[b]Own definition.
[c]In Paper II, only drugs classified as narcotics in the Swedish Medicines Information Engine (FASS) were included, as well as five additional drugs with evidence on addictive properties: caffeine, codeine, nicotine, pregabalin, and dextropropoxyphene.
[d]Excluded from Papers I-II.

Preventability

In Papers I-III, preventability was defined according to the Hallas criteria from 1990 (62), which were originally used for assessing the avoidability of drug-related hospital admissions. The criteria were chosen because they had been widely used for assessing the preventability of ADEs in different settings (75,105,167,180-191). The Hallas criteria include four avoidability categories (Table 4), of which definitely and possibly avoidable are considered preventable in Papers I-III. In Paper III, the original preventability categories of the criteria were employed, while Hallas' descriptions for avoidability were used for formulating questions on preventability in Papers I-II. In Paper IV and the Appendix Paper, no criteria for the definition of preventability were set.

Table 4. Hallas' avoidability[a] categories for defining preventability[a] in Papers I-III.

Hallas' avoidability[a] category	Description for Hallas' avoidability[a] category	Preventability[a] in Papers I-III
Definitely avoidable	The drug event was due to a drug treatment procedure inconsistent with present day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account.	Preventable
Possibly avoidable	The prescription was not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands.	
Not avoidable	The drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice.	Not-preventable
Unevaluable	The data for rating could not be obtained or the evidence was conflicting.	

[b]Avoidability and preventability are considered synonymous in this thesis.

3.2 Data sources

As different data sources are complementary and ADEs of differing nature are detected through them (43), different study designs were combined in this thesis (Table 5).

Table 5. Overview of study designs, data sources and measurements.

Paper	Study design	Data source	Study population	Study year	Main outcome measure	Analyses
I	Modelling study	Selected physician expert panel (n=53)	Panel of physicians (n=19)	2010	Estimated probability of ADEs and preventable ADEs among current patients	Mean probabilities
II	Cross-sectional survey study	Postal questionnaire, LISA database, Swedish Prescribed Drug Register (n=14 000)	Adult general population in Sweden (n=7099)	2010	Self-reported ADEs and preventable ADRs and STEs during the past month	Descriptive
III	Retrospective medical record study	Medical records, Care Data Warehouse of Östergötland, LISA database, Swedish Prescribed Drug Register (n=5025)	Adult general population in the Östergötland county council (n=4970)	2008	ADEs and preventable ADEs during three months	Descriptive
IV	Systematic literature review and meta-analyses	Citations in seven bibliographic databases (n=5770)	Original research articles (n=22), with outpatients (n=48797) and inpatients (n=24128)	-2010	Preventable ADRs among healthcare visits	Meta-analysis
Appendix Paper	Systematic literature review	Citations in seven bibliographic databases (n=5770)	Original research articles (n=143)	-2010	Methods for assessing the preventability of ADEs	Systematic literature review

ADE Adverse drug event; *ADR* Adverse drug reaction; *STE* Sub-therapeutic effect of drug therapy; *LISA* Longitudinal integration database for health insurance and labour market studies.

National registers of population characteristics and dispensed drugs (Papers II and III)

Statistics Sweden (SCB) holds the Total Population Register and the LISA (longitudinal integration database for health insurance and labour market studies) database, among other registers. The Total Population Register is produced by the Swedish Tax Agency (192), and its data is transferred to SCB. It includes the unique personal identity number (PIN) and demographic variables, including data on residency in Sweden. The PIN is given to every resident in Sweden, and is the same throughout life. The same PIN is used in other registers and enables data linkage

between the registers (193). The LISA database covers all Swedish residents aged 16 years or more, and contains data from the national population register and further demographic and socioeconomic variables, such as country of birth, level of education and level of income (194).

The National Board of Health and Welfare holds several national health registers, among them the Swedish Prescribed Drug Register (SPDR) (195). The SPDR covers all prescribed drugs that are dispensed in pharmacies since 2005. Dispensed drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system (196). In addition to the ATC code, data on each dispensed drug include the dispensed amount, product name, and costs. Data on patients include the PIN, age, and sex. In addition, prescribing date, prescriber information, dispensing date, and information on reimbursement are recorded. The SPDR does not include drugs bought over-the-counter, drugs used in hospitals, or drugs that are used in outpatient care but administered in hospitals or other healthcare facilities. The PIN is missing in 0.3% of dispensed drugs, because providing it is not compulsory at the time of dispensing (although necessary for reimbursement) and persons without residency have no PIN. The coverage of multi-dose dispensed drugs is partially incomplete, and thus medicines used in residential care are partially missing. As data quality on patients' exact prescribed dosage is given only in free text in the SDPR, dose is commonly estimated based on the defined daily dose (DDD) (196).

Regional data on outpatient and inpatient care (Paper III)

The Care Data Warehouse of Östergötland (VDL), a county council in Sweden, includes administrative data on all healthcare resources provided by the county (197). All inpatient and public outpatient care in all medical specialities are recorded, as well as private outpatient care reimbursed by the county. Even though a small part of private care might be missing (personal communication from Mr. Lars Svensson, Östergötland County Council), private outpatient care (including dental care) in total constituted 3% of all healthcare expenditure in 2008 in Östergötland (198). Thus, the coverage of the VDL is considered full. Variables used from the VDL included the PIN, date of care, type of care, and the profession of the caregiver.

In Östergötland, all inpatient and public outpatient medical records of nurse and physicians consultations are stored centrally in an electronic medical record database. Private primary care is not included. In general, medical records are considered an important source of information for detecting ADEs (43), although information on drug use has been found partly inaccurate in electronic medical records (199).

Bibliographic databases (Paper IV and Appendix Paper)

The Cochrane database of systematic reviews, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Excerpta Medica Database

(EMBASE), the International Pharmaceutical Abstract (IPA), the Medical Literature Analysis and Retrieval System Online (MEDLINE), PsycINFO, and Web of Science are bibliographic databases on published evidence, including research in health sciences. A range of databases are commonly used in systematic reviews of evidence in healthcare (200,201), as none of the databases covers all evidence. Citations are organised according to index terms that vary across the databases. In two commonly used databases, MEDLINE and EMBASE, the index terms are called Medical Subject Headings (MeSH) and EMTREE (Elsevier's Life Science Thesaurus) medical index terms, respectively. The databases are commonly searched using the index terms (201), but can also be searched using other search fields, such as titles and abstracts of the citations.

3.3 Study designs

Modelling study using an expert panel of physicians (Paper I)

A conceptual model on DRM with a decision tree was modified from an American study (21). Using the model (eSupplement 1) and modified Delphi methodology (202), perceptions of an expert panel of physicians were collected. Physicians active in drug and therapeutics committees were recruited in six strata, with desired number of participants in each stratum to gain representation from outpatient and inpatient care, different specialties, academic and non-academic, as well as rural and urban healthcare. When an invited physician in a stratum declined participation, another physician in the stratum was invited. The recruitment finished when a pre-defined number of approximately 20 stratified participants was gained. From a total of 53 invited physicians, 19 (36%) representing the six strata consented, forming the expert panel.

Physicians working in outpatient care (n=11) provided estimates for outpatients, and physicians working with inpatients (n=8) for inpatients. In the decision tree (Appendix 1), the physicians estimated proportions of patients with DRM, which was divided into NMPs and TF. NMPs included ADRs, DD and intoxications by overdose, while TF included STEs and UTIs. These were described (Table 3) for the physicians orally and in the decision tree. Physicians also estimated the proportions of patients with preventable DRM, which were defined in the decision tree according to Hallas' definitely and possibly avoidable cases (Table 4) (62).

Cross-sectional survey to the general public (Paper II)

A cross-sectional, population-based study linked survey data and national register data from the LISA database and the SPDR, using the PIN. The survey was mailed to a random sample of 13 921 residents aged 18 years or older, who were already registered in Sweden on 1st January 2010. The sample size was based on expecting 10% of adults to report ADRs during one month (91), 10% of these ADR being

preventable (26,80), and a 60% response rate (91). Requiring a maximum length of a 95% confidence interval of +/-0.3% unit, the calculated minimum number of respondents was n=7043, which was doubled to n=14 000 individuals allowing more detailed analyses. The sample was drawn from the Total Population Register.

Questions on experienced ADEs during the past month were developed by the research group based on earlier studies (26,80,91). Although recall periods in previous studies vary from two weeks (91) to one year (26), a one-month period was chosen to promote the recollection of both serious ADEs and less memorable, non-serious ADEs, and to enable detecting cases in a generally healthy population. The definitions for each ADE category (Table 3) were not provided in the survey, as the target audience was the general public. Instead, questions on each ADE category were carefully formulated for laymen to comprehend (eSupplement 2.1). Based on Hallas' descriptions for definitely and possibly avoidable cases (Table 4) (62), questions on the perceived preventability of self-reported ADRs and STEs were formulated (eSupplement 2.1). The survey was pilot-tested in different populations (health professionals, administrative personnel, elderly, and immigrants) for face and content validity. The survey, its introductory letter (eSupplement 2.2) and a prepaid return envelope were mailed by SCB in October 2010. A postcard reminder was sent to non-respondents in October 2010, and reminders with a re-posted survey in November 2010 and January 2011. In total 7099 study individuals (51%) returned the survey to SCB. SCB linked the survey responses to data on the respondents' dispensed drugs from SPDR, and age and sex from the LISA database.

Aggregated sociodemographic variables (sex, marital status, area of residence, country of birth, level of education, and income) were retrieved from the LISA database for respondents and non-respondents, to compare their characteristics.

Retrospective medical record study (Paper III)

A population-based retrospective study was conducted in the county council of Östergötland. A random sample of 5025 residents aged 18 or more on 31st December 2007 was drawn from the Total Population Register and observed retrospectively for three months in 2008. A three-month period was considered sufficient for detecting enough cases for intended analyses, and yet practically feasible. The sample size was based on an expected 6% ADE prevalence among persons with healthcare encounters (ca 50% of the general population) and +/-5% precision. To manage seasonal variation, the study population was randomly divided into four groups for each quarter of the year.

Using the PIN, data on the study individuals' dispensed drugs were retrieved from the SPDR, and data on healthcare encounters from the VDL. Using data from the VDL, individuals who had healthcare encounters (nurse or physician, visit or telephone contact, outpatient or inpatient, specialised or not, excluding dental care) during the three-month study period were identified, and their electronic medical records retrieved and scrutinised manually to detect ADEs. When electronic

medical records were missing, the healthcare providers were contacted for paper copies. Assessment of ADEs was performed during 2009-2012 in several steps using standardised, pilot tested data extraction sheets for primary (eSupplement 3.1) and secondary reviews (eSupplement 3.2). In the primary review, pharmacists extracted pre-determined information on suspected ADEs from the medical records during the three-month study period, and up to nine months before and three months after the study period. Data on dispensed drugs from the SPDR were used to facilitate the assessment. In the secondary review, a clinical pharmacologist and a pharmacist performed independent assessments, based on the extracted data in the primary review, the causal relationship between each suspected ADE and drug therapy and detect possible additional ADEs, using the Howard criteria (Table 6) (203). For ADEs with at least possible causality, the clinical pharmacologist and the pharmacist independently judged preventability according to Hallas (Table 4) (62), whether the ADE contributed to a hospitalisation (62), and seriousness (51) based on suspected serious ADEs indicated by a pharmacist.

Table 6. Howard criteria (203) for assessing the causality between suspected events and drug therapies.

Howard criteria for causality
(1) Known adverse drug reaction, toxic reaction, response to omission of treatment or inadequate treatment.
(2) Reasonable temporal relationship between commencement or cessation/omission of treatment and onset of problem.
(3) Risk of further problems likely to be reduced by dose reduction or increase, discontinuation, closer monitoring or commencement of treatment.
(4) Not explained by any other known condition of predisposition to the patient, or this condition/predisposition is likely to be exacerbated by the presence/absence of the drug.
(5a) For drug toxicity: • symptoms re-appeared upon re-exposure; • laboratory tests showed toxic drug levels or drug induced metabolic disturbances that explained the symptom; • symptoms resolved on dose reduction or discontinuation of the drug. (5b) For drug omission: • symptoms resolved upon re-introduction of the drug or dose increase.
If 5 criteria fulfilled then definite. If 4 criteria fulfilled then probable. If 3 criteria fulfilled then possible. If 2 or less criteria fulfilled then either, not drug related or unevaluable.

After reviewing the medical records, relevant variables were transferred to an ADE dataset, including a patient identifier, symptoms, drug substances, ADE category (Table 3), and levels of causality (Table 6), preventability (Table 4), contribution to hospitalisations, and seriousness. The ADE dataset and the data from the VDL and the SPDR were combined with age and sex from the LISA database, also for persons without healthcare encounters during the study period. As 25 persons became deceased or migrated before the end of study period, and medical records

could not be adequately reviewed for 30 persons, in total 4970 study individuals (99%) could be included in the analysis.

The following sociodemographic variables retrieved from the LISA database were compared between the study individuals and the adult general public in Sweden: sex, marital status, area of residence, country of birth, level of education, and income.

Systematic review and meta-analysis (Paper IV and Appendix Paper)

Seven databases (Cochrane, CINAHL, EMBASE, IPA, MEDLINE, PsycINFO and Web of Science) were searched in September 2010, using the databases' index terms and other commonly used terminology on ADEs and preventability. References of included original articles and relevant review studies were also retrieved. Original peer-reviewed research articles were selected according to pre-determined inclusion and exclusion criteria. Outcome measures of included studies had to include the frequency of ADEs or synonymous concepts and the assessment of their preventability. Original studies published in other languages than English were excluded. A total of 5770 citations were found in the database search. After removal of duplicate records, and applying the inclusion and exclusion criteria on titles, abstracts, and full-texts articles, 142 articles were included.

Meta-analysis on preventable adverse drug reactions (Paper IV)

Further inclusion and exclusion criteria were applied for pooling the results of the studies, as pooling requires standardised outcome measures (201). The most precisely defined outcome measure among the 142 articles - ADRs - was chosen to be pooled. To avoid inconsistent estimates and decrease heterogeneity, ADRs had to be defined according to the WHO (46), or according to a similar definition (51). Small changes in wording could be overlooked. Included studies had to sufficiently report the percentage of patients with preventable ADRs or the preventability of ADRs. After applying the further inclusion and exclusion criteria, 22 articles were included in the meta-analysis, representing outpatients with 48 797 emergency visits or hospital admissions and 24 128 inpatient. Data on ADRs and preventable ADRs were extracted (eSupplement 4).

Systematic review of methods for preventability assessment (Appendix Paper)

For the systematic review of methods for assessing the preventability of ADEs, one additional article was included from reference lists. Thus, the total number of included articles was 143. From the included articles, study characteristics were extracted (eSupplement 5) and measurement instruments for defining the preventability of ADEs identified.

3.4 Analyses

Prevalence of adverse drug events (Papers I, II and III)

The proportions of patients with ADEs estimated by the physician expert panel were calculated separately for outpatients and inpatients, using respondents' mean estimates with standard deviations (Paper I). The use of means and standard deviations was considered appropriate, because the response distributions were reasonably symmetrical (although not apparent due to the small sample size) and because means and medians did not differ notably. Because the sample was not random, 95% confidence intervals were not calculated.

The one-month prevalences in the survey study (Paper II) and three-month prevalences in the medical record study (Paper III) were calculated with 95% confidence intervals for all ADEs, using the general population in the denominator. To investigate the influence of varying the denominator, the ADE prevalences were calculated in the survey study (Paper II) for respondents with self-reported drug use during the past month and in the medical record study (Paper III) for individuals with dispensed drugs during six months before the study period. In addition, the prevalences were calculated for survey respondents with self-reported healthcare encounters during the past month (Paper II), and in the medical record study (Paper III) for individuals with healthcare encounters during the three-month study period.

Nature of adverse drug events (Papers II and III)

In the survey (Paper II) and medical record (Paper III) studies, the prevalences of persons with the different ADE categories were calculated with 95% confidence intervals. The proportions of the different ADE categories of all ADEs, at event level, were also reported. Drugs associated with ADEs were reported descriptively, with 95% confidence intervals. Drugs were categorised according to the Anatomical Therapeutic Chemical (ATC) Classification System (196), including the most common main groups, pharmacological subgroups and chemical substances. The main organ systems and individual symptoms affected by ADEs were categorised according to the Medical Dictionary for Regulatory Activities (MedDRA) (204). Organs affected by ADRs (Paper II), and by all ADE categories (Paper III) were calculated.

In the medical record study (Paper III), the seriousness of ADEs and its categories was reported, including the proportion of serious events among all ADEs (event level analysis) and the prevalence of serious ADEs (person-level analysis). The prevalence of hospitalisations contributed by all ADEs was also reported.

To investigate the characteristics of persons with ADEs, prevalences of ADEs and its categories were reported in age groups (18-44, 45-64, and ≥65 years) and compared using χ^2 or Fisher's exact test (Papers II and III). In this thesis, the prevalences of ADEs and its categories were also reported by sex.

Potential for preventing adverse drug events (Papers I-IV and Appendix Paper)

In the expert panel study (Paper I), the mean proportions of patients with preventable ADEs among all patients and among patients with ADEs were calculated separately for inpatients and outpatients, with standard deviations. The use of means and standard deviations was considered appropriate, for the same reasons as for the proportions of patients with ADEs. In the absence of a random, representative sample, 95% confidence intervals were not calculated.

At ADE level, the preventability of ADRs and STEs were calculated in the survey study (Paper II), and the preventability of all ADEs and their categories in the medical record study (Paper III). In the preventability calculations, the preventability of each event was dichotomised (preventable or not) and the number of preventable events divided by the number of all ADEs of the same category. In this thesis, the original preventability categories were also reported descriptively, which were *preventable*, *not preventable* or *don't know/unevaluable* in the survey study, and *definitely avoidable*, *possibly avoidable*, *not avoidable* and *unevaluable* in the medical record study.

At person level, one-month prevalences in the survey study (Paper II) and three-month prevalences in the medical record study (Paper III) were calculated for preventable ADEs and their categories, with 95% confidence intervals.

To investigate the nature of preventable ADEs in the survey (Paper II) and medical record (Paper III) studies, associated drugs, affected organs and seriousness were calculated as for all ADEs.

The meta-analyses of previous studies (Paper IV) were performed using DerSimonian and Laird random effects model with the estimate of heterogeneity being taken from the inverse variance random effect model (205). The percentage of patients with preventable ADRs (analysis unit healthcare visit) was calculated by dividing the reported number of healthcare visits with preventable ADRs by the total number of healthcare visits. The preventability of ADRs (analysis unit ADR) was calculated by dividing the number of preventable ADRs by the total number of ADRs. The summary measures for the percentage of patients with preventable ADRs and for the preventability of ADRs were calculated separately for ADRs occurring in outpatients and for ADRs present among inpatients during hospitalisation, as used drugs and expected ADRs differ in outpatient and inpatient settings. As the analyses using healthcare visits or ADRs as analysis units could only include articles for which these data were available, articles included in the analyses using healthcare visits as analysis unit could differ from the analyses using ADRs as analysis unit.

In the systematic review on methods for assessing the preventability of ADEs (Appendix Paper), unique measurement instruments were classified and compared. The process of assessing the preventability of ADEs in each article was assessed

based on reported actions that may influence the validity and reliability of the measurement (206-208) (eSupplement 5).

3.5 Ethical considerations

The risk of intrusion to the participants' personal integrity was considered in the survey (Paper II) and medical record studies (Paper III), as sensitive data on the participants were collected and handled. To avoid delivering PINs to the research group, SCB administered the survey, linked the survey responses to register data, and de-identified the combined dataset. Data linkage was also done by SCB in the medical record study. Locating medical records required PINs, which were replaced with new identifiers after the record review. SCB kept the code between the PINs and the new identifiers. Identifying individuals in Papers I-III was also minimised through confidential handling and storing of data, presenting only aggregated data in publications, and the researchers committing to professional secrecy. Even though the medical record and survey studies involved accessing, collecting and analysing sensitive information on the participants, the expected value of the research results for improving healthcare in the future motivates the risk of intrusion of the personal integrity (209).

Physicians participated in the expert panel study voluntarily, after an oral consent (Paper I). Respondents on the survey study consented voluntarily to participate by returning the survey (Paper II). The introductory letter (eSupplement 2.2) sent with the survey followed the principals of the Declaration of Helsinki (210). No informed consents from the participants of the medical record study (Paper III) were obtained, and the individuals were not informed about being study subjects. Announcements were distributed in the local media, although no one contacted the research group. Retrieving sensitive information without the participants' consents was considered justified, because participation could not change their healthcare or health status and the results were expected to improve care for future patients (209).

Permissions for using register data were gained from the register holders. No ethical approval was necessary for the expert panel study, as no sensitive information on individuals was collected and the physicians answered in their professional role. According to The Act Concerning the Ethical Review of Research Involving Humans (209), the medical record study (Paper III) received ethical approval in December 2008 (644-2008) from the Regional Ethical Review Board in Gothenburg, and the survey study (Paper II) in May 2010 (238-2010). The meta-analysis and literature review (Paper IV and Appendix Paper) did not involve ethical considerations, as aggregated published results from bibliographic data were used.

4 Results

4.1 Prevalence of all adverse drug events

The physician expert panel estimated that 51% of their current outpatients and 54% of inpatients suffer from at least one ADE (Table 7; Paper I). In the survey study (Paper II), 19.4% of the adult general public reported having experienced one or more ADEs during the past month. Scrutinising medical records (Paper III), 12.0% of the general public were found to suffer from ADEs during the three-month study period. Compared to the general population, the prevalence of all ADEs was higher for individuals with dispensed drugs and for individuals with healthcare encounters, both in the survey (Paper II) and medical record (Paper III) studies.

Table 7. Prevalence of all adverse drug events (ADEs), by varying the denominator and data source.

	Physician estimated mean proportions of patients (Paper I)		Self-reported 1-month prevalence (Paper II)	3-month prevalence in medical records (Paper III)
Denominator	Outpatients % (SD)	Inpatients % (SD)	% (95% CI)	% (95% CI)
General population	-	-	19.4 (18.5-20.3)	12.0 (11.1-12.9)
Among individuals with drugs	-	-	22.7 (21.7-23.8)	18.3 (16.9-19.7)
Among individuals with healthcare encounters	51 (22)	54 (17)	32.7 (28.9-36.5)	24.5 (22.8-26.2)

ADE Adverse drug event; *CI* Confidence interval; *SD* Standard deviation.

4.2 Nature of adverse drug events

Categories of adverse drug events

When the prevalences of ADEs were calculated by ADE category, ADRs and STEs were reported by equally many survey respondents (approximately 8%) and detected in equally many persons medical records (approximately 6.5%) (Table 8; Papers II and III).

At event level, self-reported ADRs, STEs, and UTIs each constituted, respectively, 32.8%, 28.9%, and 30.7% of all self-reported ADEs (Paper II). In the medical records (Paper III), ADRs represented 52.4% of all ADEs, STEs 38.8%, and UTIs 5.3%. DD constituted 6.7% of all self-reported ADEs (Paper II), and DD and DA

2.6% of all ADEs detected from the medical records (Paper III). In both Papers II and III, 0.8% of all ADEs were DIs.

Table 8. Prevalence of categories of adverse drug events (ADEs), by data source.

ADE category	Self-reported 1-month prevalence (Paper II) % (95% CI)	3-month prevalence in medical records (Paper III) % (95% CI)
Adverse drug reactions	7.8 (7.2-8.4)	6.9 (6.2-7.6)
Drug intoxications from overdose	0.2 (0.1-0.3)	0.1 (0.0-0.2)
Drug dependence or abuse	2.2 (1.9-2.6)[a]	0.4 (0.2-0.6)
Sub-therapeutic effects of drug therapy	7.6 (7.0-8.2)	6.4 (5.8-7.1)
Morbidities due to drug-related untreated indication	8.1 (7.5-8.7)	0.9 (0.7-1.2)

ADE Adverse drug event; *CI* Confidence interval.
[a]Drug dependence exclusively.

Drugs associated with events

Drugs for the nervous system contributed to 31-39% of all ADRs and STEs (Table 9), according to both self-reports (Paper II) and medical records (Paper III). Of nervous system drugs, psychoanaleptics (mainly composing of antidepressants) were associated with 15.4% of ADRs in the self-reports and 19.8% of ADRs in the medical records, while analgesics were present in 16.6% of self-reported STEs and in 12.1% of STEs in medical records. Drugs for the cardiovascular system contributed in 19.2-29.6% of all ADRs and STEs, apart from self-reported STEs (7.0%). Of cardiovascular drugs, agents acting on the renin-angiotensin system, beta blocking agents, and diuretics were each present in 9.1-12.9% of ADRs and STEs in the medical records. Of cardiovascular drugs in the survey study, the most common sub-groups were agents acting on the renin-angiotensin system, beta blocking agents, and lipid modifying agents, each present in 3.3-4.4% of all self-reported ADRs.

Nervous system drugs were associated with 93.7% of self-reported DD cases (Paper II), and 100.0% of DD and DA cases in medical records (Paper III). Hypnotics and sedatives were present in most (53.5%) of the self-reported DD cases (Paper II), while anxiolytics (38.5%) and hypnotics and sedatives (38.5%) were equally common among DD and DA detected in medical records (Paper III). Drugs for the nervous system were associated with 66.7% and 62.5% of DIs in the survey (Paper II) and medical record studies (Paper III), respectively.

Table 9. Most common drug classes associated with adverse drug reactions (ADRs) and sub-therapeutic effects of drug therapy (STEs), and preventable ADRs and STEs, by data source.

	All events				Preventable events			
	ADRs %		STEs %		Preventable ADRs %		Preventable STEs %	
Drug class[a]	Self-reported (Paper II)	Medical records (Paper III)	Self-reported (Paper II)	Medical records (Paper III)	Self-reported (Paper II)	Medical records (Paper III)	Self-reported (Paper II)	Medical records (Paper III)
Cardiovascular system	19.2	29.6	7.0	28.3	20.9	37.8	9.0	31.4
Nervous system	33.2	39.3	32.0	30.4	30.9	43.7	35.9	21.5
Alimentary tract and metabolism	4.0	7.2	9.4	14.2	0.7	6.7	9.6	20.4
Blood and blood forming organs	2.8	7.4	1.3	1.8	2.9	9.6	1.8	2.9
Genito urinary system and sex hormones	6.3	5.4	3.2	1.6	7.9	1.5	4.2	0.6
Respiratory system	6.6	4.7	9.8	7.1	3.6	5.2	7.8	4.7
Antiinfectives for systemic use	5.0	3.5	3.2	6.3	4.2	1.5	2.4	8.1
Musculo-skeletal system	7.2	5.6	14.9	9.7	3.6	8.2	10.8	9.3
Systemic hormonal preparations[b]	5.4	3.9	1.9	3.7	3.6	1.5	4.8	3.5

ADR Adverse drug reaction; *STE* Sub-therapeutic effect of drug therapy.

[a]Ordered according to the most commonly dispensed drugs in the survey study (Paper II).

[b]Excluding sex hormones and insulins.

Organs affected by events

ADRs reported by the general public (Paper II) and detected in medical records (Paper III) were most frequently gastrointestinal (26.9% respective 21.6%) and general disorders (17.5% respective 12.3%), such as fatigue. STEs were most frequently vascular (18.9%), psychiatric (15.5%), or musculoskeletal (12.6%), while UTIs were most commonly psychiatric (17.3%) or vascular (13.5%) (Paper III).

Seriousness

In total, 9.5% of ADEs detected from the medical records were serious (Paper III). The seriousness varied by ADE category from 6.0% for ADRs to 62.5% for intoxications, but the large confidence intervals hindered comparing seriousness between the ADE categories. At person-level, 1.2% of the general population suffered from serious ADEs during three months. ADEs contributed in hospitalisations for 0.6% of the general population during the three-month period, corresponding 22.1% of all 136 hospitalised persons.

Person demographics

Both in the survey and medical record studies (Table 10), the overall ADE prevalences were higher among women than men.

Table 10. Prevalence of adverse drug events (ADEs), by ADE category, data source, and sex.

	Self-reported 1-month prevalence		3-month prevalence in medical records	
ADE category	Female % (95% CI)	Male % (95% CI)	Female % (95% CI)	Male % (95% CI)
Any ADE, in the general population	**22.1 (20.8-23.4)**	**16.2 (14.9-17.5)**	**14.1 (12.7-15.4)**	**9.8 (8.6-11.0)**
Adverse drug reactions	9.3 (8.4-10.2)	6.1 (5.3-6.9)	8.6 (7.5-9.7)	5.1 (4.2-5.9)
Drug intoxications from overdose	0.2 (0.1-0.4)	0.2 (0.0-0.3)	0.2 (0.0-0.5)	0.0 (0.0-0.2)
Drug dependence or abuse	2.8 (2.3-3.4)[a]	1.5 (1.1-1.9)[a]	0.5 (0.2-0.8)	0.3 (0.2-0.6)
Sub-therapeutic effects of drug therapy	8.8 (7.9-9.7)	6.1 (5.3-7.0)	7.3 (6.3-8.3)	5.6 (4.7-6.5)
Morbidities due to drug-related untreated indication	8.5 (7.6-9.4)	7.6 (6.7-8.5)	1.1 (0.7-1.5)	0.8 (0.5-1.2)

ADE Adverse drug event; *CI* Confidence interval.
[a]Drug dependence exclusively.

Based on the self-reports (Table 11; Paper II), the prevalence of all ADEs did not differ by age group, but the prevalence of DD was higher among the elderly (≥65 years) and the prevalence of STEs among young adults (18-44 years). When detected from the medical records (Paper III), the prevalence of all ADEs, ADRs

and STEs was higher among the elderly (≥65 years) compared to younger adults (Paper III).

Table 11. Prevalence of adverse drug events (ADEs) in age groups, by ADE category and data source.

ADE category	Age 18-44 years % (95% CI)	Age 45-64 years % (95% CI)	Age ≥65 years % (95% CI)	P Value[b]
Self-reported 1-month prevalence (Paper II)				
Any ADE[a], in the general population	**19.8 (18.2-21.4)**	**19.4 (17.8-21.0)**	**18.9 (17.2-20.5)**	**0.73**
Adverse drug reactions	7.6 (6.5-8.6)	8.0 (6.9-9.0)	7.9 (6.7-9.0)	0.86
Drug intoxications from overdose	0.1 (0.0-0.3)	0.3 (0.1-0.5)	0.2 (0.0-0.4)	0.49
Drug dependence	1.0 (0.6-1.3)	2.2 (1.7-2.8)	3.7 (2.9-4.5)	<0.001
Sub-therapeutic effects of drug therapy	9.0 (7.9-10.1)	7.5 (6.5-8.5)	6.1 (5.1-7.1)	0.001
Morbidities due to drug-related untreated indication	8.5 (7.4-9.6)	8.4 (7.3-9.5)	7.3 (6.2-8.4)	0.28
3-month prevalence in medical records (Paper III)				
Any ADE[a], in the general population	**5.9 (4.9-6.8)**	**13.1 (11.5-14.8)**	**22.2 (19.8-24.6)**	**<0.001**
Adverse drug reactions	3.4 (2.7-4.2)	6.7 (5.5-7.9)	13.8 (11.8-15.8)	<0.001
Drug intoxications from overdose	0.1 (0.0-0.3)	0 (-)	0.3 (0.0-0.7)	0.04
Drug dependence or abuse	0.3 (0.1-0.5)	0.6 (0.2-0.9)	0.3 (0.0-0.7)	0.46
Sub-therapeutic effects of drug therapy	3.0 (2.3-3.7)	7.6 (6.3-8.9)	11.4 (9.6-13.3)	<0.001
Morbidities due to drug-related untreated indication	0.6 (0.3-1.0)	1.1 (0.6-1.6)	1.4 (0.7-2.1)	0.08

ADE Adverse drug event; *CI* Confidence interval.

[a]As one person could have multiple ADEs, the combined prevalences were lower than the sum of the prevalences of the ADE categories.

[b]For testing the statistical significance between all three age groups using $\chi 2$ test, with the exception of using Fisher's exact test for drug intoxications from overdose due to low number of cases.

4.3 Potential for preventing adverse drug events

Occurrence of preventable adverse drug events

The physician expert panel estimated that ADEs were preventable among 24% of outpatients with ADEs, and 31% of inpatients with ADEs (Table 12; Paper I), but the large standard deviations indicate low precision. The survey respondents perceived 19.2% of their self-reported STEs and ADRs, combined, preventable (Table 12; Paper II). Judged from the medical records (Paper III), 38.8% of all ADEs were preventable.

Table 12. Potential preventability of adverse drug events (ADEs), by ADE category and data source.

ADE category	Physician estimated[a] (Paper I) Outpatients % (SD)	Physician estimated[a] (Paper I) Inpatients % (SD)	Self-reported (Paper II) % (95% CI)	Medical records (Paper III) All % (95% CI)	Medical records (Paper III) Serious % (95% CI)	Literature (Paper IV) Outpatients[b] % (95% CI)	Literature (Paper IV) Inpatients % (95% CI)
All ADEs	**24 (11)**	**31 (15)**	-	**38.8 (35.7-41.8)**	**55.9 (45.8-66.0)**	-	-
Adverse drug reactions	-	-	16.4 (13.9-18.9)	26.3 (22.4-30.1)	54.8 (36.3-73.4)	52 (42-62)	45 (33-58)
Drug intoxications from overdose	-	-	-	100.0 (67.6-100.0)	100.0 (56.6-100.0)	-	-
Drug dependence or abuse	-	-	-	92.3 (75.9-97.9)	87.5 (52.9-97.8)	-	-
Sub-therapeutic effects of drug therapy	-	-	22.4 (19.4-25.4)	45.1 (40.1-50.2)	43.2 (27.9-58.4)	-	-
Morbidities due to drug-related untreated indication	-	-	-	76.9 (65.1-88.8)	80.0 (37.6-96.4)	-	-

CI Confidence interval; *NA* Not available; *SD* Standard deviation.

[a]Proportion of patients with preventable ADEs among all patients with ADEs of the category.

[b]Outpatients being hospitalised or visiting emergency care.

According to the physician expert panel (Paper I), 12% of all outpatients and 16% of all inpatients suffered from preventable ADEs, but the standard deviations were large. In the medical record study (Paper III), 5.6% of the adult general public experienced one or more preventable ADEs, corresponding to 11.4% of individuals with healthcare encounters.

Nature of preventable adverse drug events

Categories of preventable adverse drug events

When preventable ADEs were investigated by ADE category, the survey respondents perceived that 16.4% of their ADRs and 22.4% of STEs were preventable (Table 12; Paper II). Also in the medical record study (Paper III), ADRs were estimated less preventable than STEs or the other categories of ADEs. In the meta-analysis (Paper IV), 52% of ADRs among outpatients being hospitalised or visiting emergency care and 45% of ADRs among outpatients were preventable, although the included original studies were found heterogeneous ($p<0.001$). No studies in primary care were identified.

The prevalence of preventable STEs (Paper II: 1.8%; Paper III: 3.1%) was slightly higher than the prevalence of preventable ADRs (Paper II: 1.3%; Paper III: 2.1%). In the meta-analysis (Paper IV), preventable ADRs were present in 2.0% of outpatients visiting emergency care or being admitted to hospital. The proportion of inpatients with preventable ADRs during hospitalisation could not be estimated precisely and no studies in primary care were identified.

Drugs associated with preventable events

By large, drug classes associated with preventable ADEs were similar to drug classes associated with all ADEs, both according to self-reports and medical records (Table 9, Papers II and III). Similarly to all ADRs and STEs, nervous system drugs contributed to 22-44% of preventable ADRs and STEs, and cardiovascular drugs to 21-38% of preventable ADRs and STEs, apart from self-reported preventable STEs. In the medical record study, however, some drug classes associated with preventable ADRs and STEs differed from all ADRs and STEs: drugs for blood and blood forming organs and the musculoskeletal system were more frequent among preventable ADRs, and drugs for the alimentary tract and metabolism among preventable STEs.

Organs affected by preventable events

Analogously to all ADRs, preventable ADRs most frequently affected the gastrointestinal system or were general disorders (Papers II and III). In the medical record study (Paper III), preventable STEs frequently affected the vascular, psychiatric, and musculoskeletal systems, as for all STEs, but endocrine disorders, including hyperglycaemia, were more common among preventable than all STEs.

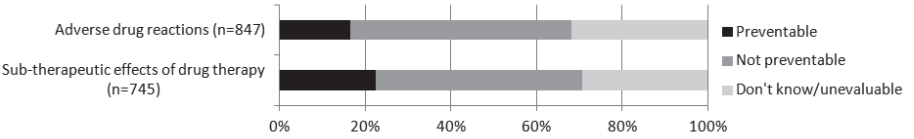
Preventable serious events

According to an evaluation of the medical records (Paper III), 55.9% serious ADEs were preventable. In the general population, 0.7% suffered from preventable

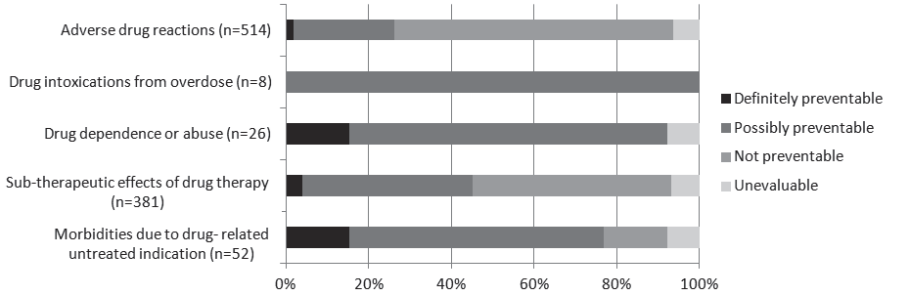
serious ADEs. These preventable serious ADEs contributed to hospital admissions for 0.4% of the general population during the three-month period, corresponding to 14.0% all 136 hospitalised persons.

Preventability assessment

In the survey study, the respondents answered *don't know* to the question on preventability or the answer was unevaluable for 31.8% of ADRs and 29.4% of STEs (Figure 5). In the medical record study, few ADEs were judged *definitely preventable,* in particular ADRs, DIs and STEs. Preventability was judged unevaluable for 6-8% of ADRs, DDs, DAs, STEs and UTIs in the medical record study.



5a. Self-assessed preventability by survey respondents



5b. Preventability assessment from medical records

Figure 5. The preventability of adverse drug reactions and sub-therapeutic effects of drug therapy perceived by the respondents of the survey study (**5a**), and the preventability of all adverse drug event categories judged by a clinical pharmacologist and a pharmacist in the medical record study (**5b**).

In the systematic review (Appendix Paper), 18 unique instruments for determining the preventability of ADEs were identified from the literature (62,65,80,81,211-224). The instruments fell under four groups: instruments using a definition of preventability only (n=3) (81,218,219), instruments with a definition of preventability and an assessment scale for determining preventability (n=5) (220-224), instruments with specific criteria for each preventability category (n=3) (62,65,80), and instruments with an algorithm for determining preventability (n=7)

(211-217). In the identified measurement instruments, the preventability categories varied from dichotomous (Yes/No) to four-point ordinal categories, including descriptors such *definitely*, *probably*, *probably not*, and *definitely not* preventable. Despite differing levels of structure and wording in defining preventability, all instruments shared the same basis for defining preventability: whether an error or sub-standard care had resulted in an ADE. Of actions to standardise the assessment of preventability, performing a pilot study was reported in 15% (n=21) and the use of a standardised protocol in 13% (n=18) of the included articles. The reliability of the preventability assessment was tested in 27% (n=39) of the articles, and 11% (n=16) of the articles referred to a previous reliability assessment. Reliability ranged from poor to excellent. Three per cent of the articles mentioned assessing validity but no sensitivity or specificity analyses or negative or positive predictive values were presented.

5 Discussion

5.1 Prevalence of all adverse drug events

The findings of this thesis demonstrate that ADEs are common in the adult general population, beyond hospitals and specific outpatient settings as found previously (18-20,29,31,32), although the relatively inclusive definitions for ADEs and their categories contributed to the high ADE prevalences. Swedish physicians estimated that roughly half of their current outpatients and inpatients experienced ADEs. This estimate was lower than previous estimates by Swedish pharmacists (24), and higher than by American pharmacists (21). Even though the panellists did not reach consensus and the panellists' interest in drug safety probably resulted in overestimations, the expert panel studies combined suggest that ADEs are more common in the entire healthcare system than previously found in observational studies (18-20,29,31,32). In the survey study, one-fifth of the adult general public reported ADEs during the past month, a relatively high proportion compared to previous studies on self-reported ADEs (26,80,101,166,172,175). Despite possible over-reporting, the prevalence of self-reported ADEs is unlikely to be an overestimation due to recall bias, underreporting of asymptomatic ADEs, and non-response bias concerning frail or institutionalised persons who are likely to have a high ADE burden. The three-month ADE prevalence in the medical record study was 12% for the general public and 25% for persons with healthcare encounters. This was slightly higher than in most previous studies in sub-populations of outpatients (18,26,80,96,101,166,172,175), probably also due to access to all medical records, including before the study period, enhancing the case detection. However, the retrospective assessment of dispensing and medical records exclusively probably resulted in an underestimation (18,19). Considering also the expert panel's high estimations, the 19% one-month prevalence of self-reported ADEs and especially the 12% three-month prevalence of ADEs in the medical records are probably not overestimations, with the ADE definitions used in this thesis. Although the prevalence of ADEs varies depending on the context and research methods (19), the high ADE prevalence in the adult general population in Sweden demonstrates that ADEs are a significant health concern across care settings.

5.2 Nature of adverse drug events

Categories of adverse drug events

The high frequency of several categories of ADEs in this thesis underlines that ADEs burden society beyond ADRs, which are traditionally emphasised in

recommendations for preventing ADEs (225,226). ADRs and STEs were the most frequent in the survey and medical record studies, consistent with previous studies separating the ADE categories (54,55,57,73-75), both in terms of prevalences of persons experiencing ADEs and the numbers of events. Thus, ADRs exclusively constituted less than half of all ADEs. In both studies, ADRs and STEs were also equally common. Compared to previous evidence specifically on STEs of chronic conditions (227), however, the prevalence of STEs in this thesis is probably underestimated. These results warrant an increasing emphasis on the range of ADEs in national and international policies, research, and practice to tackle ADEs.

As detection methods and data sources influenced the identified ADE categories in the survey and medical record studies, the ADE categories should in future research be investigated combining data sources. The markedly higher prevalences of self-reported UTIs and DD compared to those detected from the medical records indicate that patient involvement is required for detecting the spectrum of ADEs experienced by people. As the survey responses were, however, affected by non-response, reporting, and recall biases, and the validity of the survey instrument, self-reports should be compared with data from for example medical records and direct observation (228-231) for the same study population, to gain a more complete understanding of the occurring events.

Associated drugs and affected organs

In this thesis, the most commonly used drug classes caused most ADEs in the general population, as argued previously in studies in outpatient settings (71,80), illustrating that most ADEs in the general population do not originate from a short list of high risk drugs, such as certain antithrombotic agents or antiepileptics (232,233). In the survey and medical record studies, drugs for the nervous system caused one-third of ADEs, and the drug class has been commonly attributed to ADEs in primary care in previous studies (71,102,234), although these drugs have not been mentioned or have constituted a smaller proportion of ADEs in studies among various outpatients (18,31,80,96) and inpatients (29,84,86,94,185). In the medical record study, cardiovascular drugs also constituted approximately 30% of ADRs and STEs, in accordance with previous studies in primary (102,234), other outpatient (18,31,87), and inpatient (29,84,86) care. Cardiovascular and nervous system drugs had in the survey and medical record studies the highest dispensing prevalences in the general population, and the two drug classes have previously topped the annual numbers of dispensed prescriptions (195). In the survey study, the underreporting of asymptomatic ADEs from cardiovascular drugs, in particular STEs, probably resulted in underreporting them.

However, the various ADE categories identified in this thesis were caused by partially different drugs and affected partially different organ systems, indicating that categorising ADEs provides nuanced information on their nature. Within the nervous system drugs, ADRs from antidepressants and STEs of analgesics dominated, according to the survey and medical record studies. Although antidepressants and analgesics have been associated with ADEs before (18,31,71),

the differing pattern between ADRs and STEs has not been discussed in previous studies on all ADEs. Previous studies on exclusively ADRs in primary care have, however, found antidepressants dominating (70), and STEs of analgesics are well reported in the literature on pain management (60).

ADRs most commonly affected the gastrointestinal or the central nervous systems (including nervous system and psychiatric disorders, fatigue and dizziness), similarly to previous research in primarily outpatient settings (31,91). ADRs causing psychiatric disorders were not, however, as common as psychiatric disorders due to STEs and UTIs, such as depression, anxiety and sleep disorders. In the medical record study, ADRs, STEs and UTIs also commonly affected the cardiovascular system (including cardiac or vascular disorders), hypotension and related dizziness being frequent among ADRs, while hypertension dominated cardiovascular STEs and UTIs. Previous research has found ADEs to commonly affect the cardiovascular system, but without distinguishing the ADE categories (31).

Associated drugs and affected organs for ADEs in the general population, detected through self-reports and medical records, partially differed from ADE identified in previous studies in specific outpatient populations and in hospitals (18,31,84,94,185), illustrating that prioritising ADEs in specialised care would disregard a large quantity of ADEs of different nature. Previously commonly reported ADEs from anti-infectives (18,31,84,94) were much less common among the general population. ADRs present at the time of or during hospitalisation have previously been commonly associated with antithrombotic agents, drugs used in diabetes, systemic corticosteroids, antineoplastic agents, opioids, and inhaled beta-agonists (84,94,185), but these drugs caused ADRs less commonly in the general population. Of cardiovascular drugs, ADEs from diuretics and beta-blocking agents have previously been highlighted in hospitals (84,94,185), but no pharmacological subgroup dominated ADEs in the general population.

ADEs affected the electrolyte, renal, endocrine and hematologic functions less commonly in the general population compared to patients of outpatient clinics and hospitals (31,93,94,185). On the contrary, STEs and UTIs causing vascular and psychiatric disorders, and STEs resulting in musculoskeletal and endocrinal disorders were common among the general public in the medical record study, unlike in previous studies investigating all ADEs in specific outpatient or inpatient settings (31). These differences in associated drugs and affected organs, by care level, were somewhat expected due to known discrepancies in patients' age and morbidity, the nature of care, and drug use, and also due to the inclusive definition for ADEs in this thesis. In addition, ADEs common in outpatient clinics or hospitals may have been underestimated in the general population due to possible reporting and recall biases in self-reports and information bias in medical records, and the inclusion of all medical records both before and after the study period, probably facilitated detecting longer-term, non-acute ADEs.

Seriousness

The proportion of serious ADEs in the general population was expectedly lower in the medical record study than previously found in hospitals (81,95), in accordance with previous studies in ambulatory care (80,96). Reasons for the discrepancy in the seriousness by settings are probably the same as for the differing drugs and organs, mentioned previously. Among persons with serious ADEs in the medical record study, ADEs contributed to hospitalisations markedly more commonly than found previously (19,29), probably influenced by the relatively low frequency of hospitalisations in Sweden (235). These results further imply that clinically serious ADEs are concentrated in hospitals. Although most ADEs in the general population are not clinically serious, they cause other consequences excluded in this thesis, such as costs from lost productivity and additional healthcare (236), as well as worsened perceived health, worry, and discomfort in individuals' daily lives (25-28).

The varying seriousness between the ADE categories in the medical record study supports categorising ADEs for describing their impact on individuals and the healthcare system. STEs being equally or more serious than ADRs has been rarely described in previous research on all ADEs (63,104,191). As expected (90), most DIs identified in the medical records were serious, although the low number of cases caused imprecise estimates. The high proportion of serious DD and DA cases was also expected considering the criteria for seriousness (significant disability/incapacity). These differences by ADE category facilitate the understanding of the clinical seriousness of ADEs, and probably also the social and economic impact of ADEs.

Person demographics

The survey and medical record studies demonstrated that the overall ADE prevalence was considerable in all age groups of adults, strengthening the argument that ADEs are widely distributed in the general population. However, ADEs were more common among the elderly in the medical record study, but equally reported by young, middle-aged and elderly adults in the survey study. These results are in accordance with previous studies revealing ADEs detected from medical records, often in combination with other detection methods, more common among the elderly (63,97,98), but finding no association between age and self-reported ADEs (102), or finding older age protective of reporting ADRs (103). The discrepancy may be due a non-response bias in studies relying on self-reports, if frail or institutionalised elderly with high burden of ADEs did not respond. Alternatively, the elderly may be less likely to report ADEs, possibly due to declined cognition, differing illness perception compared to younger adults (237), or inability to differentiate ADEs from other health conditions. As the ADE prevalences by age group in the medical record and survey studies were not adjusted for other factors, such as socioeconomic characteristics, healthcare utilisation, and drug use, multivariate analysis facilitates understanding how the higher prevalence among the elderly is affected by other factors. When the characteristics of persons with ADEs

detected from the medical records were further analysed using multivariate logistic regression, experiencing ADEs was no longer associated with older age, after adjusting for sex, marital status, level of education, healthcare encounters, and number of dispensed drugs (238).

The demographics of persons experiencing ADEs differ by ADE category, based on results of this thesis and additional analyses (238). ADEs were more common among women than men in the survey and the medical record studies of this thesis, as found previously (63,75,92,97-101). This discrepancy by sex may be due to the higher utilisation of medicines (195) and health services (239) by women. In addition, a larger proportion of elderly women than men has been described to report physical health concerns, but the difference disappears when other sociodemographic and clinical characteristics are considered (240). In the multivariate logistic regression analysis on ADEs detected from the medical records, female sex was no longer associated with experiencing ADEs of any category, after adjusting for sociodemographic characteristics, healthcare encounters, and dispensed drugs (238). When the multivariate analysis was stratified by ADE category, however, experiencing ADRs was associated with female sex. The distribution by age group also differed in the survey and the medical record studies, for example for ADRs and STEs, although associations by age group vanished in the medical record study after adjusting for other person characteristics (238).

5.3 Potential for preventing adverse drug events

Occurrence of preventable adverse drug events

The findings of this thesis verify that a significant proportion of ADEs in the entire healthcare system and the general population could potentially be prevented. The 39% preventability estimate in the medical record study was more consistent with most previous observational studies (18,20,29,31,32,70) than the lower estimates by the physician panel and the general public. The physician experts' estimates were also lower than previous estimates by Swedish pharmacists (24), indicating a perhaps unconscious underestimation if the physicians perceived acknowledging substandard care to reflect poorly on their practice. As the Swedish pharmacist panel's previous estimate (24) was of similar magnitude with the 39% preventability judged from the medical records, the pharmacists' preventability estimate was probably not largely overestimated. The survey respondents' lower preventability estimates were probably caused by the under-representation of seriously ill and hospitalised patients and the respondents' limited capability to judge preventability against clinical data. Although the diverse definitions for preventability and limited methods for assessing it, discussed in the following paragraphs, hinder exact

estimations, it is evident that many ADEs are preventable, based on this thesis and prior research (18,20,29,31,32,32,89).

Consequently, a large proportion of patients and the general population experienced potentially preventable ADEs according to this thesis. In particular, the finding of the medical record study that preventable ADEs contributed to 14% of all hospital admissions was higher than in other studies (32,89). The high prevalences of preventable ADEs originate mainly from the higher prevalences of all ADEs, whereas preventability estimates were more comparable to previous findings (18,20,29,31,32,32,89). As discussed previously, the inclusive definition for all ADEs probably increased prevalences in this thesis, and the physician panellists' interest in drug safety may have resulted in overestimations. However, the inability to detect non-recorded, preventable ADEs in the medical records most likely led to underestimating their prevalence (18). Thus, the 6% three-month prevalence of potentially preventable ADEs detected from the medical records is probably not an overestimation, considering the used definition for ADEs. This prevalence corresponds to over 400 000 adults in Sweden (among 7.3 million adults in 2007) suffering from potentially preventable harm from medicines, during a three-month period, which warrants increased action on developing preventive measures.

Nature of preventable adverse drug events

The varying potential preventability by ADE category and seriousness, found in this thesis, further reinforces acknowledging the range of ADEs in research and clinical practice on preventing ADEs. The finding of the medical record study that a larger proportion of serious ADEs and ADEs leading to hospitalisations appear potentially preventable, compared to all ADEs combined, was consistent with previous research reporting higher preventability for serious ADEs (96) and ADEs among hospitalised or emergency care patients (18,20,29,31). ADEs in hospitals appeared also more preventable according to the physician expert panel, but the standard deviations were large. When investigated by ADE category, serious ADRs in particular were more frequently preventable than all ADRs, while preventability did not differ by seriousness for the other ADE categories. The finding of the meta-analysis that approximately half of ADRs at hospital admission, in emergency care, or during hospitalisation were preventable further suggests that serious ADRs are more preventable than all ADRs, because ADRs are commonly serious in these settings (63,189). In the survey and medical record studies, a larger proportion of STEs than ADRs appeared potentially preventable, in accordance to previous studies on ADEs in emergency care (63,104). Even though studies on ADEs rarely describe the preventability of STEs and UTIs, the potential for preventing morbidities due to under-prescribing, omitting doses in institutions, or non-adherence by the patient is widely described elsewhere (227,241-243). In the medical record study, most cases of DIs, DD and DA were judged potential preventability, which was expected considering previously research (105) and the used definition for preventability (62). These results imply that prevention efforts targeted exclusively to serious ADRs, which have gained most attention in the

prevention of ADEs (225,226), would oversee a considerable amount of potentially preventable ADEs, which may be clinically less serious but cause other significant consequences to individuals and society (25-28,236).

The similarity of potentially preventable ADEs and all ADEs, in terms of associated drugs and affected organs, in this thesis and prior studies (96) implies that preventable ADEs "just" represent a proportion of all ADEs, hindering recommending the prevention of specific ADEs. The limitations in assessing preventability may, however, have masked differences. The majority of preventable ADEs reported by the general public and detected in the medical records were also associated with nervous system and cardiovascular drugs, with similar frequencies of the pharmacological subgroups. As for all ADEs, the differing pattern in associated drugs by ADE category, for example antidepressants dominating preventable ADRs and analgesics preventable STEs, has not been recognised in previous research on preventable ADEs (18,31). In accordance with previous research (96), potentially preventable ADRs among the general population also most commonly affected the gastrointestinal, central nervous and cardiovascular systems. Moreover, potentially preventable psychiatric and cardiovascular STEs and UTIs were frequent, similarly to all ADEs. Despite these similarities, some potentially preventable ADEs, such as ADRs of antithrombotic agents, had disproportionally high frequency in the medical record study, consistent with previous evidence in ambulatory care (31), warranting further investigating contributing factors behind these preventable events.

Preventability assessment and potential for improvement

The insecurity in determining preventability in the medical record and survey studies together with diverse, limited methods for assessing preventability, as identified in the literature review and by others (49), warrant improving the preventability assessment in the future. The sub-optimal assessment of preventability most likely contributed in the heterogeneous preventability estimates in the meta-analysis of this thesis and other literature (18,20,29,31,32). Apart from measuring the magnitude of preventable harm imprecisely, sub-optimal preventability assessment probably hinders characterising the nature of preventable ADEs, identifying their contributing factors, and measuring the impact of interventions to prevent ADEs. As the instruments used in the articles of the literature review had scattered reliability and unknown validity, more scientifically rigorous methodology for the measurement is required. Thus, the existing instruments should be improved or newly developed for measuring the preventability of ADEs more accurately and precisely in the future.

In addition to further developing instruments for assessing the preventability of ADEs, improving the assessment requires clarifying the definition and categorisation of ADEs, in relation to other adverse events in healthcare. The differing nature and potential preventability by ADE category in the survey and medical record studies indicate that dividing ADEs into categories prior to preventability assessment would improve the understanding of preventable ADEs,

while describing preventability exclusively for all ADEs could mask differences between the categories. ADEs do not, however, occur in isolation from other adverse events in healthcare, as ADEs are part of all adverse events and medication errors part of all errors, which may share latent failures (244). Although ADEs are considered in the WHO's framework on patient safety (38), the ADEs categories are currently insufficiently recognised in the framework.

For developing instruments for assessing the preventability of ADEs, a clear, shared definition for preventability must be established, based on a thorough investigation of the literature and international collaboration. A starting point could be the shared basis for defining preventability, identified in the literature review: whether an error or sub-standard care resulted in an ADE. Further development of the definition for preventability should consider the ADE categories illustrated in this thesis, previous work on conceptualising the preventability of ADEs and medication errors (44,48,50,245), as well as concepts within patient safety as a whole (38-40,246). Although violations are rarely mentioned in the literature on preventable ADEs (247), violations are addressed in patient safety literature (42,68) and should therefore be considered in the preventability of ADE. Different scenarios for the preventability of various ADE categories should be described, considering their varying pharmacological nature. Pharmacological predictability and preventability in practice should be distinguished, as some use the concepts interchangeably (248). As involving patients in detecting preventable adverse events is increasingly emphasised (102,231,249), the definition for preventability should also consider errors and violations in drug use by patients and their carers. However, the possibility of assessing all ADEs using a single instrument should be evaluated, as the differing preventability by ADE category identified in this thesis and the diversity of possible scenarios may hinder assessing all ADE categories together. In the development work, the application and feasibility of any definitions and instruments should also be examined in different research and practice settings, including self-assessment by patients. Finally, the validity and reliability of any new instrument should be established.

When the preventability of ADEs is conceptualised, preventability due to errors, violations, or sub-standard care in the light of the current evidence on effects of drugs should be distinguished from preventability in the future through improved understanding of drug effects and further drug development (Figure 6). This thesis investigates the former form of preventability, which is commonly considered as part of patient safety. Others investigate the latter form of preventing ADEs: in the future through improving the knowledge of, for example, an unknown ADR, which enables revising treatment guidelines or developing drugs with a more advantageous safety profile. Studies contributing on the latter form of preventing ADEs are commonly referred to as drug safety studies. For example, old age and a long treatment period were discovered as risk factors for flucloxacillin-associated jaundice in the 1990's (250). The research contributed to preventing future ADRs, because warnings could subsequently be introduced in treatment guidelines. Today, an elderly person's jaundice during a long-term flucloxacillin treatment, without

monitoring hepatic function, could be judged preventable, but not in the 1980's, when the ADR and its risk factors were unknown. Further, judging the case preventable would depend on the existing treatment guidelines in the particular setting. Thus, distinguishing studies on drug safety from preventing ADEs due to errors, violations or substandard care illuminates how preventability, as studied in this thesis, depends on the current evidence and treatment guidelines, which vary over time and between health systems. This distinction is important for finding a common language for preventing negative drug effects.

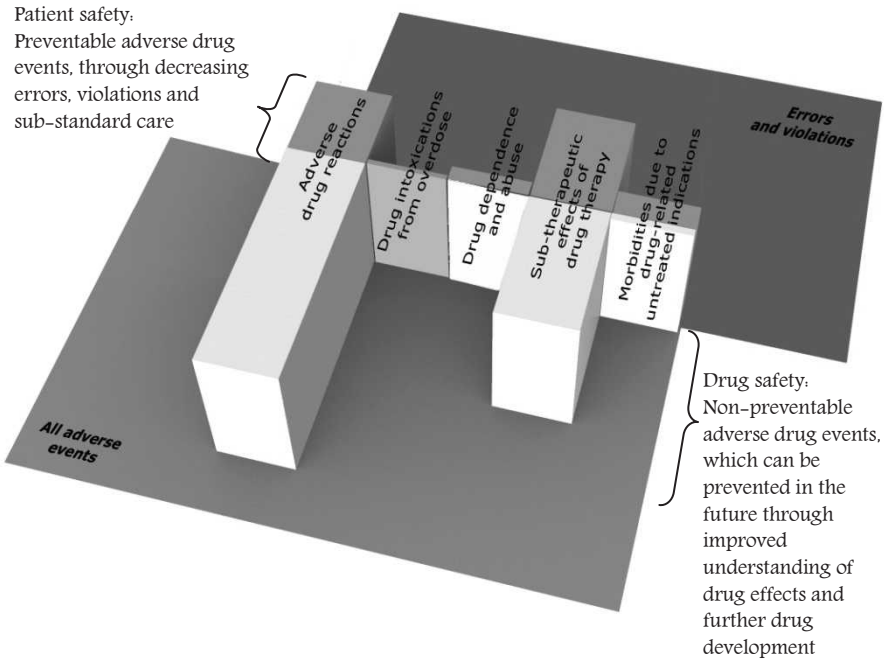


Figure 6. Distinguishing preventability in patient safety and drug safety, illustrated using the results of the medical record study. The bars represent the categories of adverse drugs events, and the size of the bars the proportions of the event categories.

The current categorisation of ADEs, from non-preventable to preventable events as identified in the literature review, could be improved to provide more information on active failures, and ultimately on the prevention of ADEs (Figure 7). The identified explicit instruments establish preventability dichotomously or in an ordinal scale, without further detailing the unsafe acts. According to the Organisational Accident Causation Model, safety can be improved by identifying and addressing the latent failures and triggering factors in the system (41,68,69), i.e.

contributing factors in the WHO's framework (38), which in turn requires understanding of the active failures. Thus, including descriptions of active failures, i.e. unsafe acts, in an instrument for preventability assessment could enhance the identification of the triggering factors and latent failures, such as staff performance, communication, workload, and patient behaviour related factors. Errors and contributing factors should not be categorised as mutually exclusive, as reasons for adverse events commonly involve multiple factors (39). Information on the stage of the drug therapy process (43), where an unsafe act was committed, should also be considered. Although assessing the triggering factors and latent failures as part of the preventability assessment in epidemiological studies is probably impossible, the preventability assessment could better prepare for further investigating the underlying causes, which require other methods such as the root cause analysis (251). Finally, laypersons' perceptions on active failures should be considered in the preventability assessment, because clinical data often lack information on, for example, errors in drug use outside care units.

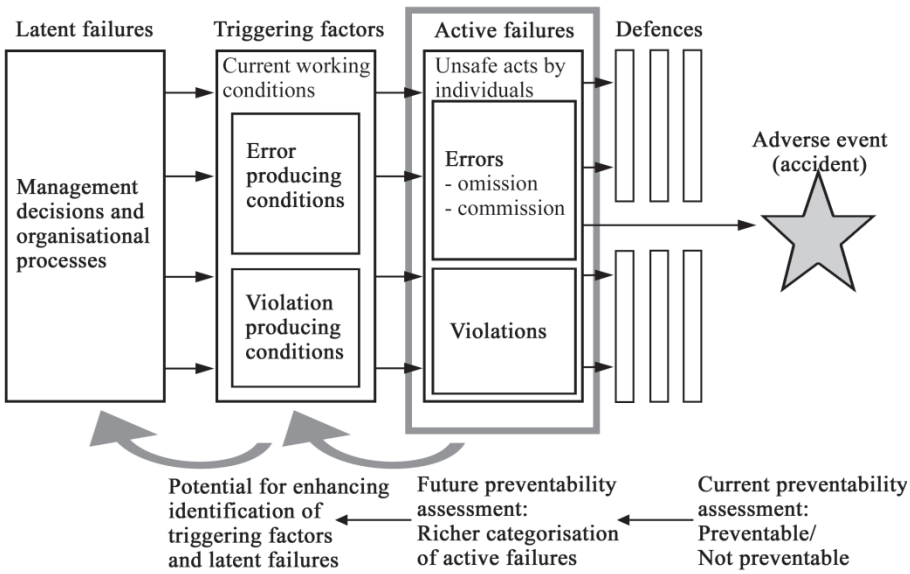


Figure 7. Potential for enriching the preventability assessment of ADEs, towards classifying active failures to facilitate identifying triggering factors and latent failures, illustrated in the Organisational Accident Causation Model modified from Reason, and Taylor-Adams and colleagues (41,68,69)

Preventing adverse drug events

The significant burden of potentially preventable ADEs described in this thesis reinforces prioritising ADEs in patient safety, allocating resources on preventing ADEs, and the need for large-scale efforts to redesign safer, higher quality healthcare systems to adequately tackle the problem (252-254). Based on the results of this thesis and a recent study on adverse events in Swedish hospitals (255), ADEs are one of the most common patient safety hazards in Sweden, as in hospitals in other countries (16,17). Thus, preventing ADEs is fundamental for improving patient safety as a whole.

Actions in the entire healthcare system are required for preventing ADEs, including primary care, other outpatient care, and self-care by patients, because potentially preventable ADEs from widely used drugs concern a wide range of the population and occur in all care settings, causing harm of varying consequences. The need for improving safety in primary, other outpatient, and self-care settings has recently gained more attention (102,231,249,256), as patient safety has mainly been studied and developed in hospitals and from care givers' perspective. Despite the high preventability of serious ADEs, found in this thesis and by others (81,96), non-serious events shall also be prevented (72). Addressing primarily serious ADEs common in emergency care and hospitals, as suggested by some (89,225,226), could lead to overseeing a large quantity of less serious preventable events that are not resource intensive individually, but collectively consume considerable resources (72), causing both direct healthcare costs and productivity loss (236). Focusing on serious cases, the prevalence of potentially preventable serious ADEs in the medical record study represents 51 000 adults in Sweden within three months (among 7.3 million adults in 2007). But also inspecting non-serious ADEs that could potentially be prevented reveals how widespread preventable ADEs are. The prevalence of self-reported preventable ADRs and STEs in the survey study corresponds to 210 000 adults monthly (among 7.4 million adults in 2010), and the prevalence of potentially preventable ADEs from the medical records to 400 000 adults every three months (among 7.3 million adults in 2007). Thus, targeting serious ADEs would oversee this high burden of potentially preventable, less serious ADEs among the general population, justifying preventing both serious and less serious ADEs in the entire health system. However, the differing nature of ADEs in the general population, according to the survey and medical record studies, compared to specific outpatient and inpatient populations (18,31,84,93,94,185), demonstrates that the burden ADEs differs in different settings, probably requiring partially different preventive strategies. For example, long treatment episodes for less acute conditions in outpatient care require longer-term monitoring of treatment effects, such as ADRs and STEs of antidepressants and antihypertensives, compared to short treatment episodes in hospitals.

Interventions for preventing ADEs should be carefully selected based on understanding their contributing factors, probably with an increasing focus on general interventions for improving the organisation of care for all patients. Currently, preventable ADEs may be inadequately understood, as definitions for

ADEs and preventability are diverse and ambiguous (43,47-50) and their preventability assessments sub-optimal. As investigating contributing factors requires understanding of the occurring incidents (38), and knowledge of the contributing factors is required for developing preventive interventions (178), the limited understanding of preventable ADEs may have influenced the ineffectiveness of interventions in decreasing ADEs or improving health outcomes (140,144-146,148,150-152,155,156,159,160,163-165). Considering the commonness of ADEs in this thesis and the likelihood of ADEs sharing contributing factors with each other and other adverse events (38,244), introducing general interventions that prevent several adverse events simultaneously may have the highest potential for improving overall safety.

Patient safety strategies targeted at specific events are also necessary. Some such interventions have showed impressive success (257), while others have gained an established position in healthcare, such as monitoring warfarin patients. However, developing preventive interventions for various ADEs, for example by drug class, could consume more resources than available, both time and money, and may be inadequate for achieving transformational improvements in overall safety.

In addition to improving the organisation of care for error prevention, examples of defences for detecting and addressing errors include, for example, medication reconciliation for correcting discrepancies in information on medication use between care units and patients (153-156). Although defences are also needed, because no organisation is immune to errors or adverse events, interventions targeted at already-occurred errors require careful consideration before implementation. Firstly, developing separate defences for various ADEs, for example for drug classes frequently associated with ADEs, could be infeasible in practice and result in fragmented care, as argued previously (117). This is because such interventions would be provided to most patients, due to the commonness of drugs causing ADEs, and many patients would receive multiple interventions over time, due to increasing chronic drug use. Secondly, introducing multiple defences may increase complexity in patient care, increasing the possibility of errors.

For these reasons, preventing ADEs more successfully in the future probably requires systematic strategies to design safer health systems than seen to date, the commitment of clinicians and care units, collaboration with patients, researchers and safety experts, and strong political will and leadership. The systemic approach in patient safety (41,68,69) for preventing ADEs is in accordance with the population approach for preventing illness in public health (107-110). Both consider targeting individuals inadequate for improving health, and emphasise a wider approach: developing the system or society for decreasing risks for all. Prevention efforts in patient safety should probably not exclusively focus on risk groups either, such as persons with multiple medicines, because many preventable ADEs still occur among persons at lower risk, limiting the risk group strategy's capability of achieving the greatest effect, as described for improving public health (107-110). Both public health and patient safety are challenged by the inadequate prioritisation of and resource allocation on prevention (109,110,123,258). Thus,

shifting the focus from treatment to prevention remains a challenge also for preventing ADEs. The results of this thesis on the high burden of preventable ADEs and their varying nature are anticipated to motivate increasing resource allocation on preventing this unnecessary harm from drug therapies for improving the health of the population.

5.4 Methodological considerations

Combination of study designs and data sources

The several methodological approaches used in this thesis can be argued to strengthen the validity of the findings, as the main results were comparable. By large, the prevalences of ADEs, the proportions of the ADE categories, the most frequent drugs and patient outcomes, estimates for potential preventability, and the insecurity in the preventability assessment were similar, or differences could be elucidated.

Data sources for detecting ADEs have been found complementary (43,80,86,231,259), including medical records, voluntary reports of health professionals or patients, and surveys and interviews to patients, care givers and health professionals. The data sources used in this thesis also complemented each other. For example, STEs of cardiovascular and anti-diabetic drugs could mainly be detected from medical records, while STEs of analgesics were more common in self-reports. A weakness of this thesis is, however, that the results of the survey and medical record studies could not be combined, which would have enhanced the understanding of the occurring ADEs among the general population (43,80,86,231,259). When the studies were designed, the choice of using different populations was conscious, due to several reasons. Firstly, combining the samples would have required informed consent also from the participants of the medical record study, which would have decreased its representativeness. Secondly, a large population sample of medical records could, feasibly in practice, only be scrutinised retrospectively from previous years. If self-reported ADEs had been surveyed for the same time period, recall bias would have decreased the validity of the self-reports.

Defining and assessing adverse drug events

Although a common definition for an ADE (81) was used in this thesis, the diversity and ambiguity in defining ADEs in the literature hinder comparison across studies (50), and should be considered when the results of this thesis are interpreted. Due to the ambiguity of the previously used categories for ADEs, ADEs were divided into categories in this thesis (Table 3), unlike in most previous studies. The results of this thesis demonstrate that the division was valuable and provided nuanced information on ADEs. However, the categorisation and the relatively inclusive definition for ADEs, leading to a higher overall prevalence of

ADEs, must be considered when the results of this thesis are compared to other studies. In the survey and medical record studies, the ADE prevalences did decrease when the ADE definition was changed to mimic previously used definitions, but the prevalence of ADEs remained notable and did not change the drawn conclusions.

Even though the used ADE categorisation was considered to add value, it was not flawless. DA was included in ADEs in the medical records study, but excluded in the expert panel and survey studies, limiting the comparability of the studies in this thesis. However, the inclusion of DA was unlikely to influence the overall prevalences considerably, as DA was relatively uncommon in the medical records study, as in previous studies (53,88). In the survey study, the definition for DD differed from the other studies, as dependence was limited to addictive drugs in the survey study, due to a high frequency of misinterpreting the question as *being dependent on a drug* and therefore reporting of drugs such as insulin. However, only one case of DD, on a cinnarizine/phenylpropanolamine combination drug, detected in the medical record study would not have been included in addictive drugs in the survey study, suggesting that the differing definitions had minor impact on the prevalence of DD and ADEs.

Nonetheless, definitions for DD, DA and addiction are debated in the literature (260,261), and their inclusion in ADEs should be elaborated in future research. Also the distinction between DIs and ADRs, through whether an overdose was involved, was somewhat arbitrary, because intoxications may also occur without an overdose, such as digoxin intoxication due to digoxin-diuretic interaction. Further, determining an overdose depends on applied guidelines and how strictly these are interpreted, for example whether one additional tablet constitutes an overdose. Therefore, alternative definitions for DIs and ADRs should be considered in future research, such as the European Union's current definition for an ADR (262), which also includes reactions resulting from medication errors and drug use against the authorised product information.

ADEs could not be investigated in the meta-analysis, because standardised definitions are required when results of original studies are pooled (201). Thus, ADRs and their preventability were chosen as an outcome measure, as ADRs were defined the most consistently among articles on ADEs. Because of the used standardised definitions for ADRs (46,51), the meta-analysis in this thesis provides more consistent estimates on preventable ADRs than previous reviews. In the literature review on methods for assessing preventability, all studies on ADEs regardless of the used definition were considered, but the relationship between a negative health outcome and medication therapy had to be assessed for inclusion.

In addition to definitions for ADEs, methods for assessing causality between a drug therapy and an adverse event have been described as challenging (263), and there is no universally accepted method. In the expert panel study, the physicians estimated probabilities of ADEs in a decision tree, based on a generic question on ADEs. A modified Delphi technique for reaching consensus among the expert

panel was considered justified because no empirical data on ADEs in the entire healthcare system was available at the time of conducting the study (264). A better consensus on the probabilities of ADEs may have been reached if more than two Delphi rounds had been performed (265), although forcing consensus is not desired either and could lead to *collective ignorance rather than wisdom* (265). Therefore, the accuracy of the physicians' perception could even improve by the researchers' avoidance to influence the panellists' estimations. Instead, the lack of consensus and therefore imprecise estimates were likely mainly due to the questions referring to each physician's own practice, when variation is unavoidable. In hindsight, Delphi methodology was probably inappropriate for the research question, because reaching consensus was impossible using questions referring to the participants' own practice and in the pilot study physicians considered more general questions impossible to answer.

In the survey study, laymen assessed the causality for their ADEs, based on a generic question that was tested for face and content validity. As described in Paper II, some respondents still misinterpreted the questions, probably underreporting expected ADEs and ADEs accepted by the patient, such as frequent urination as an ADR from diuretics. In the medical record study, previously introduced criteria for assessing ADEs (203) were used. Although validity was not assessed, the causality assessment was likely to be facilitated by access to medical records in all healthcare units also before the study period, but challenged by the retrospective nature of assessing medical and dispensing records exclusively (18,19), as non-recorded cases would have been overseen. Aware of this limitation, a retrospective study design was chosen, because recruiting people prospectively based on a representative population sample and collecting data in various healthcare units would have been practically infeasible and resulted in drop-outs. In the meta-analysis, the causality of ADRs was assessed in the original studies. As in other studies in the field, the varying and limited methods to establish a causal link between a drug therapy and an adverse event (263) must be considered when interpreting the results.

Defining and assessing preventability

Common criteria for assessing the preventability of ADEs, the Hallas criteria (62), were used in the first three Papers of this thesis, which improves the comparability of the studies with each other and to prior studies using the same criteria. Even though all studies with preventability assessment were considered for inclusion in the meta-analysis, most included studies used the Hallas (62) or other well-established criteria (211). The Hallas criteria was expectedly also captured in the literature review on methods for assessing the preventability of ADEs. However, choosing the Hallas criteria for the first three Papers was not influenced by the results of the meta-analysis or the literature review on methods, as the literature studies were completed after choosing the Hallas criteria for the other studies. The preventability estimates may have been lower if other preventability criteria had been chosen, because Hallas considers ADEs *possibly preventable* if they were

avoidable by effort exceeding the obligatory demands (62), while other criteria more exclusively determine only erroneous treatment preventable (65,80,81,211-224). As described and elaborated in other parts of this thesis, the current methods for assessing preventability by health professionals or researchers vary and have limited scientific rigour. Due to the limitations of the assessment, the term *potentially preventable* is used throughout this thesis instead of *preventable*.

In this thesis, all of the used ADE categories could be judged preventable but were not automatically considered preventable. However, it could be debated that all DIs and UTIs should automatically be preventable, as an error has occurred if an overdose has been administered or if an indicated drug was not initiated. All DIs were also considered preventable in the medical record study, as in previous studies (105), but the fact that only a part of UTIs were judged preventable probably reflects the insufficiency of the preventability assessment. Thus, the preventability of UTIs can be seen as an underestimation.

Other definitions and categorisations

Widely accepted, international classifications were used in the survey and medical record studies when drug classes (196), organ systems (204) and seriousness (51) were defined and categorised. Despite using operational manuals to standardise these categorisations and several assessors for determining seriousness in the medical record study, some cases would have been misclassified. However, the proportion of serious ADEs is probably not overestimated, because the assessment was conservative. Further, some differences in drugs and organs associated with ADEs between this thesis and previous studies were caused by differing drug and organ classifications, in addition to differing detection methods and definitions.

Sampling and selection bias and representativeness

In the expert panel study, the panellists were strategically sampled and selected to represent different specialties and both outpatient and inpatient care, but the composition and small size of the panel probably influenced the results (265). Selecting physicians active on drug and therapeutics committees was considered necessary for improving accurate interpretation of the decision tree and the definitions, but the physicians' prior interest in drug therapies and adverse events probably resulted in overestimations, in particular considering the 36% participation rate. Thus, the panellists' estimations are not representative of all Swedish physicians' perceptions, and the results of the expert panel study must be interpreted with caution.

The survey and medical record studies were the first to investigate the prevalence of all ADEs in the general population. Sampling error was not a concern, as the samples were drawn by Statistics Sweden (266). Selection bias was not a significant concern in the medical record study, as few persons' records were missing (0.6%). As the county council of Östergötland is reasonably representative of Sweden, the findings of the medical record study are by large generalisable to adults in Sweden.

However, the underrepresentation of persons born outside Sweden in the study population of the medical record study and the absence of a city with over 200 000 inhabitants in Östergötland somewhat limits generalisability to the entire nation. The results on self-reported ADEs in the survey study are not generalisable to all Swedish adults, due to the high proportion of elderly, women, persons with high socio-economic status and Swedish origin among respondents (51% response rate). Although the response rate was lower than expected (60%) in the power calculation, based on a study from 2004 (91), it was in line with the declining response rates of surveys (267). For example, the response rate to the National Survey of Public Health has declined from 61% in 2004 to 52% in 2009 (268). The decreasing response rates of postal surveys warrant using other methods, such as telephone surveys, in future studies on self-reported ADEs.

The use of seven databases and a wide range of search terms increased the likelihood of capturing relevant articles in the meta-analysis and the literature review. However, unpublished studies and studies published in other languages than English may have been overlooked. As study selection was done by one researcher in the literature review and the reliability of the selection was not assessed, some relevant articles may have been overlooked. Although the systematic data extraction procedure was likely to improve the objectivity of the meta-analysis and the literature review, the interpretation of the original studies may have been influenced the results. A limitation of the literature review is that only reported information on the preventability assessment in each article was extracted and authors of original articles were not contacted for complementary information.

The influence of used denominators in prevalence calculations is another important consideration when interpreting the ADE prevalences found in this thesis and comparing the prevalences to other studies. In the survey and medical record studies, the ADE prevalences were expectedly higher among persons with healthcare encounters or drug use, compared to the general population. Strengths of the survey and medical record studies were that the denominator could be varied in the sensitivity analyses.

6 Conclusions

The significant prevalence of ADEs across age groups of the adult general population demonstrates that ADEs are a considerable public health concern. Further, the prevalence of potentially preventable ADEs in the general population emphasises the importance of preventing ADEs in the entire health system. Although serious ADEs in hospital and emergency care appear more preventable than all ADEs, the markedly larger quantity of non-serious ADEs justifies resource allocation on all potentially preventable ADEs across healthcare. However, the required preventive strategies are likely to vary between settings, as the nature of ADEs in the general population partially differed from ADEs in outpatient clinics and hospitals.

The ADEs identified in this thesis demonstrate that ADEs are a heterogeneous group of events differing in nature. ADRs, STEs and self-reported UTIs were the most prevalent. Among them, gastrointestinal and central nervous system ADRs and STEs of hypertension and diabetes drugs burdened the general population the most. This heterogeneous nature of the ADE categories demonstrates that categorising ADEs enhances the understanding of their nature.

The diverse and limited methods for assessing the preventability of ADEs enforce improving their assessment. Establishing a clear definition for preventable ADEs could be the basis for developing one or more measurement instruments for more accurate and precise measurement in the future. The instrument could include characterising unsafe acts leading to preventable ADEs, which could enhance investigating and addressing their multi-factorial underlying causes in the healthcare organisation.

At least one-fifth of ADEs were potentially preventable in the adult general public. As preventability varied by ADE category, the ADE categories should be considered when investigating the prevention of ADEs. However, the high frequency of potentially preventable ADEs from commonly used drugs suggests that developing system-level strategies to improve the process of care for all patients, addressing reasons for several event types simultaneously, may result in greater improvement in safety than introducing separate prevention strategies for specific ADEs. Moreover, the high burden of preventable ADEs reinforces large-scale efforts to redesign safer, higher quality healthcare systems to adequately tackle the problem.

7 Future perspectives

Based on this thesis, several areas for future research were identified. First, the diverse nature of ADEs and the varying definitions for their preventability demonstrate the necessity of clarifying the definitions for ADEs and preventable ADEs. The harmonisation of the concepts requires international collaboration and thorough investigation. Clear, shared definitions would enhance the comparison of studies, improve the understanding of ADEs and their preventability, and thus facilitate developing preventive strategies.

Second, the diverse and limited methods for assessing the preventability of ADEs warrant improving the measurement. Based on shared definitions for ADEs and their preventability, new instruments for measuring preventability should be developed and their validity and reliability investigated. The characterisation of unsafe acts leading to preventable ADEs could be included in the preventability assessment, to enhance further investigating the underlying causes of preventable ADEs.

Third, the burden, nature and preventability of ADEs should increasingly be investigated in the entire healthcare system, in particular in primary care, as previous research is mainly conducted in hospitals. Preventive strategies should also be studied and developed in the entire healthcare system and in the community, where most preventable ADEs occur. For improving the understanding of prevention of ADEs, from both clinical and patient perspectives, future studies should investigate ADEs and their preventability using both self-reports and clinical data for the same population sample.

Finally, future research on preventing ADEs should recognise the importance of investigating the underlying causes of preventable ADEs, combining qualitative and quantitative methods. Numerous studies on the burden of ADEs and preventable ADEs describe the occurring events, mainly in hospital settings, but little is known about the contributing factors that caused them. A thorough understanding of the causes for preventable ADEs is the ground for developing preventive interventions.

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