Risk factors associated with use of medication in an elderly population

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Objectives: To study the use of medications in an elderly population and the risk factors for adverse drug events (age, gender, socioeconomics, multi-morbidity and polypharmacy).

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Results: Use of medications varies among individuals depending on gender, age and socioeconomic status, which is not dependent on level of multi-morbidity (paper I). Use of medications with increased risk of falling as opioids, dopaminergic agents, anxiolytics, antidepressants and hypnotics/sedatives increase the risk of hip fracture after adjustment for age, gender and multimorbidity level. However, no association was found to cardiovascular medications with increased risk of falling (Paper II). Number of chronic conditions and number of medications is more important for the risk of hospitalization, than the use of PIM (Paper III). Use of PIM has decreased in all strata of the variables age, gender, number of chronic conditions and polypharmacy when comparing two cohorts of patients 75 years and older in Blekinge. Polypharmacy has not increased significantly despite an increase in number of chronic conditions (Paper IV).

Conclusion: Factors, as gender, age and socioeconomics are affecting the use of medication to some extent even after adjusting for multi-morbidity. The results show that it is possible to improve quality of medication use in the elderly by decreased use of PIM in elderly, in a relative short period of time. Use of risk medications, should be evaluated in the context of the patient's multi-morbidity and whole medication treatment.

Key words Use of medication, elderly, potentially inappropriate medications, fall-risk increasing drugs, multi-morbidity, risk factors, adverse drug events

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MADE IN SWEDEN

To my loving and supporting family, I love you all

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Abbreviations

ACG	Adjusted Clinical Group
ADE	Adverse drug event
ATC	Anatomical Therapeutic Chemical classification system
CDWÖ	Care Data Warehouse in Östergötland
CI	Confidence interval
DDD	Defined Daily Doses
FRIDS	Fall-risk increasing drugs
IRR	Incidence Rate Ratio
NBHW	Swedish National Board of Health and Welfare
OR	Odds Ratio
PHC	Primary Health Care Centers
PIM	Potentially inappropriate medication
RUB	Resource Utilization Band
WHO	World Health Organization

Word definitions

Adjusted Clinical Groups	Summary measure of morbidity burden focused on stratification and classification of patients into groups according to diseases and conditions, age and gender.
Number of chronic conditions	Summary measure of morbidity were the number of chronic conditions are summaries on an individual level
Polypharmacy	Use of five or more medications at the same time

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Original Papers

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. **Thorell K**, Skoog J, Zielinski A, Borgquist L, Halling A: Licit prescription drug use in a Swedish population according to age, gender and socioeconomic status after adjusting for level of multi-morbidity. *BMC Public Health.* 2012 Jul 31;12:575.

II. **Thorell K**, Ranstad K, Midlöv P, Borgquist L, Halling A: Is use of fall risk-increasing drugs in an elderly population associated with an increased risk of hip fracture, after adjustment for multimorbidity level: a cohort study. *BMC Geriatr*. 2014 Dec 4;14:131.

III. **Thorell K**, Midlöv P, Fastbom J, Halling A: "Importance of potentially inappropriate medications, number of chronic conditions and medications for the risk of hospitalisation in elderly: a case-control study" Submitted after revision.

IV. **Thorell K**, Midlöv P, Fastbom J, Halling A: "Use of potentially inappropriate medication and polypharmacy in elderly: a repeated cross-sectional study" Submitted

Introduction

The life expectancy in Sweden has increased during the last century. Decline in infant mortality from the beginning of 1900's and onwards has been one of the main causes for the increase. Today the infant mortality is so low that the increased life expectancy has more to do with decreased mortality in the elderly [1]. The medical developments in the last decades have enabled health care to cure or treat diseases and treat symptoms better than ever. This leads to a growing elderly population, which leads to new challenges for the health care system [2].

Today modern medicine can cure and treat more diagnoses and symptoms which leads to an increased number of medications being used by one patient. The multimorbidity and use of medications increases with age. The risk of side effects and adverse drug events increases with age and increased use of medications [3].

The elderly population is a very heterogenic population. The difference between a healthy elderly population with few morbidities and medicines compared to the multimorbid elderly population with polypharmacy is large and so is the need for health care. One of the largest challenges for health care systems is how to manage the increasing need for care in an aging population.

Pharmacoepidemiology

The study of the use and effects of drugs in a large number of people is often how pharmacoepidemiology is described. Here the methods from epidemiology interact with the concept of evaluation of rational drug use from the clinical pharmacology. This relatively young research area, from the beginning of the 1960's, complements randomised clinical trials to evaluate drug treatments risk-benefit ratio.

Randomised clinical trials (RCT) are seen to be the gold standard to evaluate effect and safety in drug treatments. This is since the study design makes it ideal for obtaining an unbiased estimate of the benefits of drug treatment or risks of adverse outcomes. However, RCTs can only answer to a certain degree, the question regarding the risk-benefit ratio of a drug treatment. This is because RCTs have a high internal validity but, limited external validity. Therefore, it means that their results apply well to the specific population included in the study but cannot be applied fully to the total population in the real world. Observational postmarketing studies are needed to get a more complete picture of the risks with new marketed drugs. The thalidomide disaster in the 1960's raised the need for more studies on safety of drug use [4]. It has now evolved to include studies on rational drug use, health-economics and effectiveness of drug treatment.

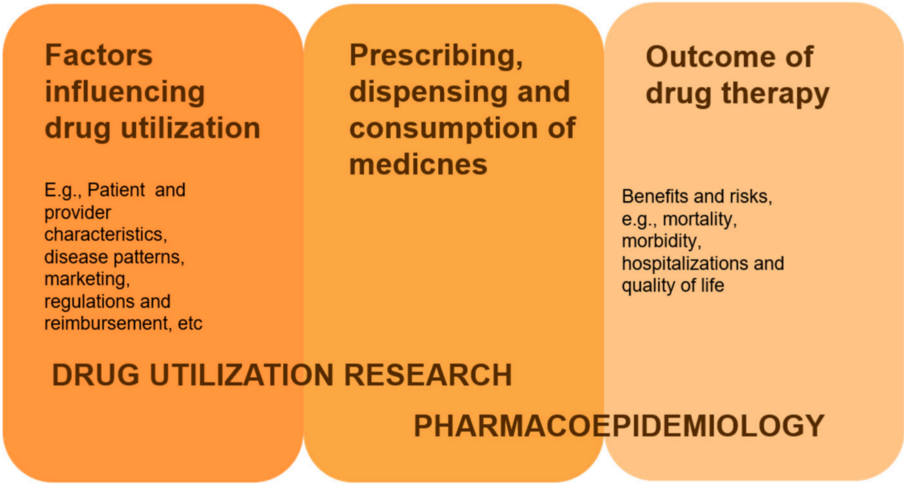

Figure 1. Traditional descriptions of drug utilization research and pharmacoepidemiology
Source: B. Wettermark et al. 2016 [5]

The last decades development of electronic population-based databases has led to pharmacoepidemiology growing rapidly. The new opportunities that have emerged have led to what is called drug utilization research, with the main purpose of improving drug use. In drug utilization research factors influencing drug utilization for example; patient and/or providers characteristics, disease patterns, marketing, regulation, and reimbursement factors, are analysed (figure 1). Pharmacoepidemiology and drug utilization research study "real-world" effectiveness and attempt to quantify risk of drug treatment [5].

Population based registers

Sweden has a long history of routinely collecting information about dispensed medications and building population-based databases like the Swedish Prescribed Drug Register. Databases have historically been developed for the need of administrative data and economical purposes. In time, researchers and health care personal have found new perspectives and opportunities [6, 7]. All this data can, and is, being used to compare medication treatment and medical results between different county councils, or units within the county, or even between countries.

Patient care records have historically been kept in paper form, but nowadays in Sweden most of the patient care data is stored electronically in different health care records. Using data from electronic patient records is still evolving in pharmacoepidemiology. Electronic patient records contain information that can provide a wealth of information for research purposes. Sweden has several different electronic patients records and some county councils have established data warehouses to store individual level data from them. A data warehouse is a database where all the information is linked together, for example with a personal identification number, data is added consecutively, and never written over or deleted. It comprises of information from multiple sources. The purpose for a data warehouse is to store information as raw data for analytic purposes.

Medication treatment in elderly

Aging is associated with physiological changes that affect how medicines are distributed in the body, their metabolism, and elimination. This can prolong; medications half-life, increase the potential for drug toxicity, and the likelihood for adverse drug reactions. For example, the proportion of fat in relation to the proportion of water increases, leading to an increased volume of distribution and half-life of fat-soluble medications. Decreased renal function can reduce the elimination of medications that have their major elimination through the kidneys. This can lead to prolonged half-life and the accumulation of medication in the body, therefore increasing the risk of adverse drug events (ADE). Elderly people may also have an altered response to medications, eg. an increased risk of orthostatic blood pressure when using vasodilators due to attenuated response from baroreceptors [2].

Side effects and adverse drug reactions from the use of medications is usually divided in to type A or type B reactions. Type B reactions are unpredictable and cannot be explained by the pharmacological properties of the medication. The majority of side effects and adverse drug reactions are type A reactions. This means that they originate from the pharmacological properties of the medication and are therefore predictable and preventable to a certain degree [8-12].

The saying “start low go slow” is often used when discussing medical treatment in the elderly. As we age, the morbidities and use of medication increases. This, in combination with altered pharmacokinetics and pharmacodynamics properties, increases the risk for ADE in an elderly patient.

An adverse drug event can be a hip fracture due to a fall caused by medications. Or an unplanned hospitalization due to an adverse drug reaction like an altered effect of the medication due to drug-drug interaction, or drug-diagnose interactions. Studies have found that between 10-30% of all unplanned hospital admissions for all ages are related to medication treatment and that the risk increases with age [8, 9, 12, 13]. Pirmohamed *et al.* found that up to 72% of medication related hospitalizations are avoidable [9]. However, the cause of an ADE is multifaceted and complex. Among many other factors, polypharmacy and the use of potentially inappropriate medications (PIM) have been found to increase the risk of ADE [2, 8, 9, 12, 13].

Quality indicators for medication use in elderly

To improve the medication quality in elderly and reduce the risk of ADE in elderly, different recommendations have been developed regarding potentially inappropriate prescribing (PIP) and how to handle them clinically. The term potentially inappropriate prescribing is commonly used for medical treatment that can be inappropriate for the individual in relation to diagnoses, other medication and physiological state. PIP increases the risk of a ADE if the medical treatment is not evaluated regularly [14, 15]. Internationally, the Beers criteria and the Screening tool of older persons potentially inappropriate prescribing (STOPP) are the most commonly used quality criteria's in research [16, 17].

The Swedish National Board of Health and Welfare have created a Swedish version, "Quality indicators for good drug therapy in elderly", to evaluate quality in medication treatment, and to follow up PIP. The quality indicators are developed for an elderly population of 75 years and older. From this report the first indicator 1.1 "Medicines that should be avoided unless there are special reasons" have been defined, in Sweden, as potentially inappropriate medication. The report also includes an indicator that define medications with an increased risk of falling in the elderly, "Medications and certain symptoms". These two definitions for PIP in elderly are used in this thesis and are described further below [14].

Potential Inappropriate Medication

PIM is generally defined as medications that have increased risk of side effects, that when used by older patients, outweigh the clinical benefits of the drug. Particularly when there are safer or more effective alternatives. The purpose of the indicators is to facilitate the follow-up of medical treatment. As the name states, it is medicines that should be avoided in patients 75 years and older because of the higher risk of side effects unless there are special reasons. If prescribed the prescriber should have a well-founded indication and the treatment should be evaluated at regular intervals.

The following drug groups and substances are included in the definition of the 2010 version of "Medicines that should be avoided unless there are special reasons": long acting benzodiazepines, tramadol, propiomazine and medicines with anticholinergic effect. The proportion of patients using PIM should be low. All mentioned medications have well-known side effects in elderly due to age-related physiological changes [14].

Long acting benzodiazepines

Hypnotics and sedatives called long acting benzodiazepines are associated with day-fatigue, cognitive impairment, muscle weakness, impaired balance and falls. Diazepam, nitrazepam and flunitrazepam are included in this group [14].

Tramadol

In older patients, tramadol has an increased risk of confusion and nausea. It should not be combined with other medications which also affects the serotonin system. This because of an increased risk of serotonergic syndrome [14].

Propiomazine

Propiomazine is a sedative medication that can give day-fatigue and extrapyramidal symptoms in the elderly [14].

Medicines with anticholinergic effect

In this group medications for incontinence, hydroxyzine, tricyclic antidepressant and some antipsychotics are the most common medications with anticholinergic effects among elderly in Sweden. They can cause cognitive impairment from mild memory issues to confusion. The risk increases with age but patients with Alzheimer dementia are particularly exposed [14].

Fall risk-increasing drugs

Medications are one of the main causes for falls in elderly. There are several medications that can be classified as fall risk-increasing drugs (FRIDs). FRIDs increases the risk of falling through orthostatic hypotension, impaired balance, dizziness or decreased reaction time. They can be divided into two groups, cardiovascular medications and psychotropic medications.

Cardiovascular medications

Here vasodilators used in cardiac diseases, antihypertensive agents, diuretics, beta-blocking agents, calcium channel blockers and renin-angiotensin system inhibitors are included.

Psychotropic medications

Here medications with increased risk of falling including those that affect the central nervous system are included e.g. opioids, dopaminergic agents, antipsychotics (lithium excluded), anxiolytics, hypnotics, sedatives and antidepressants, and alpha-adrenoreceptor antagonists.

Polypharmacy

Polypharmacy is the use of multiple medications at the same time. There is no clear definition on polypharmacy regarding the number of medications. However, when using five or more medications at the same time the risk of ADR increases exponentially. Therefore, the use of five medications or more at the same time is often used as a cut off for polypharmacy. The term excessive polypharmacy occurs in some studies and is used for the use of ten or more medications at the same time. Polypharmacy is associated with an increased risk of ADE due to the increased risk of drug-drug interactions[18, 19].

Polypharmacy is not wrong per se and is sometimes a necessity in patients with multimorbidity. Due to the developments in medicine in past decades, today we can treat and cure more diagnoses than ever before. More and more treatments are a combination of several medications acting on different parts of a system, giving the desired health outcome. For example, combining different blood pressure medications or different antipsychotic medications [20]. For the purpose in this thesis we use the definition for polypharmacy as the use of five or more medications at the same time.

Multimorbidity

The concept of the coexistence of several morbidities in one person at the same time has been defined in several ways. The term, comorbidity, is often used to describe the relation of a morbidity to a specific index condition. Multimorbidity is used to describe the presence of multiple morbidities in one person at the same time without any relation to an index condition. Morbidity burden is the collected burden of morbidities, gender, age, frailty and health-related attributes in an individual [21]. Depending on what the purpose is, different concepts are used to measure multimorbidity.

In this thesis two different methods to measure multi-morbidity are being used, the ACG-case mix system [22] and number of chronic conditions [23].

Adjusted Clinical groups case mix-system

The ACG case-mix system was developed by Barbara Starfield and colleagues at the John Hopkins University [15]. It was developed to estimate utilization of care in children and then modified to include adults also. The ACG case-mix system aims to estimate multi-morbidity and predict utilization of health care in the population to predict costs of health care utilization in an individual or population.

All registered diagnoses for an individual, for a fixed period of time, are used to group and estimate the individual's multi-morbidity level based on the patients diagnoses characteristics. An individual's diagnoses are grouped in ACG groups based on five clinical dimensions:

- Duration of the condition
- Severity of the condition
- Aetiology for the diagnosis
- Diagnostic certainty
- Need for specialist care

All individuals in the same ACG have the same degree of multi-morbidity but not per se the same diagnoses. The ACG's are categorised in to six Resource Utilization Band's (RUB). RUB 0 includes patients with no need for health care and patients in RUB 5 have a very high need for health care. For example, preventive interventions correspond to RUB 1, a single chronic diagnosis could correspond to RUB 3 and a certain combination of chronic diagnoses corresponds to RUB 4 or RUB 5.

The ACG case-mix system calculates a multi-morbidity burden for the individual according to a specific algorithm. Its main purpose is to predict the need for health care in a population and in the individual [22].

Number of chronic conditions

At the Aging Research Centre in Stockholm, A. Calderòn-Larrañaga et.al. developed a clinical driven method to measure multi-morbidity in older populations [23]. Diagnoses coded in ICD-codes on a 4 digit-level have been evaluated and discussed on the following key features for the disease:

- Duration e.g. the prolonged or lasting for a specific time
- Development e.g. The progression, the recurrence or the persistence of the disease

- Reversibility of symptoms and of pathological alterations
- Treatment both pharmacological, nonpharmacological, and care setting
- Consequences e.g. disability, quality of life, etc.

The chronic diseases were then clustered according to pathophysiological pathway, treatment, prognosis, and prevalence to create broader chronic conditions groups. The result was 60 chronic conditions groups. Multi-morbidity was then estimated by counting the number of chronic conditions according to each patient. In this method all diagnoses are equal, and the complexity of the multi-morbidity is estimated. The aim for the method is to be a standardized, transparent and feasible method for estimating multi-morbidity in an older population.

Other factors affecting use of medication

Factors other than those that are strictly medical are of importance to medication use. Gender is a variable where there is a difference between males and women in medication use. Women are more likely to use medication than men according to findings in several epidemiological studies. The differences cannot fully be explained by gender related-morbidity [24, 25].

Socioeconomics also effects the prevalence of medication use in a population. Socioeconomic status is generally assessed by education and income in health care research [26, 27]. Individuals with low socioeconomic status have a higher multi-morbidity than individuals with higher socioeconomic status [28]. Studies of inequalities in medication used in an older population due to socioeconomic factors have come to inconclusive results. A low educational level is often related to an increased use of medications, and inappropriate drug use [29, 30]. However, there are medication treatments where the use increases with high education level e.g. use of anti-migraine, erectile dysfunction, hormone replacement, osteoporosis and antibiotics medication [31, 32] .

As discussed earlier physiological changes that occur as we age can affect the pharmacological response, metabolism, and elimination of medications. The prevalence of multi-morbidity in the population is increasing with age [33]. This can be illustrated by the fact that individuals 65 years or older in Sweden constituted for 20% of the total population [34] but accounted for 58 % of all prescribed medications in 2010 [35]. Age is therefore in pharmacoepidemiologic studies divide into different age categories to take this into consideration. Usually the population is divided into intervals relevant for the study outcome in question. However, there are some commonly used cut offs for the elderly, 65 years or 75 years of age. In this study we use the cut off of 75 years and older due to that the quality criterias are constructed from this age cut off.

Aims

The general aim of this thesis was to study the use of medications in an elderly population and the risk factors for adverse drug events (age, gender, socioeconomics, multi-morbidity and polypharmacy).

Specific aims:

- To analyse the odds of medication use among individuals in the population and the rate of medication use among patients depending on gender, age and socioeconomic status after adjustment for multimorbidity level (Paper I).
- To explore the association between the use of fall risk-increasing drugs in combination with multimorbidity level and the risk of hip fracture in the elderly (Paper II).
- To study the association of potentially inappropriate medication, the number of chronic conditions and the number of medications as useable risk factors for unplanned hospitalisation in elderly patients (Paper III).
- To study the prevalence of PIM in a population and in different strata of the variables age, gender, number of chronic conditions and number of medications and how that prevalence and relation changed over time (Paper IV).

Methods

This thesis contains four register-based studies on two different populations form Östergötland and Blekinge County. An overview of the studies is presented in table 1.

Table 1. Overview of the study designs in the four studies

Paper	I	II	III	IV
Design	Cohort	Cohort	Case-control	Repeated Cross-sectional
Participants	Individuals ≥20 years from Östergötlands County (N= 313 977)	Individuals ≥75 years from Östergötlands County (N= 38407)	Individuals ≥ 75 years from Blekinge County (N= 5720)	Individuals ≥ 75 years from Blekinge County population 1, 31/3 2011 (N1= 15 361) and population 2, 31/12 2013(N=15 945)
Outcomes	Use of medications and costs	Odds for hip fracture during use of fall risk-increasing drugs	Odds for hospitalisation during use of potentially inappropriate medication	Change in proportion of potentially inappropriate medication and polypharmacy in stratified varibles gender, age, polypharmacy and number of chronic conditions. The odds ratio to have potentially inappropriate medication 2013.
Data collection methods	Data from CDWÖ and the Swedish National Pharmacy Register	Data from CDWÖ and the Swedish National Pharmacy Register	Data from patient records and regional register on dispensed medicines for inhabitants in Blekinge County	Data from patient records and regional register on dispensed medicines for inhabitants in Blekinge County
Data package	Stata 10	Stata 13	Stata 14	Stata 14
Data analysis	Zero-inflated negativ bionomial regressions	Multivariate logistic regression	Multivariate logistic regression	Chi-square test Multivariate logistic regression

Study population and data collecting

Paper I and II

In Östergötland county there lived about 400 000 inhabitants in 2006. It is situated about 200 km southwest of Stockholm. The age demography in Östergötland is similar to that of the rest of Sweden. The mean age of Östergötland was 41,0 years in 2006 compare 40,9 years for the hole of Sweden [36].

The Care Data Warehouse in Östergötland

The CDWÖ was established in 1998 to register information from the hospitals in the county. In 1999 the information from the primary health care centres (PHC), both public and private, began. In 2000 private specialist clinics were included. The data warehouse includes administrative data on the patients and on the consultations or hospitalization. For each consulting to a doctor and hospitalization, the main diagnosis and up to 10 secondary diagnoses are registered. In PHC it is possible to register up to 10 unranked diagnoses.

From the CDWÖ information on the patients age, gender and diagnoses from 2006 was collected. Information about hip fractures was collected from 2007.

The Swedish Prescribe Drug Register

The Swedish prescribe drug register (SPDR) with personal identification number was established in July 2005. It covers the total population of Sweden and contains information on all prescribed and dispensed medications on an individual level. If the medication is only prescribed but not dispensed it is not in the SPDR. The SPDR does not cover information on over the counter medications. On an individual level the SPDR holds information on age, gender and an unique identifier on the patient as well as the prescriber's profession and practice [37].

Information about medication use were collected from SPDR for 2006 for study I and III. All information on medications were grouped according to the anatomical therapeutic and chemical (ATC) system [38].

Statistics Sweden

The first population survey in Sweden was as early as in 1749, and in 1914 Statistics Sweden gave out their first ever year-book about population composition. Ever since, Statistics Sweden has kept a population register for presenting size and composition of the population, stratified according to sex, age, marital status, income, educational level etc. Statistic Sweden is in charge of producing, developing and communicating official statistics [36]. Information on income and education level were collected from Statistics Sweden.

Paper III and IV

Blekinge is located in the southeastern corner of Sweden. It is one of the smallest counties in Sweden with only 152 315 inhabitants in 2013. The population in Blekinge had a higher mean age compared to the rest of Sweden. The mean age in Blekinge was 43.4 years in 2013, compared to 41.2 years in the whole of Sweden [36].

For paper III and IV individuals aged 75 years and older listed to a primary health care center in Blekinge 2011 and 2013 were included. Information on age, gender, diagnoses and unplanned hospitalizations were collected from the patient records of Blekinge county council. Diagnoses from both primary and secondary care were used.

Data on medication use was collected from the county councils register on dispended medicines for all inhabitants in Blekinge, which was received from the Swedish eHealth Agency. The register contains the same data on prescribed medicines as the SPDR, but the coverage is limited to the residents in the county and the dose text is missing [6, 39]. Medicines were classified according to the ATC-system [38].

Procedure

Paper I and II

In paper I the total population aged 20 years or older (n=313 977) was included and in paper II the population 75 years and older (n=38 407) was included. Information on medication use was collected from the SPDR during 2006. Multi-morbidity level was estimated with the ACG case-mix system with diagnoses from the CDWÖ from 2006 being used. The ACGs were collapsed into six RUBs, zero to five, in order to reflect the need of health care. Individuals in no need of health care according to the ACG algorithm were placed in RUB 0, and individuals with a very high need for healthcare were placed in RUB 5. The ACG case mix system uses age and gender only to a certain degree when estimating the need of health care. However, it is not a complete consideration and therefore we adjust for age and gender in the analyses too. Information on hip fracture was collected from the CDWÖ during 2007. The following diagnose codes were used, S72.0, S72.1 and S72.2.

In paper I income and education level were used as socioeconomic factors and were collected from Statistics Sweden. Due to the high degree of missing data of educational levels for individuals ≥70 years, that was excluded from the analyses of education level. Income was categorised into quartiles from the lowest to the highest income level. Education was divided into four categories according to years of education: 1. Primary school not completed (<9 years). 2. Primary school completed (9-10 years) 3. Secondary school (10-12 years) 4. Higher education (>12 years).

In paper I the use of medication, stated as defined daily doses (DDD), and total cost of medication as a dependent variable in 2006. DDD is a fixed measurement for each medication based on the average dose per day for its main indication. The WHO determines the DDD [38].

In paper II four models were created to analyse the odds of hip fracture during the use of FRIDs; Model A was unadjusted; model B was adjusted for age; model C was adjusted for age and gender; and model D was adjusted for age, gender and multimorbidity level.

Paper III

Paper III was a case-control study and individuals 75 years or older listed to a primary care center in Blekinge during 2013 were included. Individuals with at least one unplanned hospitalization during 2013 to a medical, geriatric and palliative or an orthopaedic ward were classified as cases. Each case was then matched 1:1 on age (birth year) and gender to a control to form risk sets. Information about unplanned hospitalizations was collected from the electronic patient records for the included individuals. The date of the first unplanned hospitalisation for each case was set to be the index date for each risk set.

Multi-morbidity was measured as the number of chronic conditions based on diagnoses for a two-year period before 2013 [23]. If a diagnosis was recorded more than one time it was only counted once. Number of chronic conditions were divided into five intervals; none chronic conditions, one, two to four, five to seven and eight or more chronic conditions.

The number of medications were obtained from the county council local register on prescribed dispensed medication. A three-month period was used to construct a medicine list on prescribed collected medicines on an index date for each risk set. If the same drug was dispensed more than once it was counted only once. Since the county councils register of dispended medicines does not contain the dose text, we used Defined Daily Doses (DDD) to calculate the duration of the drug exposure for every individual. We assumed 0.9 DDDs for regularly used medicines based on calculations for regularly used medicines in an elderly population [40]. The number of medications and use of PIM defined according to definition by NBHW [14], was gained from the constructed medication list for each risk set at index date. The number of medications were categorised into five intervals; no medication, 1 to 4, 5 to 9, 10 to 14 and 15 or more and use of PIM in to two, use or no-use.

Paper IV

To the repeated cross-sectional study in paper IV two cohorts were included; cohort one was individuals listed at a primary care center the 31st March 2011 and cohort two was individuals listed the 31st December 2013. All included individuals were of the age of 75 years or older. Age was categorised into four groups: 75-<80, 80-<85, 85-<90 and ≥90. Information on diagnoses was collected from the electronic patient record for a two-year period before inclusion of each cohort. Multi-morbidity was estimated with number of chronic conditions [23], as described under paper III. Use of medication was obtained from the county register of dispensed prescribed medication. The medication list was constructed in the same way as in paper III. For cohort one the medication use was considered for the 31st March 2011 and for cohort two for the 31st December 2013. Polypharmacy was defined as the use of five or more medications at the same time and use of PIM (according to definition by NBHW) in to two categories, use or no-use [14].

Statistical analyses

The statistical analyses in Paper I was carried out using STATA version 10, and in Paper II STATA version 12 was used. In Paper III and IV STATA version 14 was used for the statistical analyses (Stata Corporation, Texas, USA). For descriptive analyses of the cohorts in paper I, III and IV, chi2- test was used. A significance level (α) of 0.05 (*) and 0.001 (**) was used.

Paper I

Zero-inflated negative binomial regression, was the best statistical fit for our data due to the high number of non-users of medication in the population [41]. It is a combined model; one analysis is logistic regression and answers the question of what the odds are to belong to individuals in the population with no risk of medication use (DDD==0) and gives an odds ratio (OR) with 95% confidence intervals. The inverted odds ratio was the odds of medication use when at risk (DDD>=0). The second analysis is similar to Poisson regression and answers the question of what the effect is of increasing the independent variable, by one unit among patients at risk of medication use and gives an incidence rate ratio (IRR) with 95% confidence intervals. This provided two analyses of medication use and medication costs for individuals in the population and two analyses for patients. The dichotomous models for medication use and medication costs for individuals gave similar results, therefore we only used the one for medication use (DDD).

We generated four different models for each analysis: Model 1; adjusted for multi-morbidity, Model 2; adjusted for multi-morbidity, gender, Model 3; adjusted for multi-morbidity, gender and age.

Paper II

To analyse the odds ratio of having a hip fracture during 2007 during use of FRIDs, multivariate logistic regression was used. This is an extension of the simple regression in which two or more independent variables (age, gender and multi-morbidity level) are taken into consideration simultaneously to predict a value of the dependent variable (FRIDs) for each subject. Four models were created to analyse each FRID; Model A was unadjusted; model B was adjusted for age; model C was adjusted for age and gender; and model D was adjusted for age, gender and multimorbidity level. The odds ratio of having a hip fracture during the use of multiple FRIDs or multiple psychotropic FRIDs or cardiovascular FRIDs was also analysed. The odds ratio (OR) was presented with 95% confidence intervals.

Paper III

All variables were used as categorical. Five different models were created to analyse the importance of the variables, use of PIM, number of medications, and number of chronic conditions for an unplanned hospitalization. Model A to C was univariate analyses for each included variable; model D adjusted for number of chronic conditions; model E adjusted for number of chronic conditions- and medicines. Conditional logistic regression was used since it was a matched case-control study, and the results were presented as odds ratio (OR) with 95% confidence intervals (95%Cls).

Paper IV

All variables were used as categories in the analyses. For the descriptive analysis of the cohorts, use of medications was divided into three strata; no-medication, use of 1 to 4 and use of five or more. However, for analysis of polypharmacy in different strata, use of medication was divided into two categories; zero to four medications (<5, no-polypharmacy) and five or more medications (≥5, polypharmacy).

We then described the cohorts from use of PIM in different strata of the variables age, gender, number of chronic conditions and polypharmacy and analysed the differences between the 2011 and 2013. The cohorts were then described and analysed from use of polypharmacy in different strata of the variables age, gender and number of chronic conditions. The cohorts were compared using chi-square test. A significance level (α) of 0.05 (*) and 0.001 (**) was used.

Logistic regression was used to analyse how the different strata of the variables from 2011 was associated to the use of PIM 2013. Here only individuals present in both cohorts were included. We created five models; model A adjusted with stratification for use of PIM, model B adjusted with stratification for PIM and age, model C adjusted with stratification for PIM, age and gender, model D adjusted with stratification for PIM, age, gender and number of chronic conditions, model E adjusted with stratification for PIM, age, gender, number of chronic conditions and polypharmacy. A significance level (α) of 0.05 (*) and 0.001 (**) was used.

Ethical consideration

All the studies in this thesis used register-based data.

Ethical consideration for Paper I and II

All personal identification numbers in data from the Swedish Prescribed Drug register had been removed by the National Board of Health and Welfare. Data from Statistics Sweden are anonymous. Data from the CDWÖ was anonymized which means that the outcome from the register cannot be linked to any individuals. The Research Ethics committee at Linköping University approved of the studies (Dnr 147/05 and 29/06)

Ethical consideration for Paper III and IV

Data in paper III and IV is based on anonymized information provided by the County Council of Blekinge. They provided the data anonymized so that no individual could be linked to the outcomes. These studies were approved by the Regional Ethical Review Board in Lund (Dnr 2015/712).

Due to the requirement of anonymized data, each individual could not be asked for consent to participate; active refusal of participation was instead applied. This was done by publishing information about the planned study in local newspapers. The advertisement outlined the studies and contained information on how to contact the data extractor by phone, email or mail in order to have the opportunity not to participate.

Findings

Main findings

- Use of medications varies among individuals depending on gender, age and socioeconomic status, which is not dependent on level of multi-morbidity. Nonetheless multi-morbidity level is the main cause for use of medication. (Paper I).
- The list of medications with increased risk of falling comprise of both cardiovascular and psychotropic medications. However, our results indicate that only opioids, dopaminergic agents, anxiolytics, antidepressants and hypnotics/sedatives increase the risk of hip fracture after adjustment for age, gender and multimorbidity level. Use of psychotropic medications, high age, female gender and multimorbidity level could be used to identify individuals that would benefit from a medication review. (Paper II)
- Number of chronic conditions and number of medications is more important for the risk of hospitalization, than the use of potentially inappropriate medication. (Paper III)
- Use of potentially inappropriate medication has decreased in all strata of the variables, age, gender, number of chronic conditions and polypharmacy. When comparing two cohorts of patients 75 years and older in Blekinge between 2011 and 2013. Polypharmacy has not increased significantly despite an increase in number of chronic conditions (Paper IV).

Male individuals had half the OR of receiving prescribed medications after adjustment of multi-morbidity, compared to females (OR 0.41 (95% CI 0.40- 0.42). However, when analysing the use of medication in the population that uses medication, males had decreased rates of medication use (IRR 0.97 (CI 95% 0.96-0.98)) but increased rates of costs (IRR 1.14 (CI 95%1.13-1.15)) compared to female patients (table 2).

Tabel. 2 Odds ratio of receiving medication treatment in the population and rate

Variables	DDD[a] OR (CI 95%)	DDD[b] IRR (CI 95%)	Costs[b] IRR (CI 95%)
Gender[1]			
female	1	1	1
male	0.41 (0.40-0.42)*	0.97 (0.96- 0.98)*	1.14 (1.13-1.15)*
Age (years)[2]			
20-29	1	1	1
30-39	1.04 (1.00-1.08)	1.07 (1.05- 1.09)*	1.07 (1.05- 1.10)*
40-49	1.26 (1.22-1.30)*	1.50 (1.47- 1.53)*	1.42 (1.39- 1.46)*
50-59	1.85 (1.78-1.88)*	2.18 (2.14- 2.22)*	1.63 (1.59- 1.67)*
60-69	3.03 (2.94-3.03)*	2.97 (2.91- 3.03)*	1.88 (1.84- 1.92)*
70-79	4.76 (4.54-5.00)*	3.68 (3.60- 3.76)*	1.95 (1.90- 1.99)*
80-	9.09 (8.33-10.00)*	4.50 (4.40- 4.60)*	1.95 (1.91- 2.00)*
Educational level[3] up to 60-69 years			
1	1	1	1
2	0.97 (0.92-1.02)	0.99 (0.96-1.02)	1.05 (1.02-1.09)*
3	0.94 (0.90-0.99)*	0.85 (0.83-0.87)*	0.96 (0.93-0.98)*
4	0.89 (0.85-0.93)*	0.78 (0.76-0.80)*	0.92 (0.89-0.94)*
Income level[3]			
1	1	1	1
2	1.16 (1.14-1.20)*	1.00 (0.99- 1.02)	0.97 (0.96- 0.99)*
3	1.06 (1.03-1.09)*	0.81 (0.80- 0.82)*	0.83 (0.82- 0.85)*
4	1.05 (1.02-1.08)*	0.73 (0.71- 0.74)*	0.71 (0.70- 0.72)*

a total population b, population that uses medications * p-value <0.05
[1]Adjusted for multi-morbidity, [2]Adjusted for multi-morbidity and gender, [3]Adjusted for multi-morbidity, gender and age

Use of medication increased with age and individuals of 80 years and older in the population had the highest odds ratio of medication use (OR 4.50 (Cl 95% 4.40-4.60). Age increased the rate of both medication use (DDDs) and costs for patients (Table 2).

Individuals with the highest educational level had 11% lower odds to use medications where compared to the lowest educational level. Individuals in the lowest income quartile had the lowest odds for medication use after adjustment of multi-morbidity, age and gender. Individuals in the second quartile of income (the next lowest income level) had the highest odds of medication use (OR 1.16 (Cl95% 1.14-1.20) (Table 2). High educational level was associated with a reduced rate of medication use (DDDs) up to 22% in the highest level, and a reduced rate of costs up to 8%. In the highest income quartile among patients the rate of medication use reduced by 27% and the rate of costs by 29% (Table 2).

Paper II

In the study population (n=38 407), 2% had a hip fracture during 2007. The highest prevalence of hip fractures was found in women (1.52%) and in individuals 85 years and older (1.19%). The majority of the population had at least one chronic diagnosis. Diuretics and beta-blocking agents were the most commonly used medications (47% and 44%, respectively). One quarter of the population used hypnotic and sedative medications and 20% used opioids. There was no use of alpha-adrenoreceptor antagonists (G04CA) in the population and hence no results were presented here.

The multivariate logistic regression exposed that cardiovascular FRIDs and psychotropic FRIDs have different risk patterns for hip fracture after adjusting for age gender and multi-morbidity (full model) (Table 3). Use of cardiovascular FRIDs was not associated with an increased risk of hip fracture in the full model (D). Though patients using psychotropic FRIDs had a higher risk of hip fracture than non-users (model D). Dopaminergic agents and antidepressants had the highest ORs for hip fracture: 1.78 (95% CI 1.24-2.55) and 1.66 (95% CI 1.42-1.95), respectively after adjustment for multi-morbidity level, age and gender. However, the OR estimation of hip fracture due to pharmacological treatment decreased every time we adjusted for an additional confounder.

Use of more than one psychotropic FRIDs had an increased risk of hip fracture, in the full model (Table 4). Use of four psychotropic FRIDs (OR 2.72 95% Cl 1.95-3.79) had the highest risk of hip fracture. Use of six or seven FRIDs also had increased ORs for hip fracture: 1.68 (95% CI 1.16-2.43) and 1.85 (95% CI 1.12-3.06), respectively.

Table 3. Odds ratio of hip fracture in patients using FRIDs

Drugs/group of drugs	Model A *OR* (CI 95%)	Model B *OR* (CI 95%)	Model C *OR* (CI 95%)	Model D *OR* (CI 95%)
Cardiovascular drugs				
Vasodilators used in cardiac diseases	1.14 (0.96-1.35)	0.99 (0.83-1.18)	1.02 (0.85-1.21)	0.89 (0.74-1.06)
Antihypertensive agents	0.99 (0.37-2.67)	1.12 (0.41-3.02)	1.29 (0.47-3.49)	1.26 (0.46-3.42)
Diuretics	1.35 (1.17-1.56)*	1.10 (0.95-1.27)	1.07 (0.92-1.23)	0.97 (0.84-1.12)
Beta-blocking agents	0.96 (0.83-1.11)	1.01 (0.88-1.16)	1.01 (0.88-1.17)	0.92 (0.80-1.07)
Calcium channel blockers	0.82 (0.68-0.98)*	0.87 (0.73-1.05)	0.88 (0.73-1.05)	0.83 (0.69-1.00)
Renin-angiotensin system inhibitors	0.89 (0.77-1.04)	0.99 (0.85-1.16)	1.02 (0.87-1.19)	0.93 (0.79-1.09)
Psychotropic drugs				
Opioids	2.03 (1.75-2.36)*	1.83 (1.57-2.13)*	1.76 (1.51-2.05)*	1.56 (1.34–1.82)*
Dopaminergic agents	1.88 (1.31-2.67)*	1.96 (1.37-2.81)*	1.99 (1.39-2.84)*	1.78 (1.24-2.55)*
Antipsychotics excluding lithium	1.80 (1.35-2.39)*	1.42 (1.06-1.89)*	1.37 (1.03-1.84)*	1.31 (0.98-1.75)*
Anxiolytics	1.75 (1.49-2.06)*	1.48 (1.25-1.74)*	1.41 (1.19-1.66)*	1.31 (1.11-1.54)*
Hypnotics and sedatives	1.75 (1.51-2.02)*	1.48 (1.28-1.71)*	1.42 (1.22-1.64)*	1.31 (1.13-1.52)*
Antidepressants	2.08 (1.78-2.43)*	1.88 (1.61-2.20)*	1.79 (1.53-2.10)*	1.66 (1.42-1.95)*

*p-value <0.05

Table 4. Risk of hip fracture in patients using multiple FRIDs, adjusted for age, gender and multimorbidity level

Number of FRIDs	All FRIDs	Cardiovascular drugs	Psychotropic drugs
	OR (CI 95%))	OR (CI 95%)	OR (CI 95%))
1	1.04 (0.76-1.41)	0.90 (0.73-1.10)	1.42 (1.18-1.71)*
2	1.15 (0.87-1.54)	0.74 (0.60-0.91)*	1.79 (1.46-2.20)*
3	1.22 (0.91-1.62)	0.92 (0.74-1.15)	2.10 (1.65-2.69)*
4	1.20 (0.89-1.62)	0.70 (0.53-0.96)*	2.72 (1.95-3.79)*
5	1.29 (0.93-1.80)	0.69 (0.38-1.26)	0.67 (0.16-2.74)
6	1.68 (1.16-2.43)*		
7	1.85 (1.12-3.06)*		
8	1.13 (0.44-2.88)		
9	2.99 (0.69-13.03)		

*p-value <0.05

The combination of high multi-morbidity level (RUB 3 to 5) and use of single psychotropic FRIDs, except for antipsychotics, increased the OR for hip fracture (dopaminergic agents OR 1.91, CI 95%1.31-2.79, antidepressants OR 1.75 CI 95% 1.47-2.09, opioids OR 1.71 95% CI 95% 1.44-2.03, anxiolytics 1.35 95% CI 95% 1.12-1.63 or hypnotics/sedatives OR 1.36 95% CI 95%1.15-1.61). Use of cardiovascular FRIDs did not have increased OR for hip fracture, irrespective of multimorbidity level. Patients using antidepressants (RUB 0-2 OR1.66 Cl 95% had increased odds of hip fracture, irrespective of multimorbidity level.

Paper III

There were 2941 patients with the minimum of one hospitalization to a medical, geriatric and palliative or orthopaedic ward during 2013. 81 were cases excluded; 78 were excluded because of incomplete data and three because of the absence of controls. In total 5720 individuals were included and formed 2860 risk sets. In the univariate analysis of hospitalisation during use of PIM the OR was 1.54 (Cl 95% 1.30-1.83) (Table 5). In the univariate analysis for number of chronic conditions the OR was significant from 2-4 chronic conditions (OR 1.27 Cl 95% 1.04-1.56) and then continued to increase with multi-morbidity. Number of medications has the strongest association for hospitalisation in the univariate analysis and the OR increased exponentially for each interval of number of medicines (5 to 9 medicines; OR 1.86 (Cl 95% 1.55-2.90) 10 to 14 medicines; OR 3.10 (Cl 95% 2.44-3.93) ≥15 medicines OR 6.93 (Cl 95% 4.25-11-30). When multi-morbidity was added to the model the association for hospitalization during use of PIM decreased (OR 1.39 Cl 95% 1.16-1.66). For number of chronic conditions, the association was significant from 2-4 (OR 1.26 (Cl 95% 1.03-1.54)) chronic conditions and was doubled for 5-7 (OR 2.30 (Cl 95% 1.86-2.85)) and for ≥8 (OR 3.94 Cl 95% 3.08-5.04). In the full model use of PIM was not associated with hospitalization. Multi-morbidity was significant from 5 to 7 chronic conditions (OR 1.86 (Cl 95 % 1.49-2.33), ≥8 chronic conditions OR 2.70 (Cl 95 % 2.08-3.51)). The strongest association for hospitalization in the full model had number of medicines. From the use of 5-9 medications the OR was doubled for each interval of number of medicine (5 to 9 medicines; OR 1.86 (Cl 95% 1.55-2.90) 10 to 14 medicines; OR 3.10 (Cl 95% 2.44-3.93) ≥15 medicines; has an OR 6.93 (Cl 95% 4.25-11-30).

Table 5. Odds ratio of hospitalization

Model A to C, are univariate analyses, model D includes PIM and number of chronic conditions and model E includes PIM, number of chronic conditions and medicines Paper III.

Variables	Model A OR (CI 95%)	Model B OR (CI 95%)	Model C OR (CI 95%)3	Model D OR (CI 95%)	Model E OR (CI 95%)
No Use of PIM	1			1	1
Use of PIM	1.54 (1.30-1.83)*			1.39 (1.16-1.66)*	1.09 (0.90-1.33)
Number of chronic conditions					
0		1		1	1
1		1.12 (0.88-1.42)		1.11 (0.88-1.41)	1.09 (0.86-1.39)
2-4		1.27 (1.04-1.56)*		1.26 (1.03-1.54)*	1.15 (0.93-1.41)
5-7		2.35 (1.90-2.90)*		2.30 (1.86-2.85)*	1.86 (1.49-2.33)*
≥8		4.06 (3.18-5.19)*		3.94 (3.08-5.04)*	2.70 (2.08-3.51)*
Number of medicines					
0			1		1
1-4			0.99 (0.82-1.18)		0.89 (0.74-1.08)
5-9			1.86 (1.55-2.22)*		1.46 (1.21-1.77)*
10-14			3.10 (2.44-3.93)*		2.05 (1.59-2.66)*
≥15			6.93 (4.25-11.30)*		3.84 (2.30-6.44)*

*p-value<0.05, PIM = Potential inappropriate medicines

Paper IV

Number of individuals in the 2011 cohort was 15 361 and for 2013, 15 945 individuals. Of these, 11 973 (78%) individuals were present in both cohorts. The mean age in both cohorts was 82 years. Prevalence of PIM decreased from 10.60% to 7.04% between 2011 and 2013 (p-value, <0.001). Five to seven chronic conditions increased from 20.82% to 23.66% and eight or more chronic conditions increased from 7.72% to 9.48% (p-value, <0.001). Use of medication increased between 2011 and 2013 (use of 1-4 medications 46.57% to 47.39% and use of ≥5 32.62% to 33.41%) while non-users decreased (20.82% to 19.19%) (p-value <0.001) (Table 6)

Table 6. Descriptive analysis of the two cohorts from 2011 and 2013, paper IV.

Variables		2011 (n)	%	2013 (n)	%	p-value
Total		15 361		15945		
Age	75- <80	6027	39.24	6472	40.59	
	80- <85	4751	30.93	4733	29.68	
	85- <90	3029	19.72	3021	18.95	
	≥90	1554	10.12	1719	10.78	<0.05
Gender	Women	8907	57.98	9167	57.49	
	Man	6454	42.02	6778	42.51	ns
Use of PIM	No	13733	89.40	14823	92.96	
	Yes	1628	10.60	1122	7.04	<0.001
Number of chronic conditions	0	2117	13.78	1762	11.05	
	1	2342	15.25	2076	13.02	
	2-4	6559	42.70	6822	42.78	
	5-7	3157	20.55	3773	23.66	
	≥8	1186	7.72	1512	9.48	<0.001
	No-medication	3198	20.82	3060	19.19	
Polypharmacy	1-4	7153	46.57	7557	47.39	
	≥5	5010	32.62	5328	33.41	<0.001

Use of PIM decreased in all strata of the variables. Among patients with multi-morbidity the highest decrease was seen in two to four chronic conditions (4.28% to 2.75%) (p-value, <0.001) (Table 7). Use of PIM decreased among patients with polypharmacy (7.36% to 4.91% p-value <0.001). The prevalence of polypharmacy increased only in patients aged 80- <85 years (10.27% to 10.50 %, p-value <0.05) and in males (12.34% to 13.47%, p-value <0.05). In all the other strata of the variables the differences were not significant.

Table 7 Use of potentially inappropriate medication in 2011 and 2013 in different strata of the variables

Variables	Categories	Use of PIM 2011		Use of PIM 2013		
		No (%)	Yes (%)	No (%)	Yes %	p-value
Age	75- <80	5442 (35.43)	585 (3.81)	6049 (37.94)	423 (2.65)	<0.001
	80- <85	4278 (27.85)	473 (3.08)	4383 (27.49)	350 (2.20)	<0.001
	85- <90	2665 (17.35)	364 (2.37)	2815 (17.65)	206 (1.29)	<0.001
	≥90	1348 (8.78)	206 (1.34)	1576 (9.88)	143 (0.90)	<0.001
Gender	Women	7815 (50.88)	1092 (7.11)	8427 (52.85)	740 (4.64)	<0.001
	Man	5918 (38.53)	536 (3.49)	6396 (40.11)	382 (2.40)	<0.001
Number of chronic conditions	0	1970 (12.82)	147 (0.96)	1689 (10.59)	73 (0.46)	<0.001
	1	2144 (13.96)	198 (1.29)	1982 (12.43)	94 (0.59)	<0.001
	2-4	5901 (38.42)	658 (4.28)	6384 (40.04)	438 (2.75)	<0.001
	5-7	2728 (17.76)	429 (2.79)	3433 (21.53)	340 (2.13)	<0.001
	≥8	990 (6.44)	196 (1.28)	1335 (8.37)	177 (1.11)	<0.001
Polypharmacy	<5	9854 (64.15)	497 (3.24)	10278 (64.46)	339 (2.13)	<0.001
	≥5	3879 (25.25)	1131 (7.36)	4545 (28.50)	783 (4.91)	<0.001

In the univariate analyses PIM, women, number of chronic conditions and polypharmacy has an increased OR for having PIM 2013. In the full model those having PIM 2011 had the highest odds of having PIM 2013 (OR 15.10 (Cl 95% 12.91-17.91, p-value <0.001)) (Table 8). Multi-morbidity was the only other variable that had a significantly increased odds of having PIM 2013 in the full model (2 to 4 chronic conditions OR 1.36 Cl 95% 1.03-1.78 and ≥8 OR 1.80 Cl 95% 1.25-2.58). Polypharmacy (OR 1.18 Cl 95% 0.99-1.40) however, did not increase the odds of having PIM compared to no-polypharmacy.

Table 8 Univariate analysesand the full model for the odds ratio for the different strata of the variables in.

Variables	Categories	Univariate analyses	Model E
		OR CI 95%	OR (CI 95%)
PIM 2011	No	1	1
	Yes	16.81 (14.43-19.58)**	15.10 (12.91-17.91)**
Gender 2011	Women	1	1
	Man	0.74 (0.64-0.85)**	0.91 (0.77-1.07)
Age 2011	75- <80	1	1
	80- <85	1.01 (0.86-1.19)	0.96 (0.80-1.15)
	85- <90	0.96 (0.79-1.18)	0.82 (0.66-1.03)
	≥90	1.34 (1.03-1.75)*	1.00 (0.74-1.35)
Number of chronic conditions 2011	0	1	1
	1	1.37 (1.02-1.85)*	1.23 (0.89-1.69)
	2-4	1.67 (1.29-2.15)**	1.36 (1.03-1.78)*
	5-7	2.20 (1.68-2.89)**	1.43 (1.06-1.93)*
	≥8	3.09 (2.24-4.25)**	1.80 (1.25-2.58)*
Polypharmacy 2011	<5	1	1
	≥5	2.63 (2.29-3.02)**	1.18 (0.99-1.40)

Model E; adjusted with stratification for PIM, age, gender, number of chronic conditions and polypharmacy

Discussion

This thesis has shown that there are several factors associated with medication use in elderly that are not dependent only on morbidity. The complexity in the elderly population is increasing with increasing medication use and multi-morbidity. Only focusing on quality criterias to a few potentially inappropriate medications will not improve quality of medical treatment for the larger part of the population. The interaction between morbidity and medication use has to be considered. However, the decrease in use of PIM shows that deprescribing in an elderly population is feasible.

Factors associated with medication use

The growing elderly population is a challenge for the health care system. Multi-morbidity, age, gender, and socioeconomics are of importance for use of medication according to this thesis. Gender differences in medication use found in this thesis are in line with other studies. They have also found that the differences remain even after excluding medication that is only related to women [25]. Some of the differences can be explained by obvious diagnosis differences between the genders. When analysing specific pharmacological groups some of the differences are obviously related to known prevalent differences between the genders [24]. Women have been found to seek more preventative health care than men but both males and women have the same rate for emergency visits [42]. Gender-related morbidity needs to be considered when analysing gender differences.

With low socioeconomic status the morbidity burden increases, therefore it is not surprising that the medication use is higher in individuals with low socioeconomic status [28]. It is interesting that socioeconomic differences remain in medication use after adjustment for multi-morbidity, age and gender. The differences are not conclusive. However, when analysing smaller pharmacological groups there are some medications that are increasing with socioeconomic status like use of antibiotics, hormone-replace treatment, anti-migraine and erectile-dysfunction medications [31]. Individuals ≥70 years were excluded when analysing education level due to missing data. However, Haider et. al. has analysed the association of polypharmacy and educational level in an older population. They found that after controlling for co-morbidity, marital status and living-situations there were no association between low education level and polypharmacy [29]. There is a complex web surrounding elderly that affects their medication use besides pure morbidity.

That age is a factor for medication use is well known and is to a great extent related to the increased prevalence of morbidities in the elderly. However, after adjusting for multi-morbidities the increased odds for medication use remained. There are several hypotheses for this. The longer a person lives with a chronic condition it progresses and therefore the need of additional medication treatment increases. The other is that prescribers are more willing to prescribe medications in elderly than recommending nonpharmacological treatment, like lifestyle changes, compared to younger individuals. Side effects from the medication treatment can be misinterpreted as a new symptom or diagnosis that require a new medication. This effect is called the prescribing cascade [43]

All the above mentioned and discussed factors are studied well in the literature regarding risk factor for medication use. However, one factor that is more complex to analyse is the meeting between the patient and prescriber resulting in prescription of medication. Men and women have been found to describe symptoms differently and that could affect the odds for medication use [44]. The same argument can be applied on both socioeconomic status and age; patients have different ways of communicating the same symptoms but our context as patients will affect the choice of treatment by the prescriber. That is not per se a bad thing because it means that the prescribers adapt the medical treatment to the individual. However, when these adaptions are more and more in line with the persons age or gender or socioeconomics rather than morbidity the risk for unequal medication treatment increases.

The term deprescribing is increasingly discussed regarding drug treatment in elderly. It has been argued that it is easier to prescribe than deprescribe medications, especially in the elderly.

This thesis has shown that a risk factor for ADR as PIM is possible to deprescribe during a relative short time period. The positive trend of the reduced prevalence of PIM users found in this thesis corresponds with results from other reports in Sweden during the same time period [45-47]. In 2005 the prevalence of PIM was found to be 17% in a Swedish elderly population and a national comparison showed that use of PIM had decreased with 44% between 2005 and 2014 [48, 49]. Use of PIM is associated with increased risk for ADRs and hospitalisation [50, 51]. Therefore, quality indicators that aim to decrease the use of PIM can lead to an improvement of quality in drug treatment in the elderly.

In this thesis it was found that the prevalence of multimorbidity increased but the prevalence of polypharmacy stayed relatively stable between 2011 and 2013. It is interesting that polypharmacy stabilises while the number of chronic conditions increases. One could think that if multimorbidity is increasing polypharmacy would follow. However, the use of medication did increase; just not polypharmacy in comparison with the rest of the population.

Number of medications, as polypharmacy, is frequently used and also found to be an independent risk factor for ADRs, while very few studies include a morbidity measurement when evaluating quality of drug treatment [52, 53]. Polypharmacy increases the risk of drug-drug interaction considerably [54]. Polypharmacy is not wrong, per se, as long as the entire medication list is evaluated, and the risk benefit ratio is considered for the individual patient; this is called appropriate polypharmacy [2, 20]. Previous studies have also shown that patients with chronic diseases and with low continuity of care use more out-of-hours primary care than other patients [55, 56]. Causes for polypharmacy and inappropriate prescribing are many, e.g. number of prescribers, communication failures and knowledge gaps of the prescriber about the patient or the medication [11, 57]. Number of medications, polypharmacy can cover many other risk factors, like underuse or overuse and inappropriate prescribing in the elderly [58]. It has been estimated that patients with polypharmacy (defined as using four or more medications) were under-treated in 42.9% of cases compared with those receiving fewer medicines (13.5%). The theory is that fear of causing ADEs is contributing to under-prescribing by prescribers in patients with polypharmacy [59].

Risk factors for adverse drug events

The cause for a drug related hospitalisation is multifaceted and complex. In the process of prescribing medication to a patient, there are many steps where single or multiple reasons can cause an ADR. Some of the most common causes are communication problems between the prescriber and patient, knowledge gaps about medications and/or patient medical history [11].

In this thesis it was found that psychotropic FRIDs increases the risk of an ADE as hip fracture, after adjustment for age, gender and multi-morbidity. This corresponds well to previous studies [60]. On the other hand no increased risk for cardiovascular FRIDs could be found which is surprising because of elderly’s decreased ability to regulate the blood pressure [2, 14]. Number of FRIDs in total did increase the risk of hip fracture first at use of six or seven FRIDs at the same time. Indicating that polypharmacy is the risk factor rather than FRIDs. Psychotropic FRIDs did increase the risk for hip fracture already at the use of one.

Use of PIM and the risk of hospitalization have been analysed before [50, 51, 61]. However, the results here differ some from earlier results. This thesis results didn’t show any increased odds for hospitalization for use of PIM in the full model with number of medications and number of chronic conditions. The used definition of PIM from the Swedish National Board of Health and Welfare is stricter in its definition and includes fewer drugs and drug classes than other definitions [14, 62]. For example, it does not include nonsteroidal anti-inflammatory drugs (NSAID) or cardiovascular drugs except for disopyramide. This means that these results cannot be directly translated to other settings where the definition of PIM is broader and more like the definition of PIP. However, since this definition has been used to evaluate quality of medication treatment in the elderly in Sweden for the last decade it is relevant in our setting. The definition used here is more straightforward and easier to evaluate in register data. However as the results here shows that the reality is more complex.

ADE as a result of drug-drug interaction or drug-diagnose interactions can also be called potentially inappropriate prescribing (PIP). The risk of PIP increases with the number of medications and multi-morbidity [3, 63, 64].

The risk benefit ratio for treatment becomes more complex to evaluate and physiological changes that affect pharmacokinetics and pharmacodynamics can appear fast in an elderly patient [2, 59]. The results of increasing risk of hospitalization with increasing number of medicines and chronic conditions confirm this.

The most common drugs causing ADEs are drugs that have well documented positive effects on reducing risk of morbidity and mortality in elderly. The most common drugs causing ADEs are antiplatelet, anticoagulants, diuretics, NSAID, antidepressant and antibacterial preparations for systemic use [65, 66]. This is not surprising as all mentioned drugs are potent with a good effect in preventing morbidity when used in the right patient, at the right time and at the right dosage. However, when used inappropriately, they can cause ADEs, especially in elderly due to their frailty [9, 13]. The majority of these drugs are not included in the definition of PIM used here. Together with our results, this indicates that decreasing use of PIM in the elderly would have very little effect on the risk of hospitalization.

New approaches are needed to improve quality of drug treatment in the elderly and possibly coordination with other care interventions. Our results indicate that the health care system needs to improve the care of patients with multi-morbidity and polypharmacy. The term appropriate polypharmacy needs to be embraced and is in clinical practice defined as evidence-based prescribing and medicines optimisation. What it means is that when choosing treatment the dosages are adjusted to the patient's physiological conditions [59].

However, only using number of medicines as an indicator for the assessment of drug-related problems has been shown to have limited value in clinical practice [18].

When combining number of medications, number of chronic morbidities and use of medications with high risk of ADE the clinical advantages increases. The results here indicate that focus should shift from decreasing use of PIM to include total medicines optimisation for each individual.

When evaluating quality of drug treatment in the elderly in register-based data, it is difficult to include and to evaluate contraindications for drug use, drug-diagnose interactions and potentially inappropriate prescribing.

The results in this thesis show that even if the use of PIM decreases, the prevalence of polypharmacy is stable while the multi-morbidity increases. The most common drug classes in patients 75 years and older with polypharmacy are not PIM (according to our definition) but cardiovascular drugs (including antithrombotic agents), analgesics and psychotropic drugs [19]. These are also the most commonly used drugs in drug-related events such as bleeding or bruising, which are associated with antithrombotic agents and dizziness or unsteadiness due to psychotropic medicines [3]. Different methods have been tested to improve drug treatment in elderly. Implementing the STOPP criteria in a hospital setting reduced the number of ADE in a study from Cork University Hospital [67]. The STOPP criteria are wider in its definition for PIM than in this thesis. The STOPP criteria are a collection of indicators to detect and stop potentially inappropriate prescribing.

The complete collection of quality criterias in "Quality indicators for good drug therapy in elderly" can be used in the same way [14]. However, evaluating the effect is more complex then measure the use of PIM when evaluating quality of care in the elderly on a population level. The Cork study shows that improvement of quality of care can be achieved through implementing different systematic methods for improving of medical treatment in individuals. There are several studies that show that using a systematic method, such as medication review, in multi-professional teams reduces the prevalence of PIP, the use of PIM and medication cost. It is a method developed not to focus on specific risk medication but a systematic approach to optimise a patient's medical treatment as a whole; diagnoses, medicines and patient's physical conditions, e.g. kidney function [68-70]. The effect is more complex to evaluate on a population level, but the clinical effect is greater.

Methodological considerations

A general limitation in this thesis is that it only included and analysed register data on diagnoses and medications. There was no information on indications for the medication prescribed and dispensed.

Prescribed dispensed medications from the pharmacies were used in this thesis. Patients had collected the prescribed medications however, the compliance to the prescribed treatment by the patient is unknown. The indication for what the medication was prescribed was also unknown.

The information of medicines in the study was register data from the county council's register that includes prescribed and pharmacy dispensed medicines for all inhabitants in Blekinge. There is no information on use of illegal drugs or over the counter drugs in this thesis. Data from the Medical Products Agency indicates that 11% of the Swedish population bought prescription drugs from non-approved pharmacies during 2011 [71].

Three different methods were used for identifying medication use in this thesis. For the first paper, DDD used to estimate medication use in the population. DDD is the assumed average maintenance dose per day for a pharmacological substance determined by the main indication in adults. There is only one DDD-value assigned to one pharmacological substance. This means that if a substance has multiple indications and in different dose ranges, the use of DDD may overestimate or underestimate the medication use in a population. Depending on which indication or treatment regime is most common.

Due to the limitations in DDD, for paper II one-year prevalence was used instead. Patients that collected one prescription of a FRID during 2006 were classified as users. The limitation with one-year prevalence is that there is a time gap between when the medication was dispensed, and the event analysed.

Paper III and IV, point prevalence was used to construct a medication list for a specific date. By constructing a medication list on dispensed prescribed drugs from a specific date and three months back for each individual, it allowed us to estimate what the patient was using on the day of interest. On the other hand, there is a possibility of underestimating medications used as needed because they are dispensed more rarely than every three months.

All three methods can lead to misclassification of medication use and exposure to risk medication. Depending on the research question and data available you should use the method best appropriate for your data. However, use of DDD in drug utilizations data only gives a rough approximation of medication use.

Multimorbidity in this thesis was measured by two different methods. ACG was based on one-year data on registered diagnoses in both primary and secondary care from the CDWÖ. ACG is constructed to give diagnoses different weights for estimating how much a diagnosis contributed to need of care or cost [22]. The time period of one year can have made us underestimate the multi-morbidity level. However, during 2006 Östergötland did not use ACG case-mix system for reimbursement whereas overestimation of the multi-morbidity level is low.

It has been found, in a Swedish setting, that 75% of the total population in a county had at least one diagnosis registered during a three year period in primary care [72]. Therefore a two year period was used for paper III and IV for estimating multi-morbidity with number of chronic conditions [23]. The recording of diagnoses in this thesis has not been validated. However, the use of registered diagnoses from both primary and secondary care was used to get as close to total coverage as possible. There is a difference between the two methods besides period of data collection. The ACG is a measurement of need of care while number of chronic conditions are a measurement of the complexity of the patient.

Confounding by indication may be present in our thesis. In this thesis importance of multi-morbidity, use of PIM, FRIDs and number of medications for the odds of having an ADE were analysed. Number of medications can be a confounder for conditions that are a cause for an ADE. Number of medications can also cover the effect by PIM since PIM is included in number of medications.

Conclusions

The elderly population is growing and factors, other than morbidity, are affecting the use of medication to some extent according to the results in this thesis. The results show that it is possible to improve quality of medication use in the elderly by decreased use of PIM in elderly, in a relative short period of time.

The causes to adverse drug events are multifaceted and multiple. Medication related problems that can lead to an ADE are as a result of the individual patient's multi-morbidity, medication treatment and physiological conditions. Use of risk medications both FRIDs and PIM, should be evaluated in the context of the patient's multi-morbidity. The complex population of the elderly with increasing multi-morbidity, and high prevalence of medication use needs systematic methods that can handle the complexity on an individual level. To improve medication treatment in the elderly population and ultimately decrease the risk of hospitalization, there needs to be more focus on implementing methods to optimise a medical treatment in relation to the individual. Systematic methods such as medication reviews that facilitates individual optimisations of medical treatment in the individual, need to be further implemented.

Future research

To be able to take care of the growing elderly population, research to understand the complexity of the elderly population must continue. As a compliment to the medical reviews the quality indicators on national, county council and care unit level needs to be evolving to be able to evaluate and compare the quality in medical treatment in the elderly. With distinct and simple quality indicators it is possible to improve the quality of drug treatment in the elderly of population level. Further research is needed to develop, improve and evaluate existing indicators and create new ones that measure quality of drug treatment in a population that can also have better clinical value for the individual patient. Indicators that facilitate follow up on multiple levels in the health care system, population, care unit or individual level need to be developed further.

Svensk sammanfattning

Sveriges befolkning blir allt äldre. Den vanligaste behandlingsformen, framför allt hos äldre patienter (>75 år) är läkemedelsbehandling. Målet med läkemedelsbehandling är att förebygga, lindra eller bota sjukdom eller symptom på sjukdom. För äldre som är multisjuka och använder flera olika läkemedel samtidigt (polyfarmaci) kan dock effekten ibland bli den motsatta. Olämplig behandling av äldre är inte ovanligt, vilken kan leda till ökad sjuklighet och dödlighet. Med polyfarmaci ökar risken för läkemedelsrelaterade problem som biverkningar och interaktioner. Läkemedelsrelaterade problem ökar risken att läggas in på sjukhus på grund av allvarliga läkemedelsrelaterade händelser. Socialstyrelsen har tagit fram kvalitetsindikatorer för god läkemedelsbehandling hos äldre. Bland dessa indikatorer finns en som heter ”Preparat som bör undvikas om inte särskilda skäl föreligger” även kallade potentiellt olämpliga läkemedel (PIM) i Sverige. Läkemedel med ökad risk för fall är också en indikator.

En patients samlade sjuklighet påverkar sannolikheten för läkemedelsanvändning och risken att drabbas av en allvarlig läkemedelsrelaterad händelse. Men andra typer av faktorer påverkar också läkemedelsanvändningen.

I den här avhandlingen har olika faktorers påverkan på läkemedelsanvändning och risk för en allvarlig läkemedelsrelaterad händelse vid användning av potentiellt olämpliga läkemedel och fallrisk ökande läkemedel studerats.

Alla studier är registerbaserade. Studie I och II är baserade på data från Östergötland och studie III och IV på data från Blekinge. Studie I inkluderades alla individer som är 20 år och äldre. Sannolikheten för läkemedelsanvändning studerades beroende på ålder, kön och socioekonomi, med variablerna utbildnings- och inkomstnivå, efter att hänsyn tagits till individernas individuella sjuklighet. Skillnader i de studerade variablerna fanns efter att hänsyn tagits till individernas sjuklighet. Ålder var den starkaste faktorn för läkemedelsanvändning men kvinnor hade större sannolikhet för läkemedelsanvändning än män. Individer med låg socioekonomi hade högre sannolikhet för läkemedelsanvändning än individer med hög socioekonomi.

Individer 75 år och äldre inkluderades i studie II. Här studerades risken att få en höftfraktur vid användning av fallriskökande läkemedel efter justering för ålder, kön och sjuklighet. Centralstimulerande fallriskläkemedel hade en ökad risk för höftfraktur med hänsyn tagen till individernas ålder, kön och sjuklighet. Ingen ökad risk för höftfraktur hittades för fallriskläkemedel som används för att behandla hjärt-kärlsjukdomar.

Till studie III och IV inkluderades individer 75 år och äldre registrerade på en vårdcentral i Blekinge 2011 och 2013. I studie III studeras vikten av sjuklighet, antal läkemedel och användningen av PIM för sjukhusinläggning efter att tagit hänsyn till ålder och kön. Sjuklighet och antal läkemedel var av större vikt för sjukhusinläggning än användningen av PIM. I studie IV studerades förekomsten av PIM i olika grupper av variablerna ålder, kön, sjuklighet och polyfarmacie mellan två populationer 2011 och 2013. Jämförelsen visar att användningen av PIM minskar i alla grupper mellan 2011 och 2013. Samtidigt ökar andelen individer med multisjuklighet och användningen av läkemedel.

Sammantaget visa resultaten i den här avhandlingen att läkemedelsanvändningen påverkas av andra faktorer än en individs sjuklighet. Faktorer som ålder, kön och socioekonomi påverkar sannolikheten för läkemedelsanvändning som inte förklaras fullt ut av sjukligheten. Användningen av PIM minskar och minskningen är oberoende av ålder, kön och sjuklighet. Användning av läkemedel med ökad risk för allvarlig läkemedels händelse som PIM och fallriskläkemedel bör utvärderas i relation till patientens sjuklighet och övrig läkemedelsanvändning. Då sjuklighet och antal läkemedel har stor och ibland större betydelse för sannolikheten att drabbas av en allvarlig läkemedelsrelaterad händelse.

Med enkla kvalitetsindikatorer är det möjligt att förbättra läkemedelsanvändningen för äldre, fortsatt forskning behövs för att förstå komplexiteten i den åldrande befolkningen. Indikatorer som underlättar uppföljning på befolkningsnivå, flera nivåer i sjukvårdssystemet och enskilda vårdenheter behöver utvecklas. Men det behövs också fortsatt utveckling av metoder och indikatorer som tar hänsyn till optimal läkemedelsanvändning för den enskilda patienten.

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