Analysis of factors of importance for drug use

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Title and subtitle Analysis of factors of importance for drug use

Background: There are differences in drug use depending on non-medical factors such as age, gender and socioeconomic status. The combined effect of these factors, with adjustment for multimorbidity, is highly relevant to study to ensure equality in drug use. *Objectives:* 1. To examine drug use related to age, gender, income and education after adjustment for multimorbidity, in an entire adult population and in a population where prescription drugs were issued only by general practitioners. 2. To analyse if gender-related morbidity explains the differences in drug use. 3. To examine to what extent the elderly may lack indication for treatment. *Methods:* Register-based methods were applied in all papers, using data from Östergötland County. To estimate multimorbidity the ACG-Case Mix was used in all papers. Drug use depending on age, gender, income- and educational level, after adjustment for multimorbidity, was analysed in the entire adult population in Paper I, and in the primary healthcare population in Paper III. In Paper II diseases tending to afflict females more frequently were identified, together with the prescription drugs used to treat these diseases. Drug use was analysed before and after exclusion of these identified prescription drugs. In Paper IV the proportion of patients 65 years or older having indication for a number of their prescription drugs, identified as inappropriate for elderly, was examined, with further analysis of what may affect the result. *Results:* Significant differences in drug use were identified depending on age, gender, income and education, despite adjustment for multimorbidity. The elderly, females and individuals with the lowest levels of income and education had higher drug use. The differences persisted when drug use in primary healthcare was examined. The gender difference in drug use decreased when prescription drugs used to treat diseases afflicting females more often were excluded from the analyses. Less than half of the patients' prescription drugs (45.1%), studied in Paper IV had indication for treatment. The oldest patients had to the lowest extent indication for treatment. *Conclusion:* The patients' age, gender, income and education affect the drug use, despite adjustment for multimorbidity. Gender-related morbidity seems to explain some of the gender difference in drug use, and lack of indication for treatment among the elderly explains some of the age difference.

Key words Drug use, prescription drug, pharmacological treatment, multimorbidity, age, gender, income, education, socioeconomic status, general practitioner, primary care

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Abstract

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Abbreviations

ACG	Adjusted Clinical Groups
ADG	Aggregated Diagnoses Groups
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CDWÖ	Care Data Warehouse in Östergötland
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability-Adjusted Life Year
DDD	Defined Daily Dose
GP	General Practitioner
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
NBHW	Swedish National Board of Health and Welfare
OR	Odds Ratio
PHC	Primary Healthcare Centre
RUB	Resource Utilization Band
SPDR	Swedish Prescribed Drug Register
SSRI	Selective Serotonin Reuptake Inhibitor
WHO	World Health Organization

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, 12:575

II. Skoog J, Midlöv P, Borgquist L, Sundquist J, Halling A: Can gender difference in prescription drug use be explained by gender-related morbidity?: A study on a Swedish population during 2006. *BMC Public Health* 2014, 14: 329.

III. Skoog J, Midlöv P, Beckman A, Sundquist J, Halling A: Drugs prescribed by general practitioners according to age, gender and socioeconomic status after adjustment for multimorbidity level. *BMC Family Practice* 2014, 15:183.

IV. Skoog J, Midlöv P, Beckman A, Sundquist J, Halling A: Indication for pharmacological treatment is often lacking: a cohort study on the quality of drug therapy among the elderly. *Submitted*

Background

Drug use is one of the healthcare system's most important methods to prevent and treat diseases. Billions of prescription drugs are consumed daily by patients all over the world, and drug use acts as an important method to relieve symptoms and cure diseases. Nevertheless, drug use is associated with great costs and may also be harmful, if the patients develop drug-related problems from their treatment. Thus, on behalf of both the patients and society it is highly important that the drug use is secure, effective and well motivated.

Drug use may be studied on several levels. In any case, drug use must originate from a patient-doctor consultation involving a health problem. Many stages are passed, before a prescription drug is recommended and later actually used. Non-medical factors such as the patients' age, gender, and socioeconomic status have proven to affect drug use. A model to study this was developed by Weitoft et al. in 2008 and is presented below in a modified form (Figure 1).

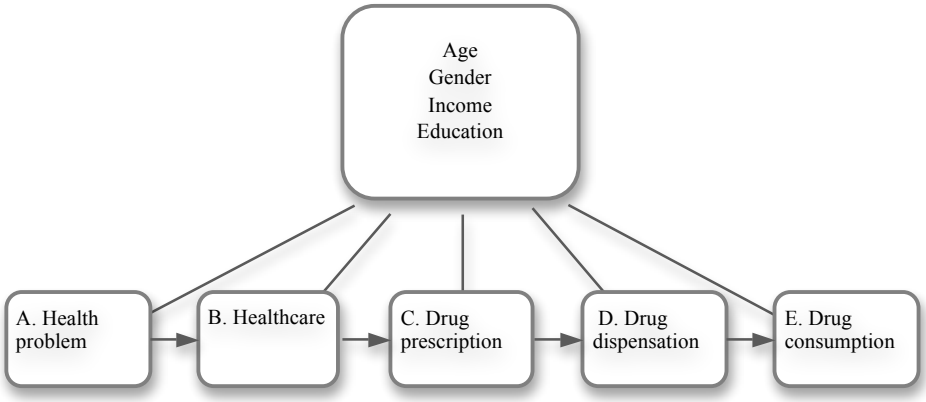

Figure 1.
Conceptual framework for examining non-medical factors on drug use. Modified from Weitoft et al. 2008 (1).

In each frame non-medical factors may influence the outcome. Former research has mainly focused on single factors, but in this thesis the overall effect of the non-medical factors is examined. Multimorbidity is considered to be an obvious factor

affecting the drug use, but despite this, the multimorbidity of the patients has scarcely been taken into account in former studies, where non-medical factors' effect on drug use has been studied. In this thesis, using register-based methods, the focus was on how age, gender, income and education, together, affected the outcome in frames C-D after adjustment for multimorbidity. Thus, epidemiological methods were used to reflect what happens during and after the patient-doctor consultation with focus on drug use.

Drug use

In Sweden, the use of prescription drugs per person has been increasing yearly up until 2011, where there was a peak in drug use. During 2012-2013 the use of prescription drugs decreased slightly, but in 2014 drug use in the adult population increased again (2). New prescription drugs are continuously released on the market, and former prescription drugs get new indications. Due to better care-taking and improved treatment in healthcare, the population in Sweden is growing older (3), which also contributes to a higher level of prescription drug use (4). Dentists and some nurses have a limited right to prescribe drugs in Sweden, but the drug prescribing is to highest extent carried out by physicians.

Drug use is a major financial expenditure to the Swedish Government. During 2013 the total costs for prescription drugs in Sweden amounted to 36.4 billion SEK (3.84 billion Euro) (5) , which in turn represent 10-12% of healthcare costs in Sweden (6).

The Swedish healthcare system

According to the Swedish Healthcare Act the goal for healthcare in Sweden is good health and care on equal terms in the entire population. Healthcare should be provided with respect for human equality and dignity. Those who are most in need of care shall be given preference (7).

In 2011 the first national prescription drug strategy was formed. One of the five long-term goals to achieve equality in healthcare was to ensure equal drug use (8).

The Swedish healthcare system is financed through taxes. The twenty county councils are responsible for providing healthcare, which in turn is divided into primary healthcare and specialised care. Private healthcare providers accounted for approximately 16.6% of the healthcare costs financed through taxes during 2013 and act both within primary healthcare and specialised care (9).

In case of health problems patients are supposed to first contact their Primary healthcare centre (PHC) in order to see a nurse or their general practitioner (GP). GPs handle the majority of the patients' healthcare problems. If there is a need for

major investigations and specialised examinations, or if in need of a second opinion, the patients are referred to specialists in secondary care.

Secondary care is essentially provided at hospitals, both as inpatient and outpatient care. The most advanced care is provided at the larger university hospitals and more regular specialised care is provided at smaller local hospitals.

In Sweden there is a high cost threshold system for drug use and the patients' expenditures for prescription drugs are to a high extent reimbursed. There is a gradual reimbursement up to 2200 SEK (232 Euro), which is the largest amount the patients pay for their prescription drugs during one year. The governmental agency, the Dental and Pharmaceuticals Benefit Agency is responsible for deciding which prescription drugs are granted reimbursement and subsequently included in the high cost threshold system (10). There is a continuous review of previous decisions, and prescription drugs that were earlier reimbursed may lose their reimbursement status.

There is also a high cost threshold system for outpatient healthcare, where the patients' expenditures for healthcare are reimbursed to a high extent. The patients pay between 100 and 400 SEK (9.5-38 Euro) for each visit, depending on level of healthcare and county. The outpatient healthcare is fully reimbursed, when the amount reaches 1100 SEK, which is the highest expenditure patients in Sweden have for healthcare during one year (11).

Prescription drug use and age

The population in Sweden and the Western countries is ageing (3,12). In 1970 the population in Sweden aged 65 years or older represented 13.8% of the total population, and in 2014 the population aged 65 years or older constituted as much as 19.6% of the total population (3). Chronic illness is more common at older age (13). When a patient has more than one chronic disease, the patient is said to have multimorbidity (14), which is associated with increased drug use (4). The patients in Sweden use on average 5 prescription drugs daily, when the entire population is examined. The number increases with age, and patients aged 70 years or older use on average 8 prescription drugs on a daily basis (15). Treating elderly and multimorbid patients with prescription drugs puts high demands on the physicians. Elderly patients are rarely included in randomised controlled clinical drug trials (16), and the benefit of drug use of elderly and multimorbid patients is often extrapolated from studies conducted on both younger and healthier patients. Physiological alterations in the elderly and multimorbid patients must be taken into consideration, as well as the high number of different physicians the elderly see and, furthermore, the interaction between two authorities involved in the care of the elderly patients. Routinely renewal of prescription drugs is another challenge to appropriate prescription drug use among the elderly.

There is no universally established definition of polypharmacy. The use of five prescription drugs daily seems after all to be accepted as polypharmacy (17). Polypharmacy increases the risk of developing 'The prescribing cascade', which is described as side effects of a prescription drug misinterpreted as a new disease or medical condition leading to prescription of a new drug (18,19), increasing the risk of additional polypharmacy among elderly and multimorbid patients. Polypharmacy also increases the risk of drug-related problems (20) such as ADRs, which is defined by the World Health Organization (WHO) as "*a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function*" (21) . Thus, ADRs include side effects of prescription drugs, lack of effect and interactions between different prescription drugs, which in turn increase the risk of need of medical care. At worst, ADRs may lead to hospital admission, and up to 30% of the elderly patients' care events are caused by ADRs (22-25).

Due to physiological changes in the body, elderly patients are more susceptible to ADRs (26). The body water decreases, leading to a higher proportion of body fat. This affects the pharmacokinetics, which may be described as the way the body affects the prescription drug (27). The increase of body fat may lead to a prolonged effect of fat-soluble prescription drugs, for example long-acting benzodiazepines, because of higher distribution volume (26,28). Renal function also decreases with age, leading to decreased elimination of prescription drugs and risk of accumulation of drugs (28). Alterations in many organ systems also contribute to the sensitivity, and this affects the pharmacodynamics, which may be described as the way the prescription drug affects the body (27). The body of elderly patients is for example more sensitive to prescription drugs acting on the central nervous system, for example anti-cholinergic drugs.

Because of high level of multimorbidity elderly patients often have many caregivers, for example PHCs, acute care hospitals and rehabilitation departments. In the majority of the county councils in Sweden there is no common medication list for the patients, i.e. every care provider has his/her own prescription drug list. Thus, a correct and complete medication list is highly dependent on good communication between the different care providers, something that unfortunately was proved to be inadequate (29,30). Many caregivers implicate many prescribers, a circumstance that may lead to further drug-related problems (31). In Sweden, since 1992, the 290 municipalities have the responsibility for the home care of those elderly patients that cannot cope themselves (32). The home care is mainly provided by nurses, assistant nurses and home help, ideally in close contact with the patients' GPs. Thus, two authorities are involved in the care of the elderly patients, putting high demands on good cooperation for the benefit of the patients.

Already in the 80s WHO started their work on improving the drug use among the elderly, and in 1997 the first report was written on this topic (33). One of the first steps towards a correct and safe drug use among elderly patients was confirmed to be

ensuring that all the prescription drugs used by the patients have an indication, i.e. correct diagnoses are linked to all of the prescription drugs the patients are using. Apart from the above, according to WHO, following criteria must, furthermore, be met before pharmacological treatment should start: 1. The treatment must have an effect on the disease, and 2. The treatment should involve few or no side effects (33).

In order to improve the quality in drug use among elderly patients efforts have been made to define criteria for appropriate drug use. The most widespread criteria are the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (34). However, many of the listed prescription drugs in the Beers Criteria are not available in Europe, and therefore many European countries have developed criteria of their own (35-37). In Sweden, the National Board of Health and Welfare (NBHW) has written a report about indicators for satisfactory drug use among elderly patients (20). The aims of the report were to act as a support to the prescribers to enhance drug use among the elderly, while at the same time serving as a basis for monitoring and epidemiological research. The report contains both diagnosis-specific and drug-specific indicators. The diagnosis-specific indicators describe proper versus irrational drug use at the eleven most common diagnoses among the elderly. The drug-specific indicators describe different treatment regimens that lead to good quality in drug use. The drug-specific indicators list for example prescription drugs that should be avoided, prescription drugs for which a correct indication is of particular importance, inappropriate regimens and dosages, and combinations of prescription drugs that may lead to harmful interactions.

The NBHW also claims that an accurate and correct diagnosis is fundamental for good quality drug use. Lack of indication to prescription drugs has unfortunately been shown to occur among elderly patients (38,39), which may increase the risk of unnecessary treatment and irrational drug use.

Drug use and gender

There are inequalities between the genders regarding health services. In Sweden, as well as in other Western countries, females tend to live longer than males (3,12). On the other hand, females tend to have a higher morbidity than males (40), which at times has been referred to as the gender paradox (41). The consulting rates differ between the genders, and females tend to seek more healthcare than males (42-44). Females are to a lesser extent included in clinical trials compared to males (45).

The differences in drug use between the genders have been investigated in several studies. Studies from the United States have shown that females purchased between 20-38% more prescription drugs than males (46,47). Likewise, European studies showed a gender difference, where females had a drug use up to 19% higher than males (48,49). Another European study showed higher risk of polypharmacy among

females compared to males (50). There is thus convincing evidence that females use more prescription drugs than males. Former studies have, however, rarely taken the patients' multimorbidity into consideration.

The quality in drug use is not equal between the genders. Females seem to be more prone to ADRs compared to males (49,51). Higher levels of polypharmacy among females as well as the fact that females are more likely to be prescribed inappropriate drugs may be explanatory factors (52,53). A higher sensitivity to ADRs may, furthermore, be explained by differences in pharmacokinetics and pharmacodynamics between the genders (54). Due to differences in for example body size, body fat, liver and renal activity, the absorption, distribution, metabolism and elimination of drugs differ between the genders, leading to generally prolonged effects of prescription drugs on females.

Females and males tend to fall ill with different diseases (55,56). A report from the Swedish National Institute of Public Health (nowadays the Public Health Agency of Sweden) in 2012 states that females to higher extent are afflicted with for example asthma, chronic obstructive pulmonary disease (COPD), cystitis, dementia, depression and anxiety disorders, insomnia, migraine, osteoarthritis, stroke and thyroid gland disorders (55). In the report, the disability-adjusted life year (DALY) was used to measure the burden of disease. The DALY concept was elaborated by the WHO and the World Bank to measure the burden of disease in the population, taking into consideration both mortality and disability (57,58). The DALY is a time-based measure that combines years of life lost due to premature mortality and years spent living in states of less than full health. DALY is the sum of life years lost due to premature mortality and years lived with disability, adjusted for severity. To put it simply, 1 DALY means one lost healthy year (57,59). It is likely that this gender-related morbidity may affect the drug use.

Drug use and socioeconomic factors

There is a social gradient in health. Individuals who are well-off have in general better health status (60) and health-related problems are more common among individuals with lower socioeconomic status (61). There is also inequality in drug use where individuals with lower socioeconomic status use more prescription drugs (17). Socioeconomics may be measured by different factors like income, education, occupation, wealth, unemployment and single households, but income, occupation and education are the most widely used measurements (61,62). In this thesis income and education were used.

Education is supposed to capture the individual's knowledge asset. Education measures socioeconomics during the transition from childhood to adulthood and it reflects social opportunities for education and remains constant during the adult life.

Education is shown to be a strong determinant of future employment and income (61). Income measures material assets. It measures directly the financial possibilities at the present time and reflects for example residence, work, food-intake and physical exercise, factors that may affect the health status of the individual (61).

Low educational level is associated with greater likelihood of drug use (1,63). Likewise, polypharmacy and inappropriate drug use are more frequent among individuals with low educational level (17). Low educational level is, furthermore, associated with noncompliance with guidelines (64). On the other hand, regarding drug treatment with statins (65), drug treatment for dementia (66) and climacteric complaints (67,68) individuals with higher socioeconomic status have higher drug use. The relationship between drug use and income is less studied but low income seems to be associated with both inappropriate drug use, and greater likelihood of drug use (69-71). As for gender, former studies on drug use according to education and income have rarely taken the patients' multimorbidity into consideration.

Drug use in primary healthcare

As in most Western European countries, the first-line healthcare in Sweden is primary healthcare. GPs work almost exclusively together at PHCs alongside specialist nurses, who to a high extent have their own surgery. In contrast to other Western Europeans countries, in Sweden, the GPs do not have a gate-keeping function. In case of health problems the individuals cannot handle themselves, they are supposed to get in contact with their GP to get a primary evaluation of their health status. In Sweden, GPs handle the majority of the diseases afflicting the patients. In case the GP needs a second opinion, or if there is a need of larger resources to investigate the health issue or disease, the GP refers to a specialist. Nevertheless, the individual is allowed to seek secondary care, both at the emergency room and at specialist clinics, without a letter of referral. When the patient seeks secondary care, the liability regarding the prescribing of drugs accompanies the patient, regardless of whether the patient was referred. Thus the prescribing of drugs is shared between primary and secondary care.

Drug use is thus initiated at different levels of healthcare in Sweden. When non-GP caregivers initiate drug use, it is not uncommon to assign the responsibility of evaluation of the prescription drug effect to the patients' GPs (72). In such cases of lacking continuity, it is important that information about the indication and expected effects, as well as whether the drug use is temporary or continuous, is passed on to the GPs. Unfortunately, the communication around the patients when transferred between different caregivers has been shown to be inadequate (29,30). Nevertheless, it is hard for any physician to evaluate the effect of a prescription drug not initiated by him-/herself and it is easy to assume that GPs do not feel certain about evaluating prescription drugs initiated by specialists and vice versa – situations that may lead to unnecessary drug use.

Primary healthcare is performed in different socioeconomic environments. GPs handle patients with a holistic and patient-centred perspective and have a unique insight into patients' context and are accustomed to consider differences in health (73). This approach may have influence on drug use.

Indexes to describe multimorbidity

Most of the studies referred to in the above regarding drug use do not take the patients' multimorbidity into consideration. There are many indexes to describe multimorbidity, for example the Charlson Comorbidity Index, the Elixhauser et al. Comorbidity Measure, and the Kaplan and Feinstein Index. The aim of the Charlson Comorbidity Index was to develop a method that could be applied in future studies to classify comorbidities that may alter the risk of mortality (74). It is based on the mortality rates of patients admitted to a general internal medicine department in New York during one month. Sixteen diseases were selected and weighted by the strength of their association with mortality, giving the patient a single comorbidity score. The Elixhauser et al. Comorbidity Measure is a further development of the Charlson Comorbidity Index and is based on all inpatient hospital stays in California during one year (75). It identified 30 comorbidities that had a great impact on short-term outcome in acute hospital patients. The Kaplan and Feinstein Index was developed as a predictor of survival in some types of cancer (76). No 'gold standard' index has been established. In this thesis the Adjusted Clinical Groups (ACG) Case-Mix System was used, which at the time of the studies was considered to be the best index to measure multimorbidity, not least because it includes medical information from both primary and secondary care. The ACG Case-Mix System has previously been described (77-80) and is currently used by 175 healthcare providers and insurance companies worldwide (81).

The ACG Case-Mix System was elaborated at the Johns Hopkins University (82). It was primarily developed to predict healthcare utilisation in children, but was later refined and modified to also include adults. The hypothesis for its elaboration was that clustering of morbidity would be a better predictor of healthcare utilisation and costs than the presence of specific diseases.

By using different building blocks, at the end, every individual is assigned a certain ACG (n=93), which predicts the healthcare utilisation and cost for that specific individual. The system assigns all International Classification of Diseases (ICD) codes (ICD-9, 9-CM, -10) to Aggregated Diagnoses Groups (ADGs) (n=32) given to an individual during a specific time period. The classification is based on five clinical circumstances:

1. Duration of the condition (acute, recurrent, chronic): For how long will healthcare resources be needed?
2. Severity of the condition (minor and stable vs. major and unstable): How many healthcare resources will be required?
3. Diagnostic certainty (symptoms vs. documented disease): To what extent will diagnostic examination be needed?
4. Etiology of the condition (infectious, injury, autoimmune, etc.): What kind of healthcare services will be used?
5. Specialty care involvement: To what extent will specialist care be required?

Thus, every ICD code is classified to one of the 32 ADGs. Each ADG is a group of ICD codes that are similar in terms of severity and likelihood of persistence. Two examples of different ADGs are 'Time limited: Minor-Primary Infectious', which could correspond to a viral infection, and 'Signs/Symptoms: Major', which could correspond to syncope. Thus, the same individual may have one or several ADGs, depending on which diagnoses the individual have. The different ADGs are then incorporated in an algorithm in which also age and gender are included. The final algorithm assigns each individual an ACG, i.e. a morbidity group with a certain expected healthcare utilisation and cost. The ACGs may further be clustered into six Resource Utilization Bands (RUBs), 0-5, please see the Method section.

Aims of the thesis

The general aim of this thesis was to describe how age, gender, income- and educational level influence the drug use among adults after adjustment for multimorbidity.

The specific aims were:

- To investigate the odds of having prescription drugs and the rate of drug use related to age, gender, income and education after adjustment for multimorbidity. (Paper I)
- To analyse whether the gender difference in Paper I can be explained by gender-related morbidity. (Paper II)
- To investigate the odds of having prescription drugs issued by GPs and the rate of drug use among patients treated by GPs related to age, gender, education and income after adjustment for multimorbidity. (Paper III)
- To examine to what extent elderly patients have indication for a number of their prescription drugs, identified by the Swedish National Board of Health and Welfare as inappropriate drugs, and if there are any differences in having indication for treatment related to age, gender, multimorbidity and income.

Methods

Data collection

Sweden has one of the oldest healthcare registers in the world; the nationwide register that registers cause of death was founded already in 1749 (83). The healthcare registers in Sweden are well known for high quality. Because of a unique personal identification number assigned to all Swedish residents, well-structured healthcare system and trustworthy registers, it is excellent to perform register-based epidemiological research in Sweden.

In all of the papers data were collected from the Care Data Warehouse in Östergötland (CDWÖ) database and the Swedish Prescribed Drug Register (SPDR) (84) . In Papers I, III and IV, data were also collected from Statistics Sweden (85).

The CDWÖ database

Östergötland County is situated about 200 km southwest of Stockholm and has about 400 000 inhabitants. The age and demography in Östergötland are similar to the rest of Sweden (86).

The CDWÖ database was established in 1998. Initially the database included information only on hospital care. In 1999 the database was expanded to include data from primary healthcare, including private PHCs. Data from each healthcare consultation, i.e. visits at PHCs, hospitals and inpatient care in Östergötland County, are transferred to the CDWÖ database once every month. Data consist of information on diagnoses according to ICD-10, personal identification number, healthcare unit visited, waiting time and staff category.

Data on the diagnoses were collected from the CDWÖ database during 2006 in Paper I-III and during 2005-2006 in Paper IV.

The Swedish Prescribed Drug Register

The SPDR was founded in 1999, and since 2005 the personal identification number is included in the register (84). The register is administered by the NBHW and holds

complete information on all prescription drugs collected at pharmacies in Sweden. Only prescription drugs that are in fact collected by patients are included in the register. In case a drug is prescribed by a physician, but not collected by the patient, the drug will not be included in the SPDR. There is no information on over-the-counter drugs in the register. The SPDR does not hold information on the individual physician level, but information about workplace and physician specialty is included.

Data were collected from the SPDR during 2006 in all of the studies.

Statistics Sweden

Statistic Sweden is an administrative agency (85). The main task is to supply statistics for decision-making, research and debate. Another task is to support and coordinate the Swedish system for official statistics. Statistics Sweden primarily serves the government and other agencies.

Data were collected from Statistics Sweden about income and education in Papers I and III and income in Paper IV.

Study participants and procedure

As described in the Background section the ACG Case-Mix System was used to estimate multimorbidity. Every patient is assigned an ACG, and the ACG Case-Mix System is further clustered into six RUBs, 0-5. Persons without need of healthcare according to ACG are placed in RUB 0 and persons with a very high degree of healthcare according to ACG are placed in RUB 5. A single chronic condition could correspond to RUB 3, and a combination of certain chronic diagnoses could correspond to RUB 4 or 5. The ACG Case-Mix System takes in consideration age and gender only to some extent. Therefore, the analyses in this thesis are adjusted for age and gender.

The individual disposable income was divided into quartiles, from the lowest to the highest, with an equal number of individuals in each quartile. The individual income includes earnings from employment and business, and income transfers (e.g., pension payments, unemployment benefits, or paid sick leave), but not capital returns.

The educational variable was divided into four levels: 1. Primary school not completed (<9 years), 2. Primary school completed (9-10 years), 3. Secondary school (10-12 years), and 4. Higher education (>12 years).

Papers I and III

All individuals aged 20 years or older in Östergötland County during 2006 (n=313 977) were enrolled. Information on the individuals' gender, age and diagnoses were collected from the CDWÖ. Multimorbidity was estimated using the ACG Case-Mix System. Information on drug use was collected from the SPDR. Information on income and education was collected from Statistics Sweden. Information on education was to a high extent incomplete in people aged 70 years or older, and therefore this group of elderly was excluded, when the effect of educational level on prescription drug use was analysed.

In paper I the utilisation of prescription drugs, stated as Defined Daily Doses (DDDs), and total costs of prescription drugs in 2006 were the dependent variables. In Paper III the utilisation of prescription drugs issued by a GP in 2006 was the dependent variable. DDD is defined by WHO as the assumed average maintenance dose per day for a prescription drug used for its main indication in adults (87). It is a fixed unit of measurement that enables comparative research on prescription drugs. The cost is defined as the National Corporation of Swedish Pharmacies' sales price to customers (AUP) during 2006 in SEKs. AUP is the sales price used by the pharmacies when selling prescription drugs. It is determined by the Dental and Pharmaceuticals Benefit Agency (10).

Paper II

As for Papers I and III, all individuals aged 20 years or older in Östergötland County during 2006 were enrolled. Information on the individuals' gender, age and diagnoses were collected from the CDWÖ, and multimorbidity was estimated using the ACG Case-Mix System. Information on drug use was collected from the SPDR.

The utilisation of prescription drugs, stated as DDDs, was the dependent variable. A report from the Swedish National Institute of Public Health (nowadays the Public Health Agency of Sweden) was used to identify diseases that tend to afflict females more frequently (55). In this report, the DALY was used to measure the burden of disease (see Background). In total, Sweden reached 1 689 959 DALYs during 2006, 835 796 for males and 854 163 for females. In this paper, diseases were selected that reached at least 7 500 DALYs in Sweden for both genders combined, and for which females had a predominance of at least 20%. Prescription drugs commonly used to treat these specific diseases were then identified using Swedish National Guidelines (Table 1) (88,89) . Contraceptive drugs are a special case. These drugs are normally used by healthy females as contraceptives and are not considered to treat any disease. They may, however, explain some of the difference in drug use between the genders and are hence identified as prescription drugs causing a gender difference in drug use. The Anatomical Therapeutic Chemical (ATC) classification system was elaborated by the WHO to enable internationally comparable studies on prescription drugs (90). Active substances are classified in different groups according to the organ or system

on which they act, and according to their therapeutic, pharmacological and chemical properties. The drugs are divided into 14 main ATC groups, and these groups are subsequently divided into five levels.

Table 1.
Prescription drugs that used to treat diseases and conditions that to a greater extent afflict females compared to males

Disease or condition	ATC code	Prescription drugs
Contraception	G03A	Contraceptive drugs
Climacteric complaints	G03C	Estrogens
	G03D	Gestagens
Thyroid gland disorders	H03AA01	Thyroid hormones
Cystitis	J01CA08	Pivmecillinam
	J01EA01	Trimethoprim
	J01XE01	Nitrofurantoin
Osteoarthritis	M01	Anti-inflammatory and anti-rheumatic drugs
	N02BE01	Paracetamol
Migraine	N02C	Migraine drugs, including triptans
Depression and anxiety disorders	N05BA	Benzodiazepines
	N05BB01	Hydroxyzine
	N05BE	Buspirone
	N06A	Antidepressant drugs, including Selective Serotonin Reuptake Inhibitors (SSRIs)
Insomnia	N05CD	Derivates of benzodiazepines (e.g. nitrazepam)
	N05CF	Benzodiazepine-related drugs (e.g. zolpidem)
	N05CM06	Propiomazine
Asthma and COPD	R03AC	Selective beta-2-stimulants and inhalable corticosteroids
	R03AK	
	R03BA02	
	R03BA05	
	R03BB01	

Paper IV

All individuals aged 65 years or older in Östergötland County during 2006 were enrolled (n=77 978). Information on the individuals' gender, age and diagnoses were collected from the CDWÖ during 2005-2006. Multimorbidity was estimated using the ACG Case-Mix System. Information on drug use was collected from the SPDR. Information on income was collected from Statistics Sweden. The individuals were further divided into 65-79 years and 80 years and above.

The proportion of the patients with correct diagnoses linked to the prescription drug was the outcome. A report from the NBHW regarding satisfactory pharmacological treatment among elderly patients was used to identify a number of prescription drugs, for which it is particularly important to have accurate and up-to-date diagnoses (Table 2). These prescription drugs were selected since there is a history of prescribing these drugs without correct indications, and because ADRs are highly associated with these drugs among the elderly. For each of these prescription drugs, diagnoses validated as accurate were classified by means of the Swedish database of prescription drugs (Table 3) (91) . Originally, the list from the NBHW also contained cox-inhibitors (NSAIDs), paracetamol and opioids. Since it is very hard to establish which diagnoses that are valid as accurate, not leaving any out, for example cancer or other chronic painful diseases, these drugs were excluded from the study.

Table 2.
Prescription drugs for which an accurate and up-to-date diagnosis is particularly important in elderly patients

Prescription drugs
Antipsychotic drugs
Proton pump inhibitors
Digoxin
Loop diuretics
SSRIs
Cox-inhibitors (NSAIDs)
Paracetamol
Opioids

Table 3.
Prescription drugs and their valid accurate diagnoses (Paper IV)

Prescription drugs	ATC codes	Accurate diagnoses	ICD-10 codes
Antipsychotic drugs	N05A excluding N05AN	Schizophrenia	F22
			F23
			F24
			F25
		Bipolar disorder	F31
		Severe aggression in	F91
		Alzheimer's disease	G30
			F00
Proton pump inhibitors	A02BC	Gastroesophageal reflux	K21
		Stomach ulcer	K25
		Ulcer in the duodenum	K26
		Ulcer in stomach or duodenum	K27
Digoxin	C01AA05	Heart failure	I50
		Atrial fibrillation	I48
Loop diuretics	C03C	Pulmonary edema	J81
		Heart failure	I50
		Hypertension	I10
		Edema	R60
		Kidney failure	N18
		Liver failure	K72
SSRIs	N06AB N06AX	Depression	F31
			F32
			F33
		Social anxiety disorder	F40
		Panic disorder	F41
		Obsessive-compulsive disorder	F42

Statistical analyses

The statistical analyses in Paper I was performed using STATA version 10, and in Papers II-IV STATA version 12 was used (Stata Corporation, Texas, USA).

Papers I and III

The best statistical method to define the data was considered to be zero-inflated negative binomial regression, since this model takes into account that a high number in the population do not use any prescription drugs (92). This model performs two analyses in parallel. One analysis is similar to logistic regression and answers the question of what the odds are for the individual to belong to the population with prescription drugs. This analysis gives odds ratios (ORs) of having prescription drugs, and 95% confidence intervals (CIs). The other analysis is similar to Poisson regression and answers the question of what the effect is of increasing the independent variable, i.e. DDD, with one unit for the individuals who already have at least one DDD. This analysis gives incident rate ratios (IRRs) for prescription drug use, and 95% CIs. In Paper I odds ratios of having prescription drug costs, and incidence rate ratios for prescription drug costs (SEK) were also analysed.

A multi-level analysis was performed in Paper III in order to examine if the differences in the drug use were dependent on the different PHCs.

In Paper I four models were generated: Model 1 adjusted for multimorbidity and gender, Model 2 adjusted for multimorbidity, gender and age, Model 3 adjusted for multimorbidity, gender, age and income, Model 4 adjusted for multimorbidity, gender, age and education. In Paper III two models were generated: Model 1 adjusted for multimorbidity, gender, age and income, Model 2 adjusted for multimorbidity, gender, age and education.

Paper II

Logistic regression was used to examine the odds of having prescription drugs, giving odds ratios and 95% CIs. The prescription drugs that were identified to treat diseases that afflict females to a higher extent, together with contraceptive drugs, were excluded from the analyses. Three models were generated. Model 1 was adjusted for multimorbidity and age. In Model 2 the prescription drugs were excluded one by one in subsequent univariate analyses, after adjustment for multimorbidity. In Model 3 all of the prescription drugs that caused a decrease in the gender difference in the univariate analyses (Model 2) were excluded, after adjustment for multimorbidity.

Paper IV

The proportion of patients with correct diagnoses linked to the prescription drugs was analysed. Data were further analysed in different strata: for males and females alone, for different age levels, for each multimorbidity level and for each income level. The outcome was compared using chi^2-test. Logistic regression was used to examine the odds ratios of having indication for the different prescription drugs. The model was adjusted for multimorbidity, age, gender and income.

Ethical considerations

All of the studies used register-based data. Regarding the Swedish Prescribed Drug Register the National Board of Health and Welfare removed the personal identification number. Data from Statistics Sweden are anonymous. Data from the Care Data Warehouse in Östergötland were anonymised which means that the outcome from the register cannot be linked to any individuals. The studies were approved by the Research Ethics Committee at Linköping University (Dnr 147/05 and 29/06).

Results

The effect of age, gender, income and education on drug use (Paper I)

The majority of the study population (66%) used prescription drugs.

The odds ratios of having costs for prescription drugs were similar to the odds ratios of having prescription drugs and are consequently not reported.

After adjustment for multimorbidity, age and income, male individuals had lower odds ratio of having prescriptions drugs (OR 0.45 (95% CI 0.44-0.46)) compared to females. Among the patients, i.e., those in the population who had at least one prescription drug, the gender difference in drug use considerably decreased (IRR 0.95 (95% CI 0.94-0.96)). Male patients had increased rates of costs compared to female patients (IRR 1.22 (95% CI 1.21-1.24)) after adjustment for multimorbidity, age and income (Table 4).

Individuals aged 80 years or older had higher odds ratio of having prescription drugs (OR 9.09 (95% CI 8.33-10.0)) compared to individuals 20-29 years old after adjustment for multimorbidity, gender and income. Patients aged 80 years or older had higher rate of drug use (IRR 4.36 (95% CI 4.26-4.45)) and costs for drug use (IRR 1.91 (95% CI 1.86-1.95)) compared to patients aged 20-29 years old after adjustment for multimorbidity, gender and income (Table 4).

Individuals with the lowest level of income had the lowest odds ratio of having prescription drugs and patients with the highest level of income had the lowest rate of drug use (IRR 0.73 (95% CI 0.71-0.74)) and the lowest costs (IRR 0.71 (95% CI 0.70-0.72)) after adjustment for multimorbidity, age and gender (Table 4). Individuals and patients with the highest level of education had the lowest odds ratio of having prescription drugs (OR 0.89 (95% CI 0.85-0.93)), the lowest rate of drug use (IRR 0.78 (95% CI 0.76-0.80)) and the lowest costs (IRR 0.92 (95% CI 0.89-0.94)) after adjustment for multimorbidity, age and gender.

The effect of gender-related morbidity on drug use (Paper II)

Gender difference in morbidity with predominance for females was identified for anxiety disorders, asthma, COPD, cystitis, dementia, depression, insomnia, migraine, osteoarthritis, stroke and thyroid gland disorders.

After adjustment for multimorbidity and age, males had lower odds ratio of having prescription drugs (OR 0.45 (95% CI 0.45-0.46)). After excluding contraceptive drugs from the analysis, the gender difference in drug use decreased (OR 0.65 (95% CI 0.64-0.66)). In the rest of the univariate analyses (Model 2) the effect was moderate, but when all of the prescription drugs that gave an OR >0.45 in Model 2 were excluded all together (Model 3), the odds ratio of having prescription drugs for males increased to 0.82 (95% CI 0.80-0.83) after adjustment for multimorbidity and age.

The effect of age, gender, income and education on prescription drugs issued by GPs (Paper III)

A total of 46% had at least one prescription drug issued by a GP.

The results for gender and age in the statistical models were quite similar for income and education, and therefore only the results for income are presented below (Model 1). For results regarding education (Model 2), please see Paper III.

After adjustment for multimorbidity, gender and income, individuals aged 80 years or older had higher odds ratio of having prescription drugs (OR 3.37 (95% CI 3.22-3.52)), and patients aged 80 years or older had higher rate of drug use (IRR 6.24 (95% CI 5.79-6.72)) compared to individuals and patients aged 20-39 years old (Table 4).

Male individuals had lower odds ratio of having prescription drugs (OR 0.66 (95% CI 0.64-0.69)) after adjustment for multimorbidity, age and income. Male patients had higher rate of drug use (IRR 1.06 (95% CI 1.04-1.09)) after adjustment for multimorbidity, age and income (Table 4).

Individuals and patients with the highest level of income had the lowest odds ratio of having prescription drugs (OR 0.86 (95% CI 0.81-0.91)) and the lowest rate of drug use (IRR 0.70 (95% CI 0.68-0.72)) after adjustment for multimorbidity, gender and age. Individuals with the second lowest level of income had the highest odds ratio of having prescription drugs (OR 1.10 (95% CI 1.07-1.13)) after adjustment for multimorbidity, gender and age (Table 4).

Individuals and patients with the highest level of education had the lowest odds ratio of having prescription drugs (OR 0.61 (95% CI 0.54-0.67)) and the lowest rate of

drug use (IRR 0.70 (95% CI 0.67-0.73)) after adjustment for multimorbidity, gender and age.

The multilevel analysis showed that only 2% of the differences seen between the different groups was dependent on the PHC level.

Table 4.
Odds ratios of having prescription drugs and incidence rate ratios for drug use in Paper I (Model 3) and Paper III (Model 1)

		Total population (Paper I)				Primary healthcare population (Paper III)	
Variables		**OR (CI 95%)**	**IRR (CI 95%)**	**Variables**		**OR (CI 95%)**	**IRR (CI 95%)**
Gender	Females	1	1	Gender	Females	1	1
	Males	0.45 (0.44-0.46)	0.95 (0.94-0.96)		Males	0.66 (0.64-0.69)	1.06 (1.04-1.09)
Age	20-29	1	1	Age	20-39	1	1
	30-39	1.02 (0.99-1.05)	1.16 (1.14-1.18)		40-59	1.76 (1.72-1.79)	2.41 (2.31-2.52)
	40-49	1.25 (1.20-28)	1.64 (1.61-1.67)		60-79	2.56 (2.49-2.62)	4.34 (4.12-4.57)
	50-59	1.82 (1.75-1.89)	2.35 (2.31-2.40)		80-	3.37 (3.22-3.52)	6.24 (5.79-6.72)
	60-69	2.94 (2.86-3.03)	3.10 (3.04-3.16)				
	70-79	4.76 (4.55-5.00)	3.59 (3.52-3.67)				
	80-	9.09 (8.33-10.0)	4.36 (4.26-4.45)				
Income level	1	1	1	Income level	1	1	1
	2	1.16 (1.14-1.20)	1.00 (0.99-1.02)		2	1.10 (1.07-1.13)	1.00 (0.98-1.03)
	3	1.06 (1.03-1.10)	0.81 (0.80-0.82)		3	0.98 (0.95-1.02)	0.78 (0.75-0.81)
	4	1.05 (1.02-1.09)	0.73 (0.71-0.74)		4	0.86 (0.81-0.91)	0.70 (0.68-0.72)

The presence of indication for treatment (Paper IV)

On average 45.1% (range 12.9%-75.8%) of the patients' prescription drugs examined in this paper had indication for treatment. Patients aged 80 years or older had indication for the prescription drugs to the lowest extent (40.8%), and patients with the highest level of multimorbidity had indication for treatment to the highest extent (52.2%).

Antipsychotics drugs

Of the patients who used antipsychotic drugs, 18.0% had indication for treatment. Patients aged 80 years or older had the lowest odds ratio of having indication for treatment (OR 0.66 (95% CI 0.54-0.82)), and patients with the second to highest multimorbidity had the highest odds ratio of having indication for treatment (OR 3.93 (95% CI 2.29-6.75)).

Proton pump inhibitors

Of the patients who used proton pump inhibitors, 12.9% had indication for treatment. Patients aged 80 years or older had the lowest odds ratio of having indication for treatment (0.82 (95% CI 0.74-0.92)), and patients with the highest multimorbidity had the highest odds ratio of having indication for treatment (OR 2.99 (95% CI 2.07-4.31)).

Digoxin

Of the patients who used digoxin, 75.8% had indication for treatment. Patients with the second lowest income had the lowest odds ratio of having indication for treatment (OR 0.84 (95% CI 0.66-1.06)), and patients with the highest multimorbidity had the highest odds ratio of having indication for treatment (OR 26.4 (95% CI 15.4-45.4)).

Loop diuretics

Of the patients who used loop diuretics, 69.0% had indication for treatment. Patients with the second lowest income had the lowest odds ratio of having indication for treatment (OR 0.93 (95% CI 0.85-1.02)), and patients with the highest multimorbidity had the highest odds ratio of having indication for treatment (OR 10.5 (95% CI 8.63-12.8)).

SSRIs

Of the patients who used SSRIs, 40.3% had indication for treatment. Patients aged 80 years or older had the lowest odds ratio of having indication for treatment (OR 0.61 (95% CI 0.56-0.67)), and patients with the highest multimorbidity had the highest odds ratio of having indication for treatment (OR 3.58 (95% CI 2.81-4.55)).

Table 5.
Characteristics of the study population in Papers I-III

Variables		N
Gender	Females	158 703
	Males	155 274
Age	20-39	99 439
	40-59	108 703
	60-79	79 802
	80-	26 033
Multimorbidity level (RUB)	0	101 835
	1	43 855
	2	64 587
	3	89 583
	4	10 901
	5	3 216
Income level	1	78 445
	2	78 445
	3	78 446
	4	78 444
Educational level*	1	21 109
	2	26 295
	3	125 581
	4	80 297

N – number of observations
* Including individuals up to 70 years old

Table 6.
Characteristics of the study population in Paper IV

Variables		N
Gender	Females	43 983
	Males	33 994
Age	65-79	51 945
	80-	26 033
Multimorbidity level (RUB)	0	14 481
	1	5 287
	2	13 466
	3	35 190
	4	7 107
	5	2 447
Income level	1	19 495
	2	19 494
	3	19 494
	4	19 494

N – number of observations

Discussion

Main findings

There are differences in drug use depending on age, gender, income and education even after adjustment for multimorbidity. The elderly, females and individuals with the lowest levels of income and education use more prescription drugs. These differences persist, when drug use in primary healthcare is examined. Gender-related morbidity seems to explain some of the gender difference in drug use. The age difference may partly be explained by lack of indication for treatment among elderly patients.

Age

The age difference regarding drug use is evident both in Papers I and III. One explanation for the age difference may be that some diseases are progressive and will require larger healthcare utilisation, including drug use. Heart failure and COPD may be examples where a progression of the disease and higher drug use are expected with higher age (93,94). Aging further leads to physiological changes in the body. One example is hypertension, as the blood pressure is expected to increase with higher age. Therefore, higher levels of drug use against hypertension are expected with higher age. The prescribing cascade was mentioned in the Background section. Since elderly patients use many prescription drugs, they are the most vulnerable to the risk of developing a prescribing cascade, because of the risk of misinterpreting a side effect of a prescription drug as a new disease (18,19). The approach to the elderly regarding drug use may contribute to the age difference. It is likely that younger individuals are recommended lifestyle changes, when possible, instead of a prescription drug. Cardiovascular disease may be used as an example, where exercise and a change of diet may be recommended as initial treatment among younger individuals (95). The results in both Papers I and III indicate that elderly may have an irrational drug use. This is partly confirmed by Paper IV, showing that the elderly lack indication for a number of their prescribed drugs. The critical criterion – to have indication for treatment – is thus not fulfilled, indicating that drug use among the elderly is not well planned or properly evaluated. Increased stress and shorter patient consultations in healthcare (96,97) may contribute to poorer evaluation and discontinuation of drug use. It has previously been stated that stopping drug use is much harder than starting

it (98), but it is essential to dare stop drug use in order not to cause polypharmacy, especially among the elderly. As important as initiating drug use is to evaluate its effect. Treatment duration, time for evaluation and responsible physician for evaluating the drug use should always be determined in advance (98). When drug use is discontinued, it is important that the physician informs the patient of the different scenarios that might arise. To do this is time-consuming and it is imperative that sufficient consultation time for informing the patient is allocated.

Even if all the patients' prescription drugs had indication for treatment, it is not guarantee that the drug use would be satisfactory. Elderly patients, often with high levels of multimorbidity, should probably not be treated according to all clinical protocols and guidelines because of risk of developing polypharmacy. Instead, physicians need to consider the context the patients live in and put this in relation to the overall clinical situation, when drug use is planned. This approach would likely lead to more satisfactory drug use among the elderly (99,100). In Paper III where prescription drugs issued by GPs are examined, the age difference is less prominent. This could be an effect of that GPs to a lower extent tend to follow guidelines (101). It could also be that GPs have a more holistic approach, (102) and because of that are better at evaluating and discontinuing drug use.

Gender

Males have considerably lower odds ratio of having prescription drugs compared to females. This is consistent with other studies (46-50,103), but it is interesting that this gender difference remains after adjustment for multimorbidity. Females seek more healthcare than males (42-44,104,105), and it has been argued that this may affect the difference in drug use. On the other hand, a patient-doctor consultation must not end with a drug prescription. Prescription drugs should only be advised and issued when needed, and when no other treatment option is available. Thus, the medical need should be in focus when prescribing drugs. It has, however, been shown that males and females describe their symptoms differently (106,107) . This may have an affect on the physician in the interpretation of the symptoms, and in the end the assessment of need for drug use. The patients' expectations of having a prescription drug have in a British study been shown to affect the drug use in positive direction. Despite different health-seeking behaviour between the genders, there was, however, no significant gender difference in the expectation of having a drug prescribed when visiting a GP (108) .

In Paper II the result indicates that the gender difference with regard to what diseases males and females are afflicted with may partly explain the gender difference in drug use. Especially the exclusion of contraceptive drugs decreases the gender difference in drug use. This is probably the reason for the less pronounced gender difference, when drug use was examined in primary care (Paper III), as prescriptions for contraceptive

drugs were issued by midwives, who at the time of the study belonged to secondary care. Theoretically, the diseases females are afflicted with may require drug use to a higher extent than the diseases males are afflicted with, which would be a good explanation for the gender difference in drug use. There is, however, no clear evidence to support that theory.

There is a large discrepancy between the odds ratio of having prescription drugs and the incidence rate ratio for drug use in both Papers I and III, which is quite interesting. Thus, there seems to be a barrier to initiate drug use among males, but once initiated the rate of drug use is nearly the same as for females. It has been indicated that males have worse compliance compared to females (109,110) , and this may be one explanation for the discrepancy. The gender-related morbidity together with the statistical model may also help to explain the discrepancy. In Paper II females were to a larger extent afflicted with anxiety disorders, asthma, COPD, cystitis, dementia, depression, insomnia, migraine, osteoarthritis, stroke and thyroid gland disorders. The majority of these diseases may be treated with only one prescription drug, for example antibiotics for cystitis, a triptan for migraine and thyroid hormone for thyroid gland disorders, giving it a 1-0 ratio, i.e. the patient may or may not use a prescription drug. This especially affects the odds ratio, but has a smaller effect on the incidence rate ratio.

Income and education

Patients with the lowest levels of income and the lowest level of education had the highest drug use, which is consistent with former studies (1,17,69). In this thesis the difference persists despite adjustment for multimorbidity. The differences are more pronounced for education. As for gender, there is a difference in consultation rate. Although in this case the results are varying, where individuals with low socioeconomic status generally seek healthcare to a lesser extent (111,112) , while consultation rates in primary healthcare are higher among individuals with low socioeconomic status (113) . Even if the medical need should be in focus for drug prescribing, as argued in the above, there is a risk that the consultation rates affect the drug use. It has been indicated that individuals with lower socioeconomic status to a lower extent have a health-enhancing behaviour (111) and to a lower extent tend to act on physicians' recommendations regarding health risks, for example smoking (114) . In many of the common chronic diseases, e.g. diabetes, hypertension and hyperlipidaemia, lifestyle changes are recommended as first-line treatment. If individuals with lower socioeconomic status to a lesser extent tend to act on these recommendations, this may lead to higher drug use among these individuals. In Paper I, individuals with the lowest level of income had the lowest odds ratio of having prescription drugs. This has previously been shown (115,116) and may be interpreted as the poorest individuals not being able to afford to collect their prescription drugs, despite the reimbursement system. This is supported by research showing that

patients with low income are more affected by price changes of prescription drugs (117) . Differences in compliance may affect the results, but poor compliance has previously rather been associated with low socioeconomic status (118) . In this thesis the differences in drug use between the different income and education levels are more pronounced in primary care, which supports a social gradient in the way primary healthcare is provided, as earlier described (119,120) . Because of the locations of PHCs in different socioeconomic environments, some effect on the level of the PHCs was expected in the multi-level analysis. However, no effect was seen, which indicates that the differences depend on the patients or the physicians. Patients' expectations and demands for healthcare have been indicated to differ between different socioeconomic groups (121) , which may influence the drug use. Previous research indicates that physicians may risk stereotyping patients (122) , which also may affect drug use.

Methodological considerations

The ACG Case-Mix System applied in all of the papers uses the individuals' diagnoses to estimate multimorbidity level. The quality of the registration of accurate diagnoses is thus of great importance. The total registration of diagnoses in the CDWÖ register is not validated. During 2006, Östergötland County did not use the ACG Case-Mix System for reimbursement, and consequently there was no financial incentive to register diagnoses. The likelihood of over-registration of diagnoses is thus low, but there is a risk of under-registration of diagnoses, which may have led to an underestimation of the effect of adjusting for multimorbidity. In Paper IV, lack of indication for treatment may have been overestimated because of substandard registration of diagnoses. On the other hand, it was not possible to assess whether the diagnoses were up-to-date, which may have led to an underestimation of lack of indication for treatment.

Another limitation is that the consultation rates were not included in this thesis as a factor affecting drug use. This would be interesting, since there is both a gender difference and a difference depending on socioeconomics in healthcare-seeking behaviour, which may have an effect on drug use. The lack of information on education for individuals aged 70 years and above ruled out the possibility of fully comparing the effect of income and education on drug use, and, furthermore, it was not possible to put income and education in the same statistical model. In Paper III, where a multi-level analysis was performed, it would have been interesting to include the level of GPs, since differences in drug use depending on the characteristics of the physicians (123,124) have been reported.

Data from the CDWÖ are from 2006 (2005-2006 in Paper IV) and may be regarded as old. On the one hand, the outcomes studied in this thesis reflect the behaviour in both physicians and patients, and to change a behavioural pattern, for example the

prescription pattern of physicians has been proven to be quite hard (125,126) . Drug costs, on the other hand, vary a lot over time, mostly due to patent loss, resulting in data on drug costs rapidly becoming outdated. Examination of drug costs was therefore limited to Paper I.

The cut-off points for the number of DALYs (7500) (Paper II) may have been set too high, and the cut-off point for gender difference in DALYs may have been set too low, which may have led to an underestimation of the effect of gender-related morbidity on the gender difference in drug use. The statistical model in Paper II was logistic regression giving odds ratio of having prescription drugs. For some of the diseases that females are afflicted with more frequently, e.g. dementia and stroke, it is most likely that the patients have multimorbidity and accordingly have treatment for other diseases as well as for dementia and stroke. Therefore prescription drugs used to treat dementia and stroke were not excluded from the statistical analyses in Paper II, which may have led to an underestimation of the gender-related morbidity on drug use.

Prescription drugs issued in primary healthcare were examined in Paper III. Some of these prescription drugs were probably originally initiated in secondary care and later iterated by GPs in primary healthcare. Hence, there is a risk that the results in Paper III do not entirely reflect the drug use in only primary healthcare, but that they also reflect the drug use in secondary care to some extent.

The information in the SPDR regards prescription drugs actually collected from the pharmacies. This mainly reflects the drug use, since it is dependent on the patients' compliance in collecting the prescription drugs, and thus differs from drug treatment, which reflects the physicians' intended treatment. Furthermore, there is no information on the extent to which the patients actually used the collected prescription drugs.

Future research

The effect of age, gender, income and education on prescription drug use was examined in this thesis. Pharmacoepidemiological methods were used to study what happens during and after the patient-doctor consultation. In the end, it is the physician who after all decides when or whether a drug is to be prescribed. The choice of prescription drug is also ultimately the choice of the physician. Previous research has shown that there is variability in how physicians prescribe drugs, where for example age and gender of the physician, and duration after qualification have been found to affect the prescribing of drugs (123,124) . To be able to affect the differences in drug use, it would be useful to examine the prescribing patterns at the physician level.

The findings suggest that drug use among the elderly to quite a high extent is unjustified with low rates of indication for treatment, especially among the oldest patients. Some of this unnecessary drug use probably derives from an aversion among physicians to discontinue drug treatment, and this field may be productive to explore. The inclusion of elderly patients in future studies on drug use and development of guidelines adapted to elderly patients are also highly relevant. The latest guidelines on diabetes may be a good example of this (127) .

The results indicate that there is a barrier to initiating drug use among males, and this has not been studied before. Future research exploring both the patients' and the physicians' thoughts and experiences in this field would be informative. The result in Paper II shows that despite adjusting for multimorbidity and exclusion of prescription drugs used to treat diseases that females are afflicted with more frequently, together with contraceptive drugs, there is still a gender difference of 18% in receiving prescription drugs. Further research, tentatively including consultation rates and compliance, would be of interest. If this research is carried out, contraceptive drugs ought to be excluded because of risk of skewing the results because of lack of corresponding drug use among males.

Conclusions and clinical implications

This thesis verifies that the patients' age, gender, income and education to a large extent unjustifiably affect drug use. Males and individuals with higher income and education have a lower drug use, while females and the elderly have a higher drug use, despite adjustment for multimorbidity. The age difference is probably a testament to unnecessary drug use, which is likely emanated from the widespread lack of indication for treatment among the elderly patients. This implicates that physicians need to become better at evaluating drug use, in particular among the elderly. The consultation times must be adapted to elderly patients, allowing the physicians, and in particular the GPs, to evaluate the drug use of the patients and thus provide conditions to keep a holistic and patient-centred perspective. Because of many caregivers among the elderly, national medication lists should be developed to ensure that both patients and physicians use the same list when evaluation of drug use is performed. In Sweden, equality is a major priority and this should also apply to drug use. The findings suggest that the medical need is not the only factor influencing drug use, but that age, gender and socioeconomic status, separately, have a high impact on drug use. Consequently, there is a risk that non-medical factors may lead to both an over- and underuse of drugs, with risk of unnecessary suffering for patients and high costs for society. Patients, physicians and decision-makers must be aware of and act on these findings to avoid future inequality in drug use.

Svensk sammanfattning

Läkemedelsanvändning är en av sjukvårdens viktigaste behandlingsmetoder för att bota och lindra sjukdom. Samtidigt kan läkemedelsanvändning innebära risker. Det finns en risk för att patienterna får biverkningar av sina läkemedel, att läkemedlen fungerar mindre bra tillsammans och att effekten därmed upphör eller förstärks. Vidare finns det risk för att läkemedlen inte används på rätt sätt, i synnerhet om patienterna använder många läkemedel. De skadliga effekterna av läkemedel kan i värsta fall göra patienterna så sjuka att sjukhusvård krävs och forskning visar att upp till 30 % av alla sjukhusinläggningar beror på negativa effekter av läkemedel. Läkemedelsanvändningen innebär också stora kostnader för staten. År 2013 uppgick kostnaden för läkemedel i Sverige till 36,4 miljarder kronor, vilket utgör ca 10-12 % av hela sjukvårdens kostnader. Om dessutom kostnaderna för sjukhusvård orsakad av läkemedel läggs till denna summa stiger beloppet avsevärt. Det är således viktigt för både patienterna och samhället att läkemedelsanvändningen är säker, effektiv och välmotiverad.

Läkemedelsanvändningen är inte jämlik, vare sig i världen eller i Sverige. Det finns skillnader i läkemedelsanvändningen i befolkningen, som beror på icke medicinska faktorer som ålder, kön och socioekonomi. Det är känt att äldre patienter, kvinnor och patienter med lägre socioekonomi använder läkemedel i högre utsträckning. Tidigare studier har sällan tagit patienternas sjuklighet i beaktande, vilket gör att en del av de uppmätta skillnaderna skulle kunna förklaras med olika sjuklighet i de olika grupperna. I denna avhandling finns ett mått på patienternas sjuklighet med i alla studierna och hänsyn tas därmed till patienternas sjuklighet. Det övergripande syftet med avhandlingen är att beskriva hur ålder, kön, inkomst och utbildning påverkar läkemedelsanvändningen i en vuxen population, när hänsyn tagits till patienternas sjuklighet, med fördjupande studier avseende ålders- och könsskillnaden.

Alla studier är registerbaserade på data från Östergötland. För beräkning av patienternas sjuklighet används ACG Case-Mix Systemet, vilket använder patienternas alla diagnoser, både från öppen- och slutenvård, för att beräkna sjukligheten. Genom en algoritm, som bland annat bygger på diagnosernas orsak, behov av utredning och behandling, tillskrivs varje patient en sjuklighetsgrupp.

I studie I och III inkluderas alla individer som är 20 år och äldre. Sannolikheten för läkemedelsanvändning beroende på ålder, kön, utbildning och inkomst beräknas, efter att hänsyn tagits till individernas olika sjuklighet. I studie I undersöks den totala läkemedelsanvändningen medan läkemedelsanvändningen i primärvården undersöks i

studie III. Trots att hänsyn tagits till patienternas olika sjuklighet fanns det stora skillnader. De äldsta individerna hade åtta gånger högre sannolikhet att ha behandling med ett läkemedel jämfört med de yngsta individerna, män hade hälften så stor sannolikhet att behandlas med ett läkemedel jämfört med kvinnor och de mest välutbildade individerna hade en klart lägre läkemedelsanvändning jämfört med individerna med den lägsta utbildningen. Resultaten var i princip desamma när läkemedelsanvändningen i primärvården undersöktes.

Studie II fokuserar på den uppmätta könsskillnaden i första studien. Alla individer som är 20 år och äldre, inkluderas för att undersöka om könsskillnaden från studie I kan bero på att kvinnor och män till viss del har olika sjukdomspanorama, d.v.s. insjuknar i olika typer av sjukdomar. Läkemedel, som används för att behandla sjukdomar som kvinnor i högre utsträckning insjuknar i, exempelvis migrän och depression, identifieras. När dessa läkemedel uteslöts från beräkningen sågs en klar minskning av könsskillnaden från studie I men samtidigt kvarstod en omotiverad skillnad mellan könen i läkemedelsanvändning på 18 %.

Studie IV fokuserar på de uppmätta åldersskillnaderna från studie I och III, vilka misstänks delvis vara beroende av att de äldre patienterna saknar indikation för en del av sina läkemedel. I denna studie inkluderas alla individer som är 65 år och äldre. Socialstyrelsen har identifierat några läkemedel för vilka det är särskilt viktigt att ha en indikation. Andelen patienter som har indikation för dessa läkemedel beräknas. I medeltal hade färre än hälften av patienterna indikation för de av Socialstyrelsen identifierade läkemedlen (45,1 %). Lägst sannolikhet att ha indikation för läkemedlen hade de patienter som var 80 år eller äldre.

Således konstateras att icke medicinska faktorer som patienternas ålder, kön, inkomst och utbildning påverkar läkemedelsanvändningen trots att sjukligheten tas i beaktande, att kvinnors och mäns något skilda sjukdomspanorama delvis kan förklara könsskillnaden samt att omotiverad läkemedelsanvändning hos de äldre patienterna delvis kan förklara åldersskillnaden.

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References

(1) Weitoft GR, Rosen M, Ericsson O, Ljung R. Education and drug use in Sweden--a nationwide register-based study. Pharmacoepidemiol Drug Saf 2008 Oct;17(10):1020-1028.

(2) The National Board of Health and Welfare. Database for prescriprion drugs. Available at: http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel. Accessed Mar 10, 2015.

(3) Statistics Sweden. Population statistics. Available at: http://www.scb.se/sv_/Hitta-statistik/Statistik-efter-amne/Befolkning/Befolkningens-sammansattning/Befolkningsstatistik/25788/25795/Helarsstatistik---Riket/26040/. Accessed Mar 10, 2015.

(4) Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011 Sep;10(4):430-439.

(5) The Swedish eHealth Agency. Prescription drug sales. 2013; Available at: http://www.ehalsomyndigheten.se/Documents/statistik/LäkemedelsförsäljningSV_Årsrapport_2013_1.0_dig.pdf. Accessed Mar 10, 2015.

(6) The National Board of Health and Welfare. Statistics for prescription drugs. 2013; Available at: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19366/2014-3-1.pdf. Accessed Mar 10, 2015.

(7) Svensk Författningssamling: Hälso- och sjukvårdslag [Swedish Code of Statutes: Healthcare Act] SFS 1982:763. Stockholm 1982. 1982.

(8) Ministry of Health and Social Affairs. National Drug Strategy, s 2011.029. Stockholm. 2011; Available at: http://www.regeringen.se/content/1/c6/17/38/05/f10289bc.pdf. Accessed Mar 10, 2015.

(9) Anell A, Glenngard AH, Merkur SM. Sweden: Health system review. Health systems in transition 2014;14:1:1-159. Available at: http://www.euro.who.int/__data/assets/pdf_file/0008/164096/e96455.pdf. Accessed Mar 10, 2015.

(10) The Dental and Pharmaceutical Benefits Agency. Available at: http://www.tlv.se. Accessed Mar 10, 2015.

(11) Swedish Association of Local Authorities nad Regions. Patient cost in Healthcare. Available at: http://skl.se/download/18.385754eb14ade5baef282d5/1421230754013/SKL+patientavgifter+2015.pdf. Accessed Mar 10, 2015.

(12) United Nations. Population growth rate. Available at: https://data.un.org/Data.aspx?d=PopDiv&f=variableID%3a47. Accessed Mar 10, 2015.

(13) Abad-Diez JM, Calderon-Larranaga A, Poncel-Falco A, Poblador-Plou B, Calderon-Meza JM, Sicras-Mainar A, et al. Age and gender differences in the prevalence and patterns of multimorbidity in the older population. BMC Geriatr 2014 Jun 17;14:75-2318-14-75.

(14) Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. J Gerontol A Biol Sci Med Sci 2011 Mar;66(3):301-311.

(15) Hovstadius B, Astrand B, Petersson G. Dispensed drugs and multiple medications in the Swedish population: an individual-based register study. BMC Clin Pharmacol 2009 May 27;9:11-6904-9-11.

(16) Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? Ann Fam Med 2006 Mar-Apr;4(2):104-108.

(17) Haider SI, Johnell K, Weitoft GR, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. J Am Geriatr Soc 2009 Jan;57(1):62-69.

(18) Geller AI, Nopkhun W, Dows-Martinez MN, Strasser DC. Polypharmacy and the role of physical medicine and rehabilitation. PM R 2012 Mar;4(3):198-219.

(19) Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ 1997 Oct 25;315(7115):1096-1099.

(20) The Swedish National Board of Health and Welfare. Indicators for satisfactory phamacological treatment among elderly patients. Available at: http://www.socialstyrelsen.se/lists/artikelkatalog/attachments/18085/2010-6-29.pdf. Accessed Mar 10, 2015.

(21) The World Health Organization. Definitions. Available at: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf. Accessed Mar 10, 2015.

(22) von Euler M, Eliasson E, Ohlen G, Bergman U. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization. Pharmacoepidemiol Drug Saf 2006 Mar;15(3):179-184.

(23) Mjorndal T, Boman MD, Hagg S, Backstrom M, Wiholm BE, Wahlin A, et al. Adverse drug reactions as a cause for admissions to a department of internal medicine. Pharmacoepidemiol Drug Saf 2002 Jan-Feb;11(1):65-72.

(24) Paul E, End-Rodrigues T, Thylen P, Bergman U. Adverse drug reactions a common cause of hospitalization of the elderly. A clinical retrospective study. Lakartidningen 2008 Aug 27-Sep 2;105(35):2338-2342.

(25) Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998 Apr 15;279(15):1200-1205.

(26) Noble RE. Drug therapy in the elderly. Metabolism 2003 Oct;52(10 Suppl 2):27-30.

(27) Fastbom J. Äldre och läkemedel. [Elderly and prescription drugs]. : Liber; 2007.

(28) Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol 2003 Aug;38(8):843-853.

(29) Midlov P, Bahrani L, Seyfali M, Hoglund P, Rickhag E, Eriksson T. The effect of medication reconciliation in elderly patients at hospital discharge. Int J Clin Pharm 2012 Feb;34(1):113-119.

(30) Moen J, Norrgard S, Antonov K, Nilsson JL, Ring L. GPs' perceptions of multiple-medicine use in older patients. J Eval Clin Pract 2010 Feb;16(1):69-75.

(31) Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother 2007 Dec;5(4):345-351.

(32) Andersson G, Karlberg I. Integrated care for the elderly: the background and effects of the reform of Swedish care of the elderly. Int J Integr Care 2000 Nov 1;1:e01.

(33) Offerhaus L. Drugs for the elderly. Second edition. World Health Organization. WHO Reg Publ Eur Ser 1997;71:1-145.

(34) American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012 Apr;60(4):616-631.

(35) Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study. Scand J Prim Health Care 2009;27(3):153-159.

(36) Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int 2010 Aug;107(31-32):543-551.

(37) Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol 2007 Aug;63(8):725-731.

(38) Hajjar ER, Hanlon JT, Sloane RJ, Lindblad CI, Pieper CF, Ruby CM, et al. Unnecessary drug use in frail older people at hospital discharge. J Am Geriatr Soc 2005 Sep;53(9):1518-1523.

(39) Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 2006 Oct;54(10):1516-1523.

(40) The Public Health Agency of Sweden. Public Health Report 2009. Available at: http://www.folkhalsomyndigheten.se/pagefiles/12982/folkhalsorapport-2009.pdf. Accessed Mar 10, 2015.

(41) Nathanson CA. Illness and the feminine role: a theoretical review. Soc Sci Med 1975 Feb;9(2):57-62.

(42) Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. Br J Clin Pharmacol 1998 Nov;46(5):505-511.

(43) Simoni-Wastila L. Gender and psychotropic drug use. Med Care 1998 Jan;36(1):88-94.

(44) The National Board of Health and Welfare. Equal care? Available at: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10285/2004-103-3_20041033.pdf. Accessed Mar 10, 2015.

(45) Geller SE, Adams MG, Carnes M. Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials. J Womens Health (Larchmt) 2006 Dec;15(10):1123-1131.

(46) Correa-de-Araujo R, Miller GE, Banthin JS, Trinh Y. Gender differences in drug use and expenditures in a privately insured population of older adults. J Womens Health (Larchmt) 2005 Jan-Feb;14(1):73-81.

(47) Roe CM, McNamara AM, Motheral BR. Use of chronic medications among a large, commercially-insured US population. Pharmacoepidemiol Drug Saf 2002 Jun;11(4):301-309.

(48) Fernandez-Liz E, Modamio P, Catalan A, Lastra CF, Rodriguez T, Marino EL. Identifying how age and gender influence prescription drug use in a primary health care environment in Catalonia, Spain. Br J Clin Pharmacol 2008 Mar;65(3):407-417.

(49) Schuler J, Duckelmann C, Beindl W, Prinz E, Michalski T, Pichler M. Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria. Wien Klin Wochenschr 2008;120(23-24):733-741.

(50) Kennerfalk A, Ruigomez A, Wallander MA, Wilhelmsen L, Johansson S. Geriatric drug therapy and healthcare utilization in the United kingdom. Ann Pharmacother 2002 May;36(5):797-803.

(51) Hofer-Duckelmann C. Gender and polypharmacotherapy in the elderly: a clinical challenge. Handb Exp Pharmacol 2012;(214):169-82. doi(214):169-182.

(52) Bierman AS, Pugh MJ, Dhalla I, Amuan M, Fincke BG, Rosen A, et al. Sex differences in inappropriate prescribing among elderly veterans. Am J Geriatr Pharmacother 2007 Jun;5(2):147-161.

(53) Gurwitz JH. The age/gender interface in geriatric pharmacotherapy. J Womens Health (Larchmt) 2005 Jan-Feb;14(1):68-72.

(54) Marazziti D, Baroni S, Picchetti M, Piccinni A, Carlini M, Vatteroni E, et al. Pharmacokinetics and pharmacodynamics of psychotropic drugs: effect of sex. CNS Spectr 2013 Jun;18(3):118-127.

(55) Allebeck P, Moradi T, Jacobsson A. The Public Health Agency of Sweden. Burden of disease in Sweden and its risk factors. Available at: http://www.folkhalsomyndigheten.se/pagefiles/12245/A20064_dalys0606.pdf. Accessed Mar 10, 2015.

(56) The Swedish National Institue of Public Health., The National Bord of Health and Welfare. The Publica Health Agency in Sweden. Public Health in Sweden 2012. Available at: http://www.folkhalsomyndigheten.se/pagefiles/12738/2012-3-6-Folkhalsan-i-Sverige-Arsrapport-2012.pdf. Accessed Mar 10, 2015.

(57) Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997 May 17;349(9063):1436-1442.

(58) Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997 May 24;349(9064):1498-1504.

(59) The World Health Organization. Definition DALY. Available at: http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/. Accessed Mar 10, 2015.

(60) Ljung R, Peterson S, Hallqvist J, Heimerson I, Diderichsen F. Socioeconomic differences in the burden of disease in Sweden. Bull World Health Organ 2005 Feb;83(2):92-99.

(61) Lynch, JW, Kaplan, GA. Socioeconomic Position. In: Berkman LF KI, editor. Socioeconomic Factors New York: Oxford University Press; 2000. p. 12-35.

(62) Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. Br Med Bull 2007;81-82:21-37.

(63) Haider SI, Johnell K, Ringback Weitoft G, Thorslund M, Fastbom J. Patient educational level and use of newly marketed drugs: a register-based study of over 600,000 older people. Eur J Clin Pharmacol 2008 Dec;64(12):1215-1222.

(64) Ringback Weitoft G, Ericsson O, Lofroth E, Rosen M. Equal access to treatment? Population-based follow-up of drugs dispensed to patients after acute myocardial infarction in Sweden. Eur J Clin Pharmacol 2008 Apr;64(4):417-424.

(65) Thomsen RW, Johnsen SP, Olesen AV, Mortensen JT, Boggild H, Olsen J, et al. Socioeconomic gradient in use of statins among Danish patients: population-based cross-sectional study. Br J Clin Pharmacol 2005 Nov;60(5):534-542.

(66) Matthews FE, McKeith I, Bond J, Brayne C, MRC CFAS. Reaching the population with dementia drugs: what are the challenges? Int J Geriatr Psychiatry 2007 Jul;22(7):627-631.

(67) Merlo J, Lynch JW, Yang M, Lindstrom M, Ostergren PO, Rasmusen NK, et al. Effect of neighborhood social participation on individual use of hormone replacement therapy and antihypertensive medication: a multilevel analysis. Am J Epidemiol 2003 May 1;157(9):774-783.

(68) Finley C, Gregg EW, Solomon LJ, Gay E. Disparities in hormone replacement therapy use by socioeconomic status in a primary care population. J Community Health 2001 Feb;26(1):39-50.

(69) Engstrom S, Magnusson H, Enthoven P, Walter L, Thorell K, Halling A, et al. Social status affects drug costs and health care costs. A registry study shows that Care Choice should take socioeconomic factors into account. Lakartidningen 2009 Nov 25-Dec 1;106(48):3248, 3250, 3252-3.

(70) Odubanjo E, Bennett K, Feely J. Influence of socioeconomic status on the quality of prescribing in the elderly -- a population based study. Br J Clin Pharmacol 2004 Nov;58(5):496-502.

(71) Lechevallier-Michel N, Gautier-Bertrand M, Alperovitch A, Berr C, Belmin J, Legrain S, et al. Frequency and risk factors of potentially inappropriate medication use in a community-dwelling elderly population: results from the 3C Study. Eur J Clin Pharmacol 2005 Jan;60(11):813-819.

(72) Hoffmann M, Lovstrom R. Lakartidningen 2015 Feb 17;112:C949.

(73) Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012 Jul 7;380(9836):37-43.

(74) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.

(75) Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998 Jan;36(1):8-27.

(76) Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974 Sep;27(7-8):387-404.

(77) Starfield B, Weiner J, Mumford L, Steinwachs D. Ambulatory care groups: a categorization of diagnoses for research and management. Health Serv Res 1991 Apr;26(1):53-74.

(78) Weiner JP, Starfield BH, Steinwachs DM, Mumford LM. Development and application of a population-oriented measure of ambulatory care case-mix. Med Care 1991 May;29(5):452-472.

(79) Zielinski A, Kronogard M, Lenhoff H, Halling A. Validation of ACG Case-mix for equitable resource allocation in Swedish primary health care. BMC Public Health 2009 Sep 18;9:347-2458-9-347.

(80) Calderon-Larranaga A, Poblador-Plou B, Lopez-Cabanas A, Alcala-Nalvaiz JT, Abad-Diez JM, Bordonaba-Bosque D, et al. Does the pharmacy expenditure of patients always correspond with their morbidity burden? Exploring new approaches in the interpretation of pharmacy expenditure. BMC Public Health 2010 May 11;10:244-2458-10-244.

(81) Skåne County. Statistics for primary healthcare. Available at: http://vardgivare.skane.se/uppfoljning/halsoval-statistik/#18341. Accessed Mar 10, 2015.

(82) The Johns Hopkins ACG System. Available at: http://acg.jhsph.org. Accessed Mar 10, 2015.

(83) The National Board of Health and Welfare. Cause of Death Register. Available at: http://www.socialstyrelsen.se/register/dodsorsaksregistret. Accessed Mar 10, 2015.

(84) The National Board of Health and Welfare. The Swedish Prescribed Drug Register. Available at: http://www.socialstyrelsen.se/register/halsodataregister/lakemedelsregistret. Accessed Mar 10, 2015.

(85) Statistics Sweden. Available at: http://www.scb.se. Accessed Mar 10, 2015.

(86) Statistics Sweden. Animated population pyramids. Available at: https://www.h5.scb.se/kommunfakta/pyramider/index.asp. Accessed Mar 10, 2015.

(87) The World Health Organization. Available at: http://www.whocc.no/ddd/definition_and_general_considera/. Accessed Mar 10, 2015.

(88) The Medical Product Agency. Treatment guidelines. Available at: http://www.lakemedelsverket.se/english/. Accessed Mar 10, 2015.

(89) The Medical Product Agency. Book of prescription drugs. Available at: http://www.lakemedelsboken.se. Accessed Mar 10, 2015.

(90) The World Healh Organization. The ATC classification system. Available at: http://www.whocc.no/atc/structure_and_principles/. Accessed Mar 10, 2015.

(91) The research-based pharmaceutical industry. Database of prescription drugs. Available at: http://www.fass.se. Accessed Mar 10, 2015.

(92) Mwalili SM, Lesaffre E, Declerck D. The zero-inflated negative binomial regression model with correction for misclassification: an example in caries research. Stat Methods Med Res 2008 Apr;17(2):123-139.

(93) Takeda A, Taylor SJ, Taylor RS, Khan F, Krum H, Underwood M. Clinical service organisation for heart failure. Cochrane Database Syst Rev 2012 Sep 12;9:CD002752.

(94) Elbehairy AF, Webb KA, Neder JA, O'Donnell DE. Should mild COPD be treated? Evidence for early pharmacological intervention. Drugs 2013 Dec;73(18):1991-2001.

(95) Gielen S, Landmesser U. The Year in Cardiology 2013: cardiovascular disease prevention. Eur Heart J 2014 Feb;35(5):307-312.

(96) The Swedish Agency for Health and Care Services Analysis. Healthcare seen from the patients' perspective - a comparison between Sweden and ten other countries. Result from the Commonwealth Fund 2014 International Health Policy Survey. . Available at: http://www.vardanalys.se/Global/Rapporter%20pdf-filer/2014/2014-11-Vården%20ur%20patienternas%20perspektiv.pdf. Accessed Mar 10, 2015.

(97) The Swedish Agency for Health and Care Services Analysis. Four areas of development for a more efficient use of physicians' time and skills. 2013; Available at: http://www.vardanalys.se/Global/Rapporter%20pdf-filer/2013/2013-9-Ur%20led%20är%20tiden.pdf. Accessed Mar 10, 2015.

(98) Boman K, Ogren JE. Drug withdrawal--clinically important but practically difficult. Lakartidningen 2002 Jul 25;99(30-31):3100-3102.

(99) Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. Arch Intern Med 2010 Oct 11;170(18):1648-1654.

(100) Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. BMC Fam Pract 2012 Jul 9;13:56-2296-13-56.

(101) Ekesbo R, Midlov P, Gerward S, Persson K, Nerbrand C, Johansson L. Lack of adherence to hypertension treatment guidelines among GPs in southern Sweden-a case report-based survey. BMC Fam Pract 2012 Jul 9;13:34-2296-13-34.

(102) Chew-Graham CA, Hunter C, Langer S, Stenhoff A, Drinkwater J, Guthrie EA, et al. How QOF is shaping primary care review consultations: a longitudinal qualitative study. BMC Fam Pract 2013 Jul 21;14:103-2296-14-103.

(103) Anthony M, Lee KY, Bertram CT, Abarca J, Rehfeld RA, Malone DC, et al. Gender and age differences in medications dispensed from a national chain drugstore. J Womens Health (Larchmt) 2008 Jun;17(5):735-743.

(104) Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. Vital Health Stat 13 2006 Feb;(159)(159):1-66.

(105) Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs 2005 Mar;49(6):616-623.

(106) Safran DG, Rogers WH, Tarlov AR, McHorney CA, Ware JE,Jr. Gender differences in medical treatment: the case of physician-prescribed activity restrictions. Soc Sci Med 1997 Sep;45(5):711-722.

(107) Hall JA, Roter DL. Do patients talk differently to male and female physicians? A meta-analytic review. Patient Educ Couns 2002 Dec;48(3):217-224.

(108) Webb S, Lloyd M. Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. Br J Gen Pract 1994 Apr;44(381):165-169.

(109) Wallach-Kildemoes H, Andersen M, Diderichsen F, Lange T. Adherence to preventive statin therapy according to socioeconomic position. Eur J Clin Pharmacol 2013 Aug;69(8):1553-1563.

(110) Mukherjee S, Sharmasarkar B, Das KK, Bhattacharyya A, Deb A. Compliance to anti-diabetic drugs: observations from the diabetic clinic of a medical college in kolkata, India. J Clin Diagn Res 2013 Apr;7(4):661-665.

(111) Fiscella K, Franks P, Clancy CM. Skepticism toward medical care and health care utilization. Med Care 1998 Feb;36(2):180-189.

(112) Fiscella K, Franks P, Gold MR, Clancy CM. Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care. JAMA 2000 May 17;283(19):2579-2584.

(113) Carr-Hill RA, Rice N, Roland M. Socioeconomic determinants of rates of consultation in general practice based on fourth national morbidity survey of general practices. BMJ 1996 Apr 20;312(7037):1008-1012.

(114) Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health Aff (Millwood) 2002 Mar-Apr;21(2):60-76.

(115) Weitoft GR, Ericsson O, Fastbom J. Prescription drugs: Health in Sweden: The National Public Health Report 2012. Chapter 18. Scand J Public Health 2012 Dec;40(9 Suppl):293-304.

(116) Fillenbaum GG, Horner RD, Hanlon JT, Landerman LR, Dawson DV, Cohen HJ. Factors predicting change in prescription and nonprescription drug use in a community-residing black and white elderly population. J Clin Epidemiol 1996 May;49(5):587-593.

(117) Lundberg L, Johannesson M, Isacson DG, Borgquist L. Effects of user charges on the use of prescription medicines in different socio-economic groups. Health Policy 1998 May;44(2):123-134.

(118) Wamala S, Merlo J, Bostrom G, Hogstedt C, Agren G. Socioeconomic disadvantage and primary non-adherence with medication in Sweden. Int J Qual Health Care 2007 Jun;19(3):134-140.

(119) Bradley CP. Factors which influence the decision whether or not to prescribe: the dilemma facing general practitioners. Br J Gen Pract 1992 Nov;42(364):454-458.

(120) Britten N, Ukoumunne O. The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: a questionnaire survey. BMJ 1997 Dec 6;315(7121):1506-1510.

(121) Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations--a questionnaire study. BMJ 1997 Aug 30;315(7107):520-523.

(122) Burgess DJ, Fu SS, van Ryn M. Why do providers contribute to disparities and what can be done about it? J Gen Intern Med 2004 Nov;19(11):1154-1159.

(123) Wun YT, Chan CS, Dickinson JA. Determinants of physicians' attitude towards prescribing. J Clin Pharm Ther 2002 Feb;27(1):57-65.

(124) Weng SS, Chen YH, Lin CC, Keller JJ, Wang IT, Lin HC. Physician characteristics and prescription drug use during pregnancy: a population-based study. Ann Epidemiol 2013 Feb;23(2):54-59.

(125) Armstrong D, Reyburn H, Jones R. A study of general practitioners' reasons for changing their prescribing behaviour. BMJ 1996 Apr 13;312(7036):949-952.

(126) Gill PS, Makela M, Vermeulen KM, Freemantle N, Ryan G, Bond C, et al. Changing doctor prescribing behaviour. Pharm World Sci 1999 Aug;21(4):158-167.

(127) Dunning T, Sinclair A, Colagiuri S. New IDF Guideline for managing type 2 diabetes in older people. Diabetes Res Clin Pract 2014 Mar;103(3):538-540.