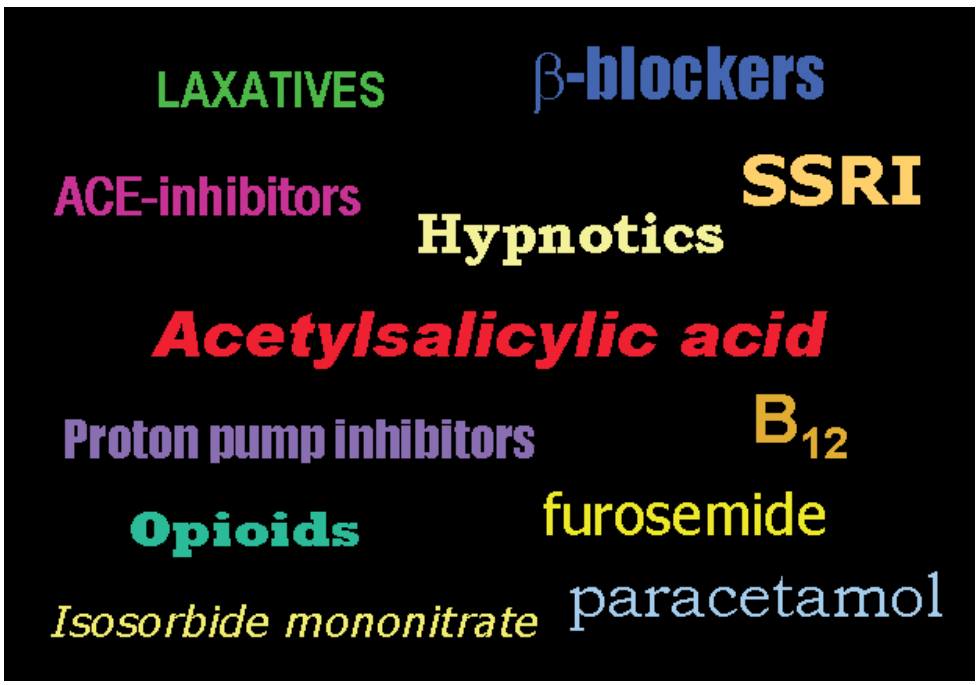
Thesis for doctoral degree (Ph.D.)
2008

Socioeconomic Differences in Drug Use Among Older People

Trends, Polypharmacy, Quality and New Drugs



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Socioeconomic Differences in Drug Use Among Older People
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SOCIOECONOMIC DIFFERENCES IN DRUG USE AMONG OLDER PEOPLE

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To my parents

ABSTRACT ENGLISH

Polypharmacy and potentially inappropriate drug use (IDU) is a major patient safety and public health concern in the elderly, resulting in an increased likelihood of adverse drug reactions, drug-drug interactions (DDI), hospitalization, poor quality of life and mortality.

This doctoral thesis investigated the complex relationship between drug use and socioeconomic position (SEP) and characterized the drug use, quality of prescribing, development of drug use over time, and use of new drugs in the elderly. The data were derived from the Swedish Panel Study of the Living Conditions of the Oldest Old (SWEOLD) project (*Studies I and II*) and from the Swedish Prescribed Drug Register (SPDR), National Inpatient Register and Education Register (*Studies III and IV*). The SWEOLD Project is a national representative, community-based study on living conditions of people aged ≥77 years in Sweden. The SPDR is a new health register which contains data on all dispensed prescriptions to the entire Swedish population. The major findings are summarized below.

Study I. The relationship between drug use and SEP (measured by education, occupation, or income), was investigated using SWEOLD 2002 survey data. Polypharmacy (use of five or more drugs) was observed in 42% of the elderly. Low education was associated with polypharmacy (OR = 1.46, 95% CI, 1.02-2.07), after controlling for age and sex. The tendency for an association between low education and polypharmacy remained (OR = 1.40, 95% CI 0.96-2.05), however not conclusive, after adjustment for age, sex, comorbidity, and marital status. We did not observe any association between occupation or income and polypharmacy.

Study II. Changes in drug use between educational groups during one decade were based on comparison of the two SWEOLD surveys (1992 and 2002). Overall drug use and mean number of drugs used per person increased between the years. The prevalence of polypharmacy increased more than twofold (from 18% in 1992 to 42% in 2002). In both SWEOLD surveys, the less educated reported polypharmacy more often (19% in 1992 and 46% in 2002) than the higher educated (12% in 1992 and 36% in 2002). Potential DDI also increased, both among the less educated (14% in 1992 to 26% in 2002) and the higher educated (18% in 1992 to 24% in 2002). These changes were most prominent among low educated women.

Study III. The association of polypharmacy with education was verified using the nationwide SPDR. In addition, relationship between excessive polypharmacy, potential IDU and educational level was investigated. The low educated had a higher probability of polypharmacy (OR: 1.11, 95% CI: 1.10-1.12), excessive polypharmacy (OR: 1.15, 95% CI: 1.13-1.17) and IDU (OR: 1.09, 95% CI: 1.09-1.17), after adjustment for age, sex, comorbidity and type of residential area (urban/rural). Low educated elderly women were slightly more likely to have polypharmacy and excessive polypharmacy and IDU than low educated men.

Study IV. The association between educational level and use of newly marketed drugs (NMD) was investigated. Use of NMD was associated with low education (OR: 0.82; 95% CI: 0.80–0.88 for <9 compared with ≥13 years of education), after adjustment for age, sex, type of residential area, and number of dispensed drugs. Decreasing educational attainment was associated with a lower probability of using most of the NMD, especially oseltamivir and ezetimibe.

Conclusions: Low socioeconomic position increases the risk of drug use, polypharmacy, excessive polypharmacy, potential IDU, and potential DDI. Polypharmacy, potential DDI, and most kinds of drugs usage have increased within a decade. Although low educated elderly have a higher drug use than high educated, the low educated use new drugs to lesser extent. Today, the main focus of medication safety programs is on clinical aspects. Future programs of rational drug therapy should also involve socioeconomic aspects surrounding drug use. This study shows that inequalities in drug use may exist even in a health care system that claims to ensure a high degree of equity.

Key words: pharmacoepidemiology, drug utilization, polypharmacy, inappropriate drug use, drug-drug interactions, new drugs, comorbidity, registers, cross-sectional, population-based, elderly, equity, socioeconomic position, education, occupation, income.

SAMMANFATTNING SVENSKA

Polyfarmaci och olämplig läkemedelsanvändning är betydande patientsäkerhets- och folkhälsoproblem för de äldre, och har samband med biverkningar, läkemedelsinteraktioner, sjukhusinläggningar, mortalitet och försämrad livskvalitet.

Denna avhandling handlar om det komplexa sambandet mellan läkemedelsanvändning och socioekonomisk position (SEP), och beskriver läkemedelsanvändningen och dess kvalitet, utvecklingen över tid samt användning av nya läkemedel hos äldre. Studierna baseras på Swedish Panel Study of the Living Conditions of the Oldest Old (SWEOLD) (*Studie I och II*) läkemedelsregistret (Swedish Prescribed Drug Register, SPDR), patientregistret och utbildningsregistret (*Studie III och IV*). SWEOLD är en nationellt representativ studie av hälsa och levnadsförhållanden för äldre ≥77 år i Sverige. SPDR är ett nytt hälsodataregister med uppgifter om alla på apoteket uthämtade receptbelagda läkemedel i Sverige. De viktigaste resultaten av studierna sammanfattas nedan.

Studie I. Sambandet mellan läkemedelsanvändning och SEP (mätt genom utbildning, yrke och inkomst) undersöktes i SWEOLD 2002. Polyfarmaci (användning av fem eller fler läkemedel) sågs hos 42%. Låg utbildning var associerat med polyfarmaci (OR = 1.46, 95% CI, 1.02-2.07) efter justering för ålder och kön. Detta var dock inte statistiskt signifikant efter att analysen även justerades för komorbiditet och civilstånd (OR = 1.40, 95% CI 0.96-2.05). Vi fann inget samband mellan yrke och inkomst och polyfarmaci.

Studie II. Förändringar i läkemedelsanvändningen under en tioårsperiod, hos äldre med olika utbildning, studerades genom att jämföra SWEOLD-undersökningarna 1992 och 2002. Läkemedelsanvändningen ökade påtagligt under denna tid. Förekomsten av polyfarmaci mer än fördubblades (från 18% 1992 till 42% 2002). Vid båda tidpunkterna var polyfarmaci vanligare hos dem med låg (19% 1992 och 46% 2002) jämfört med dem med hög utbildning (12% 1992 och 36% 2002). Potentiella läkemedelsinteraktioner ökade också i omfattning, hos såväl låg- (14% 1992 till 26% 2002) som högutbildade (18% 1992 till 24% 2002). Dessa förändringar var mer uttalade hos lågutbildade kvinnor.

Studie III. Denna studie, baserad på SPDR, verifierade sambandet mellan polyfarmaci och utbildning. Därtill undersöktes sambandet mellan omfattande polyfarmaci (användning av tio eller fler läkemedel), olämplig läkemedelsanvändning och utbildning. Äldre med låg utbildning hade en högre risk för polyfarmaci (OR: 1.11, 95% CI: 1.10-1.12), omfattande polyfarmaci (OR: 1.15, 95% CI: 1.13-1.17) och olämplig läkemedelsanvändning (OR: 1.09, 95% CI: 1.09-1.17), justerat för ålder, kön, komorbiditet och typ av bostadsort (stad/landsbygd). Lågutbildade kvinnor hade en något högre sannolikhet för polyfarmaci, omfattande polyfarmaci och olämplig läkemedelsanvändning än lågutbildade män.

Studie IV. Undersökte sambandet mellan användning av nya läkemedel och utbildningsnivå. Användning av nya läkemedel var mindre sannolik hos äldre med låg utbildning (OR: 0.82; 95% CI: 0.80–0.88 för <9 jämfört med ≥13 års utbildning), justerat för ålder, kön, bostadsort och antal läkemedel. Med lägre utbildning följde en lägre sannolikhet för användning av flertalet nya läkemedel, främst oseltamivir and ezetimib.

Slutsatser: Låg SEP innebär en mer omfattande läkemedelsanvändning och en ökad risk för polyfarmaci, omfattande polyfarmaci, olämplig läkemedelsanvändning samt potentiella läkemedelsinteraktioner. Polyfarmaci, potentiella läkemedelsinteraktioner och användning av flertalet läkemedel har ökat hos äldre under ett årtionde. Trots att lågutbildade äldre har en mer omfattade användning än högutbildade, använder de mer sällan nya läkemedel. Idag ligger fokus inom läkemedelssäkerhetsområdet på de kliniska aspekterna. Framtida satsningar på rationell läkemedelsanvändning borde dock också omfatta socioekonomiska aspekter. Denna avhandling visar att ojämlikheter i läkemedelsanvändningen kan finnas även i ett sjukvårdssystem som påstår sig erbjuda en hög grad av rättvisa.

Nyckelord: farmakoepidemiologi, läkemedelsanvändning, polyfarmaci, olämplig läkemedelsan-vändning, läkemedelsinteraktioner, nya läkemedel, komorbiditet, register, tvärsnittsstudier, populationsbaserad, äldre, rättvisa, jämlikhet, socioekonomisk position, utbildning, yrke, inkomst.

LIST OF ABBREVIATIONS

ACE	Angiontensin-converting Enzyme
ADR	Adverse Drug Reaction
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical (classification system)
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DDD	Defined Daily Dose
DDI	Drug-drug Interaction
FASS	The Swedish Medicines Compendium for Physicians
ICD	International Classification of Diseases
IDU	Inappropriate Drug Use
Kloka Listan (Wise List)	Recommended drugs list by the Drug and Therapeutics Committee of the Stockholm County, Sweden
MPA	Medical Products Agency in Sweden
NMD	Newly Marketed Drug
NSAID	Non-Steroidal Anti-inflammatory Drug
OR	Odd Ratio
OTC	Over-the-counter
RR	Relative Risk
SCB	Statistiska Centralbyrån (Statistics Sweden)
SD	Standard Deviation
SEI	Socio-Economic Index
SEK	Swedish Krona (currency)
SEP	Socioeconomic Position
SoS	Swedish National Board of Health and Welfare
SPDR	Swedish Prescribed Drug Register
SSRI	Selective Serotonin Reuptake Inhibitor
SWEOLD	Swedish Panel Study of Living Conditions of the Oldest Old
WHO	World Health Organization

DEFINITIONS

Adverse Drug Reaction	Any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis or treatment.
Anatomical Therapeutic Classification system (ATC)	Classification system for drugs administered by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway.[1]
Defined Daily Dose (DDD)	The (at any given time) assumed average maintenance dose per day for a drug, if used for its main indication in adults. Technical unit administered by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway.[1]
Formulary	A list of recommended pharmaceutical products. It may for example contain drugs in stock of a hospital or drugs eligible for reimbursement.[2]
Generic drug	A drug containing the same chemical substance as an original brand-name drug and has been introduced onto the market after patent on the brand-name drug has expired.
Medication error	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, or patient/consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use. (National Coordinating Council for Medication Error Reporting and Prevention - NCC MERP)
Over-the-counter (OTC)	Pharmaceuticals sold without prescription.
Pharmacoepidemiology	The study of the use and effects of drugs in large numbers of people.[3]
Polypharmacy	One of the most commonly used definitions of polypharmacy is the concomitant use of five or more drugs.
Rational drug use	Patients receiving medication appropriate to their medical needs, in doses meeting their own individual requirements, for and adequate period of time and at the lowest costs to them and to the community.[4]
Socioeconomic position	The hierarchical position of an individual in a society and culture.

LIST OF PUBLICATIONS

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

I. Haider SI, Johnell K, Thorslund M, Fastbom J. Analysis of the Association Between Polypharmacy and Socioeconomic Position Among Elderly Aged ≥77 Years in Sweden. *Clinical Therapeutics* 2008;30(2):419-427.

II. Haider SI, Johnell K, Thorslund M, Fastbom J. Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992-2002. *International Journal of Clinical Pharmacology and Therapeutics* 2007;45(12):643-653.

III. Haider SI, Johnell K, Ringbäck Weitoft G, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of over 600,000 older people. *Journal of the American Geriatrics Society* 2008, Accepted for publication

IV. Haider SI, Johnell K, Ringbäck 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. *European Journal of Clinical Pharmacology* 2008, In press (DOI: 10.1007/s00228-008-0549-8)

CONTENTS

1 INTRODUCTION

1.1 THE AGING POPULATION

The aging of the population has become a worldwide phenomenon with a historic increase of individuals aged 65 by 10 million per year.[5,6] During the past century, the world has seen unprecedented declines in mortality rates, followed by equally unprecedented declines in fertility rates. Due to these demographic changes, the ageing population in both developed and developing nations is set to grow rapidly. In 1990, 26 nations had more than two million elderly citizens aged 65 years and older, and the projections indicate that an additional 34 countries will join the list by 2030. In 2000, the number of old people (65+ years) in the world was estimated to be 420 million and it is projected to be nearly one billion by 2030, with the proportion of old people increasing from 7% to 12%. The largest increase in absolute numbers will occur in developing countries, where it will almost triple from 249 million in 2000 to an estimated 690 million in 2030. The developing regions' share of the worldwide aging population will increase from 59% to 71%.[6] Developed countries, which have already shown a dramatic increase in people over 65 years of age, will experience a progressive aging of the elderly population. Underlying global population aging is a process known as the "demographic transition" in which mortality and then fertility decline.[7] Decrease in fertility and increase in life expectancy have together reshaped the age structure of the population in most regions of the world by shifting relative weight from younger to older groups. By 2050, the distribution is expected to become closer to a rectangle (Figure 1).

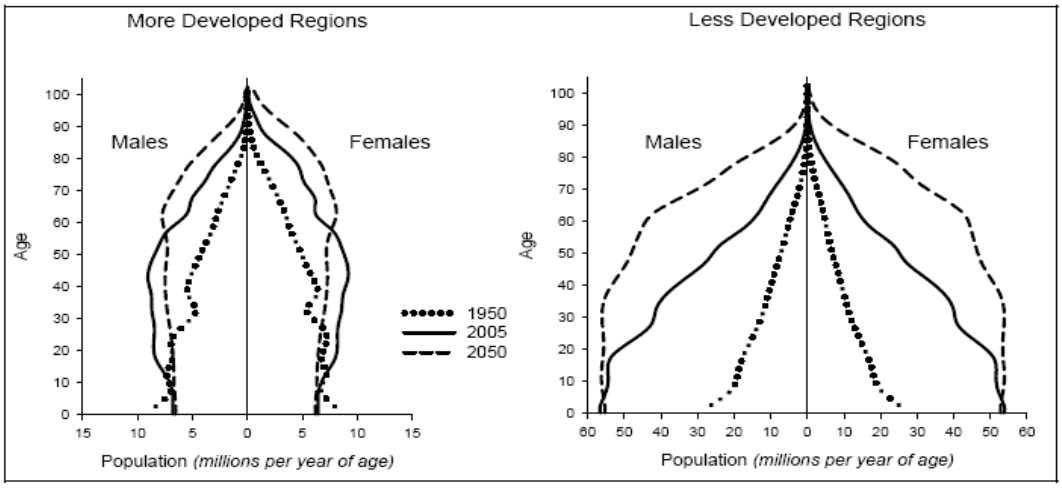

Figure 1. Age and sex distribution of the population in more developed and less developed regions, 1950, 2005 and 2050 (World Population Prospects, United Nations, 2005).

In Sweden, 17.5% of the total population is aged 65 years and older while 8.7% is 75 years and older (December 2007).[8] According to country ranking by percentage of population aged 60 and over worldwide, Sweden rank at number 4 with 24% in 2007.

Consequently, both developed and developing countries will face the challenge of coping with a high frequency of chronic conditions, which is characteristic of aging societies. These conditions impair the ability of older persons to function optimally in the community and reduce well-being among affected individuals and their families. Further, these conditions are associated with significant health care costs that must be sustained by the society at large. Thus, the global trend in the phenomenon of population aging has a dramatic impact on public health, healthcare financing and delivery systems throughout the world.[9] Due to the aging of the population, rational drug use has become a major challenge to elderly care and public health. A holistic approach to this new challenge of the 21st century will necessitate a coordinated research efforts, supported by a new partnership between industry, governments and international organizations.[5]

1.2 DRUGS AND AGING

1.2.1 Pharmacological changes with aging

As a consequence of decline in physiological functions and changes in the composition of the body, elderly are confronted with altered drug response due to pharmacokinetic (Table 1) and pharmacodynamic (Table 2) mechanisms.

1.2.1.1 Age-dependent pharmacokinetics

Pharmacokinetics is best defined as "what the body does to the drug". It includes absorption, distribution across body compartments, metabolism, and excretion. With aging, the metabolism and, in particular, excretion of many drugs decrease and the physiologic changes of aging require dose adjustment for many drugs.[10]

Drug absorption

Most drugs are absorbed from the gastrointestinal tract by diffusion and some subtle changes have been observed in the gastrointestinal tract due to aging. While some studies have not shown significant age-related differences in absorption rates for different drugs,[11] the absorption of vitamin B_{12}, iron and calcium is reduced,[12] while that of levodopa is increased. Recent studies have shown that gastric acid secretion does not change with advancing age.[13]

Due to decreased peristalsis, gastric emptying is slightly delayed in the elderly.[14] These changes might potentially affect drug absorption, but they are generally of little clinical significance.

The *first-pass metabolism* (metabolism of drugs before entering the blood stream from the gastrointestinal tract) of many drugs in the liver is reduced with ageing (see description of metabolism below).[15] As a result, the serum levels of active drugs undergoing extensive first-pass metabolism such as propranolol, can be significantly increased.[16] On the other hand, some drugs, such as several ACE inhibitors (e.g. enalapril), are prodrugs, for which decreased first-pass metabolism may result in a decreased bioavailability (amount of drug taken that reach the blood stream in active form).[17]

Drug distribution

With increasing age body water is reduced, resulting an increased proportion of body fat. This leads to an increase in the volume of distribution for highly lipophilic drugs, which may prolong their elimination half-lives. Drug binding plasma proteins, such as serum albumin (decrease) and α1-acid glycoprotein (increase), often change with aging, but the clinical effect of this on drug concentrations is unclear.[10]

Metabolism

The hepatic metabolism through the cytochrome P-450 enzyme system (phase I reaction) decreases with aging for some drugs. Clearance typically decreases 20 to 40% for these drugs (for example diazepam, amitriptyline, fentanyl, nifedipin, warfarin, and verapamil), whereas that of others is unchanged.[18] Theoretically, maintenance drug doses should be decreased by this percentage; however, rate of drug metabolism varies greatly from person to person, so individual titration is required. In contrast, age does not affect clearance of drugs that are metabolized by conjugation (phase II), for example paracetamol and oxazepam.

Excretion

The renal function continuously decline after the age of 30. Glomerular filtration rate (GFR) and renal plasma flow decrease by 6 to 10% every ten years even for persons without any disease affecting renal function.[19] This may result in accumulation and risk of adverse drug reaction (ADR), for drugs that are excreted largely unmetabolised (mainly water soluble drugs, for example digoxin) and drugs with active metabolites (for example oral blood glucose lowering drugs).

Table 1. Age-related changes in pharmacokinetics

Parameter	Change	Effect
Absorption	Increased gastric pH	Slightly decreased absorption (rarely clinically significant)
	Delayed gastric emptying	
	Reduced intestinal blood flow	
	Decreased absorption surface	
	Decreased gastrointestinal motility	
Distribution	Decreased total body water	Increased plasma concentration of water soluble drugs
	Increased proportion of body fat	Increased half-life of lipid soluble drugs
	Decreased serum albumin	Increased free fraction in plasma of highly protein-bound acidic drugs
	Increased α1-acid glycoprotein	Decreased free fraction of basic drugs
Metabolism	Decreased hepatic blood flow	First-pass metabolism and metabolic elimination of drugs can be less effective
	Impaired enzyme function	Phase I metabolism of some drugs might be impaired
Excretion	Decreased glomerular filtration rate	Renal elimination of water-soluble drugs or drug metabolites can be impaired

1.2.1.2 Age-dependent pharmacodynamics

Pharmacodynamics is defined as "what the drug does to the body" or the response of the body to the drug. Pharmacodynamic changes with aging include alterations in receptor binding, postreceptor mechanisms, adaptive homeostatic responses and, particularly among frail patients, organ pathology.. The effects of similar drug concentrations at the site of action (sensitivity) may be greater or smaller than those in younger people. Moreover, the capacity to compensate for these altered effects and to other physiological challenges decreases with higher age.[18,20]

Elderly patients are particularly sensitive to effects of anticholinergic drugs. The elderly, most notably those with dementia, are particularly prone to CNS adverse effects of such drugs and may develop cognitive impairment or delirium. Anticholinergic drugs also commonly cause constipation, urinary retention (especially in elderly men with benign prostatic hyperplasia), blurred vision and dry mouth.[18] Similarly, elderly persons are also more sensitive to

anxiolytics, opioids, and sedatives/hypnotics such as benzodiazepines, especially the long acting compounds. Table 2 summarizes some of the important pharmacodynamic changes occuring with increasing age.

Table 2. Examples of important age-related pharmacodynamic changes and their mechanisms

Pharmacodynamic change	Drugs	Consequences
Increased sensitivity of the brain	Benzodiazepines, opioids	Increased sedation, risk of cognitive impairment, delirium and falls
Reduced capacity of the brain cholinergic system	Anticholinergic drugs	Risk of cognitive impairment and delirium
Impaired baroreflex	Cardiovascular drugs, neuroleptics, antidepressants, antiparkinsonian drugs	Postural hypotension, orthostatic, reactions
Decreased number of beta-receptors	Beta-adrenergic receptor blockers	Reduced effect
Increased sensitivity in the gastrointestinal mucosa	NSAID	Increased risk of gastrointestinal bleeding

1.2.2 Drug use in the elderly

Older people experience more diseases and symptoms demanding medical treatment including drugs. The highest proportion of drug use occurs in the part of the population 75 years and older. Among these, older persons living in nursing homes and institutions are the most frequent users of drugs.[21] Table 3 highlights the prevalence and mean number of drugs in the elderly from various study populations worldwide.

The “geriatric pharmacoparadox” refers to the situation where frail elderly are often excluded from clinical trials where the safety and efficacy of drugs are evaluated, although they are most likely to require pharmacotherapy and are also among those most predisposed to adverse drug events.[22,23]

Table 3. Studies on overall drug use among older people

Author, year	Country and sample	Age, y	% users	Mean number of drugs
Chen et al,[24] 1991	England and Wales, 12489, Community-dwelling and institutionalized prescription and OTC drugs	75+	84	3.0
Laukkanen et al,[25] 1992	Finland, 1224 Community-dwelling Prescription drugs	65-84	Men 70% and women 80%,	3.4
Jörgensen et al,[26] 1994	Sweden, 4642 Different databases Prescription drugs One year prevalence	65+	78	9.9
Claesson et al,[27] 1994-1995	Sweden, 1854 Nursing home Drug lists I month prevalence	65+	-	7.7
Giron et al, [21] 1994-1996	Sweden, 681 Community-dwelling and institutionalized Home interview 14 days prevalence	81+	94	4.6
Linjakumpu et al,[28] 1999	Finland, 1596 community-dwelling Interview 7 days prevalence	64+	88	3.8

In clinical trials, the evidence supporting the use of medications is scant or even non-existing for the elderly part of population, while changes in pharmacodynamics and pharmacokinetics associated with aging support the notion that the effects of medications (both beneficial and adverse) may change with aging. Hence, it is important that careful consideration be given when prescribing drugs to elderly patients. A cautious approach in the selection of drugs, individual dose adjustment and assessment of renal, liver and other physiological functions should be implemented in clinical practice.

1.2.2.1 Patient safety issue

Patient safety has emerged as a priority for healthcare organizations and managing medicines safely is a key component of this. Most drugs are used safely and improve the quality of life. But sometimes drug related errors occur and these can lead to patient harm. National Patient Safety Agency (NPSA) in the UK defines a patient safety incident as 'any unintended or unexpected incident which could have or did lead to harm for one or more patients'. The

NPSA defines medication error as 'incidents in which there has been an error in the process of prescribing, dispensing, preparing, administering, monitoring, or providing medicine advice, regardless of whether any harm occurred'.[29-31] Drug related errors increase both cost and the number of deaths. It has been found that approximately 200 000 people in the US may die each year from medication-related problems.[32] An author from one study says "If medication related problems were ranked as a disease, it would be the fifth leading cause of death in the US".[32,33] According to one report from the UK, medication incidents, where the second most frequent type of patient safety incident reported to the NPSA from all over the UK between January 2005 and June 2006 and the three most frequently occurring types of medication error in hospitals were wrong dose, strength or frequency of medicine, omitted medicine and wrong medicine.[31] Adverse drug events have a profound impact on morbidity, mortality, and the healthcare economy, particularly among the older people. In Sweden, it has found that 12% of the patients admitted to an internal medicine clinic were ADRs related and the average cost of treating one person admitted due to ADRs was calculated to Euro 2200. In a majority of cases ADRs were preventable.[34]

1.2.2.2 Public health concern

It is reasonable to assume that as more drugs become available and longevity continues to increase, the consumption of prescription drugs by older people will increase further and thereby the incidence of potentially inappropriate prescribing. Polypharmacy and inappropriate prescribing in the elderly population is now considered a major public health issue, given its direct linkage to substantial morbidity, mortality and stretched health resources[35,36] that result from ADR.[37] Although public health programs and use of effective treatment have resulted in increased numbers of healthy elderly persons, there are also increasing numbers of elderly who are frail and vulnerable, with many comorbidities, and thus take many drugs.[38] Therefore, healthcare mobilizes resources to cope with conditions related to age, especially cognitive impairment. For example, elderly people with dementia have increased difficulty with taking drugs, and dementia impedes their ability to make autonomous decisions about their drugs, resulting in employing more resources to cope with demented persons. Due to its clinical and economic burden to patients and society inappropriate prescribing in elderly people has become an important public-health issue worldwide.

1.3 PHARMACOEPIDEMIOLOGY

Pharmacoepidemiology is the study of interactions between drugs and populations, using epidemiological methods and reasoning. Pharmacoepidemiology may be defined as the study of the utilization and effects of drugs in large numbers of people.[3] According to Hartzema et al., pharmacoepidemiology has been defined as the application of epidemiological knowledge, methods, and reasoning to the study of the effects (beneficial and adverse) and use of drugs in human populations.[39] Spitzer et al. describe pharmacoepidemiology as the study of drugs as determinants of health and disease in the general unselected population.[40] To accomplish this, pharmacoepidemiology borrows from both pharmacology and epidemiology. Thus, pharmacoepidemiology can be called a bridge spanning both pharmacology and epidemiology.[3] Pharmacoepidemiology then can also be defined as the application of epidemiological methods to pharmacological issues. There are also some areas that are altogether unique to pharmacoepidemiology, e.g., *pharmacovigilance*. Pharmacovigilance is a type of continuous monitoring for unwanted effects and other safety-related aspects of drugs that are already on the market. In practice, pharmacovigilance refers almost exclusively to the spontaneous reporting systems which allow health care professionals and others to report ADRs to a central agency.

Pharmacoepidemiology is becoming increasingly important with the global aging of populations in Western society, due to the increased prevalence of medication use among older persons. In such scenario, the evaluation of the adverse effects of concomitant use of multiple drugs has become particularly important in the elderly.

1.4 HEALTH REGISTERS IN SWEDEN - A DATA-RICH WORLD

In Sweden, population-based data on births, deaths, cancers, congenital malformations and hospital admissions have been registered at a national level in various health registers for several decades.[41] Since July 2005, information about dispensed drugs has also been available in the new Swedish Prescribed Drug Register (SPDR).[41,42] As a result of the long tradition of population-based data registration, there are unique opportunities for register-based research in Sweden. These health registers are frequently used in epidemiological studies. Besides methodological advantages with the use of register data, such as large populations and absence of recall bias, the low cost of these studies is a further major advantage. Furthermore, the unique personal identification number of each inhabitant makes it possible to link registers

to each other or to other data sources. Table 4 shows various health registers. This section focuses on the contents, usage and advantages of different national health registers.

Table 4. Health registers in Sweden

Name of register	Year of establishment
The Cancer Register	1958
The Cause of Death Register	1961
The National Inpatient Register	1964
Medical Birth and Congenital Malformation Registers	1973
Swedish Prescribed Drug Register	2005

1.4.1.1 Swedish Prescribed Drug Register

In July 2005, a national register on prescribed pharmaceuticals was established, after the Swedish parliament decision to create this register in April 2005. It contains patient identities for all dispensed prescribed drugs to the entire Swedish population (9 million inhabitants). Using the personal identification number it may be linked to the Swedish national healthcare registers as well as other population registers, mainly from Statistiscs Sweden (Statistiska Centralbyrån, SCB). The field of pharmacoepidemiology, and register based drug utilization research, dates back to 1960s when concerns about ADR and cost of drugs start to develop. Table 5 shows the timeline to the development of SPDR.

The data collection for SPDR is administered by the state-owned National Corporation of Swedish Pharmacies and then transferred to the Centre for Epidemiology (EpC) at the National Board of Health and Welfare (www.socialstyrelsen.se). All Swedish Pharmacies have standardized procedures to ensure high quality data acquisition and management. The SPDR contains the data on drugs prescribed and dispensed in ambulatory care (Table 6).

Table 5. Important years in the history of the SPDR

Year	Development
1960s	Pioneering pharmacoepidemiological surveys of prescriptions purchased by defined populations in Sweden and Czechoslovakia were initiated in the late 1960s.
1965	The first data to be collected were the drug deliveries from wholesalers to Swedish pharmacies. Since 1965, these data has been analyzed and presented by Prescription Statistics AB (Läkemedelsstatistik AB). Reports on sales of drugs in Sweden have been presented in the publication Swedish Drug Market since then.
1970s	More detailed information about drug utilization in different settings was developed in 1970s. Computerized systems for invoicing, provided statistics on drug sales to hospitals.[43] In the early 1970s, two important pharmacoepidemiologic databases were founded in Sweden in the county of Jämtland and in the munciplaity of Tierp.[44,45]
1974	The National Prescription Survey was developed to enable studies of prescription drug use in the population.[46]
1975	Sales statistics on drugs have been available since 1975. Data are captured at the wholesalers.
1978	Data on drugs linked to diagnoses has been collected from 1978 through Diagnoses and Prescription survey. This survey was closed in 2003 due to falling response rate.[47]
1987	A national prescription survey was developed to enable studies of prescription drug use in the population.[46]
1989	From 1989, the National Corporation of Swedish Pharmacies has offered physicians (individually or as a group) to follow their drug prescribing by local prescription studies, i.e. local auditing. In these studies, when a prescription has been processed at the pharmacy, the identity of the prescriber or clinic has been recorded.[48]
1989	Introduction of a National Prescription Register for Sweden to improve the possibilities of drug utilization studies. Since 1998, demographic data with information about the prescriber are routinely gathered when prescription are dispensed at pharmacies. Data are not saved at the level of individual patients.
2005	The SPDR was established in July 2005 and contains data on all dispensed prescriptions to the entire Swedish population. The new Swedish register on prescribed drugs is regulated under a legislation issued by the Swedish government (SFS 2005:363).

The SPDR is complete for the entire population in the country (patient identity data are missing for <0.3% of all items). The register does, however, not include data on OTC medications, herbal drugs, drugs used in hospitals, and only partially drugs that are used in ambulatory care but administered in day-care at hospitals. Also, the SPDR is not complete with regard to vaccines and drugs used in nursing homes (drugs dispensed from drug storerooms are not recorded).[42]

Table 6. Main contents of the SPDR[41]

Description
Data on drug
Dispensed item – substance (ATC), brand name, formulation and package
Date of prescribing and dispensing
Dispensed amount
Prescribed dosage
Type of prescription, for example ordinary or unit dose (ApoDos)
Data on patient
Patient identification number
Age
Sex
Place of residence (county, municipality and parish)
Data on prescriber
Profession, e.g. general practitioner
Education
Specialist education
Data on prescribing practice
Location (county)
Type (primary healthcare centre or hospital clinic)
Data on cost
Total cost
Cost paid by the patient
Cost paid by the county council
Difference between normal pharmaceutical costs and the generic substitution that the patient pays (if not changed to the cheaper alternative)

1.4.1.2 National Inpatient Register

The Swedish National Inpatient Register was established by the National Board of Health and Welfare in 1964-65, but most counties joined the Register later in different years, the latest one in 1987, when the register became nationwide.[41] Now, the National Inpatient Register is estimated to be 99% complete. The register contains data of all hospitalized patients in Sweden. Each record in the Register corresponds to one hospital admission and contains, in addition to the patient's identification number, the dates of admission and discharge, codes for all surgical procedures, and discharge diagnoses. The register now (for the period 1964-2006) includes 50 million discharges.[41] There are four different types of information in the National Patient Register (Table 7).

Table 7. Contents of the Swedish National Inpatient Register

Description
Data on patient
Personal identification number
Age
Sex
Place of residence (county, municipality and parish)
Data on the hospital
County
Hospital
Department
Administrative data
Date of admission
Date of discharge
Length of stay
Acute/planned admission
Admitted from
Discharged to
Medical data
Main diagnosis
Secondary diagnoses
External cause of injury and poisoning
Surgical procedures

1.4.1.3 The National Education Register

The Education Register was established in 1985 at the request of the Swedish government. Earlier registers of education at population level had been produced in the 1930 and 1970 censuses. Besides, data about education had also been collected in different surveys, e.g. the Labor Force Survey and the Survey of Living Conditions. The first version of the Register of Education refers to 1985 and since then the register is updated once a year. The register is updated annually (January 1) by Statistics Sweden, with information on the highest formal education of each Swedish citizen aged 16-74 years, based on graduation/examination-data from regular educational institutions in Sweden such as primary and secondary schools, universities etc. On January 1, 2004 the Education Register contained information for approximately 6.5 million inhabitants.[49] Table 8 shows the main variables of the register.

Table 8. Contents of the Swedish National Education Register[49]

Description
Personal identification number
Age
Sex
Place of residence (county, municipality and parish)
Country of birth
Highest education
Year of graduation

1.5 POLYPHARMACY

1.5.1 Definitions and measurements

According to Dorland's Medical Dictionary, 27th edition, polypharmacy is the "concurrent use of many different drugs". Some authors have used the term co-pharmacy to characterize the appropriate and necessary combination of drugs, and only used the term polypharmacy for the inappropriate drug combinations. In the literature, polypharmacy is usually defined in either of two ways: quantitatively or quantitatively. Quantitatively, polypharmacy has been defined in different ways such as: two or more drugs for 240 days or more,[50] concurrent use of two or more,[51] three or more[52] or four or more drugs[53] and use of ten or more drugs.[54] However, one of the most commonly used definitions of polypharmacy is the concomitant use of five or more drugs.[23,26,28,55-57] Polypharmacy is sometimes classified in more detail as minor, moderate, or major polypharmacy.[50] Qualitatively, polypharmacy has been defined differently in the literature, such as: regular daily consumption of multiple drugs as well as the use of high-risk drugs and questionable dosage,[58] and the prescription, administration or use of more medications than is clinically indicated in a given patient.[59] Qualitative definitions of polypharmacy highlights the fact that only one unnecessary drug can lead to adverse events that could have been avoided, and equally excludes an arbitrary minimum number of drugs. Fillit et al.[60] defined polypharmacy as the untoward iatrogenic sequela of the use of multiple, interacting medications. Generally, European studies define polypharmacy according to the number of drugs taken, whereas the studies conducted in the United States define polypharmacy according to whether a medication is clinically indicated or not.

Most methods used to study polypharmacy among the elderly have been based on interviews and questionnaires.[54] This type of data may, however, be influenced by recall bias (see below under Methodological Issues), which is a problem particularly for elderly patients receiving multiple drugs. The introduction of large drug databases at national level, however, allows population-based analysis without this problem.

This thesis studies polypharmacy entirely from a quantitative point of view, using the commonly employed definition of the concomitant use of five or more drugs. Elderly persons exposed to polypharmacy have thus been identified from the number of drugs in use, regardless of the clinical consequences of the drug combinations.

1.5.2 Occurrence

The prevalence of polypharmacy in the elderly has been reported to be everything between 4% and 78%.[23] Polypharmacy, defined as the use of five or more drugs, has been reported to range from 4%[50] to 34%[52] among people aged 65 years and older. The use of drugs has increased tremendously during the last decade, particularly in the elderly population. In Canada, for example, the elderly represent 12% of the population but account for almost 40% of drug use[52] and other countries report similar figures (12% of the population and 31% of prescriptions in the US,[61] 18% of the population and 45% of prescriptions in the UK[62]). A study performed in Denmark revealed that in a population of 75-year-olds, the study participants took an average of 4.2 prescription drugs and 2.5 over-the-counter drugs.[52] In the US, surveys on patients living in nursing homes revealed that they took six to eight different drugs simultaneously.[63] Polypharmacy is also common in Sweden. An earlier population-based study reported 41% of the 75 years and older persons taking five or more drugs.[64] Similarly, use of five or more different prescription drugs during 1994 was common in non-institutionalized elderly patients (39%).[26]

1.5.3 Risk Factors

Polypharmacy has been associated with different risk factors and these can be classified into three main groups: socio-demographic, health status and healthcare system characteristics. Advanced age, female gender, white race and low education are socio-demographic risk factors which increase the probability of polypharmacy.[65-67] Health status related risk factors include poor health, low level of self-rated health, multiple diseases, depression, hypertension, anemia, asthma, angina, osteoarthritis, gout, and diabetes.[23,26,68] Predictors of polypharmacy

related to the health care system are living in an institution, number of visits to a primary care provider per year, multiple providers, and supplemental insurance.[26,69]

1.5.4 Consequences of polypharmacy

Polypharmacy can be divided into three broad categories. The first is appropriate polypharmacy, when a patient takes several concomitant drugs, all of which are for recognized indications. In this case, a polypharmacologic approach for certain diseases improves therapeutic response, decreasing morbidity and mortality. The second is inappropriate polypharmacy, when a patient really takes more drugs than is necessary. The third is "redundant pseudopolypharmacy", when patients are recorded as taking more drugs than they actually take. Consequences of polypharmacy include ADRs,[70,71] drug-drug interactions (DDI),[72] drug-disease interactions, and a prescribing cascade (misinterpretation of an adverse reaction to one drug, leading to prescribing of a second, potentially inappropriate drug).[73] Polypharmacy may also lead to medication administration errors,[73] due to the consequent complexity of the drug regimen,[74] and poor medication adherence. Studies have shown that patients treated in general practice do not comply fully with the treatment proposed by the physician and that elderly patients are adherent with three out of every four of their individual drugs.[75] The use of multiple drugs also increases the risk of inappropriate prescribing,[76] and may affect geriatric syndromes with an increased risk of cognitive impairment,[77] urinary incontinence[78] and falls.[79] Polypharmacy has been shown to be associated with hospitalization.[80] and with an increased risk of mortality in the elderly.[81] Finally, polypharmacy increases healthcare costs.[82,83]

1.6 INAPPROPRIATE DRUG USE

1.6.1 Definitions and measurements

Inappropriate drug use (IDU) has been defined differently in the literature. Many other words are also used to describe inappropriate prescribing, such as poor, misprescribing, underprescribing, overprescribing, and suboptimal. Underprescribing refers to failure to prescribe drugs that are needed, overprescribing refers to prescribing more drugs than are clinically needed, and misprescribing refers to incorrectly prescribing a drug that is needed[36]. Inappropriate prescribing encompasses the use of medicines that introduce a significant risk of an adverse drug-related event, where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition. Inappropriate

prescribing also includes the use of drugs that have no clear evidence-based indication, the use of drugs at a higher frequency and for longer than clinically indicated, the use of multiple drugs that have recognized DDI and drug-disease interactions, and importantly, the underuse of beneficial drugs that are clinically indicated but not prescribed for elderly for irrational reasons.[84]

Despite the scale and severity of the problem globally, there is little agreement about how to best define IDU in older people. Three of the most important sets of values in judging appropriateness of prescribing are: what the patient wants, scientific/technical rationalism (including the clinical pharmacology of the drug), and the general good.[85] Several tools to assess the appropriateness of medication have been described and used. Inappropriateness of prescribing can be assessed by process or outcome measures that are explicit (criterion-based) or implicit (judgment-based). Explicit indicators are usually developed from published reviews, expert opinions, and consensus techniques.[86] Explicit measures are usually drug or disease oriented, and can be applied with little or no clinical judgment. The advantages of explicit criteria are that they are objective, with a high inter-rater reliability, and the disadvantages that they are rigid and do not take individual clinical situations into account. Also, explicit criteria might not take into account all factors that define high quality health care for the individual. Implicit methods are based on review of individual medications by experts in geriatric pharmacology, without given criteria. These methods have low inter-rater reliability, making comparisons between raters and comparative studies difficult.[87] Explicit measures with little clinical detail can be applied on large prescribing databases, checking each prescription not only for type of drug, but also for dose, duration of therapy, and interactions. Several sets of explicit consensus-based criteria have been developed. In 1991 Beers et al. published the first set of explicit criteria for determining IDU in nursing home residents.[88] In 1997, Beers published a revised and more comprehensive set of explicit criteria for potentially IDU in people aged 65 years and older. The revised Beers criteria were more applicable to the general elderly population regardless of their place of residence (community or nursing home) or level of frailty. The updated criteria also reflect new drugs and the availability of additional information regarding the effects of older agents in the elderly.[89] Beers criteria have been recently updated[33] and are widely used, both in the proposed and modified versions. Another set of explicit criteria was proposed and developed by McLeod et al. in Canada, called Inappropriate Prescribing in the Elderly Tool (IPET).[90] In Sweden,

National Board of Health and Welfare has developed quality indicators to evaluate the appropriateness of drug use in the elderly.[91]

1.6.2 Occurrence

Studies on elderly populations have reported prevalences of IDU between 3 and 40% using different sets of criteria.[37] Beers' criteria and McLeod's criteria were developed in the United States and Canada respectively. European-specific Europe level criteria for potentially IDU have not yet been developed, primarily because of significant differences in national drug formularies. However, few European countries such as Sweden,[91] France,[92] and United Kingdom[93] have developed quality indicators to use at a national level. A number of European studies have used Beers and McLeod criteria to investigate the prevalence of potentially IDU by the older people in Europe.[84] A Swedish population-based study of 785 community-dwelling people over the age of 75 years found that IDU was common, with a prevalence of 19%.[94] In 2005, 17% of the older people were exposed to potentially IDU and IDU was strongly connected to the number of dispensed drugs taken.[95] Similarly, a population-based survey in Finland estimated the prevalence rate of inappropriate prescribing at 12%.[96] The possible risk factors for IDU include polypharmacy,[37,97] female sex and low socioeconomic characteristics.[98]

1.6.3 Consequences of inappropriate drug use

The IDU is associated with a higher likelihood of DDI, ADR, hospitalizations, poor quality of life, and death.[36,81,94,99] One study on 3372 elderly nursing home residents in the United States, showed that those who received any potentially inappropriate medication had greater odds of being hospitalized and at greater risk of death in the following month than those not receiving a potentially inappropriate medication.[100] Few studies, however, provide the empirical evidence for the adverse effect of IDU on health outcomes at a national level.

1.7 NEW DRUG USE

1.7.1 Definition and occurrence

Different terms have been used in the literature to name newly approved drugs; such as newly marketed drugs (NMD), new drugs, newly introduced drugs, new drug prescribing and new medicines. Most studies have used 1-5 NMD to describe new drug use. For example, one

study from the US analyzed the prevalence of new generation antidepressant treatment including selective serotonin reuptake inhibitor (SSRI).[101] Another study from the Netherlands chose the introduction of rofecoxib to identify early users of rofecoxib by socio-demographic characteristics. The reason for choosing rofecoxib was that authors expected to find the influence of patients on the decision to prescribe because of its marketing and similarity to the existing non-steroidal anti-nflammatory drugs (NSAID).[102] Celecoxib and rofecoxib, was used in Finland to describe new drug use.[103] A Canadian study included celecoxib, alendronate, clopiodogrel and pantoprazole, to study the early adopters of the new drugs.[104] Previous studies have shown considerable variation between prescribers regarding early adoption of NMD.[101,105-107] The use of new and more expensive drugs is a major contributing factor to the rising costs. In many countries drug expenditure is increasing rapidly in relation to overall health care costs, due to greater variety and availability of new and expensive drugs. Despite their higher cost, new drugs do not always offer therapeutic benefits compared with older drug alternatives.[108]

1.7.2 Factors influencing the decision to prescribe new drugs

Different factors may contribute to the selection of new drugs by physicians.[106,109-111] An understanding of physician and patient behavior associated with prescribing is essential to predict the utilization of NMD. This aspect has been explored by one paper from the UK. The determinants of new drug prescribing were interconnected within four forms of physicians' knowledge: scientific knowledge, social knowledge, patient knowledge and experiential knowledge.[112] This variability in physicians' prescribing of new drugs relates not only to levels of acquired knowledge, but also to differences in subjective and ideological beliefs.[113,114] The new drug prescribing is also affected by the prescriber's surrounding social system, such as location, size and type of practice.[104,115] Patient characteristics also play a key role in prescription of NMD. For example, increasing age, poor self-perceived health, female sex, and private insurance have been linked to high use of rofecoxib.[102,116] Further, previous studies have shown that medical innovations are more likely to be adopted earlier in urban areas than in rural areas.

1.8 SOCIOECONOMIC POSITION

The term socioeconomic position (SEP) refers to hierarchical position of an individual in a society and culture. Social position is an entirely societal phenomenon; positions exist in

relation to each other and co-define each other. The idea of indicators of SEP in social epidemiology is to describe the social stratification. With this social stratification it is possible to study the relationship between resources, living conditions, and lifetime opportunities and how this affects the likelihood to achieve better health.[117] Higher SEP denotes more power in the society. Social position can be viewed in many ways. Historically, different theories on this subject have emerged. Karl Marx introduced a theory in which the individuals in society were divided in those who produced goods and those who owned and controlled the production of goods.[117] Weber, on the other hand, believed that the unequal distribution of economical means was created by stratification by class, status and political power.[117]

SEP has been found to be associated with health in numerous publications, across time periods, all around the world. Different explanations to the social divide in health have been proposed. According to the theory of social causation, a low SEP infers a higher probability for morbidity and mortality.[118,119] There may be a number of explanations to why individuals of lower SEP more often suffer from various health problems and preterm death. Lifestyle, knowledge, and resources in the lower positions might differ from that in the higher positions as well as exposure to more dangerous housing and working environments. People that have low SEP are more likely to engage in behaviors of risk and less likely to engage in behaviors that are health promoting.[120]

SEP is measured differently throughout the western world.[121] In the United States, education and income are most often used, whereas researchers in United Kingdom tend to use occupational scales. Education is most commonly used in the several European countries as a measure of SEP.[122] These differences in measurement might be due to different sociological traditions. A pragmatic approach to the choice of SEP measure is the most common in the social epidemiology. The World Health Organization (WHO) recommends the use of education, wealth, income, occupation and economic position as the measures of SEP in health interview surveys.[123] These measures are most commonly used in epidemiological studies to measure SEP.[117,122,124]

1.8.1 Measures of socioeconomic differences in drug use

In this thesis, three measures of SEP are used; education, occupation and income, as described in the method section. These three measures are described below from a theoretical and epidemiological perspective.

1.8.1.1 Education

According to WHO, education is the SEP measure of choice in health interview surveys, if it is not possible to obtain all of the preferred measures.[123] Education is used either categorized into the highest attained educational level or used as a continuous measure. Education is used as measure of SEP for several reasons: it is easy to measure, often available for all individuals, has high reliability and validity and can be collected as a continuous variable.[125] Another advantage of using educational level as a measure of SEP in social epidemiology is that educational attainment is mostly obtained prior to the onset of disease, as morbidity increases with age. This means that the diseased "keep" their social position in the society, as measured by education, whereas other measures of SEP (occupation and income).might change as a result of the onset of disease. Additionally, education is less affected by reverse causation of disease (a cause is predated by an effect), with the exception of some psychiatric disorders, than income or occupation. Winkleby and coworkers compared the relationship between different health-related behaviors and three SEP indicators – education, occupation and income – and showed that education was the indicator most consistently correlated with such behaviors[125]. Education, as measured by schooling is an important predictor of mortality and has been associated with poor physical and mental health in the general population.[126]

One drawback of using education as a measure of SEP is that educational level varies by age cohort and society.[124] The younger the individual, the higher the mean education attainment. This cohort effect makes it important to include age in all analyses using education and occupation as a measure of SEP. It should be pointed out that education is not a direct measure of position of an individual within the social stratification. Educational credentials are one way but not the only mechanism to gain access to positions in society. However, educational level in the population is important to the understanding of how society works. The level of education in general influences knowledge, attitude and access to information[127,128] and these issues are of great importance with respect to drug use. Medicine use can be regarded as a kind of lifestyle or health and illness behavior, influenced by knowledge and access to information captured by educational attainment.

1.8.1.2 Occupation

Occupation provides a comprehensive description of the individual's place in the structure of production. The intention of the occupation-based measures of SEP is to group individuals who have similar labor market and work situation.[117,129] Occupation not only reflects the exposure to hazardous working conditions or psychosocial work environment, with the

concepts of psychological demands, decision latitude, and social support, but also reflect the individual's market situation and lifetime opportunities. Occupation can be regarded as the major structural link between education and income.[128] Without good education, there are a limited number of attractive and well paid jobs. Occupation influences living conditions, privileges, prestige, power and social as well as technical skills.[127,128] One drawback of using occupation to measure SEP is the so-called *healthy worker effect*, meaning that exclusion from the labor market can distort the association between occupation and health.[130] The healthier individuals remain in the labor market, while those with diseases are excluded. This can make an occupation seem less unhealthy than it really is.[130] Some occupations may exclude individuals from the labor due to their diseases-related exclusions. These considerations make it crucial to include groups excluded from the labor market in the analysis, e.g. disability pensioners.

1.8.1.3 Income

The basic idea of using income as a measure of SEP, is that the richer has the greater possibility to add benefits that can improve health. WHO recommends using relative classifications of income such as quintiles, in order to facilitate comparisons over time and between nations.[123] Income as a measure of SEP is attractive as it is continuous and has a broad range from the very poor to the very rich individuals. However, it can be problematic in surveys based on self-reports, as respondents often perceive income level as a sensitive issue. Further, researchers have to choose between personal income or household income, which both have their pros and cons.[124] It is easiest to measure individual income, as measuring household income requires adjustment for family size. In rich nations, individual income level might be considered as a marker for social position and not merely as a material living standard.[131] Level of income might affect health through psychosocial pathways and level of social participation of the individual.[132] Hence, it is crucial to capture relative income level, that is, the individual's position in the social structure.[132] With regard to drug use, it is possible that the relative income level affects the perception of the health of individual and thus perception of the need for drug, which in turn creates differences in health and illness behavior between income groups. Differences in income can also be interpreted as a proxy for difference in purchasing power.[127,128] Regarding drugs, the relevance of purchasing power is dependent on the co-payment system for drug expenses.

One of the drawbacks of income as a measure of SEP is that, unlike education, it is not a stable measure of SEP, but reflects the current living conditions of the individual. Moreover,

income is affected by several factors including exclusion of individual from the labor market due to disease conditions. Also, the usual way of measuring income does not fully capture the economic status of the individual. In most studies, wealth or ownership of property and transfers in the informal economy are not included. Individual income as a measure must also be adjusted for the number of adults and children supported by the income.

1.9 RELATIONSHIP BETWEEN SOCIOECONOMIC POSITION AND DRUG USE

Very few studies have analyzed the association between SEP and drug use, and studies dealing with socioeconomic inequalities in drug use in the elderly have shown inconsistent results.[28,69,133-136] Moreover, within these studies, drug use has been associated differently with education, occupation and income. This indicates that education may capture different aspects of SEP than occupation and income. The most frequently used drugs have lower prevalence in higher educational level, as shown in one British study of people aged 75 years and older.[68] Table 9 summarizes selected studies on the association between overall drug use, polypharmacy and SEP. The studies have been conducted in a variety of countries.

1.9.1 Polypharmacy

One study from Ireland in 2004 reported that the relatively deprived elderly were more likely to receive suboptimal therapy and polypharmacy (Table 9).[55] Similarly, Nobili et al. found that the number of drugs taken by Italian community-dwelling elderly increased with decreasing educational level.[134] In contrast, a USA study found that more educated older women may be more likely to be exposed to polypharmacy.[137] In yet another, Finnish, study education and occupation were not associated with polypharmacy.[28]

Table 9. Epidemiological studies concerning the association between overall drug use, polypharmacy and socioeconomic position (SEP)

Author, year	Country and sample	Age, y	Analyses identified as relevant to research question	Measure (s) of drug use	Measure (s) of SEP	Results
Fillenbaum et al,[69] 1986-1987	USA, 3973 Home interview	65+	Concomitants of prescription and OTC drug use	Use of prescription or OTC drug within the past 14 days	Prescription drug: Low education OTC drug: Low education	 0 +
Fourrier et al,[138] 1988-1989	France, 3777 Home interview	65+	Sociodemographic characteristics related to number of drugs taken	Number of drugs taken regularly in the past 14 days	Low education	-
Stuart et al, [139] 1990	USA, 4066 Mail survey	65+	Social determinants of treating less serious health problems with drug	Any drug used for treating less serious health problems	Low education Low income	+ +
Chen et al,[24] 1991	England and Wales, 12489, Home interview	65+	The effects of Sociodemographic features on drug use	Current drug use and number of currently used drugs	At least one drug: Social class (Occupation) Education Using 5+ drugs: Low social class (Occupation) Education	 0 0 - 0
Nobili et al,[134] 1990-1993	Italy, 261 GP data and home interview	75+	The correlates of number of drugs taken	Number of drugs currently taken	Low education Perceived economic status	- 0
Linjakumpu et al,[28] 1999	Finland, 1596 Interview and health examination	64+	Polypharmacy among elderly	Polypharmacy: Concomitant use of 6+ drugs	Education Previous occupation	0 0
Odubanjo et al,[55] 2001-2002	Ireland, 95055 Prescribing data	70+	Quantity and quality of prescribing in different socioeconomic groups	Number of drug, polypharmacy, items/patient and potentially harmful prescribing	Number of drugs: Low SEP Major polypharmacy: Low SEP	 + +
Perry et al,[137] 1988-1994	USA, 5249 Household questionnaire	65+	Predictors of polypharmacy	Number of prescription drugs concurrently taken	Low education	+

+ = positive association, - = negative association, 0 = no association

1.9.2 Inappropriate drug use

Most studies in the elderly have associated IDU with low SEP.[98,135,140] One study with information from eight European countries, reported that potentially IDU was associated with patient's poor economic situation in home dwelling elderly (Table 10). Individuals reporting a poor economic situation had a 1.96-fold higher relative risk of receiving an inappropriate medication than the reference group. This factor was significantly associated with living in the Czech Republic (contingency coefficient, 0.38; P<.001), where 33% of patients reported a poor economic situation compared with an average of 2.9% in all the other countries.[140] In an Irish study, relatively deprived patients were more likely to receive potentially harmful drugs such as cerebral vasodilators and long-acting sulphonylurea, and potentially interacting agents such as an angiotensin converting enzyme (ACE) inhibitor and potassium sparing diuretic.[55] Similarly in France, subjects with high educational achievement were less likely to use potentially IDU, after controlling for age, gender, depressive symptoms, number of drugs used and self-rated health. The protective effect of education was more pronounced in elderly women than in elderly men.[98] Willcox et al. found that subjects covered by Medicaid were more likely to use inappropriate medication but they found no difference according to educational level.[141] In a study conducted in Québec in 1992, a higher prevalence of IDU was also observed among poor elderly subjects and among those with a low educational level.[142]

1.9.3 New drug use

Different factors may contribute to the selection of new drugs by physicians,[26,106,109,111] however, very little is known about the influence of SEP on use of new drugs in elderly [101,107]. A Canadian population-based study on persons aged ≥65 reported that newer brand-name drug prescribing modestly increased with increasing income quintile after adjusting for patient age and gender, especially for selection of newer, brand-name antipsychotics, newer generic statins and newer, brand-name ocular β-blockers.[107] Similar findings have been found in a USA study on the elderly diagnosed with depression. The new generation antidepressant treatment, including selective serotonin reuptake inhibitor (SSRI) use from 1992 to 1997, was studied. In the beginning of study period (1995-1997), SEP was positively associated with the prescriptions of these drugs. The diffusion of these new medications lagged for those with low socioeconomic status defined by education and income, but the difference disappeared by the end of the study period (1995-1997) when the SSRIs had been on the market for several years.[101] Another, Czech study based on the general population but with an ecological design,

Table 10. Major epidemiological studies concerning the association between inappropriate drug use (IDU) and socioeconomic position (SEP)

Author, year	Country and sample	Age, y	Analyses identified as relevant to research question	Measure (s) of IDU	Measure (s) of SEP	Results
Odubanjo et al,[55] 2001-2002	Ireland, 95055 Primary care prescribing data	70+	Quantity and quality of prescribing in different socioeconomic groups	Potentially harmful prescribing such as cerebral vasodilators, long-acting sulphonylurea and interacting agents	Deprived cohort	+
Fialova et al,[140] 2001-2002	Czech Republic, Denmark, Finland, Iceland, Italy, the Netherlands, Norway, and the United Kingdom, 2707 Home interview	65+	Prevalence and associated factors of potentially inappropriate drug use	Prevalence of IDU was documented using all expert panels criteria for community-living elderly persons (Beers and McLeod)	Poor economic situation	+
Lechevallier-Michel, et al,[140] 1999-2001	France, 9294 Home and study center interview	65+	Sociodemographic factors associated with potentially IDU	Inappropriate medication use was assessed using a list derived from the Beers criteria by a panel of French experts	Low education	+

+ = positive association, - = negative association, 0 = no association

found significantly higher utilization of new drugs, such as dihydropyridine calcium channel blockers and statins, in the districts with a higher percentage of university-educated inhabitants.[143] Similarly, early users of celecoxib generally had high incomes and had paid out-of-pocket for their prescriptions[104] Hence, the limited literature indicates that new drugs are more often prescribed to patient in higher socioeconomic groups (Table 11).

1.9.4 Methodological considerations

Before drawing any conclusions from this short review of the literature concerning the association of drug use with SEP, some issues need to be taken into account. First, the characteristics of the study populations are different between studies, especially regarding age and gender. Second, different methods of assessment have been used in different studies to identify drug use, polypharmacy, IDU and new drug use. These previous studies are also difficult to compare due to differences in time and place, sample size, data collection methods, measurements of drug use (OTC, prescription drugs, drug used in last 14 days or last year), and measurements of SEP. Moreover, the organizational structure of providing pharmaceuticals, including insurance and reimbursement aspects, influence the results of these studies. Also, many studies have not controlled for health status and comorbidity, which is more pronounced in the lower social classes than in the more prosperous part of the population.[117] Therefore, it is crucial to consider health status when investigating SEP in relation to polypharmacy and IDU. Further, previous studies have either focused on community-dwelling or nursing homes residents.

In summary, there is an increasing interest in the scientific world towards the association of drug use with SEP due to the high relevance of the topic, not only from a public health perspective, but also from a scientific point of view. In fact, exploring this association may help in clarifying some new pathways leading to drug use.

Table 11. Major epidemiological studies concerning the association between newly marketed drug use and socioeconomic position (SEP)

Author, year	Country and sample	Age, y	Analyses identified as relevant to research question	Measure (s) of new drug use	Measure (s) of SEP	Results
Mamdani et al,[107] 1998-1999	Canada, 128314 Medication profiles from healthcare administrative data	65+	Association between SEP as indicated by neighborhood median income level and physician drug selection between older and newer drugs	Initiation of new drugs antipsychotic, hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin), or ocular beta-blocker drug therapy	High income	+
Sambamoorthi et al,[101] 1997	USA, 1772 Merged survey data and Medicare claims from a nationally representative survey 1992-1997	65+	The diffusion of new generation of antidepressant treatment over time	Prescription of a new generation antidepressant compared to other antidepressant during the calendar year	1992-1994 High education High income 1995-1997 Education Income	 + + 0 0

+ = positive association, - = negative association, 0 = no association

2 AIMS

2.1 GENERAL AIM

The general aim of this thesis is to investigate the relationship between drug use and socioeconomic position in the elderly, with respect to extent, quality, development over time and new drugs.

2.2 SPECIFIC AIMS

The specific aims addressed in the four different studies are summarized below.

1. To investigate (i) the prevalence of polypharmacy and the most frequently used drugs in the elderly, and (ii) the association between polypharmacy and socioeconomic position, as measured by education, occupation, and income (*Study I*).

2. To assess the ten-year (1992–2002) change in drug use, polypharmacy, drug-drug interactions and the most prevalent therapeutic classes of drugs in different educational groups of elderly (*Study II*).

3. To (i) verify the association between polypharmacy and socioeconomic position, as measured by education, and to (ii) investigate whether educational attainment in the elderly is associated with excessive polypharmacy and potentially inappropriate drug use in the elderly, after controlling for age, gender, type of residential area and comorbidity. (*Study III).*

4. To examine the association between educational level and use of newly marketed drugs among elderly persons (*Study IV).*

3 MATERIAL AND METHODS

The analyses in this thesis are based on several Swedish data sources. Information on the data sources is presented in Table 12.

Table 12. Data sources for this thesis

Studies	Study Period	Research question	Data source (s)
Study I	2002	The prevalence of polypharmacy, most frequently used drugs and SEP	SWEOLD 1992
Study II	1992 and 2002	Trends in drug use, polypharmacy, DDI and most prevalent therapeutic classes of drugs over ten years	SWEOLD 1992 and SWEOLD 2002
Study III	2005	The association of polypharmacy, excessive polypharmacy and IDU with education	SPDR Inpatient Register Education Register.
Study IV	2005	The association between educational level and use of NMD	SPDR Inpatient Register Education Register.

3.1 THE SWEOLD PROJECT (STUDY I AND II)

3.1.1 Study population

The Swedish Panel Study of the Living Conditions of the Oldest Old (SWEOLD) is a population-based study of elderly persons in Sweden. The SWEOLD is originating from the Level of Living Survey (LNU). The LNU is a nationally representative sample of about 6000 individuals aged 18-75.[144] The LNU was first carried out in 1968 with follow-ups in 1974, 1981, 1991, and 2000. The SWEOLD is an interview survey of individuals previously included in the LNU sample, but who have passed the upper age limit of 75 years.[145] Thus the SWEOLD is targeted towards the oldest old part of Swedish population. The SWEOLD has been conducted three times, 1992 (SWEOLD I), 2002 (SWEOLD II) and 2004 (SWEOLD III) (Fig. 2).

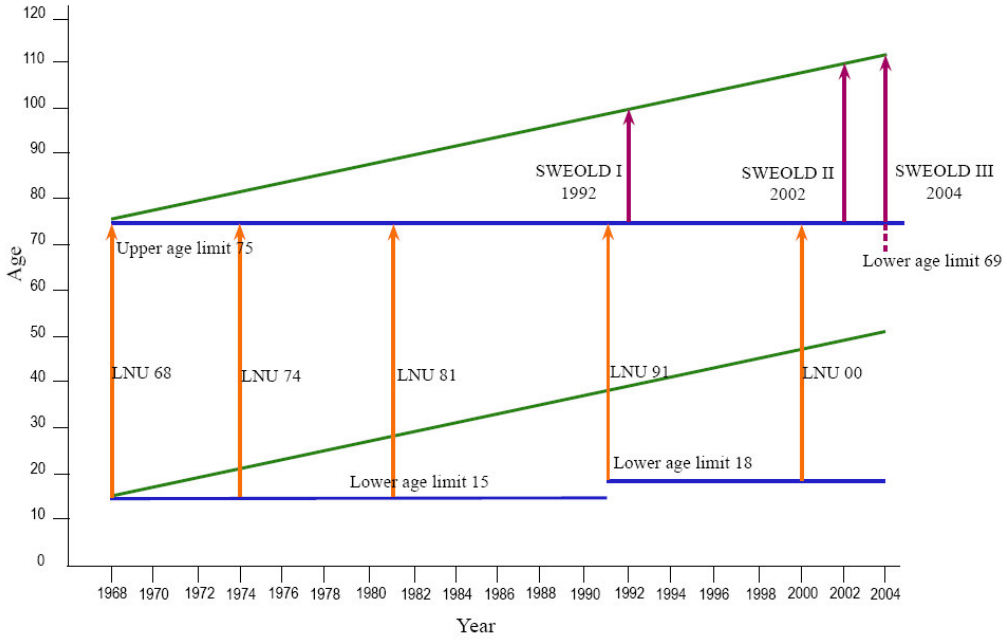

Figure 2. A schematic picture describing the LNU and SWEOLD studies

3.1.2 Data collection

Participants were randomly selected from the Swedish Person and Address Register (SPAR) and the postal address of each individual was traced. Great effort was made by the interviewers to locate and contact the subjects. Identical questionnaires were used for both 1992 and 2002 surveys. Non-response was greater in 2002 (11.5% compared to 4.5% in 1992). SWEOLD I and II can be seen as national representative samples of survivors of the birth cohorts 1892–1925 and comprise approximately 1 per thousand of the Swedish general population aged 77 and older.[145]

For both these SWEOLD surveys, the participants went through an extensive examination including an interview and various physical and cognitive ability tests. Professional interviewers conducted structured interviews with participants. Most participants were interviewed directly in their homes; however, proxy (i.e., a relative, caregiver, or medical staff) and telephone interviews were carried out when necessary. The most common reasons for proxy interviews were indisposition due to illness, weakness, or dementia. The most common reasons for telephone interviews were illness and reluctance to being visited. The distribution of interview mode (direct, telephone, proxy) changed only marginally between the two surveys. The interview questions covered data on demographics, medical history, living conditions, education, occupation, income and medicine use.

3.1.2.1 Sociodemographic characteristics

Data on demographic variables (e.g., age, sex, living situation, and marital status) were collected directly from the subjects in case of direct interviews and from relatives or care personnel in case of indirect interviews. Living situation was dichotomized into community residing (own homes, sheltered accommodation, old people homes) or residing in an institution (group living for the demented, nursing home).[146] Marital status was classified into married/living with someone, not married, divorced/separated or widow/widower.

3.1.2.2 Socioeconomic position

SEP was measured by education, occupation and income. Education was dichotomized into less or equal to 8 years of schooling (elementary or compulsory education) and more than 8 years of schooling (upper secondary and higher education). Occupation was coded according to the Swedish socioeconomic classification system: Socioeconomic Index (SEI), compiled by Statistics Sweden. The SEI classification system of occupations has been adjusted to international standards and has been utilized in several studies on Sweden.[147]

Occupation was categorized into two groups: blue-collar workers (unskilled workers, skilled workers, farmers) and white-collar workers (lower white collars, middle white collars, upper white collars). In detail, white-collar workers covered lower white collars (assistant non-manual employees such as technicians, secretaries, and nurses), middle white collars (intermediate non-manual employees such as teachers, physicians, and dentists) and upper white collars (upper-level executives in private enterprises or organizations with at least 100 employees or in public service and executives).

Income was measured as the household equivalent disposable income, gathered from a number of official registers, mainly tax records. Data from these registries were linked at the individual level (using the unique Swedish personal identification number). The household equivalent disposable income includes both the respondent's and the spouse's income from work (if any), capital, pensions and other cash benefits. While married or cohabiting couples often have two incomes, their costs of living are not usually twice that of single person. In order to counter overestimation of income for married or cohabiting, an equivalent scale was used to adjust the income of two-person households by a factor of 1.55.[81] Derived from previous evidence in Sweden,

income for one year was divided into two levels: low (<100,000 SEK) and high income (>100,000 SEK)[81] (1 US $ corresponds to approximately 6.9 SEK).

3.1.2.3 Comorbidities

Data on medical history or comorbidities were obtained during interview with the participant. Comorbidity was measured by an index based on self reported data on diseases/symptoms of the elderly. The participants were asked "Have you had any of the following diseases or symptoms during the last 12 months?" followed by a list of both diseases and symptoms. "No" was coded as 0 and "Yes, mild problems" and "Yes, severe problems" were coded as 1. The participants reported 19 diseases/symptoms in total. These were further merged to form 7 main disease areas. The participants who had a diseases/symptoms score of more than 2 were regarded as having comorbidity. This measurement of comorbidity has been used earlier and is described in detail elsewhere.[148]

3.1.3 Measurement of drug use

Data on drug use for the two weeks prior to the interview were collected. The participants were asked during the interview (both visit, proxy and telephone), to give information on brand name, strength, dosage form and frequency. In cases when visit interviews were made, drug prescription lists and containers were examined for confirmation. If the participant was living in an institution, the information was collected from a nurse, relative, caregiver or medical records. Both prescription and non-prescription drugs were recorded. 'Drug use' was defined as the use of prescribed or over-the-counter (OTC) drugs on a regular basis at the time of the interview and 'as needed' at any time during the 2 weeks prior to the interview. Information about herbal medicines was also gathered. However, it was not possible to classify these medicines according to the Anatomical Therapeutic Chemical Classification (ATC) System. Therefore, herbal medicines were not included in the analysis. The drug data in this thesis comprise the main ATC groups A-V (see below).

An experienced pharmacist or nurse entered and revised the entry of drug data. A custom designed software (Monitor) was used to automatically classify the drugs according to the ATC system and for identifying IDU, including potential DDI. To ensure the quality and quantity of data, the author checked the data entry with original data sheets for both SWEOLD surveys.

Drugs were classified according to the ATC system, as recommended by the World Health Organization.[149] The purpose of the ATC system is to serve as a tool for drug utilization research to improve the quality of drug use. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (Norway), and has been in use for statistics since 1975. The ATC system divides drugs into different classes according to the organ or system on which they act and/or their therapeutic and chemical characteristics (Table 13). Drugs are classified into groups at five different levels.

Example of ATC system:

The complete classification of metformin illustrates the structure of the ATC code:

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Oral blood glucose lowering drugs (3rd level, pharmacological subgroup)
A10B A	Biguanides (4th level, chemical subgroup)
A10B A02	Metformin (5th level, chemical substance)

Table 13. Main groups of the ATC system

First level	Level description
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

3.1.4 Assessment of polypharmacy and drug-drug interactions

Polypharmacy was defined as concurrent use of five or more drugs. This method of assessing polypharmacy has been previously used and evaluated.[51] Drugs were

differentiated and counted at the fifth level of the ATC code (eg furosemide: C03C A01).

Potential DDI for *Study II* were identified using the classification proposed by Sjöqvist (Table 14), which is continuously revised and published on a yearly basis in the Swedish medicine compendium called FASS (www.fass.se).[150] The Sjökvist DDI-system identifies four levels of clinical relevance (A-D) and four levels of evidence (1-4). The potential DDI considered to be of clinical relevance (C and D) were included in this thesis. C-interactions include those which can modify the pharmacological effects or cause ADRs, but can be controlled by dose adjustments and/or by determination of plasma concentration of the drug. D-interactions may have serious clinical consequences, like serious ADRs, suppressed effect, or are difficult to control with dose adjustment. Potential DDI of type C and D were detected by processing drug use data in the custom designed software (Monitor).

Table 14. Classification of DDI by clinical relevance

DDI class	Clinical relevance
A	Probably no clinical relevance.
B	Clinical relevance not completely assessed.
C	The interaction may modify the effect of the drug; however this can be mastered by individual dose adjustment, and/or by determination of the plasma concentration of the drug.
D	The interaction may have serious clinical consequences, such as severe adverse effects, no effects, or may be difficult to control by individual dose adjustment.

3.2 THE SWEDISH PRESCRIBED DRUG REGISTER (STUDY III AND IV)

In July 2005, a national register on dispensed pharmaceuticals was established: the SPDR. The SPDR contains data on all dispensed prescriptions to the entire Swedish population (9 million inhabitants)[42] and can be linked to other Swedish population registers by using the personal identification number.

3.2.1 Data collection

The data collection is administered by the state-owned National Corporation of Swedish Pharmacies and then transferred to the Centre for Epidemiology (EpC) at the National Board of Health and Welfare (www.socialstyrelsen.se).[42] All Swedish Pharmacies have standardized procedures to ensure high quality of data acquisition and management.

3.2.2 Measurement of drug use

All dispensed drugs were classified according to the ATC system.[109] Information included patient identity, date of filling, brand name, quantity of drug dispensed and dosage. The information on drug use was collected from the SPDR during a three month period for each individual. This period was selected on the assumption that the maximum quantity of prescribed drugs supplied to the patient is for a period of 90 days. Thus, drugs prescriptions filled during three months, approximately correspond to the current use of prescribed drugs during that period, in this case August-October 2005.[51]

3.2.3 Assessment of polypharmacy, IDU and use of NMD

3.2.3.1 Polypharmacy

Most European studies have defined polypharmacy according to the number of medications taken by the patient. We defined polypharmacy as concurrent use of five or more drugs and excessive polypharmacy as concurrent use of ten or more drugs.[23,28]

3.2.3.2 Potential IDU

Determination of potential IDU was based on four quality indicators developed by the Swedish National Board of Health and Welfare: concurrent use of three or more psychotropic drugs (ie, neuroleptics, anxiolytics, hypnotics/sedatives, antidepressants), use of at least one long-acting benzodiazepine (ie, diazepam, nitrazepam, flunitrazepam), use of at least one anticholinergic drug, and at least one potential clinically relevant DDI (Table 15).[66]

Table 15. Drug-specific quality indicators introduced by the Swedish National Board of Health and Welfare and used in the present study

Indicators for the evaluation of the quality of drug therapy among the elderly, extracted and translated from the quality indicators proposed by the Swedish National Board of Health and Welfare
Proportion of individuals taking long-acting benzodiazepines: Includes diazepam, nitrazepam and flunitrazepam
Proportion of individuals taking anticholinergic drugs: Drugs with potent anticholinergic properties (urinary and gastrointestinal antispasmodics, anticholinergic antiemetics, antiarrhythmics class Ia, anticholinergic anti-Parkinsonian drugs, low potency antipsychotics, cyclic antidepressants, first-generation antihistamines)
Proportion of individuals taking three and more psychotropic drugs: Includes antipsychotics, anxiolytics, hypnotics-sedatives. and antidepressants
Proportion of individuals with potential drug/drug interactions, category C or D: DDI category C or D according to the Swedish classification system described in the annual publication of Pharmaceutical Specialities in Sweden (FASS) Category C (1-4): DDI that could lead to a changed effect or ADR but which can be managed with individual dosage and/or measurements of plasma concentration. Category D (1-4): Drug combinations that should be avoided *Note: The lower the proportion of each indicator, the better the quality of drug therapy*

3.2.3.3 Data on newly marketed drugs

The Medical Products Agency (MPA) is the Swedish national authority responsible for approval of new drugs. Use of newly marketed drugs (NMD) was defined as use of at least one drug among products approved by the Swedish Medical Products Agency (MPA) in 2000-2004. Only new chemical entities and with at least 350 users were included in the study.

For each new drug, a reference drug class was selected, for example all antiglaucoma preparations and miotics (S01E) were used as reference drug class for the new drug brinzolamide (S01EC04), and all anti-dementia drugs (N06D) for galantamine (N06DA04).

3.3 OTHER NATIONAL REGISTERS (STUDY III AND IV)

In. the present studies, information from the national inpatient register and education register is used.

3.3.1 The Inpatient Register

The Swedish inpatient register contains diagnoses and dates of admission of all hospitalized patients in Sweden. The registry was established in parts of Sweden in 1964. The coverage has since then gradually expanded to include all of Sweden from 1987 onwards and is now estimated to be 99% complete. Diagnoses from the inpatient register were used to calculate a measure of comorbidity burden based on the individuals' history of all hospitalizations over the 7 years prior to measurement of drug use. Information was obtained about all hospital discharges during the years 1998-2004 and these were classified according to the primary diagnosis (the main cause for hospitalization, based on the judgment of the responsible clinician) registered. The comorbidity coding was performed by using the *International Classification of Disease, Tenth Revision* (ICD10) in each patient record and weighted according to the method developed by Charlson et al.[151] and modified by Deyo et al.[152] The Charlson Comorbidity Index (CCI) is derived by summing the weights assigned to all health problems leading to hospital admission from a predefined list of 17 medical conditions such as cerebrovascular disease, congestive heart failure and liver disease. For every individual registered in the SPDR, we created a dichotomous variable for having any hospital discharge for any of the 17 categories of diseases during this time period.[153] The CCI weighs the number and seriousness of comorbid diseases, assigning each condition a score of 1 to 6. The weights of each comorbid condition are summed to arrive at a total score. In this study, comorbidity scores were categorized as 0, 1-2, 3-4, and 5 or more.

3.3.2 The Education Register

The Swedish education register was established in 1985 at the request of the Government. Earlier registers of the population's level of education had been produced in the 1930 and 1970 censuses. The first version of the Education Register refers to 1985. Since then the register is updated once a year. Educational attainment was classified into three categories: low education (8 years or less), medium education (9-

12 years) and high education (13 or more years). For completeness of data, information was assessed from older versions of the rducation register as far back as until 1990. Due to missing data on education for most individuals aged 90 years and older, we had to restrict the maximum age of the studied population to 89 years in this thesis.

3.4 STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS statistical package (SPSS 14.0 and 15.0 for Windows, SPSS Inc., Chicago, IL, USA).

3.4.1 Statistical tests

The main associations examined in this thesis were between SEP and drug use, polypharmacy, excessive polypharmacy, IDU and NMD use. Throughout the four studies a range of statistical tests were employed. Chi-square test and Student's t-test or analysis of variance (ANOVA) were performed to assess the statistical differences of proportions and means between groups. Logistic regression models were employed to test multivariate associations. The results are shown as odds ratios (OR) with 95% confidence intervals (CI). Table 16 summarizes the statistical analysis, the outcome variables and the independent variables that were considered in the four studies.

3.4.2 Specific analyses for each study

The statistical methods that were performed in the four studies are described below.

Study I. the chi-square tests were used for comparing categorical variables between groups of individuals and ANOVA for continuous variables. Logistic regression was performed to analyse the association between polypharmacy and SEP. The three measures of SEP (education, occupation, income) were first separately investigated in univariate analyses. As we did not observe any significant association between occupation or income and polypharmacy in the univariate analysis, we did not include occupation and income as covariates in the further logistic regression analyses. In Model i, we adjusted for age and sex, and in Model ii, we added for age, sex, comorbidity, marital status and living situation. Statistical interaction terms were created for SEP in combination with other variables. Interactions were considered significant with a P value less than 0.05. We also investigated multicollinearity for age, sex and education.

Study II. age, gender, and living situation were considered confounders in the analysis. Living situation was dichotomized as community residing or residing in an institution. Education was dichotomized into: less or equal to 8 years of schooling and more than 8 years of schooling. Statistical significance of the changes in drug use between the SWEOLD surveys in 1992 and 2002 were analysed by Student's paired-samples and independent-samples t-test. Logistic regression was thereafter performed to adjust for age and gender.

Study III. descriptive statistics were used for the frequency of drug use, polypharmacy, and IDU among the elderly. Prescribing patterns were compared using chi-square tests. Logistic regression was used to examine the association between the polypharmacy, potential IDU and educational attainment. In multivariate models we adjusted for the effect of other variables on polypharmacy and potential IDU. Firstly, we investigated the crude relation between education and polypharmacy and IDU. In model i, we adjusted for age and gender, and in model ii age, gender, type of residential area, and comorbidity. Due to the possible effect of gender on schooling, an additional analysis was performed stratified by gender. The Hosmer-Lemeshow goodness-of-fit statistic was applied to test the data's fit to the model.

Study IV. the association between educational level and new drug use was analysed using multiple logistic regression. We adjusted for the effect of potential confounders (age, sex, type of residential area, comorbidity and number of drugs) on overall new drug use and for each new drug. The Hosmer-Lemeshow goodness-of-fit statistic was applied to test the data's fit to the model.

Table 16. Statistical models used in various studies of this thesis

Studies	Model	Dependent variables	Independent variables	Procedure
Study I	Logistic regression	Polypharmacy	Education, occupation, income, age, sex, marital status, living situation, comorbidity	1st model: age and sex 2nd model: adding marital status, living situation, comorbidity Statistical interaction terms were created for SEP in combination with other variables.
Study II	Logistic regression	Polypharmacy Potential DDI Most frequently used drug classes	Education, age, sex, living situation	Adjusted for age and sex
Study III	Logistic regression	Polypharmacy Excessive polypharmacy IDU	Education, age, sex, type of residential area, comorbidity	1st model: age and sex 2nd model: adding type of residential area and comorbidity
Study IV	Logistic regression	Use of NMD	Age, sex, type of residential area number of drugs, comorbidity	1st model: age, sex 2nd model: adding type of residential area 3rd model: adding type of residential area and number of drugs

4 ETHICAL CONSIDERATIONS

4.1 THE SWEOLD PROJECT

All participants were sent a personal letter, which explained the nature of project and the importance of the participation, yet emphasizing that involvement was voluntary. Thereafter, all participants were contacted to check their availability and to book a date for personal visit by interviewee. The informed consent was obtained directly from participants during personal interviews, after explaining the aims of the project and clarifying that all information would be kept strictly confidential. For proxy interviews, a close relative was asked to provide consent, while for telephone interviews, informed consent was obtained over the phone. All waves of the SWEOLD project received approval from the Ethics Committees.

SWEOLD 1992	Uppsala University Hospital	Dnr. 24:91
SWEOLD 2002	Karolinska Institutet	Dnr. 03:413

All staff working with the SWEOLD project database follow the guidelines of the Swedish Council for Research in the Humanities and Social Sciences: the principles of autonomy and integrity, the role of consent, and the demand for research.

4.2 THE SWEDISH PRESCRIBED DRUG REGISTER

The use of data in research from Swedish registers is strictly regulated in order to protect the personal integrity. In addition, permissions from ethical research committees are also required. Only non-identifiable data were used in this thesis and the research was approved by the ethical board in Stockholm (Dnr 2006/948-31).

5 RESULTS

5.1 CHARACTERISTICS OF THE STUDY POPULATIONS

Study I and II are based on data from SWEOLD 1992 (SWEOLD I) and 2002 (SWEOLD II) surveys (Table 17). Figures from SWEOLD I and II on age, gender, and percentage of people living in institutions (13% and 15%) are representative of the Swedish population aged 77 years or older for the two survey years. In SWEOLD II, 621 (84.4%) of the invited 736 inhabitants from all over Sweden participated. The majority were women (59%). The youngest participants were 77 and the oldest was 99 years old. Women were older (83.7± 4.9 vs. 82.7±4.6 years, $p<0.01$) and less educated (72.7 vs. 61.7% with 2-7 years of education, $p< 0.001$) than men. 68% had less than 8 years of education.

Table 17. Characteristics of the study populations

	Study I	**Study II**		**Study III and IV**
Source	SWEOLD	SWEOLD		National registers
Year of data collection	2002	1992	2002	2005
Study population, n	621	512	561	626 258
Type of data collection, n (%)				
Home visit	492 (79)	439 (81)	448 (80)	
Direct telephone	47(8)	34 (6)	41 (7)	
Proxy direct/telephone	82 (13)	64 (12)	72 (13)	
Female sex, n (%)	368 (59)	311 (61)	333 (59)	377 551 (60)
Educational level >8 y, n (%)	419 (68)	395 (77)	384 (68)	345 565 (55)
Comorbidity, n (%)	305 (51)	106 (21)	178 (32)	177 430 (28)
Drug use, n (%)	548 (88)	418 (82)	494 (88)	626 258 (100)
No. of drugs, mean (SD)	4.4 (3.4)	2.5 (2.2)	4.4 (3.4)	5.8 (4.1)
Polypharmacy	362 (42)	90 (18)	237 (42)	354 362 (57)
Excessive polypharmacy	20 (3)	6 (1)	19 (4)	110 615 (18)

Study I is based on data from SWEOLD II and *Study II* on both SWEOLD I (*n*=512) and II (*n*=561) surveys. In SWEOLD II, surviving non-responders from previous LNU were included in the sample (*n*=621), resulting in 15.6% non-response rate. However, in order to obtain comparable dataset for SWEOLD I and II, LNU non-responders were excluded in *Study II*.

Study III and IV are based on drug information derived from SPDR, with data on all dispensed prescriptions to the entire Swedish population. Basic demographic characteristics of the 626 258 study subjects for Study III and IV are presented in Table 17. Mean age of the patients was 80.9 years; most were women and lived in urban areas. The majority was low educated (55%).

5.2 STUDY I

5.2.1 Drug use in general

Overall, 88% of the study participants used medications. There were significant differences ($P<0.05$) in mean number of drugs for sex, education, marital status, living situation, and comorbidity (Table 18). The mean number of drugs was higher among the elderly with low education.

5.2.2 Polypharmacy

Polypharmacy (use of five or more drugs) was observed in 42% of the elderly. Elderly living in institutions, had a significantly higher prevalence of polypharmacy than the community dwelling elderly (64% vs 38%, $P<0.05$). Participants with poor health (high comorbidity) were also more likely to be exposed to polypharmacy (Table 18). In the logistic regression analysis, low education was associated with polypharmacy (OR=1.46 (95% CI 1.02-2.07), after adjustment for age and sex. However, after additional adjustment for morbidity, marital status and living situation, the association between education and polypharmacy was not conclusive (OR=1.39 (95% CI 0.95-2.04). We did not observe any significant difference in the occurrence of polypharmacy between occupation and income groups.

Table 18 Characteristics of the SWEOLD 2002 sample of 621 elderly people

	Drug use %	Mean number of drugs (95% CI)	P-value	Polypharmacy %	P-value
Age					
77-79 years	86.7	4.0 (3.5-4.5)	0.276	39.9	0.643
80-84 years	87.2	4.4 (4.0-4.9)		41.6	
85+ years	90.9	4.6 (4.1-5.0)		44.5	
Sex					
Men	86.6	3.9 (3.5-4.3)	0.002	38.7	0.149
Women	89.7	4.7 (4.4-5.1)		44.6	
Education[a]					
More than 8 years	88.2	4.0 (3.6-4.5)	0.048	35.9	0.024
Less or equal to 8 years	88.5	4.6 (4.0-5.0)		45.6	
Occupation[a]					
White-collar workers	87.5	4.4 (4.0-4.7)	0.999	43.6	0.461
Blue-collar worker	89.5	4.4 (4.0-4.8)		40.7	
Income					
High Income	88.0	4.3 (3.9-4.7)	0.945	41.0	0.544
Low Income	88.8	4.6 (4.2-4.9)		43.4	
Marital Status					
Not married	86.0	3.7 (2.8-4.7)	0.001	30.2	0.051
Married/living with someone	89.1	3.7 (3.4-4.1)		37.6	
Divorced/separated	81.1	4.6 (3.1-6.1)		40.5	
Widow/widower	89.1	4.9 (4.5-5.3)		47.2	
Living Situation					
In community	88.5	4.0 (3.8-4.3)	0.001	38.4	0.001
In institution	88.0	6.3 (5.4-7.2)		64.1	
Comorbidity[a]					
No	83.7	3.2 (2.9-3.5)	0.001	27.6	0.001
Yes	93.1	5.4 (5.0-8.9)		54.8	
Total	88.5	4.4 (4.1-4.6)		42.2	

P-values indicate significance level by ANOVA

[a]The numbers of individuals with missing values were 7 for education, 4 for occupation and 22 for Multiple diseases/symptoms.

5.2.3 Most frequently used drugs

The most frequently used drugs were antithrombotic agents (42%), beta-receptor blocking agents (28%), and high ceiling diuretics (28%) (Figure 3). The lower educated elderly used higher proportions of the investigated therapeutic drug classes (particularly high ceiling diuretics, analgesics, and antidepressants) except for antithrombotic agents, laxatives and cardiac glycosides, which were equally or slightly more common in high educated elderly.

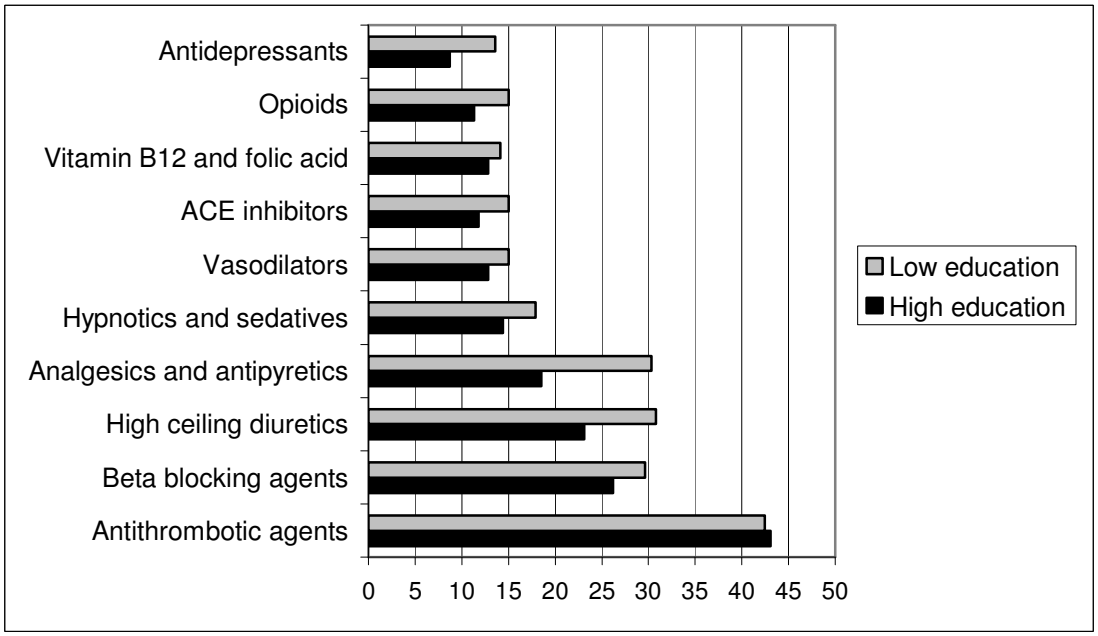

Figure 3. Top ten most frequently used therapeutic drug classes and proportion of users

5.3 STUDY II

5.3.1 Trends in drug use

The prevalence estimates of drug use in SWEOLD 1992 and 2002 are shown in Table 19. The 1992 survey showed that 82% of the Swedish elderly used at least one drug, while in the 2002 survey this proportion had increased to 88%. During the same time the mean number of drugs used per individual increased from 2.5 to 4.4. There were significant increases in mean number of drugs between the surveys for both educational groups after controlling for age and gender.

Table 19. Drug use, polypharmacy and DDI 1992 - 2002

	Mean number of drugs		Polypharmacy %		DDI, %	
	1992	2002	1992	2002	1992	2002
Total	2.5	4.4	17.6	42.4	17.0	24.6
Gender						
Men	2.2	3.9	10.9	21.9	10.9	21.9
Women	2.7	4.7	20.9	26.4	20.9	26.4
Age groups						
77-79	2.3	3.9	13.2	37.5	14.7	20.5
80-84	2.5	4.5	16.1	41.9	17.0	28.1
85+	2.9	4.7	23.3	45.5	18.9	23.0
Education						
More than 8 years	2.1	4.1	12.2	36.0	13.9	26.2
Less or equal to 8 years	2.7	4.6	19.2	45.6	17.7	24.0
Housing						
In community	2.5	4.0	17.2	38.2	17.2	24.0
In institutions	3.1	6.6	20.7	67.1	15.5	28.0

5.3.2 Prevalence of polypharmacy

Polypharmacy increased more than twofold during the 10 year period between the two SWEOLD surveys (18% in 1992 to 42% in 2002). Polypharmacy increased in both men and women, but more in men. Although polypharmacy increased significantly in both educational groups, the increase was more pronounced in high educated elderly after controlling for age and gender (Table 19). This study also showed a trend of increasing polypharmacy with increasing age.

5.3.3 Occurrence of potential DDIs

Overall, elderly exposed to one or more potential DDI increased significantly from 17% in 1992 to 25% in 2002. Potential DDIs increased in both men and women, with higher prevalence in women during both study periods. Regarding education, the most obvious change was found among the high educated elderly. Potential DDIs increased twofold among people with more than 8 years of schooling (14% in 1992 to 26% in 2002), while this increase was less in low educated elderly (18% in 1992 to 24% in 2002). In SWEOLD 2002 survey, overall the most prevalent potential type C DDIs were the combination of furosemide with digoxin or enalapril, while the most common potential type D DDIs were acetylsalicylic acid with diclofenac or ketoprofen.

5.3.4 Most frequently used drugs

During both SWEOLD surveys, drugs for the nervous system, cardiovascular system, alimentary tract, and blood and blood-forming organs, made up the largest proportion. The most obvious increase was observed in antithrombotics agents, beta-receptor blocking agents, ACE inhibitors and vitamin B_{12} and folic acid. Both high and low educated elderly reported an increased use of most types of drugs between 1992-2002, after controlling for age and gender. For the high educated, the most pronounced increase in drug use was observed for antithrombotics agents, beta blocking agents, high ceiling diuretics, and ACE inhibitors. The only exception was exposure to analgesic and antipyretics drugs which decreased somewhat, although not statistically significantly, from 23% in 1992 to 19% in 2002. For the low educated, the highest increase in drug use was seen for antithrombotics agents, ACE inhibitors, and antidepressants, while analgesics and antipyretics treatment showed almost no change. The high educated elderly reported greater increase in high ceiling diuretics, drugs for peptic ulcer and gastro-oesophageal reflux disease and laxatives, than the low educated. On the other hand, hypnotics and sedatives, antidepressants as well as vitamin B_{12} and folic acid became more common over time among the low educated, compared to the high educated.

5.3.5 Gender and most frequently used drugs

The use of most classes of drugs increased more between 1992-2002 among the high compared to the low educated men, except for hypnotics and sedatives, antidepressants and vitamin B12 and folic acid. The only decrease in any drug class was visible for analgesic and antipyretics drugs among low educated men. In contrast, the use of most classes of drugs increased more among the low compared to the high educated women, except for vasodilators. The only decrease in any drug class was visible for analgesic and antipyretics drugs among high educated women.

5.4 STUDY III

5.4.1 Polypharmacy and excessive polypharmacy

This study from SPDR confirms our findings in *Study I* regarding the association between polypharmacy and education. Polypharmacy was common among the 626 258

study subjects, with prevalence of 57% during the 3-month study period, and 18% had excessive polypharmacy (use of ten or more drugs). Polypharmacy was particularly prevalent in the oldest old (63%), females (58%), people living in urban areas (56%) and in individuals with high comorbidity (85%). A similar pattern was found for excessive polypharmacy in the study population. The lowest educated group had the highest mean number of drugs, as well as frequency of polypharmacy (57%) and excessive polypharmacy (19%). The "dose-response" effect of education on polypharmacy was evident; compared to the higher educated group, the probability of polypharmacy and excessive polypharmacy increased, moving from high to medium to low educated subjects. Low education was associated with higher probability of polypharmacy (11% increase in the odds of polypharmacy) and, especially, excessive polypharmacy (15% increase in the odds), even after adjustment for age, sex, type of residential area and comorbidity (Table 20).

Table 20. Odds ratios (OR) of polypharmacy, excessive polypharmacy and inappropriate drug use in relation to education

	Medium Educated (n = 171 876, 27.4%)	**Low Educated (n = 345 565, 55.2%)**
	OR (95% CI)*	**OR (95% CI)***
Polypharmacy	1.06 (1.04-1.07)	1.11 (1.10-1.12)
Excessive Polypharmacy	1.08 (1.05-1.10)	1.15 (1.13-1.17)
IDU	1.04 (1.01-1.05)	1.09 (1.07-1.17)
≥3 Psychotropic Drugs	1.11 (1.07-1.15)	1.18 (1.15-1.29)
Long-acting benzodiazepines	0.99 (0.95-1.05)	1.03 (1.01-1.06)
Anticholinergic drugs	0.95 (0.92-0.97)	0.96 (0.93-0.99)
DDI	1.07 (1.05-1.09)	1.17 (1.16-1.19)

*Adjusted for age, sex, type of residential area and comorbidity

5.4.2 Potentially inappropriate drug use

About one-third of the participants fulfilled at least one criterion of potential inappropriate drug use. Increasing age, being a woman, living in a rural area and higher comorbidity score were associated with the highest frequencies of IDU. Regarding individual measures of IDU, 5.6% used three or more psychotropic drugs, 5.3% long-

acting benzodiazepines, 7.2% anticholinergic drugs and 25% had at least one potential DDI. Low educated elderly persons were more likely to be exposed to at least one IDU than high educated (36% vs 32%). The same frequency pattern was found for the four individual quality indicators. Logistic regression analyses showed that low educational attainment was associated with a higher probability of at least one IDU, use of three or more psychotropic drugs and DDI, after controlling for age, sex, type of residential area and comorbidity. The opposite relationship prevailed for anticholinergic drugs and in the case of long-acting benzodiazepines, no association was observed (Table 20). There was a 9% increase in the odds of an IDU for low educated elderly persons relative to high educated (OR 1.09; 95% CI, 1.07-1.17). In the analyses stratified for sex, low educated men and low educated women had higher probabilities of at least one IDU, three or more psychotropic drugs, and potential DDI, compared to medium and high educated men and women, respectively. Increasing age and higher comorbidity was associated with a higher risk of potential IDU.

5.4.3 Most frequently used drugs

The majority of patients were taking a cardiovascular drug (70%). The most common drug groups were antithrombotic agents (B01A, 44%), followed by beta blocking agents (C07A, 35%), hypnotics and sedatives (N05C, 22%), high ceiling diuretics (C03C, 22%) and analgesics and antipyretics (N02B, 21%). The most common main therapeutic drug classes are presented in Table 21. From this table, significant differences by education can be seen. Logistic regression analyses showed striking differences in the utilization of beta blocking agents, high ceiling diuretics, analgesics and antipyretics, vasodilators (more frequently used by low educated) and hypnotics and sedatives, lipid modifying agents (more frequently used by high educated) (Table 21).

Table 21. The association between the use of most frequent drug groups (decreasing order of frequency) and education. Data from the SPDR 2005 (n= 626 258)

ATC Class	Drug group	Education, y	OR (95% CI)*	
B01A	Antithrombotic agents			
		< 9	1.10	(1.08-1.11)
		9-12	1.05	(1.03-1.07)
		≥ 13	Ref	
C07A	Beta blocking agents			
		< 9	1.22	(1.20-1.23)
		9-12	1.09	(1.08-1.11)
		≥ 13	Ref	
C03C	High ceiling diuretics			
		< 9	1.58	(1.55-1.61)
		9-12	1.24	(1.22-1.27)
		≥ 13	Ref	
N05C	Hypnotics and sedatives			
		< 9	0.90	(0.89-0.92)
		9-12	0.98	(0.96-1.00)
		≥ 13		
N02B	Analgesics and antipyretics	< 9	1.49	(1.46-1.52)
		9-12	1.25	(1.22-1.28)
		≥ 13	Ref	
C10A	Lipid modifying agents	< 9	0.90	(0.88-0.92)
		9-12	0.96	(0.94-0.98)
		≥ 13	Ref	
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease	< 9	1.09	(1.07-1.11)
		9-12	1.06	(1.04-1.09)
		≥ 13	Ref	
B03B	Vitamin B12 and folic acid	< 9	1.20	(1.18-1.23)
		9-12	1.11	(1.09-1.14)
		≥ 13	Ref	
N06A	Antidepressants	< 9	1.13	(1.10-1.15)
		9-12	1.06	(1.03-1.08)
		≥ 13	Ref	
A06A	Laxatives	< 9	0.97	(0.95-0.99)
		9-12	0.93	(0.91-0.96)
		≥ 13	Ref	
C01D	Vasodilators	< 9	1.38	(1.35-1.41)
		9-12	1.22	(1.19-1.25)
		≥ 13	Ref	

ATC Class	Drug group	Education, y	OR (95% CI)*	
C09A	ACE inhibitors	< 9	1.27	(1.24-1.29)
		9-12	1.10	(1.08-1.13)
		≥ 13	Ref	
C08C	Calcium channel blockers with mainly vascular effects	< 9	1.17	(1.15-1.20)
		9-12	1.07	(1.05-1.10)
		≥ 13	Ref	
N02A	Opioids	< 9	1.26	(1.23-1.28)
		9-12	1.15	(1.12-1.18)
		≥ 13	Ref	
N05B	Anxiolytics	< 9	1.27	(1.24-1.30)
		9-12	1.11	(1.11-1.17)
		≥ 13	Ref	

*Adjusted for age, sex and comorbidity

The fifteen most frequently used therapeutic drug classes

5.5 STUDY IV

This paper sought to identify socioeconomic differences in the use of newly marketed drugs between 2000-2004. Data on 626 258 elderly persons from the SPDR, linked to the national inpatient register and the education register, were analyzed.

5.5.1 Overall new drug use

The mean number of drugs was 5.8, with low educated elderly using a higher number of drugs than high educated. In total, 45740 (7.3%) elderly persons aged 75-89 years were dispensed at least one NMD. The logistic regression analysis showed that NMD use was more common among younger elderly, men, people living in the capital of Sweden, Stockholm and with higher comorbidity index scores, after adjustment for age, sex, education, type of residential area, and comorbidity (Table 22). A total of 18 drugs met the inclusion criteria of a Swedish market introduction between 2000-2004 and having at least 350 users in our dataset. Overall, the most common new drugs were esomeprazole (1.5%), brinzolamide (0.8%), and travoprost (0.6%). The use of NMD relative to drugs in the reference class was highest for tiotropium (52.6%) and lowest for rosuvastatin (0.4%) as shown in Figure 5.

Table 22. Odds ratios (OR) of newly marketed drugs use

	NMDs users		OR*	(95% CI)
	n	%		
Age, y				
75-79	19791	7.6	Ref	
80-84	16764	7.4	0.93	(0.92-0.95)
85-89	9195	6.5	0.80	(0.78-0.82)
Sex				
Male	18278	7.3	Ref	
Female	27462	7.3	0.97	(0.95-0.98)
Educational Level, y				
≥ 13	8775	8.1	Ref	
9-12	13119	7.6	0.93	(0.90-0.95)
< 9	23846	6.9	0.84	(0.83-0.86)
Type of residential area				
Rural (H5+H6)	6343	7.2	Ref	
Urban (H2-H4)	31590	8.1	1.07	(1.04-1.10)
Stockholm (H1)	7786	7.1	1.20	(1.17-1.24)
Charlson comorbidity index score				
0	29963	6.7	Ref	
1-2	13353	8.5	1.30	(1.28-1.33)
3-4	2088	11.3	1.76	(1.69-1.84)
≥5	336	13.7	2.19	(1.97-2.43)

*Adjusted for age, sex, education, type of residential area and comorbidity

5.5.2 Education and new drug use

The low educated elderly persons had the highest mean number of drugs, while they had the lowest proportions of new drug use (Table 22). Highly educated used new drugs to a greater extent than low-educated, only etoricoxib and bimatoprost was more common among low educated. The greatest educational difference in new drug use was observed for oseltamivir (30% for high educated as compared to 5.0% for low educated). In the multivariate analyses (Figure 4), the "dose-response" effect of education on most new drugs was evident, except for brinzolamide, darbepoetin alfa, etoricoxib, bimatoprost and solifenacin. Low education was associated with lower probability of new drug use, even after adjustment for age, sex, education, type of

residential area and no. of drugs. Association between education and new drug use remained the same after adjustment of comorbidity (adjusting for age, sex, education, type of residential area and comorbidity); however results are not shown since the ORs were quite similar to model ii and model iii). Number of dispensed drugs was significantly associated with use of NMD. The likelihood of using NMD increased 16 percent with each additional drug used by the elderly (OR: 1.16; 95% CI: 1.15-1.16). Furthermore, low educated elderly women had a slightly lower probability of new drugs use than low educated men and type of residential area also played a role independent of education.

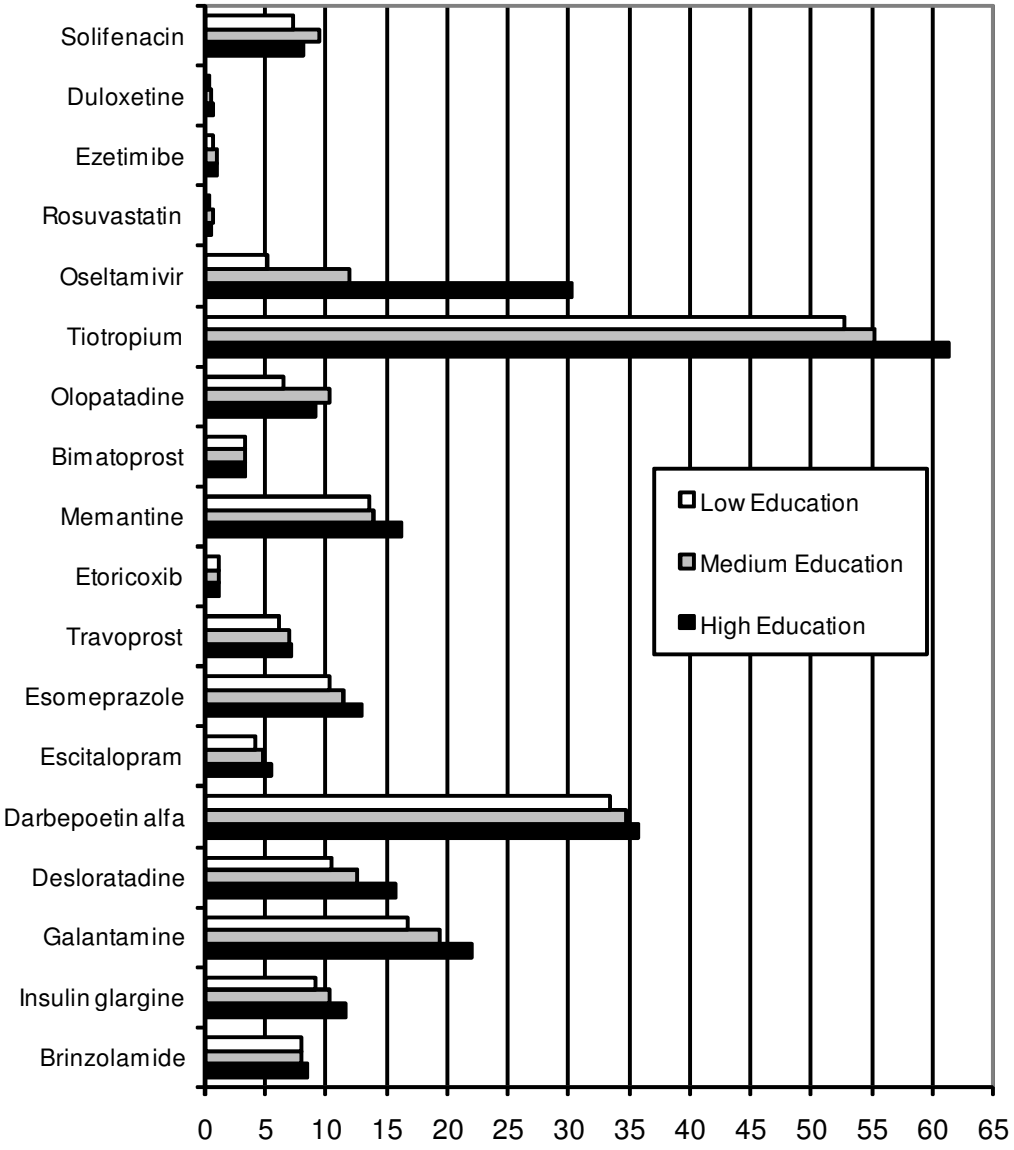

Figure 4. Frequency of newly marketed drugs stratified by educational groups.

6 DISCUSSION

6.1 MAIN FINDINGS

The main findings from this thesis can be summarized as follows:

6.1.1 Overall drug use

In *Study I, II and III,* we found that more than 80% of the elderly persons use at least one drug. The levels of drug use in the present study are similar to earlier findings from Sweden.[21,64] In line with previous studies,[154] the likelihood of drug use tended to grow with increasing comorbidity. Elderly persons living in institutions, e.g. nursing homes, had a higher mean number of drugs (6.3 drugs) than home-dwelling elderly (4.0 drugs) (*Study I and II*), mainly reflecting the higher comorbidity and functional limitations among the nursing home residents. This figure was slightly lower than found in two previous studies in Sweden where the average number of drugs used was 7.7 and 8.8, respectively,[27,64] which might be explained by differences in the measurement of drug use and time periods.

There were differences in drug use by educational level, even after controlling for age, sex, comorbidity, marital status and type of residential area (*Study III*). The mean number of drugs was higher among elderly with low education and low education increased the risk of drug use, which is consistent with previous findings.[69,137,139] However, our results do not further clarify to what extent the socioeconomic differences in drug use are due to patient or prescriber related factors.

6.1.2 Trends in drug use

Time trends showed that the proportion of the elderly population with drug treatment increased, as well as the average number of drugs, prevalence of polypharmacy and DDI, among elderly persons between 1992 and 2002 (*Study II*). The average number of drugs used by the community-dwelling elderly increased from 2.5 to 4.0 and for elderly living in institutions from 3.1 to 6.6 between 1992 and 2002. This partly reflects the increased use of existing drugs, but also the adoption of new drugs introduced on the market, such as ACE-inhibitors and SSRI antidepressants. This increase in drug use is in concordance with results from many other studies.[21,50,155-157] In Finland, the

prevalence of polypharmacy increased from 54% to 67% between 1998 and 2003 in a cohort aged 75 years and older,[157] and polypharmacy increased from 19% to 25% between 1991 to 1999 among community-dwelling elderly.[28]

We found that low educated elderly reported increase in the use of most types of drugs to a greater extent than high educated between 1992-2002, after controlling for age and gender. For the low educated, the highest increase in drug use was seen for antithrombotics agents, ACE inhibitors, and antidepressants, while analgesics and antipyretics treatment showed almost no change. For the high educated, the most pronounced increase in drug use was observed for antithrombotics agents, beta blocking agents, high ceiling diuretics, and ACE inhibitors. The high educated elderly reported greater increase in use of high ceiling diuretics, vasodilators, drugs for peptic ulcer and gastro-oesophageal reflux disease and laxatives compared to the low educated. Contrary to an earlier Swedish study,[156] we observed a decrease in the use of analgesic and antipyretic drugs. Further, when looking into differences between educational groups, this decline was seen only in the high educated. The increase in use of laxatives could reflect a higher prevalence of constipation in elderly persons, which in turn could partly be due to a higher use of drugs with constipation as a common side effect, e.g., opioids and calcium channel blockers. However, it could also be due to a higher inclination among physicians to prescribe these drugs.

6.1.3 Most frequently used drugs

The most frequently used drugs in our sample of elderly (*Study I*) were antithrombotic agents, beta blocking agents and high ceiling diuretics. The lower educated elderly used higher proportions of most investigated therapeutic drug classes (particularly high ceiling diuretics, analgesics, and antidepressants) except for antithrombotic agents, laxatives and cardiac glycosides, which were equally or slightly more common in high educated elderly. This pattern was largely similar in *Study III*. One British study of people aged 75 years and older found that a higher use of respiratory and central nervous system drugs (except hypnotics and anxiolytics) in lower social class and among lower educated.[68] Similarly, a Swedish ecological study on an urban Swedish population aged 15-64 years found increasing utilization of different ATC main groups (A, C, J, N and R) with decreasing area-based measure of SEP.[158] We found that the use of antidepressants was most common among the least educated. This is in

accordance with the expected social gradient in the burden of disease, as depression is more prevalent in lower socioeconomic groups.[159,160] Lipid lowering drugs were used to lesser extent by low educated elderly (*Study III*), which may represent an example of relative underprescription.[143,161]

6.1.4 Polypharmacy

Polypharmacy (use of five or more drugs) was observed in approximately half of the study populations (*Study I and III)*. In the literature, the prevalence of polypharmacy in the elderly has been reported to be between 4% and 78%.[23]

Education was associated with polypharmacy and excessive polypharmacy (use of ten or more drugs) after adjustment for age, sex, marital status, type of residential area and comorbidity (*Study III*). However, we did not observe any significant difference in occurrence of polypharmacy between different occupational and income groups (*Study I*). Elderly living in institutions, urban areas, of female gender, with advanced age and high comorbidity were more likely to be exposed to polypharmacy.

Further, polypharmacy increased more than twofold during the 10 year period among the SWEOLD elderly (18% in 1992 to 42% in 2002). Although polypharmacy increased significantly in both high and low educated, the increase was more pronounced in the high educated participants. Our findings regarding higher polypharmacy in low educated elderly are consistent with previous studies, from Ireland[55] and Italy.[134] Nobili et al. found that the number of drugs taken by Italian community-dwelling elderly increased with decreasing educational level.[134] In an Irish study on elderly people in primary care found that the relatively deprived cohort was more likely to be exposed to major polypharmacy (> or = five drugs) compared with monotherapy.[55] On the contrary, a study from the US found that highly educated older women may run the highest risk of polypharmacy.[137] In contrast, education and occupation were not associated with polypharmacy in a Finnish study.[28]

6.1.5 Inappropriate drug use

In *Study III*, almost one-third of the study population had at least one potential IDU. Low educational attainment was associated with a higher probability of at least one IDU, use of three or more psychotropic drugs and potential DDI, after controlling for age, sex, type of residential area and comorbidity. The association with education

tended to be stronger for ≥3 psychotropic drugs than the other individual IDU measures. The opposite relationship prevailed for anticholinergic drugs, and no association was observed for long-acting benzodiazepines. These results are in agreement with findings from previous studies in the elderly which have associated IDU with low SEP.[98,135,140] One study with information from eight European countries reported that potentially IDU was associated with patient's poor economic situation among home dwelling elderly.[140] Similarly, in France, subjects with high educational achievement were less likely to use potentially IDU (compared with 13.0% of men with a high educational level, 27.9% of women with a low educational level used at least one potentially inappropriate medication after controlling for age, gender, depressive symptoms, number of drugs used and self-rated health.[98] In another study conducted in Quebec, a higher prevalence of IDU was also observed among poor elderly subjects and among those with a low educational level.[142] In our study, increasing age, being a woman, living in a rural area and higher comorbidity were associated with the highest frequencies of IDU.

6.1.6 New drugs use

In *Study IV*, 7.3% of the elderly persons aged 75-89 years were dispensed at least one NMD. The literature on NMD use in old age is scarce and previous studies have only investigated a few NMDs, which makes it difficult to compare our finding to others. Our analysis showed that NMD use was more common among younger elderly, people living in the capital of Sweden, Stockholm, and with higher comorbidity index scores. The main finding was that elderly with a low level of formal education had a lower probability of being dispensed a new drug than the high educated elderly, irrespective of age, sex, type of residential area, comorbidity and number of drugs used. The consistency of our findings regarding 18 selected NMDs are in concordance with a Canadian population-based study on persons aged 65 and older, which reported that newer brand-name drug prescribing modestly increased with increasing income quintile, especially for selection of newer, brand-name antipsychotics, newer generic statins, and newer, brand-name ocular β-blockers.[107]

Most studies on NMD use include all age groups and not specifically the elderly. One study found a significantly higher utilization of new drugs, such as dihydropyridine calcium channel blockers and statins, in a district with a high percentage of university-

educated inhabitants.[143] Similarly, early users of celecoxib generally had high incomes and had paid out-of-pocket for their prescriptions.[104] Another study from the US on a noninstitutionalized civilian population also found higher use of new drugs in higher socioeconomic groups.[162] The reasons for the differences in health outcomes by several measures of SEP are being debated. Nevertheless, our findings regarding 18 differrent NMDs clearly indicate that the diffusion of new drugs into medical treatment favor one education group relative to another.

6.1.7 Gender differences

The mean number of drugs was higher among females (6.0 drugs) compared to males (5.5 drugs) in *Study III*. A particularly high prevalence of polypharmacy was observed in females (58%) and a similar pattern was found for excessive polypharmacy. There was a 32% increase in the odds of polypharmacy for females relative to males (OR 1.32; 95% CI, 1.31-1.33), after adjustment for age, type of residential area and comorbidity. This is in line with previous findings from Sweden[21,64,163,164] and other countries.[66,68,134,165] These gender differences in the elderly may be explained by differences in morbidity and symptoms. Females have for example a higher prevalence of thyroid disease, osteoporosis with pain and chronic venous insufficiency, whereas males are affected by ischemic heart disease earlier than females. However, there may also be gender-related differences in healthcare utilization, health behaviour and physicians' treatment biases.[166,167]

6.1.8 Measures of SEP differently related to drug use

There is still an ongoing discussion on what measures of SEP to use when studying socioeconomic inequalities in health.[122,168-170] One of the most commonly used measure is education. In *Study I*, we used all the three most commonly used measures of SEP (education, occupation and income). Although different dimensions of SEP are interrelated, it has been suggested that each capture different aspects of the social situation of an individual.[125] These three measures produce collinearity if they are included in the same statistical model, which will disturb the analysis. Therefore, we used them in separate analyses for drug use and polypharmacy. *Study I* demonstrated that education was associated with polypharmacy, after controlling for age and sex, although not statistically significant after additional adjustment for marital status, living

situation and comorbidity. However, there were no significant differences whatsoever in the occurrence of polypharmacy between different occupation and income groups. These results are in line with a study by Winkleby et al.[125] who found that higher education was the SEP measure most consistently correlated with health-realted behaviour. Therefore, we focused on education as a measure of SEP in the three subsequent studies. Education captures behaviour, knowledge and attitudes of the elderly[127,128] and these issues are of great importance with respect to drug use (see below). Educational level also captures purchasing power to some extent, through its correlation with occupation and income.[117]

6.2 METHODOLOGICAL ISSUES

The four studies in this thesis were retrospective cross-sectional studies based on population surveys and nation-wide registers. Limitations and validity of measures used in the analysis will be discussed below.

6.2.1 Study design

The cross-sectional nature of the data in this thesis is a important limitation because of the difficulty in determining whether the drug exposure preceded or followed the occurrence of the outcome.[171,172] In elderly populations, however, education has already been attained before the drug use, it seems unlikely that their educational attainment would be influenced by diseases mainly occurring later in life. However, drug use is probably a response to disease in most elderly patients. Another issue is the retrospective characteristic of the study design, which has implications for the quality of the exposure information (see section about information bias below).[173]

6.2.2 Bias

A systematic error that leads to incorrect estimates of the association between the exposure and outcome is called bias. Bias may be introduced through the study design, data collection and data analysis.[172]

6.2.2.1 Selection bias

Selection bias arises when the data come from samples that are not representative. The SWEOLD surveys (S*tudy I & II*) represent approximately 1 per thousand of the Swedish population aged 77 years and older for the studied years. The participants were

selected randomly across Sweden and the surveys include both institutionalized and home-dwelling elderly. Proxy interviews were carried out for unhealthy individuals. Therefore, most people who had reduced physical and cognitive function were included. Age and gender distribution reflected national figures for both survey waves in 1992 and 2002.[174] Also, refusals did not differ between participants as regards the major demographic features. Response rates in the SWEOLD studies were high; 96% in 1992 and 89% in 2002.[175]

S*tudy III & IV* were based on the SPDR linked to the national inpatient register and the national education register, covering the whole Swedish population aged 75 years and older. Thus, the participants should adequately reflect the elderly population in Sweden. It should be pointed out that elderly who were not dispensed any drugs during the study period were not registered in the SPDR and, therefore, not included in the analyses. This may imply that the healthiest among the elderly were excluded. However, they constitute only a small proportion. The upper age limit of the study population was restricted to 89 due to incomplete data on education for individuals 90 years and older. Hence, the analyses were based on the elderly aged 75-89 years registered in the SPDR, which corresponds to 85% (626 258/736790) of the Swedish population aged 75-89 years in September 2005.

6.2.2.2 Information bias

Information bias can happen at any time during a study. For *Study I and II*, information on drug used was based on personal interviews, which may lead to incomplete recall of the actual drug use.[176,177] There is then a risk of *recall bias* wich is one of the most important types of information bias. We were not able to analyze the impact of recall bias in detail, as we did not have register information on medicine use to compare the SWEOLD data with. However, we do not expect there to be systematic bias with respect to SEP, since earlier studies have reported high reliability and validity in surveys with self-reported drug use.[178] A Dutch study among low and middle income groups found that concordance between survey and register data differed little between socioeconomic groups.[179] Also, the question regarding current drug use as "use of drugs during last 2 weeks" might have limited recall bias due to the short recall time. Further, in these studies the respondent were asked to bring drug containers and prescriptions to the interview, to verify the current use of drugs.

Drug use data in *Study III and IV* were obtained from data on drugs dispensed at the pharmacy, which circumvents the potential recall bias that may arise in survey data. Lau et al. compared pharmacy records with data from home inventories, and reported a high correlation between the two data sources when the exposure time-window for pharmacy records was 3 months, as in *Study III and IV*.[180] However, not all prescriptions are filled at the pharmacy and not all drugs purchased are actually used. Another limitation is that the SPDR contains prescription data only, and therefore is incomplete for OTC drugs, such as salicylic acid, paracetamol, ibuprofen, some anti-ulcer drugs, laxatives and some antitussive drugs. Also, the SPDR does not contain data about drugs prescribed in hospital and dispensed from drug storerooms (used in some nursing homes). Therefore, the actual number of individuals with polypharmacy is likely to be higher than the figures calculated in this thesis.

The measure of comorbidity in *Study III and IV* was collected from the National Inpatient Register and was not biased by self-report, but it was limited to inpatient care. Hence, it only covers the most serious morbidity. Information bias in the measurement of educational level was minimized by collecting this information from the national Education Register. Also, educational level remains relatively stable over time for older persons.

6.2.3 Confounding

Confounding is one of the central issues in epidemiological research, leading to distortion in estimating the association between an exposure and outcome. Confounding is the mixing of effects between the exposure, the outcome and a third variable known as confounder.[3,172] Drug use, polypharmacy, and IDU are closely associated with risk factors that are also related to the SEP of the elderly. These potential factors include demographic, healthcare system-related and patient health-related factors and could be important determinants of the increased risk of polypharmacy and IDU in people with lower SEP. In our studies, major potential confounding factors were included and their effects were controlled by multiple regression models and stratified analyses. Possible confounders, including age, sex, marital status, living situation (community dwelling or living in institution), self-reported health, comorbidity, type of residential area (urban or rural) and number of drugs, were taken into account. However, even after controlling for many variables,

residual confounding may still be an issue. There may be factors we have not been able to account for. For example, previous research papers have shown that the NMD prescribing may be affected by the prescriber's surrounding social system, such as location, size and type of practice.[104,115] Contextual factors (e.g., therapeutic traditions) at health care centers may also be relevant when physicians select a new drug for the patient, as previously suggested.[68] We have, however, included type of residential area in the analysis, which may capture a crude confounding effect related to the living environment.

6.2.4 Random error

Random error, or chance, leads to lack of precision and is a main concern of epidemiological studies, which may lead to incorrect results. Reduction in random error and increase in the precision can be achieved by increasing the study sample size and modifying study design to increase efficiency.[172] In *Study I and II,* the statistical power was limited, due to the small number of subjects in the stratified analyses and therefore, random error might have played a role. *Study III and IV*, on the other hand, were based on one of the largest study samples of older people in Sweden. Nevertheless, the role of random error cannot be completely ruled out in the stratified analyses, where smaller groups are examined, although unlikely.

6.2.5 Generalizability

Generalizability is the validity of the inference that the findings of a study pertain also to people outside the studied population.[181] High response rates are needed to ensure generalizability and for extrapolating the findings to a wider population. However, there is no consensus on acceptable response rates.[182,183] A response rate of les than 70% has traditionally been considered poor and to be interpreted with caution.[183] The figures from SWEOLD (*Study I and II*) on age, sex, and percentage of people living in institutions are representative of the elderly Swedish population, and the response rates were high. The study population in *Study III and IV* covered the majority of the population aged 75-89 years in Sweden. However, still, nation-specific regulations and therapy traditions surrounding drugs may make it difficult to generalize the results from this thesis to other countries.

6.2.6 Strengths

One of the main strengths of this thesis is the use of two different types of data collection (the SWEOLD surveys and the SPDR). Drug use can be measured by several different methods at the population level. There are two major methods of data collection; self-reported drug use by surveys and register data, which have both been covered in this thesis.

Sweden has an extensive tradition of using administration-based registry data, both for the presentation of official statistics and research. Generally, register databases have proved their value as powerful research tools and studies comparing drug exposure according to different sources have demonstrated register data as one of the most accurate sources of drug use information.[3,51,180] Advantages of these databases include rapid, cost-saving and efficient access to information on drugs and health services on large populations with diverse exposures. Additionally, some sources of bias, such as recall bias, response bias and selection bias may be kept at a minimum. This is the first dissertation using the newly established SPDR. The main strengths of the register-based analyses in this thesis lie in their nearly full population coverage and the linkage of different registers. Most prescription databases in other countries are developed for administrative purposes and cover large populations. However, the populations are often selected and represent only subgroups of the total population.[180,184-186]

Data from the SWEOLD surveys have been used in many different research papers.[148,187-191] In relation to the main sociodemographic variables, the study population may be regarded as representative of the elderly population aged 77 years and older in Sweden.[145] In order to ensure this, SWEOLD includes institutionalized and cognitively impaired individuals, and proxy interviews. Response rates for both SWEOLD surveys were high compared to other population based surveys. Also, the SWEOLD surveys included information on OTC drugs, which are lacking in the SPDR. In addition, the SWEOLD covered some possible confounders, such as living conditions, which were not available in the register studies.

6.3 POSSIBLE MECHANISMS

Taken together, all studies included in this thesis support the idea that the risk of drug use, polypharmacy and IDU is increased, while the probability to be treated with

NMD is decreased, in older people with low education. There are many possible mechanisms through which education could affect drug use, IDU and use of NMD.

6.3.1 The relationship between education and health

Understanding how the educational composition of the elderly population will influence drug use is important for good monitoring, planning and interventions for drug use in the society. Highlighting differences in drug use due to educational level seems to be one step forward in the management of drug treatment for the elderly.

However, the pathway between education and drug use is not straightforward, but rather very complex and diverse. Different causal mechanisms behind the association may have different effects on the relationship between drug use and educational attainment of older people. Material resources may be one explanation, as these will probably have a direct effect on health. Better educated older people generally have greater material resources (higher pension income) than those with low education. Health related behavior is another possible explanation. Middle-aged people in Sweden with high educational attainment smoke less, eat better, and exercise more than those with low education.[192] Finally, high educated people act faster in adapting new technologies, are better prepared to comply with treatments,[193] and are able to manage chronic conditions better than low educated.

Social differences in drug use may be caused by social differences in health status. It is well established that health-related problems are more frequent among the lower social classes than among the more prosperous part of the population.[117] This difference in health status produces different levels of medical need. Given equal access to drugs and similar health and illness behavior in different socioeconomic groups, social differences in health status can result in similar differences in drug use.[194,195] However, the social differences in drug use identified in our studies are probably not entirely due to social differences in health status, as a measure of health status (comorbidity) was adjusted for in the analyses.

6.3.2 Patient related factors

Patients' knowledge about their treatment, health and expectations may play a role. Educational level of elderly may also have a an impact on demand and expectations for new and better drug treatments. Elderly people with high educational level may

have a better knowledge about different types of drug treatments, new drugs and also know better how to use these resources in order to improve health. Arguably, patients with high education may have greater access to drug information and may be more active in the patient-physician communication. Thus, patient educational level may influence patient convenience, acceptability and request for a drug.[196] One example from *Study IV* is oseltamivir, which showed the strongest association with high education among the NMDs. Oseltamivir is an antiviral drug that is used in the treatment and prophylaxis of both Influenzavirus A and Influenzavirus B, and is more costly than the alternatives [197]. With increasing fears about the potential for a new influenza pandemic, oseltamivir received substantial media attention. Governments, corporations, and even some private individuals stockpiled the drug. Thus, one potential explanation of greater oseltamivir use among higher educated individuals (medical professionals, managers etc) is better awareness of treatment alternatives and better communication skills.[116]

A possible explanation for social differences in drug use is differences in predisposing characteristics between socioeconomic groups. Different attitudes, values, and knowledge about health between socioeconomic groups lead to differences in health and illness behavior. Given identical health status and access to drugs in socioeconomic groups, reactions to similar symptoms and diseases may vary between socioeconomic groups and result in differences in drug use.[194,195] Social differences in health and illness behavior between educational groups may be present and may explain the results in this thesis, since we could not control for them in our analyses.

6.3.3 Influence of access to prescribed drugs

Pharmaceuticals are subsidized in Sweden and all residents who have spent 1800 SEK on their drug therapy are eligible to get free prescribed drugs for the remaining of a 12 months period through the social welfare system.[198] Differences in access to drugs may result in social differences in drug use. The access to drugs depends on the structure and function of healthcare system, e.g. reimbursement of pharmaceuticals and health insurance policies. If purchasing power is important to access to drugs, social differences can emerge, as low income elderly people might not be able to pay for drugs. In Sweden, where drugs are subsidized, financial difficulties with paying for the

medicines may, however, not play a major role for the observed differences in drug use in this thesis.

6.3.4 Prescriber related factors

The variability in the nature and meaning of knowledge among prescribers for different socioeconomic groups can also play a role. This aspect has been explored by one paper from the UK,[112] stating that new drugs come into practice from hospital doctors' awareness of new drugs to the assimilation and interpretation of evidential sources. In their study, the determinants of new drug prescribing were interconnected within four forms of knowledge: scientific knowledge, social knowledge, patient knowledge and experiential knowledge.[112] This variability in physicians' prescribing of new drugs relates not only to levels of acquired knowledge, but also to differences in subjective and ideological beliefs.[113,114] Bradely et al. found that patient social class and education influenced GPs' prescription habits.[199]

There may be additional mechanisms than those mentioned above responsible for creating social differences in drug use, polypharmacy, IDU and use of NMDs and these suggested mechanisms may interact with each other.

7 CONCLUSIONS

- This thesis has identified inequalities in trends, quantity and quality of drug use, and use of newly marketed drugs among older people in Sweden, a country where the public health policies have tried to minimize these inequalities.

- Drug use was high, with 9 out of 10 elderly persons using at least one drug and a mean number of 4.4 drugs. Most elderly persons were exposed to polypharmacy (concurrent use of five or more drugs). The low educated elderly had a higher probability of polypharmacy and excessive polypharmacy (concurrent use of ten or more drugs).

- Advanced age, female gender, widow/widower, low level of self-rated health, multiple diseases, living in an institution and living in urban areas increased the probability of polypharmacy.

- For most kinds of drugs, the lowest socioeconomic groups had the highest prevalence of use.

- The overall drug use, mean number of drugs used, and potential drug-drug interactions have increased during 1992-2002 among the elderly. Polypharmacy increased more than twofold during this period. These changes were most prominent among low educated women.

- Inappropriate drug use was common and low educational attainment was associated with an increased likelihood of inappropriate drug use in elderly persons.

- Use of newly marketed drugs was more common in high educated elderly persons and increasing educational attainment was associated with increased possibility of a prescription of a newly marketed drug.

8 IMPLICATIONS

Drugs are commonly used by the elderly and pose a large burden on health sevices in the society. Moreover, the absolute number and the proportion of older people who use drugs are expected to further increase over the next few decades. This thesis provides a better insight into how educational level of the elderly is related to the quantity, quality and use of new drugs. The major findings are of scientific relevance for theoretical aspects, clinical practice, public health, and prevention of inequities in drug use.

In Europe, socioeconomic inequalities in health have been an important public health policy issue and concerns have been raised for effective strategies to reduce socioeconomic inequalities in health.[200] A similar emphasis and approach could be designed for socioeconomic inequalities in drug use. Concerning clinical practice, it is important that drug therapy is carried out without bias due to the SEP of the patient. SEP was associated with polypharmacy and IDU, suggesting that interventions to reduce inequalities may focus on low socioeconomic groups of elderly.

The findings in this thesis suggest that the majority of elderly Swedes today have polypharmacy and the use of drugs in elderly people is often inappropriate. Also, despite the introduction of universal access to healthcare and subsidized pharmaceuticals for all, it appears that there are still socioeconomic differences in the quantity and quality of drug use. Several studies recommend interventions to improve the appropriateness of prescribing in elderly patients, such as training in geriatric pharmacotherapy, development of geriatric medicine services, pharmacist involvement in patient care, and computerized decision support.[201] We will also argue for an increased focus beyond pharmacological appropriateness. One such approach is to build a strong communication between prescribers and their patients, regardless of the SEP of the patient. Good communication and concordance between patients, their relatives and health care personnel is essential for medication safety.

9 FUTURE DIRECTIONS

There is convincing evidence of an increased use of drugs in people with low SEP. Although there have been numerous studies and quality improvement programs involving quality and quantity of drug use in the elderly, most have focused on clinical aspects. We were not able to use clinical information for assessing the appropriateness of the polypharmacy and new drug use in the elderly patients. Therefore, future research is warranted for assessing the appropriateness of polypharmacy and new drugs in different socioeconomic groups. Qualitative studies are needed to study patient and prescriber related factors and how they interplay.

All persons get all their drugs cost reimbursed over a certain limit in Sweden. The maximum annual out-of-pocket amount is 1800 SEK. There is a need for further research to evaluate whether the current reimbursement system impacts drug use and its variation in different socioeconomic groups of elderly.

With the introduction of the SPDR in July 2005, a new and exciting era for pharmacoepidemiological research has been opened up for national and international researchers.[42] The SPDR represents one of the largest population-based pharmacoepidemiological databases in the world. By employing record linkage property of the SPDR at patient level, there is great potential to study drug use and disease associations and also the risks, benefits, effectiveness and health economical aspects of drug use. One recommendation for future research is to link the SPDR with drug safety data at the MPA and to investigate if the socioeconomic differences also exist in the ADRs and drug safety signals in Sweden. This will strengthen the social side of pharmacovigilance field.

Finally, our findings also underline the need of continuous monitoring of drug use in different socioeconomic groups and the recently established SPDR may be useful in this regard.

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12 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2008

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer´s disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer´s disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer´s disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella T. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer´s disease

Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Erika Jonsson Laukka. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.

Rehnman Jenny. The role of gender in face recognition. (Stockholm University)

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

2008

Joachim Gavazzeni. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Alessandra Marengoni. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Suvi Rovio. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Weili Xu. Diabetes mellitus and the risk of dementia: a population-based study.

Bettina Meinow. Capturing health in the elderly population: Complex health problems, mortality, and the allocation of home-help services. (Stockholm University)

Neda Agahi. Leisure in late life. Patterns of participation and relationship with health.