

Public Health Aspects of Pharmaceutical Prescription Patterns

Exemplified by treatments for prevention of cardiovascular disease

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Public health aspects of pharmaceutical prescription patterns: Exemplified by treatments for prevention of cardiovascular disease.

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ABSTRACT

Public health aspects of pharmaceutical prescription patterns: Exemplified by treatments for prevention of cardiovascular disease. Louise Silber.

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Main aim: To study patterns and trends of dispensed prescriptions, to explore what proportion of the population is exposed to some of the more prevalently prescribed pharmaceuticals, and to find possible ways of measuring drug-induced adverse symptoms in the population. Further, to illuminate conditions surrounding prescribing in primary prevention of cardiovascular disease.

Methods: In three descriptive studies of prescription patterns, prescription data at aggregate level from a Swedish county were analysed retrospectively, and proportions were calculated. Data from the first ten years of the studies were obtained from a local prescription study, and data from another five years were local data from a national prescription survey. Data from a Danish database (OPED), with data at the individual level, were used for a prescription sequence symmetry analysis, and when Swedish national prescription data at the individual level became accessible, they were used for calculations of drug prevalence in the entire Swedish population. In a qualitative analysis of interview data, a phenomenographic approach was used.

Main results: The purchase of pharmaceuticals on prescription almost doubled in the studied county in the period 1988-2002. Some common pharmaceuticals that increased to a great extent among the older part of the population were cardiovascular preventive drugs, such as antihypertensive and lipid modifying agents, and also hormone replacement therapy for women. In 2005, over half of all Swedish citizens, aged 60 or over, purchased antihypertensive or lipid modifying preparations during a six-month period. The different views that were found among GPs, regarding beliefs and practical management of primary prevention of CVD, could be interpreted as a reflection of the complexity of patient counselling in primary prevention in practice.

Conclusion: The increase in dispensed prescriptions over the 15 years and the magnitude of the prevalence of the studied pharmaceuticals, such as antihypertensive, lipid modifying and hormonal treatments, which to a great extent are used by 'healthy' people, point to the need of following-up both beneficial and harmful consequences on public health. The prevalence of preventive treatments together with the variation in views of administration of primary prevention of cardiovascular disease, also point to the need of clarification of guidelines regarding pharmaceutical primary prevention and encouragement of therapy discussions among GPs.

Key words: pharmacoepidemiology, prevalence, drug use, adverse effects, primary care, primary prevention, cardiovascular, antihypertensives, lipid modifying agents, public health, Sweden.

SAMMANFATTNING

Läkemedelsförskrivningsmönster ur folkhälsoperspektiv - exemplet primärprevention av kardiovaskulär sjukdom. Louise Silwer

Syften: Att studera mönster och trender i mängden expedierade receptläkemedel, att undersöka hur stor andel av befolkningen som använder (köper ut) olika grupper av receptläkemedel, samt att finna möjliga metoder att mäta förekomst av läkemedelsinducerade symptom och biverkningar i befolkningen. Ytterligare ett syfte var att undersöka och belysa förhållanden runt läkemedelsförskrivning i samband med primärprevention av hjärt-kärlsjukdom.

Metoder: I tre deskriptiva studier analyserades receptdata från Halland retrospektivt. I en av dem relaterades data till befolkningssiffror för uppskattning av läkemedelsprevalens. När receptdata på individnivå blev tillgängliga 2005 beräknades den faktiska läkemedelsprevalensen för vissa utvalda läkemedel. Danska data på receptexpeditioner användes för analys av förskrivningssekvenser av två läkemedelsgrupper. I en kvalitativ studie analyserades intervjudata fenomenografiskt.

Resultat: Mängden expedierade receptläkemedel nästan fördubblades i Halland under de 15 åren 1988-2002. Några av de vanliga läkemedelsgrupper som ökade mest markant bland den äldre delen av befolkningen var läkemedel för förebyggande av hjärtkärlsjukdom, som blodtryckssänkande och blodfettssänkande medel, samt hormonsubstituerande läkemedel för kvinnor. Mer än hälften av alla svenska invånare över 60 år köpte ut blodtryckssänkande eller blodfettssänkande receptläkemedel under ett halvår 2005.

De varierande synsätt som förekom bland distriktsläkarna, beträffande tilltron till möjligheterna att förebygga hjärtkärlsjukdom genom primärpreventiv behandling och beträffande hur patientomhändertagandet bör skötas i praktiken, kan tolkas som ett uttryck för komplexiteten inom terapiområdet.

Slutsats: Ökningen i mängd expedierade receptläkemedel under de 15 åren tillsammans med prevalensen av de studerade läkemedelsgrupperna som t ex blodtryckssänkande medel, blodfettssänkande medel och hormonbehandling, som i stor utsträckning används av friska individer, pekar på betydelsen av intensifierad uppföljning av såväl positiva som negativa effekter på folkhälsan. Tillsammans med variationen i synsätt på möjligheterna till faktiskt förebyggande av hjärt-kärlsjukdom genom primärprevention, visar det också på behovet av förtydligande av behandlingsrekommendationer och riktlinjer samt betydelsen av kontinuerliga terapidiskussioner bland primärvårdsläkare.

LIST OF ORIGINAL PUBLICATIONS

I. Silwer L, Johansson E, Stålsby Lundborg C. Drug prescribing in public primary care centres. Results from prescription studies 1988-1997 in the county of Halland, Sweden. *Scand J Prim Health Care* 2002;20:236-41.

II. Silwer L, Stålsby Lundborg C. Drug prescribing in primary care related to patient age. Trends in a ten-year repeated prescription study in a Swedish province. *Eur J Gen Pract* 2005;11:23-24.

III. Silwer L, Stålsby Lundborg C. Patterns of drug use during a 15 year period: data from a Swedish county 1988-2002. *Pharmacoepidemiol Drug Saf* 2005;11:813-20.

IV. Silwer L, Petzold M, Hallas J, Stålsby Lundborg C. Statins as cause of NSAID use -an analysis of prescription symmetry. *Pharmacoepidemiol Drug Saf* 2006;7:510-1

V. Silwer L, Stålsby Lundborg C, Petzold M. Prevalence of purchase of antihypertensive and serum lipid-reducing drugs in Sweden - individual data from national registers. (Submitted).

VI. Silwer L, Wahlström R, Stålsby Lundborg C. Views of primary prevention of cardiovascular disease – a qualitative analysis of interviews with Swedish GPs. (Submitted).

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ABBREVIATIONS, DEFINITIONS AND EXPLANATIONS

ATC	Anatomical Therapeutic Chemical classification. =Classification system for drugs, administered by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo
CVD	Cardiovascular disease
DDD	Defined Daily Dose =The assumed average maintenance dose per day for a drug used for its main indication in adults
DDD/TIND	Defined Daily Doses per 1000 inhabitants and day
GP	General Practitioner at primary care centres
ICD-10	International Classification of Diseases
OTC	Over-the-counter =Pharmaceuticals sold without prescription
PDD	Prescribed daily dose = The average daily dose prescribed, as obtained from a representative sample of prescriptions
SEK	Swedish krona
Pharmaceutical	=A substance used in the treatment or prevention of a disease
Drug	=A substance used in the treatment or prevention of a disease

PREAMBLE

My curiosity about how prevalent drug treatments actually are, or what percentage of the population that is exposed to pharmaceuticals, originated from observations in my daily work. My perspectives were both from behind the pharmacy counter, and from my work with feed-back reports to prescribers, particularly General Practitioners (GPs) in the county of Halland, in south-west Sweden. The feed-back reports contained analyses on numbers of dispensed prescriptions, and GPs' choices of drugs, in comparison to those of other prescribers. These comparisons were made possible by a local prescription study in Halland, lasting ten years, 1988-1997. Watching the drug cost grow, year by year, also stimulated an exploration of the prescription data, to find an explanation. Gradually, my personal interest passed from prescribing patterns or 'drug choice', from the perspective of the prescriber / general practitioner, to 'prevalence of drug exposure' in the population. My studies in Public Health and my interest in toxicology further led to expectations of possibilities of measuring adverse symptoms among drug treated individuals. Data on prevalence of adverse effects or symptoms, combined with prevalence of drug exposure, could make possible estimations of numbers of individuals who could be at risk of suffering from adverse effects. Knowledge of prevalence of adverse effects among drug users could also provide the prescriber with some counterbalance, when considering and deciding on preventive drug treatment.

1. BACKGROUND

1.1. General background

1.1.1. Pharmaceuticals, pharmacoepidemiology and public health

The most commonly used treatment in Western health care is the prescription of pharmaceuticals. How they are used will therefore have consequences for the quality and the priorities of health care, as well as for the safety of patients. The cost of pharmaceuticals as a proportion of health care expenditure varies in different countries, and the cost is increasing in some countries and decreasing in others (1).

Drug exposure and differences in the quality and quantity of drug use, can be studied through so called drug utilization research or pharmacoepidemiological research. Drug utilization was defined by WHO in 1977, as *'the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences'* (2). The main aim of drug utilization research is *'to facilitate the rational drug use in populations'*. Drug utilization research, can be divided into (i) descriptive studies, which describe patterns of drug utilization and also identifies problems deserving more detailed studies, and (ii) analytical studies, which aim at linking data on drug utilization to figures on morbidity, outcome or quality of care (2). Rational use of drugs is a complex issue with a goal that is difficult to achieve, defined as follows: *'that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community'* (3)

Pharmacoepidemiology, the bridge between epidemiology and clinical pharmacology, has been defined as *'the study of use and effects of drugs in large numbers of people'* and can be useful in providing information about the beneficial and harmful effects of drugs, thus permitting a better assessment of the risk/benefit balance for the use of any particular drug in any particular patient (4). Drug utilization research is thus an essential part of pharmacoepidemiology. Over time, the distinction between these two terms has become less sharp, and they are sometimes used interchangeably. Nevertheless, drug utilization studies mostly employ various sources of information that focus on drug sales or prescription patterns, whereas the term pharmacoepidemiology most often implies populations, in which drug use can be expressed in terms of incidence and prevalence of drugs. Drug prevalence is defined as *'the percentage of a population that is exposed to specific drugs within a given time period'*, and drug incidence is *'the percentage who started to use the drug within the selected period'* (2). In the present studies 'exposure' means: having been

dispensed at least one prescription during the defined period of time. When discussing 'drug use' or 'drug exposure', an obvious problem is that (without the aid of a surveillance camera) we can never know whether the drug was actually ingested, or if the actual intake was by the individual the medicine was intended for, at the intended doses and intervals.

Drug utilization research and pharmacoepidemiology together can increase the mass of knowledge regarding (i) pattern and trends of drug use, (ii) determinants and quality of drug use, and (iii) outcomes of drug use. To describe and present this for single drugs or categories of drugs, a common language is needed, both for drug substances/classes and for the amount. For drug substances/classes, the hierarchical Anatomical Therapeutic Chemical (ATC) classification, that has been developed by WHO, is recommended as a common language for use in research (5). For the amount of drugs, the recommended measure is usually defined daily doses (DDD), defined as the average maintenance dose of the drug, when used on its major indication in adults (5), and DDD per 1000 inhabitants and day (5), the so called 'therapeutic intensity', used as a surrogate measure for the point prevalence (6).

Pharmacoepidemiology is a branch of public health (7). Public health has been defined as *'the science and art of promoting health, preventing disease, and prolonging life through the organized efforts of society'* (8). Health promotion, which is one part of public health, has been defined as *'the process of enabling people to increase control over and to improve their health'* (mostly a social and political process) (8). Since this includes measures to prevent deterioration of health, there is a frequent overlap between the content and strategies of 'health promotion' and 'disease prevention', but disease prevention is said to *'cover measures not only to prevent occurrence of disease, such as risk factor reduction, but also to arrest its progress and reduce its consequences once established'*, an action that usually emanates from the health sector (8). Pharmaceutical treatments are widespread tools in preventive work nowadays. The optimal level of use of this tool is however unknown.

1.1.2. The Swedish population and the Swedish healthcare system

There are around nine million inhabitants in Sweden, and between 1988 and 2005, the population increased by 7% overall, and by 4% in the 65+ age group (9). The population is, according to calculations by WHO, the fourth healthiest population in the world, measured in healthy life expectancy (HALE). The life expectancy at birth is 81 years (10), and the population of Halland, a county in the south-west of Sweden, has the longest life expectancy in Sweden (11).

The provision and financing of health services for the entire population is a public sector responsibility, primarily administered by the county councils. The central government establishes basic principles for the health services through laws and ordinances. The Health and Medical Services Act of 1982 lays down that people shall be offered health services of good quality on equal terms and easily accessible to all. The services provided shall respect the patient's integrity and his right to make his own decisions. The key tasks of the National Board of Health and Welfare (Socialstyrelsen) are to evaluate the health services provided, to see whether they correspond with the goals laid down by the central government, and to draw up national guidelines for good medical practice (12).

The primary level of health care, to which people should be able to turn to with any health problem, is organized, mainly by the county councils, in health centres with general practitioners, nurses, midwives and physiotherapists (12). The number of physicians has increased over the last twenty years. In 2005, there were approximately 1800 inhabitants per physician in primary care or GP (13), and 310 inhabitants per physician (when divided by all physicians) (14). Around half of the visits to doctors in public care were primary care visits in the year 2000, and half were visits to hospital specialists (15). One fourth of the visits were to private care (publicly financed) around the year 2000, after an increase during the past 20 years (15). The proportions of private care varied from a few percent and up to more than forty percent, contemporaneously, in different counties in Sweden (13).

1.1.3. Pharmaceutical preparations in Sweden

In Sweden, the Medical Products Agency (Läkemedelsverket) is the government authority responsible for the registration and control of pharmaceutical preparations. The number of registered products doubled between 1992 and 2003, from 3000 to 6000, and had risen to 7000 by 2006 (12, 14-15). This increase was due to the change from a restrictive to a more liberal attitude towards synonymous or similar drugs, after entering the European Union in 1995. The costs for pharmaceutical preparations as a proportion of total health care expenditure increased considerably between 1990 (9%) and 2000 (15%), and has thereafter slightly decreased (14). The reimbursement system has changed several times over the last 20 years, but over the years, there has been a constant 'high-cost ceiling' (annual maximum patient payment) which is periodically updated (at present: SEK 1,800), and the actual patient out-of-pocket costs, in per cent of total cost for prescribed pharmaceuticals, has fluctuated between 22% and 28% over the years (14). The system accepts a maximum of three months supply per dispensing. The state-owned National Corporation of Swedish Pharmacies (Apoteket AB) has had the sole and exclusive right to retail medicines since 1971 (12).

1.1.4. Data sources of prescriptions and pharmaceutical sales

Data on prescriptions and pharmaceutical sales are in different studies collected from sales from wholesalers to pharmacies, from dispensed prescriptions in pharmacies, or from (computerized) patient records. From sales data, neither the age and sex of the patient, nor any data regarding the prescriber, could be accessed. Computerized record systems in primary care could make prescription patterns inside the system easily accessible, but comparisons to other categories of prescribers, outside the system, could not be made. Neither could data from record systems give answers as to what prescriptions that were actually dispensed.

In Sweden, sales data, based on sales from drug wholesalers to pharmacies, measured in DDD, have been available as routine data for about 30 years. About 20 years ago, once all pharmacies had been computerized, it became possible to perform 'local prescription studies'. This was a temporary collection of data regarding number of dispensed prescriptions, the drug, the prescriber (e.g. category and name), health care facility (category and name) and patient data such as age and sex. The possibility hereby, to actively collect data for a defined geographic area and period, by manual coding, was present for about ten years before the start of continuous routine collection of national prescription data, at aggregate level, 1996-1997. The national prescription data routinely collected since then, includes all prescription drugs, reimbursed or non-reimbursed.

Until July 2005, there had been limited possibilities in Sweden to keep databases with information on dispensed prescriptions at the individual level, to facilitate calculation of drug-prevalence. The only sources of estimation of drug prevalence earlier had been two research projects with data from smaller populations of voluntary individuals (16). For the entire population, these data have been available only since July 2005 (17). Data on self-reported drug use have been possible to retrieve from a national, recurrent survey of living conditions; an interview investigation of 7500 individuals yearly since 1974 in Sweden, the ULF study (18).

Different obstacles to measuring drug prevalence occur in different countries. Diverse pharmacy-, insurance- or reimbursement-systems divide or reduce the prescription data records, and different rules for over the counter (OTC) drug sale restrict the completeness of data. In some countries, databases with data on individuals have been established. For example in Denmark and Finland, databases that cover the entire population, at the individual level, have been established since several years (6, 19). Data from the Danish database is accessible to the public, through the Internet, since a couple of years ago (20). In

Norway individual data have been registered since 2004 (21), and in Iceland since 2002 (personal message). Published reports on drug prevalence in the general public are however scarce, and vary in ways of presenting data, both in the Swedish and in the international literature.

1.1.5. Adverse effects from pharmaceuticals

Fundamental principles of modern medical ethics are beneficence and non-maleficence (22). Pharmaceutical treatment is always accompanied by a risk of adverse effects, to an often un-known extent.

An adverse drug reaction has been defined by WHO, more than 30 years ago, as *‘a response to a drug, that is noxious and unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function’*. Several other definitions have been formulated, and one of them, a new, wider one from WHO by Edwards and Aronson 2000 is: *‘An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product’* (23). After collecting data of adverse effects, there are two different approaches: demonstrating safety and demonstrating harm, of which safety is more difficult, since it can only be demonstrated to a limited degree (24).

In Sweden, there is a system of spontaneous reporting of adverse effects to the Medical Products Agency. The medical profession is obliged to report serious and “new” side effects, and the reports are stored in the Agency’s database (25). Regarding new pharmaceutical preparations, all suspected adverse reactions should be reported. Recently, there have also been some tests with reporting from the general public (internal message, Apoteket AB). With both kinds of reporting, the patient, or in the first case even the doctor, must have associated the symptom to the ingested medicine. Based on the collected data, there are however no possibilities to calculate prevalence of common and un-serious, or rare and serious adverse effects, of a specific pharmaceutical in an unselected population.

Data on adverse effects are mainly gathered from clinical studies of new drug agents, but the designs of these studies often lead to limitations in the possibilities of finding ‘rare’ adverse effects. Participants in clinical trials are seldom representative of the general population. One example is that in the general population, the prevalence of one or more additional diseases among adults in primary health care is almost 40% (7). At the time of marketing of a new drug, the number of patients treated is of the order of a few hundred to a

few thousand. This precludes identifying adverse effects with an incidence of less than 1/100 to 1/1000. When the drug is then marketed, it may be taken by millions of people and rare adverse effects may appear. Even if the effects are rare, they may still have a substantial public health impact, if the drugs are taken by for example 100 000 new patients worldwide every day, and the reaction is disabling or life threatening. Adverse effects that appear after a relatively long exposure to the drug are especially unlikely to be identified before the marketing (7).

There is an inherent difficulty in catching ‘new’ adverse effects in the current system. Firstly, it presupposes that either the patient or the doctor has linked the symptom to the treatment, in an everyday life that is full of all sorts of symptoms and feelings. In the case of very long treatments over several decades, the prescribing doctors will change over the years. If the patient reports a symptom, the physician could check the list of adverse effects in the monograph. If the symptom is not on the list, the doctor could consider it unlikely to be caused by the pharmaceutical, and not report it to the pharmacovigilance authorities. If the symptom is listed, he may find it unnecessary to report, and the constant lack of time can make the chance of reporting even smaller. Side effects may also make health professionals uncomfortable, since it is against the fundamental principles of medical ethics to cause them, and it indirectly casts blame on the physician/prescriber (26). Those side effects that have not yet become ‘official’ will stand a smaller chance of ever becoming so, since the authorities could also be influenced by what is already on the list. In studies of consultations, physicians were more prone to consider established side effects as being ‘true’ (26). This is probably the case especially regarding minor adverse symptoms. Further obstacles could be that if the baseline prevalence of a symptom is high, as for example headache or muscle pain such as stiffness after training, it will be difficult to prove or even suspect that it was caused by the medicine (26). Nevertheless, common minor symptoms can severely affect quality of life for many individuals, and thereby have impact on public health.

There are substantial difficulties in finding the prevalence of adverse events or symptoms irrespective of method – voluntary organized reporting, cohort studies, case-control-studies or record linkage (23). An under-reporting has been shown, and also been said to be selective and unpredictable (26). The results of a French population-based study suggest that the number of hepatic adverse drug reactions in the population would be 16 times greater, than the number noted by spontaneous reporting to the regulatory authorities (27). The under-reporting appears to be considerable also in Sweden, partly because the Swedish rules do not lay absolute claim to reporting of all cases of drug-induced adverse events under suspicion (28). Other examples, of factors that make the data doubtful, are

the difficulties in judging causality from a specific drug, in the case of polypharmacy, especially among the elderly (28).

Except for the described difficulties in catching data on adverse effects, there could also be publishing bias. Investigations into possible conflicts of interest have found strong association between published statements regarding the safety and the author's financial relationships with pharmaceutical manufacturers (7).

Nearly 30 years ago, Swedish investigations showed that adverse effects from drugs, directly or in-directly caused a considerable part of the in-patient care, at the medicine departments of the university hospitals (29-30). Recent studies showed that the problem has not become less, but instead more significant (31-32). There are similar situations in other European countries, for example in Denmark (33), France and Germany and to an even larger extent in the USA (34).

1.2. Background of cardiovascular preventive treatments

1.2.1. Cardiovascular risk factors and cardiovascular risk

Cardiovascular disease is the leading cause of death in the Western world, where life expectancy is long (i.e. old populations), and the cardiovascular field of prevention is growing in pace with the increased interest and awareness of cardiovascular risk factors and risk markers. Cardiovascular diseases that could be partly prevented, or postponed, are in this context the most important forms of atherosclerotic disease, i.e. ischemic heart disease and cerebrovascular disease (stroke) (35). The major potentially modifiable risk factors associated with coronary heart disease and stroke are smoking, hypertension (various definitions or cut-off points), dyslipidemia / hypercholesterolemia (various definitions or cut-off points), abdominal obesity, stressful psychosocial factors, physical inactivity and unhealthy diet (36). Important non-modifiable risk factors are age, gender, genetic factors, and diabetes mellitus (35). Some researchers state that there is already a cardiovascular damage or defect when the 'risk markers', as blood pressure or lipids, are elevated, and that the relations of cause and effect are insufficiently known (37-38).

A majority of the adult population in Sweden, and many other Western countries, have risk factors as hypertension and hyperlipidemia (39-42). In consequence of various definitions or cut-off points for hypertension (from 160/95 to 130/80) or hypercholesterolemia (from 6.5 to 5.0 or even 4.5 mmol/l), different years and in different cultures, the proportion varies.

Cardiovascular risk can be defined as the probability of developing a cardiovascular disease within a certain period of time, generally five or ten years. Earlier, the indications for preventive treatment were mostly based on specific risk factors, such as for example elevated cholesterol levels, but nowadays the combined level of risk is more pronounced as an indication for treatment (43-44). Effective methods to identify people with the highest risk of coronary heart disease are required and guidelines have recommended the use of formal risk scoring, with an algorithm based on the Framingham equation (45). Nevertheless, the accuracy for the individual of the risk assessment tools in general, has been questioned. The grounds for the doubts are, among other things, variations between regions or countries, a secular decline in the rate of CVD, that the best predictors of cardiovascular risk are those risk factors that could not be altered (age and sex), that the algorithm is based on individuals younger than 65 years, and that the scoring should also include the individual's personal circumstances and socioeconomic status (46-47). The methods have been found to both overestimate and underestimate absolute coronary risk in different socioeconomic groups in an ordinary population, and modified versions have appeared (45, 48-50). One problem could be that many patients do not have adequate information in their records, to allow the risk of coronary heart disease to be estimated (45).

1.2.2. Prevention of cardiovascular disease

Prevention of cardiovascular disease (CVD) could be practised at different levels and with different target populations:

- 1) 'Primordial prevention', prevention of risk factors among people without risk factors yet, i.e. the whole population,
- 2) 'Primary prevention', prevention among those with risk factors but without subclinical or clinical disease, in order to reduce the incidence of disease in the susceptible population,
- 3) 'Secondary prevention', applied to those with subclinical disease, but no clinical disease, with the purpose to reduce the prevalence and / or consequences of the disease,
- 4) 'Tertiary prevention', referred to those who have clinical cardiovascular disease, in order to reduce complications or disability, and
- 5) 'Quaternary prevention' for those with severe cardiovascular disease, as rehabilitation or restoration of function. (51-53).

In other contexts, the nomenclature is built on only three or four levels – health promotion/primordial prevention, primary prevention and secondary prevention or secondary and tertiary prevention (51, 53). Some say that the distinction between primary and secondary prevention has been abandoned, in favour of

cardiovascular prevention, mandating individual risk assessment (54). Those most likely to benefit from secondary prevention are identified relatively easily. The identification of patients suitable for primary prevention is less straightforward.

Twenty-five years ago, a Professor of Epidemiology, Geoffrey Rose, described the two approaches to finding the aetiology of disease, the individual, and the population based, and also their counterparts in prevention. The first is the 'high-risk' strategy, where those individuals at the top of distribution, of e.g. blood pressure or cholesterol level (the susceptible), are identified (by screening) and given individual 'protection', i.e. the traditional medical approach to prevention. This approach leaves intact the underlying causes of incidence, and seeks instead to add some supposedly protective, unnatural factor (e.g. long-term medication). Then the responsibility is on the activists to produce adequate evidence of safety. The other is the 'population strategy', that seeks to control the determinants of incidence, in the population as a whole, by removal of an unnatural factor (exposure) and restoration of 'biological normality', i.e. the conditions to which we presumably are genetically adapted, and for which there can be some presumption of safety (for example giving up smoking). The two approaches are not usually in competition, they are both needed (55-57).

Decisions on pharmaceutical or non-pharmaceutical preventive treatment are a common occurrence in GPs' everyday work, and GPs also play the leading part at this stage (58-60). It has been argued that when a healthy person is prescribed a drug, he or she is transformed to a 'patient' (55, 61-63).

1.2.2.1. Pharmaceutical prevention

Recommended pharmaceutical preventive treatments are antihypertensives (such as diuretics, beta blocking agents, calcium channel blockers and agents acting on the renin-angiotensin system), lipid modifying agents as statins, or hydroxyl-methyl-glutharyl coenzyme A (HMG CoA) reductase inhibitors, and antithrombotic agents / platelet aggregation inhibitors (64). For a period, even hormone treatments were used in order to prevent cardiovascular events among women (65).

1.2.2.2. Non-pharmaceutical prevention

Behavioural changes are changes in eating patterns, alcohol consumption, smoking, physical activity and stress management (36, 64). These activities could also be motivated by health in general and not necessarily by a certain blood pressure or lipid-level. Then the individual would also avoid the feeling of belonging to a certain risk-group (37).

In Sweden, a project called ‘physical activity on prescription’ or ‘physical activity in disease prevention and treatment’ has been developed. The aim of this project was to provide evidence that facilitates and stimulates care providers to encourage patients regarding physical activity (66).

1.3. Summary of background

Before the beginning of the data collection of these studies, there were no national or local data on trends of numbers of prescriptions, from different categories of prescribers, or on different categories of patients (age and sex). Neither were there any possibilities to estimate the number of individuals treated with different pharmaceuticals, or the drug prevalence.

The cardiovascular field of therapy was found to be one of the most frequently occurring. “Indication” for primary prevention of CVD, i.e. a variety of risk factors, could be considered to be present in the majority of the older half of the population and consequently there would be no natural limit of prevalence of treatment, as in the case of a defined disease with limited prevalence. Cardiovascular preventive treatments, and their effects, could thereby be considered to be of great importance to public health, and antihypertensive and lipid modifying pharmaceuticals thus became the focus of this thesis.

Due to incomplete data on prevalence of drug-induced adverse symptoms in an ordinary population, there was (and is) a need of increased knowledge in this field, especially regarding frequently occurring pharmaceuticals that are meant to be used by healthy people during a long time.

2. AIM AND OBJECTIVES

2.2. Main aim

The main aim was to study pharmaceutical prescription patterns and trends from a public health perspective, to explore what proportion of the population is exposed to some of the more prevalently prescribed pharmaceuticals. Further, to illuminate conditions surrounding prescribing in primary prevention of cardiovascular disease, and to find possible ways of measuring drug-induced adverse symptoms in the population.

2.3. Specific objectives

To present prescribing patterns of general practitioners (GPs) at public primary care centres (PPCCs) in Halland, a Swedish county (I, II).

To present total drug prescription data and trends, related to population statistics, in order to estimate the prevalence of exposure of some common classes of drugs, to different groups of the population in Halland (III).

To analyse prescription symmetry regarding non-steroid anti-inflammatory drugs (NSAIDs) and statins, by analysing data from a Danish county (IV).

To investigate the prevalence of antihypertensive and serum lipid-reducing treatments, in the entire Swedish population, and to try ways of estimating the proportion of primary preventive treatments (V).

To identify and describe views of primary prevention of cardiovascular disease, among general practitioners in Halland (VI).

3. MATERIALS AND METHODS

3.1. Summary of data sources and methods



In the studies I-V, data on dispensed prescriptions were used. In the analyses they are called ‘prescriptions’, ‘treatments’ or ‘drugs’ and refer to one drug item on a prescription. In the first three studies (I-III), data were collected in Halland, a county in the south west of Sweden, with a population that increased from 250 000 to 275 000 during the years 1990-2000 which corresponds to 3% of the total population of Sweden. It has around 100 GPs, at public primary care centres from a total of 650 physicians of different specialities. In the fourth study (IV), data from a Danish database of prescription data from around half a million inhabitants of Funen is used. In the fifth study (V), prescription data from the entire Swedish population, of nine million inhabitants, is used. Data were retrieved from the new Swedish Prescribed Drugs Register, and related to national demographic population statistics (9), and also linked to individual data on cardiovascular diagnoses (I00-I99), as a main or secondary diagnosis, during 1998-2004, from the Swedish Hospital Discharge register that covers all public in-patient care in Sweden (67).

Figure 1. Location of material and data sources

In the qualitative interview study (VI), 21 GPs from Halland were purposively selected in order to ensure that views were represented from GPs of different age, gender, length of experience, recruitment area, etc.

Paper	Design	Population/Material	Data source	Main units of measurement
I	Descriptive, retrospective over 10 years	Dispensed prescriptions for the 250 000 inhabitants and from the 100 GPs and 550 other physicians in the county of Halland	Data from a local prescription study obtained from a central register at National Corporation of Swedish Pharmacies (Apoteket AB)	% prescriptions from GPs, cost in SEK/DDD (from a prescriber's perspective)
II	Descriptive, retrospective over 10 years	Dispensed prescriptions for the 250 000 inhabitants and from the 100 GPs and 550 other physicians in the county of Halland	Data from a local prescription study obtained from a central register at National Corporation of Swedish Pharmacies (Apoteket AB)	% prescriptions from GPs for patients of different ages, number of prescriptions (from a prescriber's perspective)
III	Descriptive, retrospective over 15 years	Dispensed prescriptions for the 250 000 inhabitants in the county of Halland	Data from a local prescription study and other data on dispensed prescriptions obtained from a central register at National Corporation of Swedish Pharmacies (Apoteket AB)	Prescriptions per 100 inhabitants and 3 months, DDD per 100 inhabitants and day (from a population perspective)
IV	Cohort-study; prescription sequence symmetry analysis	Reimbursed dispensed prescriptions for 400 000 inhabitants of Funen in Denmark	Odense Pharmacoepidemiologic Database (OPED), Denmark	Sequence ratio
V	Descriptive, cross-sectional	Dispensed prescriptions and cardiovascular diagnoses for 9 million inhabitants of Sweden	Health data from the Swedish Prescribed Drugs Register and the Swedish Hospital Discharge register from the Epidemiologic centre at the Swedish National Board of Health and Welfare	Drug prevalence, % of the population of different ages who purchased pharmaceuticals on prescription
VI	Qualitative, phenomenographic approach	21 GPs purposively selected	Semi-structured interviews from 21 GPs	Categories of views of primary prevention of CVD

Table I. Summary of methods, data sources and units of measurement

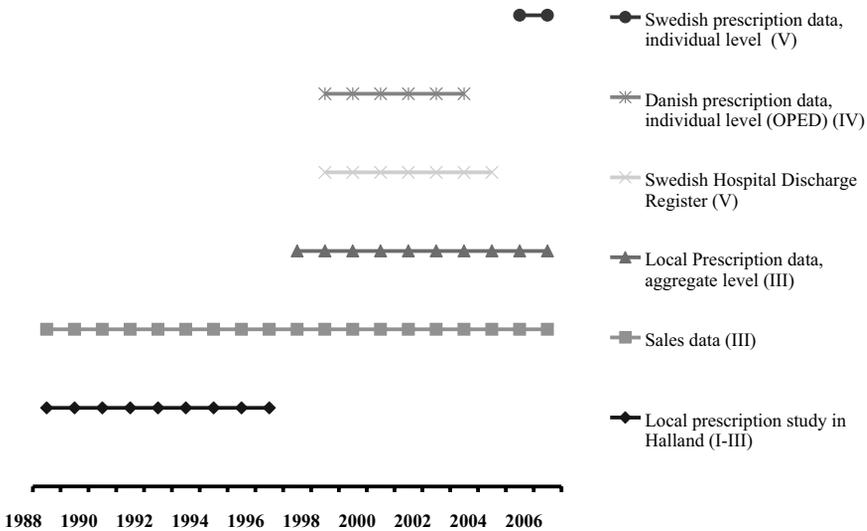


Figure 2. Data sources of the studies of this thesis (Study number in brackets).

3.2. Analyses

Studies number I and II are quantitative descriptive studies, with calculations of percentages of prescriptions, and in studies III and V, prescription data were related to population statistics. In study IV, a statistical method called prescription sequence symmetry analysis, was used. It is an analysis of symmetry regarding sequence of dispensed prescriptions among subjects who were incident users of both statins and non-steroid anti-inflammatory drugs (NSAID). The result is the sequence ratio, the ratio of number of persons with an NSAID dispensed second, vs. persons with a statin dispensed second, then adjusted for trends in dispensed prescriptions. A value above unity indicates an excess of sequences with a statin first, and NSAID second. The method has been described in detail elsewhere (68). Study VI is a qualitative explorative study, where semi-structured interviews were tape-recorded, transcribed verbatim and analysed by a phenomenographic approach. This approach aims at describing variations and similarities regarding how an experienced phenomenon is actually conceived by humans, by finding and defining different categories of meaning (69).

Studies I-III and IV can be characterized as drug utilization research, since traditionally the main questions in this field are: who the prescribers are; for whom the prescribers prescribe and what the benefits and risks of the drugs are (2). Studies I and II in particular were done from the view of the prescriber (but without any purpose of analysing or evaluating the quality of prescribing). In

studies III and V, the data were analysed in relation to the population. The studies III, IV and V include elements of pharmacoepidemiology ('the use and effects of drugs in large numbers of people'). Although unconventional, the method in study VI could be considered to belong to an extra dimension of drug utilization research, or pharmacoepidemiology.

4. ETHICAL CONSIDERATIONS

The data used in paper I-III were routine data at aggregate level from the national pharmacy database, where only year of birth and gender were collected, and no individual patient identity could be traced. No individual prescription patterns were used. Data in paper IV were gathered and analysed by statisticians connected to the Odense Pharmacoepidemiological Database (OPED), and only de-identified data were delivered for calculations outside. The calculations in paper V were based on tables of de-identified numbers of individuals and prescriptions from the new national health database, summarized by staff at the National Board of Health and Welfare, and no ethical clearance was needed according to the National Board of Health and Welfare. Study no VI was approved by The Regional Ethical Review Board in Gothenburg, Sweden, registration number 241-04. Participation was voluntary, and the participants were informed that they could withdraw from the study at any time. They were guaranteed confidentiality according to existing rules.

5. RESULTS with comments

5.1. Paper I. Drug prescribing in public primary care centres. Results from prescription studies, 1988-1997, in the county of Halland, Sweden.

In this paper, the GPs' share of the total of dispensed prescriptions of different groups of drugs, and the changes in these patterns, were explored.

5.1.1. Specific background

Pharmaceutical statistics had mostly been presented in numbers of DDD as the unit of measurement before, since this was the measure that sales data could be counted in. For instance when looking at the pharmaceutical prescribing work, from the perspective of the prescriber, it seemed appropriate to get knowledge of the number of prescriptions, even though not all of them are dispensed. A local prescription study, three months each year for ten years, made possible the analysis of data from a GP perspective.

5.1.2. Main findings

The number of prescriptions from GPs in public primary care centres increased considerably during the ten years, both in absolute and relative numbers, reflecting the intentional shift in patient consultations towards primary care. Cardiovascular drugs (C) were the pharmacological main group prescribed in greatest quantity, measured in DDD, and the majority of the dispensed prescriptions of cardiovascular drugs, were prescribed by GPs, over the ten years studied. Cardiovascular groups of drugs, which became more frequent in primary care during the years, were lipid modifying agents, angiotensin converting enzyme (ACE) inhibitors, calcium channel-inhibitors and beta-blocking agents.

5.2. Paper II. Drug prescribing in primary care related to patient age. Trends in a ten-year repeated prescription study in a Swedish province.

In this paper, dispensed prescriptions from primary care were related to patient age, and the trends discovered were presented.

5.2.1. Specific background

The findings from Paper I stimulated an analysis of the number of prescriptions and number of DDD, for different age groups, and also to an attempt to relate the number of GP prescriptions to the total numbers of prescriptions, as the unique possibilities were at hand through the local prescription studies.

5.2.2. Main findings

The GP-part of the total number of prescriptions for the elderly increased, and for children the GP-part decreased, over the ten years. In the over 60 age groups cardiovascular drugs were most frequent (from the original analysis, not published in the brief research letter). The 70-79 age group was the target of the highest number of prescriptions per ten-year interval, and half of the drugs to people over 70 were drugs for cardiovascular or nervous disorders.

5.3. Paper III. Patterns of drug use during a 15-year period. Data from a Swedish county 1988-2002.

In this paper, patterns of dispensed prescriptions were related to the number of individuals of different ages, and the trends for a 15-year period were presented.

5.3.1. Specific background

After having analysed GP prescriptions in relation to the total of prescriptions, there was a subsequent interest in relating the dispensed number of prescriptions and number of prescribed DDD, to the number of inhabitants of different ages and gender. The point was to get a general view of how common different kinds of drug treatments are, and the trends over the years, since prescription data in 2002 were available from a period of 15 years. The limitation of exclusively using DDD per 1000 inhabitants and day, as an estimate of prevalence, had been stated in a document from the Centre for Drug Statistics Methodology of WHO (2). Due to the general Swedish reimbursement rules for 3 month-periods, the combination of number of DDD with number of prescriptions could supplement the picture of prescription patterns, especially for short treatments and treatments for children, where number of DDD only could give an inadequate picture.

5.3.2. Main findings

The total drug exposure in the population of Halland, approximately doubled during the 15-year period, measured in DDD per 100 inhabitants and day, and almost as much, measured in number of dispensed prescriptions per 100 inhabitants. Multiplied therapeutic intensity or “prevalence” was found for antithrombotic drugs, agents acting on the renin-angiotensin system, hormone replacement therapy, serum lipid-reducing agents, antidepressants, and for drugs for acid related disorders, among people of 60 years and over.

When trying to estimate the drug prevalence, from number of prescriptions per 100 inhabitants and 3 months and DDD per 100 inhabitants and day in combination, it was estimated that nearly 30% of the women of ages 15-69 were exposed to sex hormones in 2002. The calculations, for the population of 60 and over, could also allow for some estimations, e.g. that around 27% used an antithrombotic drug in these age groups, and that the prevalence of use of serum lipid-reducing agents could be approximated at between 10% and 14%. Estimations of prevalence of for example proportion of users of any antihypertensive treatment were more difficult, since many patients are treated with more than one drug. (Unfortunately, there was a mistake in the text in paper III, where the ATC code for lipid modifying agents, C10, was placed among antihypertensive treatments, on p 819.)

5.4. Paper IV. Statins and cause of NSAID use – an analysis of prescription symmetry.

In this paper, data on dispensed prescriptions of statins (C10AA) and NSAIDs (non-steroid anti-inflammatory drugs) (M01A) were used for an analysis of the ratio of the number of persons with an NSAID prescribed second versus the number of persons with a statin prescribed second.

5.4.1. Specific background

One of the aims of this thesis was to find possible ways of measuring drug-induced adverse symptoms in the population. This interest originated from experienced gaps in the knowledge and research interest, in the areas of measuring so called ‘harmless’ adverse symptoms induced by common drug treatments. Muscle pain/myalgia, which is one of the established adverse effects from lipid modifying statins, could serve as an example of an adverse effect/symptom with unknown frequency. Carried to extremes, one example of a potential scenario worth avoiding could be as follows: A healthy person taking lipid modifying statins gets muscle pain without connecting it to the treatment, and then gets a prescription of an NSAID, and after that experiences gastrointestinal problems and gets a prescription of a proton pump inhibitor (PPI). The result of this good intention could be an “ill” person, and large expenses for care and pharmaceuticals. These speculations motivated the plans of trying to determine excess frequencies of adverse symptoms in the population, without the need of knowledge or diagnosis of an adverse event from drug treatment.

At that time prescription data at the individual level were available in Denmark but not in Sweden, so we turned to Denmark, to try the Odense Pharmacoepidemiological Database (OPED) and the prescription sequence symmetry analysis that was developed there (68). By using the method prescription sequence symmetry analysis, where prescriptions for ordinary populations are analysed, it would be possible to find an excess of analgesic treatments after statin treatments, without relying on the patient or doctor associating the pain to the statin treatment. Prescribed NSAID (M01A) served as a proxy for pain. A myalgia-provoking effect of statins would generate an excess of persons starting statins first, which is a non-symmetrical distribution of prescription orders. The study period was chosen to be a homogenous period of time, without major reforms or changed guidelines, and the resulting sample-size was suitable.

5.4.2. Main findings and comments

No excess in sequences of statin -> NSAID over the opposite was found, indicating no measurable exceptional occurrence of muscle pain among statin users. In retrospect, there were some shortcomings in the design of the study; other analgesic drugs than M01A, such as acetylsalicylic acid or paracetamol were not included in the final analysis due to practical reasons regarding ATC-classification, and a large proportion of analgesic pharmaceuticals are sold OTC and could not be included. Hence, the result did not reflect the complete purchase of analgesics.

5.5. Paper V. Prevalence of purchase of antihypertensive and serum lipid-reducing drugs in Sweden - individual data from national registers.

In this paper, prescription data at the individual level were related to population statistics and also to data on diagnoses from the hospital discharge register.

5.5.1. Specific background

In paper III, drug prevalence was estimated from calculations and combinations of number of prescriptions per 100 inhabitants and 3 months, and number of DDD per 100 inhabitants and day. Whether the observed increase in drug prevalence, measured in DDD / 100 inhabitants, was due to an increase in prescribed daily doses (PDD), increase in prescribed (or dispensed) quantity per individual or increased number of individuals, could not be confirmed without having access to figures of the true numbers of individuals who purchased the drugs. When the legal conditions were changed in Sweden, and collecting pharmaceutical data at the individual level was approved, individual data on drug purchase were collected from the 1st July 2005, and a national health database was established (17).

Cardiovascular drugs in general and preventive treatments such as lipid modifying and antihypertensive in particular, had been found to be frequently prescribed in the initial studies. When the opportunity arose to get access to the actual numbers of recipient individuals of different age and gender, it was taken, in order to calculate the drug prevalence. Individual data also confer possibilities to find data on individuals, who combine two or more treatments in the same field of therapy, and who should not be counted twice or three times, when the aim is to find the prevalence of, for example, antihypertensive treatments. Data in the new prescription database could also be linked to data in other registers as the register of in-patient care/hospital discharge diagnoses. Since there is no national database of out-patient diagnoses, it seemed to be of interest to find what percentage of individuals who had been discharged after cardiovascular

disease, in order to estimate the proportion of primary preventive treatment. As a complement, the number of individuals, who combined purchase of antihypertensive or lipid modifying agents with vasodilating nitrate preparations, was analysed. The result was an additional indicator of cardiovascular disease and hence secondary or tertiary prevention, since some of the patients with cardiovascular disease more than seven years earlier, were probably not included in data from the hospital discharge register.

5.5.2. Main findings

Two thirds of the Swedish population aged 75 and above, half of the population aged between 65 and 74, and one fourth of the population aged between 45 and 64, purchased prescribed antihypertensive or lipid modifying preparations over a period of six months. Lipid modifying agents were purchased by around 20% of the older population.

Among Swedes aged 60 and above, 53% purchased antihypertensive or lipid modifying pharmaceuticals, and 30% purchased the pharmaceuticals without having been hospitalized for a coronary or cerebrovascular event during the previous seven years, or having purchased prescribed nitrate vasodilators over a period of six months.

5.6. Paper VI. Views of primary prevention of cardiovascular disease – a qualitative analysis of interviews with Swedish GPs.

In this paper, interviews with GPs regarding their experiences of patient counselling in primary prevention, and their views and beliefs regarding this matter, were analysed qualitatively by a phenomenographic approach, to describe the spectrum of views.

5.6.1. Specific background

Preventive cardiovascular treatments were found to be dispensed frequently and the majority of the prescriptions originated from GPs. GPs have an important role in the information and decisions regarding prevention of cardiovascular disease (13). Therefore, it seemed logical and interesting to explore GPs' views and beliefs regarding the risk of cardiovascular disease, the chances of primary prevention of cardiovascular disease, and how the decision-making is experienced.

5.6.2. Main findings

Two overarching domains emerged during the analysis of the interviews. One was reliance on research data regarding predictability of actual risk and possibilities of primary prevention of cardiovascular disease. The other was responsibility, and how the allocation of this was conceived, regarding primary prevention of CVD. The views within each field were grouped and categorized.

The GPs had different views and beliefs, ranging from being convinced of a real risk to the individual to strongly doubting it, from relying firmly on protection from disease by pharmaceutical treatment to strongly doubting its effectiveness in individual cases, and from reliance on prevention of disease by non-pharmaceutical interventions to a total lack of reliance on non-pharmaceutical measures. We also found that views varied in terms of how to treat patients of different ages, to what extent one could or had the right to expect the patient to make lifestyle changes, and of responsibilities regarding information of adverse effects and length of treatment. This might be interpreted as a reflection of the complexity of patient counselling in this field of therapy.

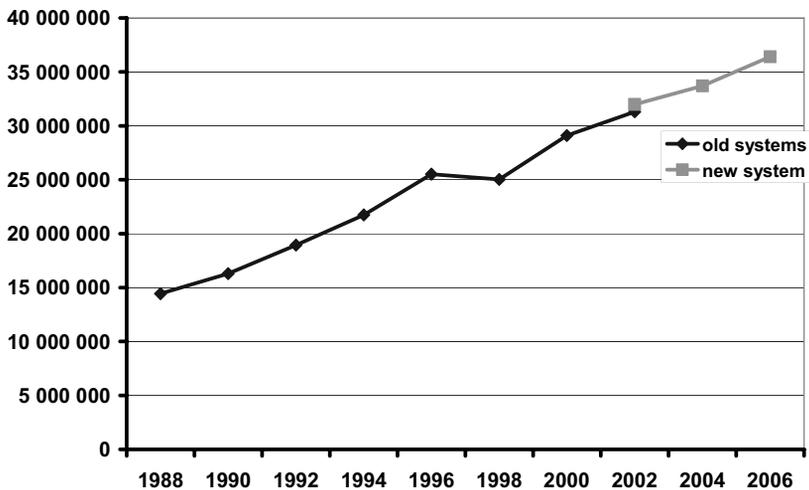
5.7. Unpublished data and calculations on drug prevalence

5.7.1. Unpublished qualitative data

In connection to our qualitative interview study of views and experiences of primary prevention among general practitioners (paper VI), we also interviewed patients about their thoughts and views. In some of these interviews, and to some extent also among the GPs, the preventive pharmaceutical treatment seemed to be understood as ‘protection’ from disease, and experienced adverse effects as something unavoidable when you want to be protected from cardiovascular disease.

5.7.2. Overall trend of pharmaceuticals on prescription

The total pharmaceutical sales continued to increase in Sweden the years after 2002.



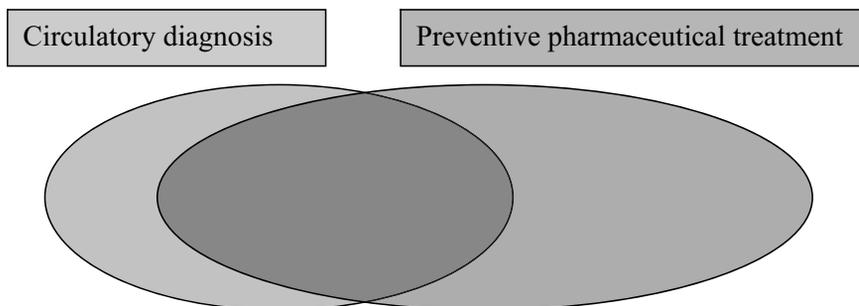
Source: National Corporation of Swedish Pharmacies, (Apoteket AB).

Figure 3. Trend for prescription data from pharmacies in Halland, 3 months, 1988-2006 (DDD).

5.7.3. Complementary data on cardiovascular prescriptions

In the entire Swedish population of all ages, 7% purchased at least one prescription of lipid modifying pharmaceuticals (C10), during a six-month period. The prevalence of antihypertensive or lipid modifying agents (C03, C07-C10) was 17%. Among these drug-treated, 6.5% had an in-patient diagnosis of diabetes mellitus the previous seven years. More than 1 million individuals (69%) of those who purchased these pharmaceuticals did not have any in-patient diagnosis of cardiovascular disease.

Around 600,000 individuals aged 60 years or over, were found to have a cardiovascular hospital discharge diagnosis as an indicator of a cardiovascular event, 1998-2004. Only around 430,000 of them purchased a prescription of antihypertensive or lipid modifying agents, during 6 months.



The 12-month prevalence of antihypertensive and/or lipid modifying treatment was 59% among individuals aged 60 years or over. In paper V, the 6-month prevalence was 53%.

	6 months %	12 months %
Diuretics, C03	24.8	28.8
Betablocking agents, C07	28.4	32.0
Calcium channel blockers, C08	13.4	15.6
Agents acting on the renin-angiotensin system, C09	20.9	25.7
Serum-lipid reducing agents, C10	18.3	21.5
Any or a combination of the groups above (C02, C03 or C07-C10)	52.9	58.7
(Number of individuals	1,131,796	1,254,481)

Table 2. Proportion of individuals of 60 years or more who purchased preventive cardiovascular treatments during 6 months and 12 months.

The finding, that the treatments were more prevalent during a 12-month period than during a 6-month period, led to deeper analyses of the successive 3-month prevalence during the year, and a steadily increasing prevalence was found. The prevalence of agents acting on the renin-angiotensin system increased by 14% and the prevalence of lipid-modifying treatments increased by 12%, from the first to the fourth 3-month period of the new database. Thus the prevalence of the pharmaceuticals in focus of this study, continued to rise.

5.7.4. Miscellaneous data on 12-month prevalence

After getting access to the numbers of individuals that purchased drugs in Sweden, through the new database with individual prescription data, more data on prevalence of the most common drug groups among different age groups were gathered 2005-2006. The 12-month prevalence of hormone treatments (G03) among women, between the ages of 15-69 turned out to be 31%, despite a decrease during recent years. The 3-month prevalence of antibacterials (J01) in the entire population of all ages was 8%, and the 12-month prevalence was 24%. Around 12% of all men and 8.5% of all women of 60 years or more purchased an antidiabetic treatment (A10) during 12 months. In the population of all ages, the corresponding proportion was 3.5%.

6. DISCUSSION

6.1. Prescription patterns and prevalence

6.1.1. Trends in prescription patterns

The volume of pharmaceuticals, measured in DDD, and the ‘therapeutic intensity’ in DDD per 1000 or 100 inhabitants, approximately doubled 1998-2002, and continued to rise thereafter. Whether this was due to an increase in prescribed daily doses (PDD), more drugs in combination for each individual, or an increased number of individuals, could not be confirmed when there were no prescription data at individual level. The number of dispensed prescriptions increased considerably as well. The dispensing of e.g. lipid modifying drugs was multiplied during the 15 years. In Ireland, where a steep increase in the number of dispensed DDD of lipid modifying drugs 2000-2003 was analysed, one third was explained by an increase in PDD and two thirds were explained by more patients being treated (132).

The highest pharmaceutical exposure was generally found in the oldest groups of the population, those who seldom are included in controlled clinical studies.

6.1.2. Prevalence of cardiovascular treatments

In the recently established Swedish health database, answers to questions of how common the use of specific pharmacological or therapeutic classes of drugs actually is, could be found. High prevalence was found for cardiovascular treatments such as antihypertensive and lipid modifying agents. Two thirds of the Swedish population aged 75 years and over, half of the population between 65 and 74, and one fourth of the population between 45 and 64 purchased prescribed antihypertensive or lipid modifying preparations during six months. Among all individuals in Sweden, aged 60 or over, 53% purchased one or more antihypertensive or lipid modifying agents treatments during 6 months and nearly 60% purchased during a 12-month period.

When looking at all ages over a six-month period, a prevalence of 17% of antihypertensive or lipid modifying treatments was found. According to recently presented data, a similar prevalence of ‘preventive cardiovascular treatments’ (in fact all drugs in group C) of 18% was found in Norway. Also for lipid modifying pharmaceuticals separately, the same proportion, 7% of individuals of all ages, was found in the Swedish and Norwegian databases (70). Lipid modifying agents were purchased by around 20% of the senior population, although the benefits of lipid modifying treatment for older people have been questioned due to lack of evidence of effectiveness (64). Among other things,

there are indications that high cholesterol weakens in its relationship to heart disease with age, and loses (and in older age reverses) its relation to mortality (71). It has also been put forward that basing treatment decisions on absolute risk, would result both in lipid modifying treatment of elderly people with hypertension, but without hyperlipidemia, and in non-treatment of young subjects with hyperlipidemia and relatively high risk of coronary disease. Basing the recommendations on absolute risk reduction would correspondingly mean that lipid modifying treatment would be prescribed to patients that will experience the most benefit (72-73).

6.1.3. Prevalence of miscellaneous treatments

Around 30 % of Swedish women of 15-69 years were treated with sex hormones (contraceptives and hormone replacement therapy) in 2005, and this result was found in spite of the reduction in quantities of dispensed hormonal preparations in recent years (74). A similar prevalence was found in the Danish database (20). Adding prescriptions of contraceptive pills, to those of hormone replacement therapy, is quite unique, since contraceptive pills seldom are included in prescription data, due to reimbursement rules. Considering both the environmental and the human consequences, it is interesting to group together the users of these therapies, and look at the prevalence as one. The environmental consequences, of the dispersion of female sex hormones and similar agents in water, such as for example disease or disturbed reproduction among fishes and aquatic organisms, and the sex reversal of 'male' tadpoles, are current topics of discussion and fore-warnings of future effects (75-78). The medical consequences for the users, related to the total duration of treatment, are among other things increased risk of cancer (79-80).

Antibacterials were, according to our unpublished data, used by 24% of all citizens in Sweden during a 12-month period. In Denmark, the corresponding percentage was approximately 30% (20). This proportion is of great interest, since the nature of antibacterial treatment – quite short treatments, but of different lengths – has made the estimation of number of recipients, from DDD, extra difficult.

6.2. Methodological considerations of the studies of patterns of dispensed prescriptions and the linkage to diagnoses

These studies are characterized by an explorative line of action. Due to scarcity of earlier data on drug prevalence, formulation of hypotheses was for most of the studies of no interest or not possible. The data used were collected as routine data and not as specific research data. Over the years, there have been a number of technical alterations in the internal system of statistics of the National

Corporation of Pharmacies in Sweden. At the times of changes in the system, overlapping analyses were made to check possible divergence. Changed rules for reimbursement, and classifications of prescriptions, have also affected the way data are caught and sorted, inside the system.

From the beginning in 1988, the data used derive from a local prescription study in Halland, including all prescriptions from prescribers in Halland, March to May each year, for ten years. This made possible the collection of patient age (year of birth) and gender, at a time when the common data collection of drug statistics was based on drug sales from the wholesalers to the pharmacies, and not on dispensed prescriptions. The local prescription studies, involved manual coding regarding prescribers of all prescriptions in all pharmacies, during three months from March to May each year, for ten years, 1988-1997. The three-month period was decided before this research started. The extra work this meant to the staff, also in very hectic situations, implies risks for the quality of data regarding the origin of the prescription. The date of birth and the sex of the patient, were routinely collected, but could at that time, before the introduction of compulsory registration of the civic registration number, also be incorrectly registered. Due to the lack of data on home addresses at that time, individuals living outside the county, visiting pharmacies inside the county, could be included, and inhabitants of Halland could purchase pharmaceuticals outside the county, and hence not be included. Prescribers outside Halland were coded separately, and were not included in the analyses (paper I-III). Conversions and calculations of number of DDD of different pharmacological groups, according to the ATC-system, were made centrally in the national records.

From 1997, most of the data was obtained from a continuous national registration of all prescriptions, from which information was extracted on those dispensed from pharmacies in Halland to inhabitants of Halland. In the local prescription study, covering the ten preceding years, all prescriptions from prescribers in Halland, dispensed in pharmacies in Halland, were included, even if the patient did not have a permanent address in Halland. Comparing data, registered in the local prescription study to data from the national continuous study, during 1996 and 1997, showed a difference below 5% for the sum, even though this did not eliminate the possibility that there were greater differences at detailed levels, due to the unknown flow of pharmacy customers.

In 1997 there was a dip in the curves of dispensed prescriptions, which was preceded by a planned reform of the reimbursement system and a hoarding of drugs at the end of 1996. Individually packed doses of pharmaceuticals used in nursing homes were not included in the prescription data until 1999, and caused a distortion in the curves that year. The individually packed doses, added 6.8% DDD to the sum of DDD from ordinary prescriptions in 1999. Due to changes in

financial conditions for the clinics, more pharmaceuticals used in hospitals could have been dispensed on prescriptions some years, instead of on requisition forms. Nevertheless, the continuous increase in pharmaceutical purchase was confirmed by sales data from the wholesalers. These data are more robust, in the way that they are not affected by changes in data collection in the pharmacies. However, they also include OTC pharmaceuticals.

All these factors put together point to the fact that the routinely collected longitudinal data were not suitable for statistical analyses of small changes, but rather for overall trends.

The population statistics from Statistics Sweden (SCB) (9) were used as denominators to calculate the frequency of prescriptions and defined daily doses per inhabitant for different groups of the population in Halland. The new prescription database with data at the individual level include all dispensed prescriptions in Swedish pharmacies and could hence be regarded as data on 'true' drug prevalence.

Estimating drug prevalence from prescription data at aggregate level (paper III) was not free from objections, having the answers from individual data at hand. DDD is a unit of measurement full of limitations. When studying trends at ATC-levels higher than the chemical substance (5th level), there will be different PDD and also DDD for different drugs. Also for a specific agent, the PDD could be related to the response in a specific patient. This is also the case for some of the studied drugs. A great proportion of combined products in an ATC group will also disturb the analysis.

The term 'prevalence' has become more and more intricate during the studies. In the literature, the period prevalence, of half a year or a whole year, has sometimes been said to be the 'indeterminate' sum of two populations: those that already were drug users by the beginning of the period, and those that became users during the period, and the point prevalence would be preferred from an epidemiological point of view, even though it is more difficult to estimate from prescription data (81). Nevertheless, in this first study of 'true' drug prevalence from data from the new Swedish database (paper V), it was of great interest to know this 'sum', the proportions of individuals that purchased these drugs at least once, over the six-month period.

The quality of the Hospital Discharges Register is checked regularly. The data cover at least 96% of the diagnoses from discharges. The quality of the diagnoses have been considered quite low before 1997, when the ICD-10 was implemented, and steps to increase the correctness of the coding was taken. Regarding the study of cardiovascular diagnoses, and the efforts to calculate the

prevalence of primary prevention, it would of course have been preferable to have diagnoses from a longer period of time. On the other hand, it would not seem very probable that a great proportion of the pharmaceutically treated individuals should have had a cardiovascular event and hospital discharge before 1998, due to the extreme increase in pharmaceutical purchase after that year. Most of the pharmacological groups chosen, C03, C07, C08 and C09, also have other indications than hypertension, and prescriptions were prescribed for those conditions to an unknown extent. There is some estimation of these percentages from the year 2000: C03: 80%, C07: 55%, C08: 78% and C09: 61% for hypertension (15). These figures are not very reliable, but the other indications/diagnoses that they are used for are included in the cardiovascular diagnoses in the study anyhow, and thus indicate secondary prevention.

6.3. The role and responsibility of the GP

General practitioners, as a category, had a key role in drug prescribing in Halland, especially for older inhabitants. In the case of prescriptions regarding prevention of cardiovascular disease, the role was also confirmed by the studies. GPs thus have an important role, also confirmed elsewhere (13), in the information given about and decisions regarding prevention of cardiovascular disease. These facts were the motives to explore GPs' views and beliefs regarding the administration of primary prevention of cardiovascular disease. We found a wide variation in views and beliefs regarding risk, and regarding possibilities of pharmaceutical prevention and non-pharmaceutical prevention. A variation was also found regarding treatment of patients of different ages, the possibility or right to urge life-style change on the patient, and of the responsibilities regarding information of adverse effects and length of treatment. The variation in views, that we found in our study, could be seen as an indicator of complexity in dealing with screening and information, and of administration, of primary prevention of cardiovascular disease. Since the studied preventive treatments turned out to involve a large proportion of older persons, the decision-making, information and follow-up of these cases, probably consume a great part of health care time / resources from primary care.

This complexity is also described in other studies. Patients are nowadays regarded as consumers, who are expected to be involved in decisions about their medical care. WHO has stated that patient involvement in care is not only desirable, but it is a social, economic and technical necessity. Shared decision-making is important in cardiovascular diseases, particularly in primary prevention where the risks and benefits of treatment may be quite similar (44). To be able to participate in the decision, the patient must be aware of possible harms and benefits of the choices they face, and the associated probabilities (82-83). Good risk communication is considered a prerequisite for patient

involvement in the decision, but the interpretation of probabilistic epidemiological data for the individual case, may be considered problematic (84-86). In our study, the presentation of test results and risks in mathematical terms or numbers was described as too complicated and not very useful. Also in a Dutch qualitative study of consultations in cardiovascular primary preventive care and interviews of patients, it was found that patients' understanding of prevention of cardiovascular disease was often insufficient, and that the risk table and the multi-factorial approach were difficult to understand (87). Nevertheless, presentation in mathematical terms, as points on a scale or as a number, is by other authors considered to be fundamental to preventive medicine (88). The fact that the word 'prevention' means both 'to slow down the course of an illness' and 'protection from illness', is probably not always completely clear, or borne in mind, by the patients. Communicating the message of risk reduction, when prevention of cardiovascular disease means postponement of disease or lowering the probability of getting ill by some per cent, seems to be a challenging task.

In one study of patients in primary prevention, their 'required risk reduction' was greater than the 'achievable risk reduction' that the cholesterol-lowering or antihypertensive medication could provide. In the same study, 18% of the participants would refuse medication, regardless of the risk reduction offered (89). Risk reduction through drugs is often presented as favourably as possible. For example in one often cited study, the use of terms of a relative risk reduction, as a 35% reduction in primary endpoints (MI and death), corresponded to an absolute risk reduction of 1.1 percentage points. It has been found that when patients are fully aware of the 'pros' and 'cons', and of the uncertainties of treatment effects, they often opt for a conservative approach (90). This can lead to difficulties when individual choice is at odds with public policy. However, in other circumstances it could result in fewer people being subjected to the risks of unnecessary treatment (91).

Prescribing drugs for healthy people, when both the benefit and risks for the individual are unknown, is a professionally challenging situation. Geoffrey Rose put forward the view that preventive medicine, and especially primary prevention, confronts physicians with other questions at issue than their traditional role of doing the best for the individual (56).

6.4. Consequence of prevalence of preventive cardiovascular treatments on public health

6.4.1. Prevalence of treatment and prevention of disease

The aims of this thesis do not include any evaluation of beneficial effects of preventive treatments. We found that the prescribing of antihypertensive drugs increased considerably during the 15 years studied. The levels of blood pressure have been constant in Sweden during the past two decades (92), but the definition of 'hypertension' has changed over the years and a greater proportion of individuals could now be defined as having indication for treatment. The drug treated percentage of the population is not always the same as the percentage with indication for treatment. It has also been reported from other countries that the percentage of the population taking medication increased despite constant prevalence of hypertension (93).

A study of barriers to implementing cardiovascular risk reduction guidelines in six European countries showed that less than half of cardiologists and primary care physicians used guidelines, or a risk calculator, to determine total risk (94). This could mean overestimation of risks, and hence pharmaceutical treatment, by those who did not use the calculators. In a study of doctors' ability to assess coronary risk, they accurately estimated the relative risk of a specific patient (compared with the average adult), but systematically overestimated the absolute baseline risk of developing coronary disease, and the risk reductions associated with specific interventions (95). Inflated perception of cardiovascular risk, and the benefit of risk-modifying medical treatment, has also been reported in other studies (96).

Even the practical use of formal risk scoring could mean an overestimation of risk and pharmaceutical treatment, due to failings in the algorithms, as mentioned above. From Norway it was reported that the implementation of the European guidelines could imply a doubling of the numbers of Norwegian adults on cardiovascular medication for primary prevention (97). In Norway, it was also found that 76% of individuals aged between 20 and 79 have an "unfavourable" cardiovascular disease risk profile, according to guideline definitions. The point prevalence of individuals with cholesterol and/or blood pressure above the recommended cut-off points increases with age. By the age of 24, the prevalence reaches 50% and by the age of 49, it reaches 90% (98).

The proportion of prescribed prescriptions that have been purchased is sometimes used as a measure of compliance or adherence to treatment (99). If the adherence was as low as generally considered, around 50% (100), and the purchase prevalence we found is the proportion of the prescriptions that is filled, the actual prescribing would be twice as frequent.

In primary prevention with patients without symptoms there could be even more concerns regarding low adherence to treatment. As discussed in our qualitative study, compliance among asymptomatic individuals to take pharmaceuticals

regularly for decades could be related to fear of disease or death. Low adherence could indicate experiences of adverse effects, difficulties in risk communication or that the patient is not frightened enough to take the medicine regularly for decades. Hence, in asymptomatic individuals, a feeling of health and well-being would hardly be combined with high compliance/adherence to treatment.

6.4.2. 'Medicalization'

Official policies have expressed the importance of preventive work, but also added that with current practice there is a risk that prevention is medicalized (101). Medicalization is the process whereby natural conditions of life, or symptoms, are transformed into medical problems to be treated.

Continuous preventive treatments theoretically mean continuously increasing prevalence of drug use. It has been suggested that medicine and public health need each other, to "confront the challenge to health system quality, brought on by the commercialization of health care" (52).

6.4.3. Possible adverse effects from pharmaceutical prevention

For the pharmaceutical drugs in focus, both perceptible but 'harmless' symptoms and serious, sometimes non-perceptible, effects occur. A complication, regarding acceptance of harmless adverse effects in primary prevention, could be that one can not be sure that those with adverse effects are those that have the benefit in the long run and avoid getting seriously ill (102). The exploration and test of 'new' methods of finding frequency or excess frequency, of 'harmless' adverse symptoms by a method that did not presuppose diagnosing the adverse effect or connecting it to the treatment (paper IV), was an interesting and instructive experience.

6.4.3.1. Lipid modifying agents and adverse effects

Our findings did not show any excess in NSAID-use after statin prescription, as an indicator of increased frequency of muscle pain among statin users. According to a recent French study, only 39% of people experiencing muscle pain from statins, used analgesics (103). Such a fact or the use of other analgesic drugs, not included in the analysis as mentioned above, could have influenced our results.

Nevertheless, it is well documented that statins affect muscular tissue adversely, and that their use is associated with clinically important muscle symptoms such as pain, cramps and weakness, even in the absence of the 'marker', an elevation of serum creatine kinase (CK) levels (104-107). In a study of 22 statin-treated

professional athletes with familial hypercholesterolemia, only six individuals tolerated the treatment (108).

The frequency of myalgia is mostly reported to be “low” (from 1 ‰ – up to 7%), although it has not been properly evaluated in an unselected population. The reason for the low frequency reported could be that light pain is a frequent symptom that most people have experienced in everyday life. Approximately 7% of all Swedes (more than 600 000 individuals) were found to have purchased a lipid modifying pharmaceutical during a year. If the frequency of muscle pain among statin users would be around 7%, as suggested in some other publications, more than 42 000 individuals in Sweden could be in pain from these pharmaceuticals. By calculating the prevalence: incidence rate for statins, from Danish individual prescription data, a surprisingly low rate has been found (i.e. low prevalence despite high incidence) that shows the lack of persistence with statin treatment (81). The same has been found in other countries (109-110). Whether the lack of persistence with treatment is caused by adverse symptoms, or some other reasons, is unknown.

Muscle weakness, which occurs even without other muscle symptoms, is especially disastrous for individuals with other neurological diseases. It also manifests itself in difficulties with walking and rising from a toilet or a chair, but the frequency is unknown (71,111). Symptoms that, like muscle pain and cognitive problems, are common in the elderly population, are even more difficult to distinguish, and may be misattributed to ageing and being underappreciated (71, 111-112). There have also been hopes of possibilities to prevent or delay Alzheimer’s disease by statin treatment (113). Interactions with other drugs, as well as co-morbid conditions, increase the risk of adverse effects (105, 114). From our study (paper V) it was calculated that one in five of the older population of Sweden purchased lipid modifying pharmaceuticals (mainly statins). The exposure could involve disability and loss of self-esteem, among a potentially large number of older people, and further consequences could be needs for extra health care and home-help, hospitalization or institutionalization (71), and thereby unnecessary costs.

Serious liver injury is the most common reason for stopping the development of a new drug and for withdrawing a marketed pharmaceutical (28, 115). Taking a medicine every day, for decades, puts liver and renal functions to a severe test. Increased levels of ALT (alanine aminotransferase) of more than three times the normal upper limit have been reported among 2% of statin-treated individuals (116). Thus, of 600 000 individuals as found in our study (paper V), 12 000 could be at risk of hepatotoxicity. For elderly people with other concomitant diseases and drug treatments, the risk is considered to be generally higher. As randomized trial data confirm that lowering cholesterol no longer extends life in

the elderly, the importance of considering adverse effects from statins in this group increases (71). In the case of preventive treatment of healthy people, attention to adverse effects is even more important. While we strive to minimize and eliminate preventable risks, adverse reactions from medications remain an ever-present challenge (115).

A well-known serious adverse effect from statins is rhabdomyolysis, the destruction or degeneration of muscle tissue, accompanied by the release of breakdown products into the bloodstream, and sometimes leading to acute renal failure (117-119). Increased risk of cancer has been reported, an effect that could be especially pronounced among older people, who are expected to harbour a large number of neoplastic and preneoplastic lesions (120). Also reduced risk (prevention) of cancer from statins has been reported (71, 121).

6.4.3.2. Antihypertensive agents and adverse effects

Antihypertensive pharmaceuticals have been shown to decrease the frequency of symptoms from blood pressure, but add other symptoms, linked to the pharmaceutical treatment (122).

Low diastolic pressure was reported to be associated with higher risk of dementia in individuals over age 75, perhaps by reducing cerebral perfusion (123). The same has been reported for individuals of these ages who used antihypertensive drugs (124). The risk of dementia among older subjects, from 85 years of age, who used antihypertensive medication, was reported to decrease with increasing blood pressure. This suggests an inverse association between blood pressure and risk of dementia in elderly persons on antihypertensive medication (125). There have also been indications of an opposite effect (126), but a systematic review did not result in convincing evidence of prevention of dementia or cognitive impairment by blood pressure lowering (127). Also a U-shaped relationship, between level of pulse pressure and incidence of dementia, has been suggested (126).

There has been a discussion of possible increased risk of cancer in people treated with antihypertensive agents, as calcium channel blockers (128). Recently, verapamil has been reported to be associated with an increased risk of cancer in the elderly (129).

6.4.4. Public health politics / policy and cardiovascular treatments

Government policy, for example taxes on food of different content quality, taxes on fuel and energy, and work environment regulations that stimulate or impede physical activity, influences health or disease promotion. Recent studies in both

the United States and Europe have shown that government policy, as well as the interests of the food industry, continues to promote CVD (130). There are companies and alliances between multinational companies, with conflicting political interests in preventing or inadvertently promoting cardiovascular disease, by e.g. production of potato chips combined with cardiovascular and diabetes research, or a combination of production of sweet drinks and anti-diabetic treatments. In the same spirit, a continuation of the market for nicotinic supplements could be based on the fact that young people continue to start smoking.

6.4.4.1. Cardiovascular trends in Nordic and other high-income countries

The incidence of cardiovascular disease falls in many high-income countries. For example in Finland, there was exceptionally high risk of cardiovascular disease in the 1960s and 1970s. In parallel with voluntary and governmental prevention programs, the level of risk factors and CVD attack rates have shown a dramatic improvement during 25 years (131), but the decline has slowed in recent years (132). In an issue of Preventive Medicine from 1999, impressions and findings from different parts of the world are gathered. Decrease in cardiovascular disease incidence is reported from e.g. Netherlands and Japan, where the change has been linked to decrease in smoking and changes in eating patterns (133-134). In Sweden, the prevalence of smoking fell from more than 30% in 1984, to below 20% in 2001 (16-74 years, age-standardized) (135).

6.4.4.2. Cardiovascular trends in low- and middle-income countries

Gradually the low- and middle-income countries are becoming subject to the same risks that have contributed to the high incidence of cardiovascular diseases in the earlier industrialized countries. A rapidly developing 'second-wave epidemic' of cardiovascular disease is flowing through low- and middle-income countries and the former socialist republics (36, 136-138).

The life expectancy at birth increases in many low- and middle-income countries, due to decreasing mortality rates from acute infectious diseases, and a higher proportion of individuals reaching middle and old age (138). The stage at which cardiovascular diseases may be considered to be 'actively emerging' was, according to WHO in 1988, corresponding to a life expectancy level between 50 and 60 years (139). Contributory causes include apart from demographic shifts with altered population age profiles, recent industrialization and urbanization accompanied by altered diets, tobacco use and diminished physical activity (140-142). Cardiovascular disease or chronic disease has traditionally been categorized as non-communicable disease. Nevertheless, it could also be considered communicable at the risk factor level, since modern dietary patterns,

and physical activity patterns, are risk behaviours that travel across countries, and are transferable from one population to another (143). Disadvantageous intake of food, by seeking food or drinks with high caloric density, could be considered a natural survival strategy among undernourished or starving people. There is also susceptibility for developing CVD among poor people, which is a probable effect of foetal under-nutrition and low birth weights (140, 144).

WHO states, that in low- and middle-income countries, there are considerable health benefits for both men and women, at all ages, in stopping smoking, reducing cholesterol and blood pressure, eating a healthy diet and increasing physical activity (145). Transforming attitudes towards 'behaviourally appropriate' customs, such as smoking, eating snacks and drinking soft drinks, in many low- and middle-income countries so that they are perceived as 'behaviourally inappropriate', in line with Rose's recommendations from 1985 (55), would probably make a great difference. A new information booklet from WHO, on prevention of cardiovascular disease, is a promising step (146).

Low- and middle-income countries seem to be the next target for the marketing of preventive drugs. One of the consequences could be that resources would be allocated to the identification and treatment of risk factors among wealthy groups, instead of to primordial prevention for the whole population. To avoid 'parallel-import', prices on patented products are nowadays often as high in low-income countries as in high-income countries (147). Current economic trends urge liberalization of markets, and follow the assumption that free flow of trade, finance and information, will produce the best outcome for economic development (7).

6.4.4.3. Prevention, prevalent treatments and possible implications for health economy

Economic policy is an important determinant of population health. True primordial prevention of CVD, may require regulation of the domestic and international market forces, which produce and distribute CVD risk factors and their determinants. The market does not bear the cost of the poor health that it generates, and primordial prevention of CVD, may need to concern itself with societal mechanisms for holding these market forces accountable (148).

The importance and cost-effectiveness of prevention is often stated and also discussed. The most cost-effective, affordable and sustainable way, to cope with the chronic disease epidemic worldwide, is considered to be the public health approach of primary prevention (143, 149). Nevertheless, there is sometimes an intentional confusion on the pharmaceutical market, regarding cost-effectiveness of primary prevention.

Economic analyses are sometimes dependent on strong assumptions and hypothetical benefits, not observed within the time periods of the trials, but from extrapolations at the end of the trial, rather than the modest benefits estimated from within it (147). The cost-effectiveness is calculated to be very different at various levels of risk (150-151). The present use of pharmaceuticals at gradually lower levels of risk will necessarily be followed by a lower effectiveness of prevention (37).

In practice, doctors also have responsibilities to other patients and potential patients within the collectively funded health care system (152). They have to bear in mind that the choices of some patients, may eliminate options for other patients, because the resources that had been available have been consumed. This has been exemplified by a large-scale use of statins that may result in too few resources for competing health needs and other effective treatments, since it will benefit only a minority of those who take them for a long time (150). In Sweden, statins were purchased by more than 600 000 individuals and for example in the United States; about 15 million individuals are estimated to take statins (150). In Canada 1% of total healthcare expenditure is spent on statins, and 2% of healthcare resources are spent on the entire public health sector, which is responsible for population health strategies for all conditions, as well as immunizations (57).

Increased public health at the primordial level could result in lower profit for pharmaceutical companies in the future. Turning more and more healthy people into permanent pharmaceutical customers, would be a way to neutralize this development, while non-recurrent treatments, such as vaccinations for poor people, would not be expected to be given priority.

6.4.5. The future

In high-income countries, it is in the prevention of disease that most research now takes place, and the increasing number of patients, included in the clinical trials (of e.g. statins), indicate the increasingly small treatment effects that are of interest (147). For the individual physician, there will be small chances of evaluating the benefit of the preventive treatments, when even more healthy individuals, with smaller statistical risks, are treated pharmaceutically. Regarding primary prevention, there are examples of calculations of numbers needed to prevent, in the range 90-99 mm Hg diastolic blood pressure, that give figures as if one GP must work for 29 years, to prevent one single case of coronary disease, by antihypertensive treatment (37).

More screening is a recurrent topic. There are ethical dimensions to screening due to the risk of doing harm (22, 98, 153). The ways of taking care of the findings, motivating the patient, preventing the feeling of illness, or later experienced adverse effects, are subsequent topics (61, 154). Pre-hypertension, a condition present in about 70 million Americans (155) has recently been recommended to be treated pharmaceutically, to prevent hypertension. In one study, 208 of 409 pharmaceutically treated participants developed hypertension, and in the placebo group 240 of 400 individuals developed hypertension. The result was presented as 15.6 % relative risk reduction (156).

The idea of a ‘Polypill’ has been spread since 2003. This is a denomination for a pill containing statin, diuretic, beta-blocker, ACE-inhibitor, acetylsalicylic acid and folic acid, to treat all persons above 55 years of age without specific risk factors, to prevent cardiovascular disease (57, 157). Calculations were made to find the right price to be ‘cost-effective’ (158-159). Also a ‘Polymeal’ with the content of wine, fish, dark chocolate, fruits, vegetables, garlic, and almonds, has been estimated to reduce cardiovascular disease events by 76% (160). Another new pharmaceutical niche, proposed from patients, seems to be drugs that help changing life-style (87).

6.4.5.1. Future research

The establishment of the Swedish Prescribed Drugs Register of data at the individual level has made the Swedish pharmacoepidemiological reality full of future prospects. We have got the tool to measure the prevalence of purchase of pharmaceuticals in different combinations and in different groups of the population (even if there are no data on actual intake). In the future, there will hopefully also be possibilities to compare groups of individuals; those exposed to pharmaceuticals with those that are not exposed, to extend the knowledge of positive and negative effects of for example cardiovascular preventive pharmaceuticals. Investigating the relative risk of developing cancer and other serious adverse effects would be of high priority.

For finding prevalence of common ‘harmless’ drug-induced adverse symptoms, the pharmacy counter would be a useful location for a questionnaire of experienced symptoms. Data could be directly transferred to a database in the pharmacy computer. A pilot study of recipients of dispensed statins has been performed, but the possibilities of catching matched controls in a corresponding way, was not present at that time. From the collected data, calculations of possible “excess-frequencies” of adverse symptoms, among individuals taking the pharmaceutical, could then be done.

Probable obstacles, that could be foreseen, to collection of complete and valid data, could be that more and more pharmaceuticals are sold OTC or via Internet. The ‘unexposed’ group of individuals could then be mixed with exposed individuals. Nevertheless, pharmacoepidemiology will be one essential tool to meet future challenges. Hopefully, some authority will realize the importance of collecting population data of effectiveness and adverse effects of pharmaceuticals, since the chances are small that a private company will take this responsibility. A complete population database with well-documented exposures to medicines, outcomes and potential risk factors, would be the ultimate aim, even though a drive towards increased confidentiality may work against the interests of public health in relation to drug safety (24).

Risk-communication is a key-field for prevention, and has recently been studied in depth regarding female hormone treatment, where often symptoms also are involved (161). In the case of primary prevention of CVD among asymptomatic people, the communication is even more problematic, and future research and development of guidelines will be necessary. The balance of reaching high compliance to preventive treatment on one side, and maintenance of feeling of health and well-being among individuals on the other, would be a challenging field of research.

6.4.6. Final reflections

Professor Rose wrote about the second type of mass preventive measure (from page 16): “...that consists not in removing a supposed cause of disease, but in adding some other unnatural factor, in the hope of conferring protection. The end result is to increase biological abnormality by an even further removal from those conditions to which we are genetically adapted”. For coronary heart disease, such measures include all forms of long-term medication: “Long-term safety cannot be assured, and quite possibly harm may outweigh benefit. For such measures as these, the required level of evidence, both of benefit and (particularly) of safety, must be far more stringent” (55).

Applying Rose’s reasoning on the high prevalence of preventive cardiovascular pharmaceuticals found in our studies, could give the impression that what Rose calls the ‘high-risk’ approach, has been extended to a majority of the older population, and become like a ‘population strategy’, that would give small benefit to each individual (55). He wrote: “Of course, the higher the prevalence of ‘high-risk’ status, the greater the potential benefits to the community from treating all those at high risk, but total costs rise disproportionately and the policy starts to lose all meaning if it has to embrace a large part of the population” and also that “The purpose is to assess reversible risk – not risk factors” (162).

Consensus is prevailing regarding the importance of prevention. Whether the prevalent prescribing of cardiovascular preventive pharmaceutical treatments will save more suffering than it causes, the future will tell. When the majority of the population over 60 is treated with preventive drugs, possible harmful effects could become visible as consequences on public health, at some stage. Then it would be advisable to set up an early-warning system so as not to be taken by surprise.

Sometimes the good of the purpose of an intervention blurs the vision of the experts, as in the case of the so called ‘oestrogen catastrophe’ from the middle of the 90s. To vindicate women’s health and well-being, hormone replacement therapy (HRT) was prescribed generously, without former restrictions, even for prevention of cardiovascular disease and osteoporosis, and without enough documentation of risks and benefits. This line of action resulted in a large number of ‘extra’ cancers (163-164).

Even in the case of cardiovascular ‘health for all’, with the aim of equalization of non-equalities in global cardiovascular health, there could be a risk of rash recommendations and insufficient clear-sightedness regarding drawbacks. To prevent a course of events, similar to that for hormone replacement therapy, it would be advisable to learn from history and follow the recommendations from the group of researchers that reviewed the factors that led to that ‘catastrophe’, here called ‘the HRT saga’ (164).

“Recommendations for future scientific research and clinical practice, building on an interdisciplinary analysis of the lessons from the HRT saga:

- *Require greater transparency regarding funding of scientific and medical training, research, and publications, especially to expose potential conflicts of interest arising when funders stand to gain economically from the issues, activities, and products they are either: (a) underwriting, or (b) attempting to obfuscate.*
- *Require the protocols and results of all drug trials, regardless of study phase or findings, to be registered in publicly accessible registries that can be freely and easily searched.*
- *Apply the precautionary principle to ‘preventive medicine’ and ‘risk reducing’ drugs, plus challenge the growing consensus, fuelled by the pharmaceutical industry, that it is ‘acceptable’ to increase disease risk in currently healthy persons by prescribing drugs intended to prevent future illness.*
- *Do not conflate biology with ‘biomedicine’’: pharmacological interventions typically are based on reductionist models, but complex evolved biological systems are unlikely to respond in a simple ‘cause and effect’ way (or in any one way) to any particular biomedical intervention.*
- *Challenge the ideology that science can render life ‘risk free’ and that all risk can be quantified.*
- *Increase economic, professional, and structural incentives for physicians to have time to practice truly preventive medicine with their patients, to address social and*

economic obstacles hindering their ability to live healthy lives, and also to make complex medical decisions with their patients, including decisions regarding termination of treatment and acceptance of mortality.

- *Encourage development of organizations and venues where experts and lay people can critically evaluate scientific evidence and obtain funding to: (a) research, explore, and scientifically test alternatives to the biomedical tendency to interpret embodied transitions, such as menopause, principally from the perspective of disease narratives, and (b) expose and provide education to counter manipulation of expert and lay opinion by sectors and people who benefit from sale of biomedical interventions (including pharmacological agents)” (164).*

7. CONCLUSIONS

The purchase of pharmaceuticals on prescription almost doubled in Halland, over the studied years. Some cardiovascular preventive treatments, and hormone replacement therapy for women, were some of the common drugs that increased to a great extent, among the older part of the population. Prescriptions of cardiovascular treatments primarily emanated from primary care.

The different views that were found among GPs, regarding beliefs and practical management of primary prevention of CVD, could be interpreted as a reflection of the complexity of patient counselling in primary prevention in practice. These findings also point at the need of clarification of guidelines regarding pharmaceutical primary prevention and encouragement of therapy discussions among GPs.

Over half of all Swedish citizens, of 60 years or more, purchased antihypertensive or lipid modifying pharmaceuticals during 6 months in 2005. The magnitude of the prevalence of the studied pharmaceuticals, such as antihypertensive, serum-lipid modifying agents and hormonal treatments, which to a great extent are used by healthy people, points to the need of following-up of harmful as well as beneficial consequences on public health.

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- 1983:1 Hälsa för alla i Norden år 2000. Föredrag presenterade på en konferens vid Nordiska hälsovårdshögskolan 7–10 september 1982.
- 1983:2 Methods and Experience in Planning for Family Health – Report from a seminar. Harald Heijbel & Lennart Köhler (eds).
- 1983:3 Accident Prevention – Report from a seminar. Ragnar Berfenstam & Lennart Köhler (eds).
- 1983:4 Själv mord i Stockholm – en epidemiologisk studie av 686 konsekutiva fall. Thomas Hjortsjö. Avhandling.

1984

- 1984:1 Långvarigt sjuka barn – sjukvårdens effekter på barn och familj. Andersson, Harwe, Hellberg & Syrén. (FoU-rapport/shstf:14). Distribueras av Studentlitteratur, Box 141, SE-221 01 Lund.
- 1984:2 Intersectoral Action for Health – Report from an International Workshop. Lennart Köhler & John Martin (eds).
- 1984:3 Barns hälsotillstånd i Norden. Gunborg Jakobsson & Lennart Köhler. Distribueras av Studentlitteratur, Box 141, SE-221 01 Lund.

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- 1985:1 Hälsa för äldre i Norden år 2000. Mårten Lagergren (red).
- 1985:2 Socialt stöd åt handikappade barn i Norden. Mats Eriksson & Lennart Köhler. Distribueras av Allmänna Barnhuset, Box 26006, SE-100 41 Stockholm.
- 1985:3 Promotion of Mental Health. Per-Olof Brogren.
- 1985:4 Training Health Workers for Primary Health Care. John Martin (ed).
- 1985:5 Inequalities in Health and Health Care. Lennart Köhler & John Martin (eds).

1986

- 1986:1 Prevention i primärvården. Rapport från konferens. Harald Siem & Hans Wedel (red). Distribueras av Studentlitteratur, Box 141, SE-221 01 Lund.
- 1986:2 Management of Primary Health Care. John Martin (ed).
- 1986:3 Health Implications of Family Breakdown. Lennart Köhler, Bengt Lindström, Keith Barnard & Houda Itani.
- 1986:4 Epidemiologi i tandvården. Dorthe Holst & Jostein Rise (red). Distribueras av Tandläkarförbundet, Box 5843, SE-102 48 Stockholm.
- 1986:5 Training Course in Social Pediatrics. Part I. Lennart Köhler & Nick Spencer (eds).

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1987

- 1987:1 Children's Health and Well-being in the Nordic Countries. Lennart Köhler & Gunborg Jakobsson. Ingår i serien Clinics in Developmental Medicine, No 98 och distribueras av Blackwell Scientific Publications Ltd, Oxford. ISBN (UK) 0 632 01797X.
- 1987:2 Traffic and Children's Health. Lennart Köhler & Hugh Jackson (eds).
- 1987:3 Methods and Experience in Planning for Health. Essential Drugs. Frants Staugård (ed).
- 1987:4 Traditional midwives. Sandra Anderson & Frants Staugård.
- 1987:5 Nordiska hälsovårdshögskolan. En historik inför invigningen av lokalerna på Nya Varvet i Göteborg den 29 augusti 1987. Lennart Köhler (red).
- 1987:6 Equity and Intersectoral Action for Health. Keith Barnard, Anna Ritsatakis & Per-Gunnar Svensson.
- 1987:7 In the Right Direction. Health Promotion Learning Programmes. Keith Barnard (ed).

1988

- 1988:1 Infant Mortality – the Swedish Experience. Lennart Köhler.
- 1988:2 Familjen i välfärdsstaten. En undersökning av levnadsförhållanden och deras fördelning bland barnfamiljer i Finland och övriga nordiska länder. Gunborg Jakobsson. Avhandling.
- 1988:3 Aids i Norden. Birgit Westphal Christensen, Allan Krasnik, Jakob Bjørner & Bo Eriksson.
- 1988:4 Methods and Experience in Planning for Health – the Role of Health Systems Research. Frants Staugård (ed).
- 1988:5 Training Course in Social Pediatrics. Part II. Perinatal and neonatal period. Bengt Lindström & Nick Spencer (eds).
- 1988:6 Äldretandvård. Jostein Rise & Dorthe Holst (red). Distribueras av Tandläkarförlaget, Box 5843, SE-102 48 Stockholm.

1989

- 1989:1 Rights, Roles and Responsibilities. A view on Youth and Health from the Nordic countries. Keith Barnard.
- 1989:2 Folkhälsovetenskap. Ett nordiskt perspektiv. Lennart Köhler (red).
- 1989:3 Training Course in Social Pediatrics. Part III. Pre-School Period. Bengt Lindström & Nick Spencer (eds).

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- 1989:4 Traditional Medicine in Botswana. Traditional Medicinal Plants. Inga Hedberg & Frants Staugård.
- 1989:5 Forsknings- och utvecklingsverksamhet vid Nordiska hälsovårdshögskolan. Rapport till Nordiska Socialpolitiska kommittén.
- 1989:6 Omstridda mödrar. En studie av mödrar som förtecknats som förståndshandikappade. Evy Kollberg. Avhandling.
- 1989:7 Traditional Medicine in a transitional society. Botswana moving towards the year 2000. Frants Staugård.
- 1989:8 Rapport fra Den 2. Nordiske Konferanse om Helseopplysning. Bergen 4–7 juni 1989. Svein Hindal, Kjell Haug, Leif Edvard Aarø & Carl-Gunnar Eriksson.

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- 1990:1 Barn och barnfamiljer i Norden. En studie av välfärd, hälsa och livskvalitet. Lennart Köhler (red). Distribueras av Studentlitteratur, Box 141, SE-221 01 Lund.
- 1990:2 Barn och barnfamiljer i Norden. Teknisk del. Lennart Köhler (red).
- 1990:3 Methods and Experience in Planning for Health. The Role of Women in Health Development. Frants Staugård (ed).
- 1990:4 Coffee and Coronary Heart Disease, Special Emphasis on the Coffee – Blood Lipids Relationship. Dag S. Thelle & Gerrit van der Stegen (eds).

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- 1991:1 Barns hälsa i Sverige. Kunskapsunderlag till 1991 års Folkhälsorapport. Gunborg Jakobsson & Lennart Köhler. Distribueras av Fritzes, Box 16356, SE-103 27 Stockholm (Allmänna Förlaget).
- 1991:2 Health Policy Assessment – Proceedings of an International Workshop in Göteborg, Sweden, February 26 – March 1, 1990. Carl-Gunnar Eriksson (ed). Distributed by Almqvist & Wiksell International, Box 638, SE-101 28 Stockholm.
- 1991:3 Children's health in Sweden. Lennart Köhler & Gunborg Jakobsson. Distributed by Fritzes, Box 16356, SE-103 27 Stockholm (Allmänna Förlaget).
- 1991:4 Poliklinikker og dagkurgi. Virksomhetsbeskrivelse for ambulent helsetjeneste. Monrad Aas.
- 1991:5 Growth and Social Conditions. Height and weight of Stockholm schoolchildren in a public health context. Lars Cernerud. Avhandling.
- 1991:6 Aids in a caring society – practice and policy. Birgit Westphal Victor. Avhandling
- 1991:7 Resultat, kvalitet, valfrihet. Nordisk hälsopolitik på 90-talet. Mats Brommels (red). Distribueras av nomesko, Sejrøgade 11, DK-2100 København.

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1992

- 1992:1 Forskning om psykiatrisk vårdorganisation – ett nordiskt komparativt perspektiv. Mats Brommels, Lars-Olof Ljungberg & Claes-Göran Westin (red). sou 1992:4. Distribueras av Fritzes, Box 16356, SE-103 27 Stockholm (Allmänna förlaget).
- 1992:2 Hepatitis virus and human immunodeficiency virus infection in dental care: occupational risk versus patient care. Flemming Scheutz. Avhandling.
- 1992:3 Att leda vård – utveckling i nordiskt perspektiv. Inga-Maja Rydholm. Distribueras av shstf-material, Box 49023, SE-100 28 Stockholm.
- 1992:4 Aktion mot alkohol och narkotika 1989–1991. Utvärderingsrapport. Athena. Ulla Marklund.
- 1992:5 Abortion from cultural, social and individual aspects. A comparative study, Italy – Sweden. Marianne Bengtsson Agostino. Avhandling.

1993

- 1993:1 Kronisk syke og funksjonshemmede barn. Mot en bedre fremtid? Arvid Heiberg (red). Distribueras av Tano Forlag, Stortorget 10, NO-0155 Oslo.
- 1993:2 3 Nordiske Konference om Sundhedsfremme i Aalborg 13 – 16 september 1992. Carl-Gunnar Eriksson (red).
- 1993:3 Reumatikernas situation i Norden. Kartläggning och rapport från en konferens på Nordiska hälsovårdshögskolan 9 – 10 november 1992. Bjarne Jansson & Dag S. Thelle (red).
- 1993:4 Peace, Health and Development. A Nobel seminar held in Göteborg, Sweden, December 5, 1991. Jointly organized by the Nordic School of Public Health and the University of Göteborg with financial support from SAREC. Lennart Köhler & Lars-Åke Hansson (eds).
- 1993:5 Hälsopolitiska jämlikhetsmål. Diskussionsunderlag utarbetat av WHOs regionkontor för Europa i Köpenhamn. Göran Dahlgren & Margret Whitehead. Distribueras gratis.

1994

- 1994:1 Innovation in Primary Health Care of Elderly People in Denmark. – Two Action Research Projects. Lis Wagner. Avhandling.
- 1994:2 Psychological stress and coping in hospitalized chronically ill elderly. Mary Kalfoss. Avhandling.
- 1994:3 The Essence of Existence. On the Quality of Life of Children in the Nordic countries. Theory and Practice. Bengt Lindström. Avhandling.

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1995

- 1995:1 Psykiatrisk sykepleie i et folkehelseperspektiv. En studie av hvordan en holistisk-eksistensiell psykiatrisk sykepleiemodell bidrar til folkehelsearbeid. Jan Kåre Hummelvoll. Avhandling.
- 1995:2 Child Health in a Swedish City – Mortality and birth weight as indicators of health and social inequality. Håkan Elmén. Avhandling.
- 1995:3 Forebyggende arbeid for eldre – om screening, funn, kostnader og opplevd verdi. Grethe Johansen. Avhandling.
- 1995:4 Clinical Nursing Supervision in Health Care. Elisabeth Severinsson. Avhandling.
- 1995:5 Prioriteringsarbeite inom hälso- och sjukvården i Sverige och i andra länder. Stefan Holmström & Johan Calltorp. Spri 1995. Distribueras av Spris förlag, Box 70487, SE-107 26 Stockholm.

1996

- 1996:1 Socialt stöd, livskontroll och hälsa. Raili Peltonen. Socialpolitiska institutionen, Åbo Akademi, Åbo, 1996.
- 1996:2 Recurrent Pains – A Public Health Concern in School – Age Children. An Investigation of Headache, Stomach Pain and Back Pain. Guðrún Kristjánsdóttir. Avhandling.
- 1996:3 AIDS and the Grassroots. Frants Staugård, David Pitt & Claudia Cabrera (red).
- 1996:4 Postgraduate public health training in the Nordic countries. Proceedings of seminar held at The Nordic School of Public Health, Göteborg, January 11 – 12, 1996.

1997

- 1997:1 Victims of Crime in a Public Health Perspective – some typologies and tentative explanatory models (Brottsoffer i ett folkhälsoperspektiv – några typologier och förklaringsmodeller). Barbro Renck. Avhandling. (Utges både på engelska och svenska.)
- 1997:2 Kön och ohälsa. Rapport från seminarium på Nordiska hälsovårdshögskolan den 30 januari 1997. Gunilla Krantz (red).
- 1997:3 Edgar Borgenhammar – 65 år. Bengt Rosengren & Hans Wedel (red).

1998

- 1998:1 Protection and Promotion of Children's Health – experiences from the East and the West. Yimin Wang & Lennart Köhler (eds).
- 1998:2 EU and Public Health. Future effects on policy, teaching and research. Lennart Köhler & Keith Barnard (eds) 1998:3 Gender and Tuberculosis. Vinod K. Diwan, Anna Thorson, Anna Winkvist (eds)

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Report from the workshop at the Nordic School of Public Health, May 24-26, 1998.

1999

- 1999:1 Tipping the Balance Towards Primary Healthcare Network. Proceedings of the 10th Anniversary Conference, 13-16 November 1997. Editor: Chris Buttanshaw.
- 1999:2 Health and Human Rights. Report from the European Conference held in Strasbourg 15-16 mars 1999. Editor: Dr. med. Stefan Winter.
- 1999:3 Learning about health: The pupils' and the school health nurses' assessment of the health dialogue. Ina Borup. DrPH-avhandling.
- 1999:4 The value of screening as an approach to cervical cancer control. A study based on the Icelandic and Nordic experience through 1995. Kristjan Sigurdsson. DrPH-avhandling.

2000

- 2000:1 Konsekvenser av urininkontinens sett i et folkehelsevitenskapelig perspektiv. En studie om livskvalitet hos kvinner og helsepersonells holdninger. Anne G Vinsnes. DrPH-avhandling.
- 2000:2 A new public health in an old country. An EU-China conference in Wuhan, China, October 25-29, 1998. Proceedings from the conference. Lennart Köhler (ed)
- 2000:3 Med gemenskap som grund - psykisk hälsa och ohälsa hos äldre människor och psykiatrisjukskötarskans hälsofrämjande arbete. Birgitta Hedelin. DrPH-avhandling.
- 2000:4 ASPHER Peer Review 1999. Review Team: Jacques Bury, ASPHER, Franco Cavallo, Torino and Charles Normand, London.
- 2000:5 Det kan bli bättre. Rapport från en konferens om barns hälsa och välfärd i Norden. 11-12 november 1999. Lennart Köhler. (red)
- 2000:6 Det är bra men kan bli bättre. En studie av barns hälsa och välfärd i de fem nordiska länderna, från 1984 till 1996. Lennart Köhler, (red)
- 2000:7 Den svenska hälso- och sjukvårdens styrning och ledning – en delikat balansakt. Lilian Axelsson. DrPH-avhandling.
- 2000:8 Health and well-being of children in the five Nordic countries in 1984 and 1996. Leeni Berntsson. DrPH-avhandling.
- 2000:9 Health Impact Assessment: from theory to practice. Report on the Leo Kaprio Workshop, Göteborg, 28 - 30 October 1999.

2001

- 2001:1 The Changing Public-Private Mix in Nordic Healthcare - An Analysis
John Øvretveit.

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- 2001:2 Hälsokonsekvensbedömningar – från teori till praktik. Rapport från ett internationellt arbetsmöte på Nordiska hälsovårdshögskolan den 28-31 oktober 1999. Björn Olsson, (red)
- 2001:3 Children with asthma and their families. Coping, adjustment and quality of life. Kjell Reichenberg. DrPH-avhandling.
- 2001:4 Studier av bruket av dextropropoxifen ur ett folkhälsoperspektiv. Påverkan av ett regelverk. Ulf Jonasson. DrPH-avhandling.
- 2001:5 Protection – Prevention – Promotion. The development and future of Child Health Services. Proceedings from a conference. Lennart Köhler, Gunnar Norvenius, Jan Johansson, Göran Wennergren (eds).
- 2001:6 Ett pionjärbete för ensamvargar
Enkät- och intervjuundersökning av nordiska folkhälsodoktorer examinerade vid Nordiska hälsovårdshögskolan under åren 1987 – 2000.
Lillemor Hallberg (red).

2002

- 2002:1 Attitudes to prioritisation in health services. The views of citizens, patients, health care politicians, personnel, and administrators. Per Rosén. DrPH-avhandling.
- 2002:2 Getting to cooperation: Conflict and conflict management in a Norwegian hospital. Morten Skjørshammer. DrPH-avhandling.
- 2002:3 Annual Research Report 2001. Lillemor Hallberg (ed).
- 2002:4 Health sector reforms: What about Hospitals? Pär Eriksson, Ingvar Karlberg, Vinod Diwan (ed).

2003

- 2003:1 Kvalitetsmåling i Sundhedsvæsenet.
Rapport fra Nordisk Ministerråds Arbejdsgruppe.
- 2003:3 NHV 50 år (Festboken)
- 2003:4 Pain, Coping and Well-Being in Children with Chronic Arthritis.
Christina Sällfors. DrPH-avhandling.
- 2003:5 A Grounded Theory of Dental Treatments and Oral Health Related Quality of Life.
Ulrika Trulsson. DrPH-avhandling.

2004

- 2004:1 Brimhealth 1993-2003
- 2004:2 Experienced quality of the intimate relationship in first-time parents – qualitative and quantitative studies. Tone Ahlborg. DrPH-avhandling.

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2005

- 2005:1 Kärlek och Hälsa – Par-behandling i ett folkhälsoperspektiv.
Ann-Marie Lundblad. DrPH-avhandling.
- 2005:2 1990 - 2000:A Decade of Health Sector Reform in Developing Countries
- Why, and What Did we Learn?
Erik Blas. DrPH-avhandling
- 2005:3 Socio-economic Status and Health in Women
Population-based studies with emphasis on lifestyle and cardiovascular disease
Claudia Cabrera. DrPH-avhandling

2006

- 2006:1 "Säker Vård -patientskador, rapportering och prevention"
Synnöve Ödegård. DrPH-avhandling
- 2006:2 Interprofessional Collaboration in Residential Childcare
Elisabeth Willumsen. DrPH-avhandling
- 2006:3 Innkøms-CTG: En vurdering av testens prediktive verdier, reliabilitet og
effekt. Betydning for jordmødre i deres daglige arbeide
Ellen Blix. DrPH-avhandling

2007

- 2007:1 Health reforms in Estonia - acceptability, satisfaction and impact
Kaja Põlluste. DrPH-avhandling
- 2007:2 Creating Integrated Health Care
Bengt Åhgren. DrPH-avhandling
- 2007:3 Alkoholbruk i tilknytning til arbeid – Ein kvalitativ studie i eit folkehelsevitskapeleg
perspektiv
Hildegunn Sagvaag. DrPH-avhandling
- 2007:4 Public Health Aspects of Pharmaceutical Prescription Patterns – Exemplified by
Treatments for Prevention of Cardiovascular Disease
Louise Silwer. DrPH-avhandling