The Nordic Countries as a Cohort for Pharmacoepidemiological Research

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Abstract: The Nordic countries have a long tradition of registry-based epidemiological research. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. In recent years, each country has established a national database to track prescription drugs dispensed to individuals in ambulatory care. The objectives were to present an overview of the prescription databases established in the Nordic countries, as well as to elaborate on their unique potential for record linkage and cross-national comparison of drug utilization. Five Nordic countries collect drug exposure data based on drugs dispensed at pharmacies and have the potential to link these data to health outcomes. The databases together cover 25 million inhabitants (Denmark: 5.5 million; Finland: 5.3 million; Iceland: 0.3 million; Norway: 4.8 million; and Sweden: 9.2 million). In 2007, the registries encompassed 17 million prescription drug users (68% of the total population). We provide examples of how these databases have been used for descriptive drug utilization studies and analytical pharmacoepidemiological studies linking drug exposure to other health registries. Comparisons are facilitated by many similarities among the databases, including data source, content, coverage and methods used for drug utilization studies and record linkage. There are, however, some differences in coding systems and validity, as well as in some access and technical issues. To perform cross-national pharmacoepidemiological studies, resources, networks and time are needed, as well as methods for pooling data. Interpretation of results needs to account for inter-country heterogeneity and the possibility of spurious relationships. The Nordic countries have a unique potential for collaborative high-quality cross-national pharmacoepidemiological studies with large populations. This research may assist in resolving safety issues of international interest, thus minimizing the risk of either over-reacting on possible signals or underestimating drug safety issues.

There is an urgent need to assess the effectiveness and safety of drugs used in routine medical practice. Despite recent changes in regulatory demands, new drug development techniques and new models for disseminating medicines in the healthcare system, post-approval observational studies remain necessary to study drug effects, safety and cost-effectiveness [1]. This is particularly important as clinical practice differs substantially from the context of randomized clinical trials in terms of numbers and characteristics of patients, length of drug exposure, dosage and compliance [1,2]. An epidemiological approach to drug use and safety allows assessment of how drugs function in the real world.

Since the 1970s, the Nordic countries have used data on wholesale drug distribution to assess nationwide time trends in drug utilization and to make regional and international comparisons [3,4]. Few other countries have access to such comprehensive longitudinal national data. However, individual-level data are crucial both to accurately measure drug exposure in the population and to permit linkage of records to outcomes.

Europe’s first computerized prescription-level tracking system was established in Northern Ireland in 1966 [5]. Since the early 1970s, Sweden has recorded outpatient prescriptions in the county of Jämtland and in a small community called Tierp [6,7]. In Canada, the province of Saskatchewan created one of the first public databases to collect individual-level prescription data for its population of 1 million people already in 1975 [8]. The United States also has several large automated databases with individual-level data on drug use [1]. However, most of these American claims databases were set up by health insurance organizations for administrative purposes and cover only selected populations. In Europe, many databases have been developed primarily for research purposes. The General Practice Research Database in the UK, established in 1987, is one of the most commonly used data resources in pharmacoepidemiological research and collects health information, including drug prescriptions in patient records, from over 460 primary healthcare practices, covering about 5% of the UK population [9].
Netherlands [10] and Scotland [11] have established databases containing data on prescriptions dispensed by pharmacies, but neither of them cover the entire population of the countries.

During the late 1980s, pharmacies in the Nordic countries gradually computerized their records of dispensed prescriptions which made it possible to collect data efficiently. National prescription databases, containing data on drugs dispensed at pharmacies (exposure data) to individuals receiving ambulatory care, have been available since 1994 in Finland and Denmark, since 2004 in Norway, since 2005 in Sweden and since 2006 in Iceland [12–18]. Although healthcare systems are not organized identically in the Nordic countries, they have similar parameters. All five countries have a tax-supported public health service with universal coverage. All citizens, independent of socioeconomic status, have unrestricted access to health services, including partial or complete reimbursement of purchased medicines.

This article provides an overview of data collection procedures and content of the Nordic countries’ prescription databases. In addition, we discuss their unique potential for cross-national record linkage and for analytical pharmacoepidemiological studies.

Data Collection Procedures and Content of the Nordic Prescription Databases

Each Nordic country has a nationwide prescription database containing electronically submitted information on prescriptions dispensed by pharmacies. In total, the databases cover the countries’ 25 million inhabitants (fig. 1). In addition, Denmark has two regional prescription databases established for research purposes. Data from the autonomic region Åland Islands are included in the Finnish data, but the data from the autonomic regions of the Faroe Islands and Greenland are not included in the Danish data. The data collected are determined by country-specific regulations but all include information on the prescriptions together with information from different administrative registries. In most countries, data are transferred electronically monthly from pharmacies to the prescription database. According to the legislation of each country, no informed consent is required for collection of the prescription data, but individuals may see information about themselves if they make an enquiry. The Finnish Prescription Registry originates from an administrative need for reimbursement decisions. Thus, it is used primarily for decision-making. When the registry data, however, are used for research purposes, the possible findings cannot be used for decisions concerning individual patients. In Iceland, they may use the register for individual supervision of both patients and prescribers. The national prescription databases in Denmark, Norway and Sweden cannot be used for supervision of either individual patients or prescribers.

Variables.

Data included in the databases fall into four main categories (table 1): (1) Patient-specific data (personal identifier, age, gender, place of residence); (2) Prescriber data (personal identifier, age, gender, profession, physician speciality, practice/clinic); (3) Drug data (e.g. the Nordic article number (which provides the trade name, pharmaceutical form, strength and package size), number of packages, Anatomical Therapeutic Chemical classification (ATC) code, amount in defined daily doses (DDD), prescription category, reimbursement code, prescribing date, dispensing date and price); and (4) Pharmacy data (name, licence number, municipality and county). Some countries include additional variables in their databases. Three of the main categories of data are discussed briefly below:

(1) Patient-specific data. All individuals/patients included in the prescription databases have a unique personal identifier based on their person identification number, permitting linkage between various population-based data sources. Some prescription databases routinely include the date of death and migration, while others need to be linked to this information.

(2) Prescriber data. Prescribers are also accessible in most of the databases based on either a personal identifier or an identifier of the practice or hospital department of the prescriber. Prescriber information is linked to information on medical speciality (e.g. general practitioner, internal medicine, psychiatry, etc.). Further information on the individual practice/clinic from which the prescriptions are issued is also available to some extent.

(3) Drug data. With regard to drug exposure, the Nordic article number is a unique identifier for each drug formulation of a medicinal product used in the Nordic countries. This number constitutes the link to other registries providing detailed information on dispensed drugs. The drugs are classified according to the global ATC system [19]. Numbers of DDD dispensed are recorded, as well as the number of packages and the reimbursement code. There are several challenges in using these data. Firstly, the reimbursement system differs between the countries. Secondly, the indication for the prescription is not yet recorded in the databases. However, the reimbursement code may function as a proxy for diagnosis in some cases [20]. For example, since March 2008, prescribers in Norway have had to use either the 10th edition of
Table 1.

Detailed information on the Nordic prescription databases.

<table>
<thead>
<tr>
<th>General</th>
<th>Denmark</th>
<th>Odense University Pharmacoepidemiological Database</th>
<th>Pharmacoepidemiological Prescription Database in Northern Denmark</th>
<th>Danish Registry of Medicinal Product Statistics</th>
<th>Finland</th>
<th>The Finnish Prescription Registry</th>
<th>Norway</th>
<th>The Norwegian Prescribed Drug Database</th>
<th>Sweden</th>
<th>The Swedish Prescribed Drug Registry</th>
<th>Iceland</th>
<th>The Icelandic Pharmaceutic Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population covered</td>
<td>Regional</td>
<td>1.2 million</td>
<td>Regional</td>
<td>1.7 million</td>
<td>Nationwide</td>
<td>5.5 million</td>
<td>Nationwide</td>
<td>5.3 million</td>
<td>Nationwide</td>
<td>4.8 million</td>
<td>Nationwide</td>
<td>9.2 million</td>
</tr>
<tr>
<td>Patient</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unique identifier</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Age</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Sex</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Date of death</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Emigration</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Place of residence</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Dispensed drug (drug exposure)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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</tr>
<tr>
<td>Unique identifier (Nordic article number)</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>DDD number</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Number of packages</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
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<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Non-reimbursed drugs</td>
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<td>No</td>
<td>Yes</td>
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<tr>
<td>Date of prescription</td>
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<td>No</td>
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<td>No</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Dispensing date</td>
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<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Diagnosis/indication for use</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Generic substitution done at pharmacy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>

Some databases include this information, while others access this information from another database.  
Dosage and indication as written by the doctor; for drugs belonging to special refund category: coded indication in case of certain diseases according to Finnish regulations.  
Dosage and indication as written by the doctor, ICD-10 codes or ICPC codes for the reimbursed drugs.  
Identified through a workplace code on the prescription.  
Complete coverage from 1998 onwards.  
Can be linked.
the International Classification of Diseases (ICD-10 codes) or the International Classification of Primary Care (ICPC codes) as the reimbursement code for prescriptions. The dispensing date and retail price are included in all the registries, but the prescription date is at present not included in the Norwegian and Danish prescription databases. Most prescribed medicines have received marketing approval in the Nordic countries. However, physicians may apply for a licence to prescribe drugs not yet approved for marketing. Drugs which are prescribed on this basis or by special permission from the National Medicines Agency are also included in the databases.

**Information not included.**

The majority of sales of non-prescription over-the-counter (OTC) medicines are not in the prescription databases. Only OTC medicines prescribed and dispensed to individual patients, e.g. for obtaining reimbursement in chronic diseases, are included. The indication for use and the prescribed dose are to some extent included, but only in free text not easily used for research purposes. Patient-level data on drug use in hospitals and other institutions are not collected routinely. In Denmark, individual-level information on drug use in nursing homes is included in its three databases. In Sweden, the majority of nursing homes have drugs supplied by prescription or multi-dose dispensing, and these are consequently included in its registry. Iceland started to include drugs supplied by multi-dose dispensing in 2006, but the data are complete only as of 1 January 2007. The Finnish Prescription Registry and the two regional Danish prescription databases do not include non-reimbursed medicines and can be affected by changes in the reimbursement system. None of the registries have complete data on vaccines.

**Linkage of the Nordic prescription databases to other registries and data sources.**

The Nordic countries introduced the unique civil registration code more than 50 years ago. This identifier is assigned to every person at birth or upon immigration; it is either 10 or 11 digits long and encodes date of birth and gender. The code is included in all national registries, allowing accurate linkage among them. The ubiquitous use of unique personal identifiers, making linkage possible among various population-based registries, has been the driving force behind the long tradition of registry-based epidemiological studies in the Nordic countries. Fig. 2 illustrates research possibilities conferred through linkage among the prescription databases and other available data sources.

**Data access and websites.**

Researchers may apply to the administrator of the databases in each country for use of data files. In general, the data themselves are free of charge, but costs accrue for administrative handling and file processing. Denmark and Norway have made information about users of a particular drug or drug category, disaggregated by sex, age and geography, accessible online (http://www.medstat.dk and http://www.norpd.no). More detailed information about access to each registry is available at the following websites:

- Denmark: http://www.medstat.dk and http://www.dst.dk/forsknin
- Finland: http://www.kela.fi/research
- Iceland: http://www.landlaeknir.is
- Norway: http://www.norpd.no
- Sweden: http://www.socialstyrelsen.se/Statistik/statistik_amne/lakemedel/lakemedelsregistret.htm

**Key Findings and Publications**

In 2007, the registries covered 17 million prescription drug users (68% of the population). The proportion of the population that had been dispensed prescribed medicines was 73.8% in Denmark, 68.8% in Finland, 73.7% in Iceland and 68.3% in Norway and in Sweden. In Denmark, approximately 35% of men and 20% of women did not purchase any prescription drugs during the previous year. Corresponding proportions in Iceland were approximately 30% of men and 20% of women and in Finland, Norway and Sweden about 40% of men and 25% of women. Drug use in different age groups was quite similar in the Nordic countries (fig. 3). In Finland and Norway, however, children used drugs less frequently than in the other countries. We have chosen to present sex-specific figures on statin use in the five countries as one example of utilization of a specific drug group (fig. 4). About 1.9 million people (7.6% of the entire population in the five countries) used statins during 2007. Utilization of statins among individuals aged 40–49 years varied from 2.8% in Sweden to 4.9% in Finland. Among individuals aged 60–69 years, it varied from 21.5% in Sweden to 29.1% in Finland. Differences among the Nordic countries in utilization of statins cannot be explained by variation in morbidity and further analysis is needed to explore the possible influ-
ences of reimbursement policies, guidelines and prescribing behaviour.

A large number of studies have been published, including both drug utilization studies (mainly descriptive studies) and analytical studies linking drug exposure to outcomes in patient registries, registries of road accidents, medical birth registries and cancer registries. Table 2 provides examples of drug utilization studies and table 3 presents a selection of published studies of drug effects conducted in the various Nordic countries.

Until now, there have been very few studies using data from more than one Nordic country. Bramness et al. published earlier this year a study of lithium use in three of the Nordic Countries [21]. In addition, there are also in progress Nordic studies of drug use during pregnancy involving all five Nordic countries.

Discussion

Strengths of the databases.
The Nordic prescription databases allow continuous post-marketing surveillance of drug dissemination and drug effects, the two core elements in the definition of pharma-coepidemiology. In pharmacoepidemiological research, complete and valid information on drug exposure is essential [22,23]. Pharmacy records are considered more complete than both medical records and information elicited from interviews and questionnaires [24–26]. Because only information about drugs dispensed and purchased by patients is entered into the databases, primary non-compliance is not an issue [27]. Completeness and accuracy of pharmacy records is high, due to legislation or other incentives motivating pharmacies to collect and send the data electronically to their national databases on all prescription drugs dispensed to and picked up by individuals in ambulatory care. In pharmacy records, drug use can be measured in great detail and the potential for recall and selection bias associated with survey data is eliminated [24,25]. The size of the prescription databases offers the potential for precise estimates of effect and the possibility of studying rare exposures and outcomes.

Weaknesses of the databases.
One potential weakness of the Nordic prescription databases is their lack of information about diagnosis or severity of the conditions treated. Furthermore, drugs dispensed to individuals during a hospital stay are not recorded, creating observation gaps. Some drugs are dispensed only through outpatient clinics (for example, antiretroviral drugs), and some new drug groups including some biological drugs (for example, infliximab) are mainly administered
in hospitals, and are therefore not usually included in the prescription databases. Drugs used by patients in nursing homes also are not completely recorded, leading to an underestimation of total drug use, especially in the elderly population. A general problem using dispensing data to assess drug use is also the fact that we do not know if and when the dispensed drugs are actually ingested by the patients. Information about lifestyle factors such as smoking habits and alcohol consumption, as well as detailed clinical data, are also lacking in the databases as in many other types of registries. There may also be certain problems of coding and data validity. However, the extent of this problem has been low. The proportion of prescriptions with invalid or missing personal identification codes varies among the Nordic countries, but in all cases is below 2%.

Future challenges.
The population required to detect an association between a particular drug and adverse events depends upon the type of event, the proportion of people using the drug and the magnitude of the risk. As early as 1982, Skegg and Doll pointed out that a population of at least half a million is needed to detect the commonest hazards, and as many as 5 million are required to detect rare events [28]. Nordic prescription databases cover populations ranging from 0.3 to about 9 million inhabitants, in some cases too small a number to detect rare events and thus inter-Nordic collaboration is needed. An on-going initiative aims to establish a Nordic Pharmacoepidemiological Network (NorPEN) to facilitate knowledge exchange, research and training (http://www.nhv.se/norpen). The role of NorPEN is to further the knowledge about the research capabilities...

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Research question</th>
<th>Linkage to other data sources</th>
<th>Setting</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Antithrombotic agents and gastrointestinal bleeding</td>
<td>Hospital registry</td>
<td>Funen</td>
<td>Hallas et al. [54]</td>
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<tr>
<td>Depression</td>
<td>SSRI and pregnancy</td>
<td>Medical birth registry</td>
<td>Finland</td>
<td>Malm et al. [55]</td>
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<tr>
<td>Depression</td>
<td>Antidepressants and mortality</td>
<td>Cause of death registry</td>
<td>Finland</td>
<td>Haukk et al. [56]</td>
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<tr>
<td>Analgesics</td>
<td>NSAIDs and MI</td>
<td>Hospital discharge registry</td>
<td>Finland</td>
<td>Helin-Salmivaara [57]</td>
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<td>Gastrointestinal</td>
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<td>Medical birth registry</td>
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<td>Dehlink et al. [58]</td>
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<td>Cancer registry</td>
<td>North Jutland</td>
<td>Poulsen et al. [59]</td>
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<tr>
<td>Antibiotics</td>
<td>Fluconazole use in pregnancy</td>
<td>Medical birth registry</td>
<td>North Jutland</td>
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<tr>
<td>Hypnotics</td>
<td>Benzodiazepine use in alcohol consumers predicts later opiate use</td>
<td>Population-based health surveys</td>
<td>Norway</td>
<td>Skurtveit et al. [61]</td>
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<td>Hypnotics</td>
<td>Hypnotics and risk of road traffic accidents</td>
<td>Road accident registry and Central Population Registry</td>
<td>Norway</td>
<td>Gustavsen et al. [62]</td>
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<tr>
<td>Various drugs</td>
<td>Prescribed drugs and risk of road traffic accidents</td>
<td>Road accident registry and Central Population Registry</td>
<td>Norway</td>
<td>Engeland et al. 2007 [63]</td>
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<tr>
<td>Anorectic</td>
<td>Ephedrine/caffeine and cardiovascular events</td>
<td>Patient registry</td>
<td>Denmark</td>
<td>Hallas et al. [64]</td>
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<td>NSAIDs</td>
<td>Death and reinfarction associated with use of coxibs and other NSAIDs</td>
<td>Patient registry</td>
<td>Denmark</td>
<td>Gislason et al. [65]</td>
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<tr>
<td>Cardiovascular</td>
<td>Cardiovascular drugs and suicide</td>
<td>Cause of death registry</td>
<td>Funen</td>
<td>Callreus et al. [66]</td>
</tr>
</tbody>
</table>

SSRI, selective-serotonin reuptake inhibitor; NSAID, non-steroidal anti-inflammatory drug; MI, myocardial infarction; PPI, proton pump inhibitor.

of the databases and build a network of Nordic researchers in pharmacoepidemiology. It is important to note that the NorPEN is not a governmental body and is as such unable to function as a common ‘gatekeeper’ for the Nordic prescription databases. Similarities and differences in methodology, coverage, validity and access to data will require close collaboration between researchers in the Nordic countries. A concern is that Statistics Denmark does not make prescription data available for use outside the institution. New rules for access to micro data were introduced in 2001. All data processing is actually done in Statistics Denmark. Data cannot be transferred from Statistics Denmark to the researcher’s computer but are analysed using a secure, encrypted Internet connection. Results are e-mailed back to the researcher and checked for revealing too detailed information whereby individual persons may be identified [29]. In the other Nordic countries, the prescription databases are located outside the Bureau of Statistics, and the prescription data may be sent to other Nordic countries. However, there may be some impediments in transferring e.g. socioeconomic data between the countries.

Results obtained from studies in different countries can be combined using meta-analytical techniques, possibly facilitated by coordinating studies in advance to ensure that the design, case and exposure definitions, etc. are compatible. Another solution would be to produce frequency tables with specified covariate patterns for each country and use the combined tables for regression analysis. With these approaches using aggregate data, adjustment for confounding may be incomplete and there is a risk of ecological bias. The best solution for performing a study with data from all the Nordic countries is therefore to retrieve similar data from all countries at the individual patient level. If national data are required, it is at present necessary to transfer all data to Statistics Denmark for analysis as described above. A common framework for analysing Nordic prescription data would, however, be desirable.

In 2003, Professor Stricker pointed out that it is time for Europe to start using epidemiological techniques and methodologies for a more systematic approach to drug safety [30]. The European Medicine Agency (EMEA) intends to further strengthen post-approval monitoring of medicinal products in Europe by facilitating the conduct of independent multi-centre safety studies. To this end, the Agency has established the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), based on expertise and research experience available in the fields of pharmacoepidemiology and pharmacovigilance across the EU (http://www.encepp.eu). The Nordic countries provide a unique resource for collaborative high-quality pharmacoepidemiological studies with large populations. Thus, they may contribute to resolving safety issues of international interest and protect society from either over- or under-reaction to drug safety issues.

**Conclusion**

The Nordic prescription databases cover the entire population of the five Nordic countries, about 25 million persons. They
provide valid and reliable data to study drug use and to assess beneficial or adverse outcomes of drug use in clinical practice. The databases serve as a resource for conducting longitudinal and record-linkage studies with health surveys and other registries, as well as for other analytical pharmacoepidemiological research. They also offer a sound evidence base for national decision-making in the field of drug utilization.

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