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### Registers in cardiovascular epidemiology

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## SUMMARY

The central theme of this thesis is the use of registers in cardiovascular epidemiology. This broad theme is discussed from two perspectives. Monitoring cardiovascular disease in the Netherlands using register data is our first perspective. We use data from two national registers to describe trends over time in the number of hospital admissions and deaths caused by different cardiovascular diseases, and to seek for possible explanations. The use of register data in epidemiological research is our second perspective. We discuss the opportunities and limitations associated with the use of registers in various epidemiological research. We examine the possibilities of extending the role of registers, in particular through the creation of longitudinal data by using medical record linkage techniques.

This thesis combines epidemiological illustrations of using register data to monitor cardiovascular disease with theoretical considerations on the role of registers in epidemiological research.

*Chapter 1* provides an overview of the possible role of register data in various epidemiological research, ranging from studies with a public health perspective to clinical studies. The registration process of registers is divided into a capturing process and the subsequent recording process. A patient with a particular disease has to fulfil three criteria before the patient is captured in a register: (1) the disease must trigger a registration event, (2) the registration event must occur within the target population, and (3) the registration event must be notified to the registry. The recording process determines the amount, the format, and the quality of the data recorded for each case.

We divide epidemiological research into single moment and serial studies, based on the functional difference whether the different pieces of information necessary to address the research question are present at a single capturing point in time or whether information from multiple time points are necessary. The focus in single moment studies is on measuring the frequency of occurrence of a disease in the general population, which has a more natural link to registers than serial studies.

We identify four potential sources of problems associated with the use of registers in epidemiological research. First, registers are usually limited to diseases with acute episodes leading to health care contact. This preference hampers epidemiological research into chronic conditions and functional diagnoses using registers. Second, the sensitivity and specificity of the registration process is often less than perfect, leading to missed cases and cases erroneously included. Third, registers suffer from the absence or incompleteness of historical or prospective information, which are necessary to study temporal relations. Fourth, registers frequently lack detailed and accurate clinical information to make meaningful subgroups in descriptive studies or to adjust for differences in case mix in comparative studies.

The relevance and importance of these problems differ for various types of research. We formulate a general perspective demonstrating the link between increasing data complexity for different study categories and, subsequently, a growing difficulty to use registers as data source.

*Chapters 2 through 5* describe trends over time for various cardiovascular diseases in the Netherlands.

*Chapter 2* starts with the epidemiology of stroke. Stroke is a major group within cardiovascular disease, responsible for 24% ( $n=12,595$ ) of all cardiovascular deaths ( $n=51,922$ ) and 12% ( $n=29,394$ ) of all cardiovascular hospital admissions ( $n=246,263$ ) in 1994. Age adjusted stroke mortality declined by 39% for men and by 45% for women between 1972 and 1994. The decline in stroke mortality has slowed down since 1987 in both men and women. From 1972 to 1986, the annual percentage decline was 2.7% for men (95% confidence interval (CI) -2.8 to -2.5%) and 3.4% in women (95% CI -3.6 to -3.2%). From 1987 onwards, the annual decline was 0.9% (95% CI -1.3 to -0.4%) in men and 0.5% (95% CI -0.9 to -0.1%) in women. In-hospital case fatality decreased from 32.6 to 18.4% between 1972 and 1983. From 1983 onwards, no further improvement was observed in the survival of hospitalised stroke patients. The analysis of diagnostic subgroups of stroke showed a steady decline in hospital admission rates for the ill-defined type of stroke, while the rate for thromboembolic and haemorrhagic type of stroke simultaneously increased.

There are signs that the major decline in stroke mortality was caused by a decrease in both stroke incidence and case fatality. The improved diagnostic capabilities in the hospital setting have prompted a shift in coding for different types of stroke.

Aneurysms of the abdominal aorta are studied in *chapter 3*. Ruptured aneurysms took the lives of 590 men and 166 women in 1992, corresponding to 2.3 and 0.6% of all cardiovascular deaths. Age adjusted mortality for men increased 2.6-fold between 1972 and 1992, for women 1.6-fold. Large increases were observed in admission rates for non-ruptured and ruptured aneurysms in both men and women, but the increase in non-ruptured cases exceeded by far the increase in ruptured cases. Age adjusted in-hospital case-fatality rates after surgery upon non-ruptured aneurysms halved from 13% in 1972 to 7% in 1992. Case-fatality after surgery upon ruptured aneurysms also decreased but was still 36% in 1992, despite improvements in critical care medicine.

The widespread use of ultrasound since the mid-seventies will have led to the detection of many previously unknown aneurysms, and subsequently to an increase in admissions for diagnostic work-up and surgical treatment. However, the difference in increase between men and women and the rise in the number of ruptured aneurysms suggest that a real increase in incidence occurred, especially in men.

Hospital admission rates for heart failure are examined in *chapter 4*. Chronic heart failure is a complex clinical syndrome characterised by a progressive loss in left ventricular function. Heart failure was the principal cause of admission in 13,022 men and in 12,944 women in 1993. Age adjusted admission rates rose by 48% for men and by 40% for women between 1980 and 1993. Using individual records from a subset of seven hospitals, we found that readmissions shortly after discharge were a prominent feature among heart failure patients. The proportion of heart failure patients being readmitted within the first six months after the initial discharge was 14%, rising to 26% in patients discharged alive for the second admission, and to 34% in patients discharged alive for the third admission.

Possible explanations for the observed increase in hospital admissions include the improved prognosis of patients with acute myocardial infarction and higher readmission rates induced by the longer survival of patients with heart failure. The impact of advances in diagnostic tools and of possible changes in admission policy remains uncertain.

*Chapter 5* provides an overall picture of cardiovascular disease in the Netherlands. The total group of cardiovascular disease was responsible for the death of 25,635 men and 26,694 women in 1995, which corresponds to 38% of all cause mortality in men and 40% in women. Cardiovascular disease was by far the leading cause of death, with cancer taking second place with 36,489 deaths (27%). Cardiovascular mortality showed a steady 2% annual decline between 1975 and 1995. In contrast to the decline in mortality, there was a constant increase in age adjusted hospital admission rates for cardiovascular disease with an annual growth of 1.3%. Increases were seen for coronary heart disease (2.6% annual growth), with a marked difference between chronic manifestations (5.1% growth) and acute syndromes (0.7% growth), for heart failure (2.1% growth), and for arterial diseases (1.8% growth).

These findings result in our main conclusion: 'Cardiovascular disease in the Netherlands, lower mortality but more patients with chronic conditions'. The improvements in the treatment of patients with acute myocardial infarction are a major contributor to this changing profile of cardiovascular disease from acute and fatal to chronic. These improvements have led to a growing pool of patients in which death has been postponed, but who are at an increased risk of recurrent coronary events, of other atherosclerotic manifestations, and of developing chronic heart conditions, such as heart failure and atrial fibrillation.

*Chapter 6* introduces the general principles of medical record linkage. The aim in record linkage is to identify records that belong to same person without the help of a unique personal identifier. These records have either been recorded in two different files or in the same file, but at different times. The most frequent use of record linkage in medical research has been in the context of passive follow-up of cohorts. Examples include the identification of deaths in large cohorts and trials and the identification of possible side effects of drugs in pharmaco-epidemiological studies.

In the absence of a unique and shared identification number, other personal characteristics have to be combined to identify records that belong to the same person, such as gender, date of birth, place of birth, surname, marital status, and area code. Record linkage is made complex by the fact that variables may contain errors or that they may validly change in value. Computer programmes are used to compare all records in file *A* with all records in file *B*, leading to a total number of pairs equal to the product of both file sizes. The objective is to classify each pair of records as either belonging to the same person (link) or to different persons (non-link). Values of corresponding

variables within each pair are compared to see whether they agree or disagree. In order to quantify the evidence provided by agreement or disagreement, a measure is calculated that compares the probability of agreement or disagreement among truly related records to the same probability among unrelated records. This measure is known as 'weight'. Weights from different variables are combined into an overall weight. This overall weight is a summary measure, which reflects the amount of evidence that has been gained in making a correct classification by observing a particular pattern of agreements and disagreements. This overall weight forms a natural quantitative measure for classifying pairs as links or non-links.

Record linkage has many similarities with medical diagnosis. Both are dichotomous classification problems. Patients are classified as having a particular disease or not in medical diagnosis, while pairs of records are classified as links or non-links in medical record linkage. Likelihood ratios of positive and negative test results in medical diagnosis are similar measures of information as weights in record linkage.

The added value of linked data sources in describing the long-term health consequences after acute myocardial infarction is demonstrated in *chapter 7*. The national register of hospital admissions in the Netherlands is a typical example of an event-oriented register, which hampers the identification of readmissions. We applied record linkage techniques to identify readmissions and deaths in a cohort of patients initially admitted for acute myocardial infarction.

Cardiovascular readmissions occurred regularly in patients with myocardial infarction. The highest rate (160 per 1,000 patients) was found during the first three months after the initial discharge. The overall rate was similar in men and women, but men were more often hospitalised for coronary causes and women more often for heart failure. Diabetic patients not only had an excess risk of dying (relative risk 2.3; 95% CI 1.5 to 3.6), but also of being readmitted (relative risk 1.7; 95% CI 1.4 to 2.2), especially for heart failure (relative risk 2.5; 95% CI 1.8 to 3.5). It shows the prognostic importance of the presence of heart failure symptoms during the initial admission and the development of these symptoms during follow-up. Diabetes is associated with both phenomena, which explains the unfavourable pattern of readmission and death in these patients.

The practice of direct standardisation in four medical journals is examined in *chapter 8*. Direct standardisation is frequently applied in studies comparing rates over time (see for instance *chapters 2 through 5*) to address differences in confounding factors. The absolute height of a standardised rate varies with the choice of standard, and is the *hypothetical* number of events that would have occurred if the population structure had been identical to that of the standard. The choice of standard can affect the comparison. Therefore, readers have to know which standard has been applied. This information is missing in one fifth of all articles using direct standardisation.

The *General Discussion* provides background information about some major developments in cardiovascular epidemiology. It demonstrates the progress that has been made in the understanding and treatment of cardiovascular disease. Cardiovascular disease, however, remains a major problem despite these improvements. Monitoring cardiovascular disease by means of registers continues to be important in order to confirm expected trends and to detect unexpected ones.

We elaborate on the specific role of registers in studies examining trends over time. The fundamental issue in the interpretation of trends in register data is reduced to a single question: '*is it real?*' Several mechanisms can be responsible for 'artificial' increases or decreases, not related to a true rise or fall in incidence or prevalence of the disease of interest. Possible causes of artificial trends are:

- ◆ change in target population
- ◆ change in notification behaviour
- ◆ change in interrelationship between health event and registration event
- ◆ change in classification
- ◆ change in coding practice

The first three elements relate to the capturing process of a register, the last two to the recording process.

Furthermore, we formulate some general recommendations on how to improve on the use of registers in epidemiological research. Our focus is in particular on creating longitudinal information by linking data within and across registers. The interest in longitudinal data is growing as a result of the changing profile of diseases, including cardiovascular disease. The longer survival of heart patients due to improvements in care demands long-term data to determine the exact health consequences of primary conditions. Such data are scarce. The absence of a national health care identification number

means that record linkage techniques are necessary to link data within and across data sources. Policies that protect the privacy of the individual patient while enabling medical research to proceed have to be established.

The possibilities of extending the use of national registers in the Netherlands have increased since the introduction of the 'Gemeentelijke Basisadministratie', a register containing information on actual residence. A pilot study is underway to assess its value as intermediary for linking hospital admission data with mortality data. It illustrates the efforts of adapting registers to the changing profile of (cardiovascular) diseases in the Netherlands and abroad. Given the complexity of research involving registers it demands teamwork between epidemiologists, physicians, biostatisticians, and registry personnel.

