MORTALITY AND MEDICAL CARE

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studies of mortality by cause of death in The Netherlands
and other European countries

(Sterfte en medische zorg:
studies van de sterfte naar doodsoorzaak in Nederland
en andere Europese landen)

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JOHAN PIETER MACKENBACH
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Promotor:	Prof. dr P.J. van der Maas
Overige leden:	Prof. dr G. Hennemann
	Prof. dr R.M. Lapré
	Prof. dr H.A. Valkenburg

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Contents

I General introduction

I.1 Preview

This thesis consists of a collection of papers which are all concerned with mortality. Mortality is one of the most tangible expressions of that intangible "public health": the frequency and distribution of health problems in a population. The age at which people die, the conditions they die from, and many other aspects of mortality patterns provide important information on the occurrence of health problems in populations.

The description and analysis of mortality patterns is therefore of interest to the health sciences, because differences in mortality between "times, places and persons" may suggest factors that play a causal role in the incidence or prognosis of specific health problems. The study of mortality may have a straightforward practical interest too, when it leads to the identification of health problems, geographical areas, population subgroups etc., where some kind of intervention is warranted. This may be an intervention through the health care system or through another agency, and will frequently have to be initiated by health policy makers.

There are four interrelated themes in this thesis.

I.1.1 Theme no. 1: The validity of cause-of-death statistics

The first theme is that of the validity of cause-of-death statistics as measures of the frequency of cause-specific mortality in the population. The main threat to the validity of this measurement lies in the fact that the classification of deaths by "underlying" condition is based on a reporting system involving a large number of practicing physicians. A substantial amount of "interobserver variation" is probable, due to e.g. differences in medical education, available

diagnostic facilities, care in filling out the death certificate etc. In addition, some variation in the coding of death certificates, over time as well as between countries, is likely to occur. Systematic differences in cause-of-death certification or coding may seriously bias estimates of trends or differences in cause-specific mortality.

Dutch studies of the validity of cause-of-death statistics have up to now been very scarce. In the framework of two studies of differences in certification and coding between countries of the European Community, the Dutch certification and coding process for two causes of death (Chronic Obstructive Pulmonary Disease and a number of cancers) was investigated. The over-all performance of the Dutch certification and coding process could be assessed and compared to that of other countries of the European Community. A detailed analysis of errors in certification and coding was undertaken in order to find possibilities for (further) improvement (chapter II).

I.1.2 Theme no. 2: The use of mortality data to address health care policy questions

The second theme is that of the use of mortality data to address health care policy questions. Applications of mortality analyses to health policy questions have a long history. Recent developments in health care policy in The Netherlands have provided reasons for exploring possible applications to health **care** policy questions.

Some years ago, new legislation specified increased responsibilities of national, regional and local authorities for the health care system, and gave rise to questions regarding the criteria that should be used in developing and evaluating health care policy at each of these three levels. Recent government papers have emphasized the importance of using data on the health status of the population as both starting-point and touchstone of health care policy [1].

During one of the early phases of this development an opportunity arose to study some of the conceptual and practical problems which have to be addressed before this can be put into practice. At that time, serious consideration was given to the idea of using objective guidelines for the regional distribution of financial resources. In some other countries, regional mortality data by cause of death play a prominent role in such allocation formulas, as proxies for the "need" for health care. The question arose whether these data can indeed be used as a criterion for the allocation of resources (chapter III).

The third and fourth themes are elaborations upon issues raised by the second theme. Do mortality data by cause of death only reflect a "need" for, or also an "outcome" of health care? The extent to which changes and differences in mortality rates reflect improvements in the outcome of health care services has in fact been the subject of considerable debate. The greater part of this thesis is

concerned with this debate, and with the use of mortality as an indicator of the effectiveness of health care, more specifically of "medical care".

Medical care is that part of the health care system where preventive, curative and rehabilitative services are delivered in a personal encounter between a health care professional (such as a doctor) and a client. From a mortality perspective, medical care is only one of many possible determinants, and perhaps not the most important. From a medical care perspective, however, mortality reduction is a very important objective, and an objective for which empirical evaluation at population level is feasible.

I.1.3 Theme no. 3: Time trends of cause-specific mortality and the effect of improvements in medical care

The third theme of this thesis is that of time trends of cause-specific mortality and the effect of improvements in medical care. Since the eighteenth century, mortality has declined dramatically in developed countries. The cause of this decline has been debated intensely. Some have claimed that medical care was largely responsible; others have attributed the decline to improved living conditions. The latter or "revisionist" [2] view has gained considerably in popularity in recent years.

One of the main protagonists of this view, Thomas McKeown, has shown that the mortality decline was the result mainly of a decline in incidence and case fatality of infectious diseases, and that this decline for the greatest part antedated the introduction of specific and effective medical therapies [3].

Moreover, after World War II, when the costs of health care and especially medical care began to rise dramatically in industrialized countries, the mortality decline seemed to slow down. This gave rise to the wide-spread opinion, cited recently in a Dutch government paper [1], that "the rapid increase in real terms (i.e. of health care costs, corrected for inflation, JPM) has not led to a commensurate improvement in standardized mortality rates" [4].

Both observations have had an enormous impact on the attitude towards medical care of the educated public in general and health care policy makers specifically. A certain degree of skepticism prevails, and hampers attempts to account for the denominator in the debate on the cost-effectiveness of medical care. This has therefore almost entirely focussed on the numerator. We will show that recent mortality trends by cause of death do in fact not justify such skepticism.

Chapter IV presents an analysis of changes in infectious disease mortality coincident with the introduction of antibiotics. Efficacious antibacterial drugs were introduced during the second half of the 1930's and in the 1940's, and were generally regarded as miracle drugs, curing many patients who formerly were likely to die

from these diseases. Although methodologically sound evidence on the efficacy of these drugs in reducing case fatality is scarce, there is no particular reason to doubt this impression of a whole generation of doctors. Most analyses of this question, including the one by McKeown cited above, have been of an informal nature, but the analysis presented in chapter IV is a formalized attempt to obtain quantitative estimates of changes coinciding with th introduction of antibiotics in The Netherlands.

Chapter V describes improvements in survival of cancer patients. This is another much frequented topic for debate, which is the more important as cancer is one of the major health problems of the industrialized world, and large sums of money have been spent on the development of efficacious treatment methods. For most other conditions it is not possible to study trends in survival at population level, but for cancer it is possible, thanks to the existence of incidence and survival registries in a number of countries.

A systematic approach to the study of the mortality effects of medical care requires a comprehensive list of causes of death which have become amenable to medical intervention. Infectious diseases and some forms of cancer are only a small subset of this. In 1976 Rutstein et al. published a list of diseases for which progress supposedly had been so dramatic, that any death from one of these conditions is to be interpreted as a "warning signal" of possible shortcomings of the health care system [5].

This and other lists in the same publication provided a good starting-point for a comprehensive study of the mortality effects of medical care. Chapter VI examines the issue, and presents an analysis of post-1950 mortality trends for those conditions, for which the evidence on medical care effects is relatively undisputed. Did mortality indeed decline for these conditions? Is the timing of cause-specific mortality declines consistent with the moment of introduction of the innovations? What was the over-all effect of these mortality reductions on life expectancy?

I.1.4 Theme no. 4: Regional variation in cause-specific mortality and the level of supply of medical care

The fourth and final theme is that of regional variation in cause-specific mortality rates and its relationship with the level of supply of medical care. Regional mortality differences are an intriguing phenomenon, and suggest that there is an opportunity for mortality reduction in regions with relatively high rates.

This would seem to apply even more to variation in mortality from conditions which have become amenable to medical intervention. The use of such a selection of conditions in regional mortality analyses was first recommended by a group from the Rand Corporation, as part of a wider effort to develop "Algorithms for health planners" [6]. In 1983 Charlton et al. proposed a similar idea and were the

first to publish the results of a descriptive study of geographical variation in such "avoidable" mortality; this study covered England and Wales [7]. The studies reported in chapters VII-IX form part of a series of studies in several countries of the European Community, stimulated by the dramatic nature of the geographical differences first demonstrated by these English researchers.

We have tried to contribute to a further understanding of these differences with three analyses, in which we related regional mortality rates for selected conditions to a number of other regional characteristics, including the level of supply of medical care. A recently prepared Atlas of regional variation in mortality from conditions amenable to medical intervention in countries of the European Community [8] provided material with which the association between levels of resource provision and mortality could be studied in a wide variety of settings. European Community countries differ with respect to the organization of medical care, the over-all level of resource provision, as well as the pattern and extent of regional variation in resource provision (Chapter VII).

It soon became clear that within The Netherlands, as well as within other countries, important regional differences in mortality from conditions amenable to medical intervention exist. Chapter VIII examines the relationship between regional mortality rates and the level of supply of medical care in The Netherlands. It adds a comparison with three earlier time-periods to the analysis of the situation in 1980-84, in order to see wether the dynamic evolution of mortality over time is reflected in a dynamic evolution of its association with medical care at the regional level.

Most studies of geographical variation in mortality, including the two of chapters VII and VIII, focus on cross-sectional differences in level of mortality at one or more moments in time. In The Netherlands, the development of mortality since ca. 1970 has been characterized by the rapid decline of a number of important causes of death. This applies to conditions amenable to medical intervention, but also to some other causes of death. An analysis of regional differences in the rate of mortality decline was undertaken. A description of these differences was expected to identify regions where progress has been unsatisfactory; also, associations with other regional characteristics, including changes in the supply of medical care and in socio-economic circumstances, were investigated (chapter IX).

I.1.5 The structure of this thesis

The rest of chapter I is devoted to a general introduction on the studies reported in the papers. In section I.2 the production of mortality data by cause of death in The Netherlands will be described in some detail, followed by a few notes on the use of mortality data for health policy purposes in section I.3. In section I.4 the debate

on "the role of medicine" as a factor in the decline of mortality since the eighteenth century will be reviewed. An introduction to the theme of regional mortality differences is the subject of section I.5. The general introduction is concluded by some methodological considerations (section I.6).

Chapters II-IX contain 8 different papers, which can be read independently from each other, and each of which ends with a summary for the hurried reader.

Chapter X starts with a general summary of the main findings, which differs from the separate summaries of the papers in that it emphasizes the relevance of the findings for the four general themes mentioned above. This is followed by a number of additional comments on the effect of medical care on mortality time trends and regional mortality patterns. Some material additional to that of the papers will be presented as well. Section X.4 contains a small number of recommendations.

Ignorance

Strange to know nothing, never to be sure
Of what is true or right or real,
But forced to qualify "or so I feel",
Or "Well, it does seem so:
Someone must know".

Strange to be ignorant of the way things work:
Their skill at finding what they need,
Their sense of shape, and punctual spread of seed,
And willingness to change;
Yes, it is strange,

Even to wear such knowledge -for our flesh
Surrounds us with its own decisions-
And yet spend all our life on imprecisions,
That when we start to die
Have no idea why.

From: The Whitsun Weddings
Philip Larkin

I.2 The production of mortality data by cause of death

Mortality statistics, although full of imprecisions, give a fascinating picture of (medical) "causes" of death. A study of these causes of death, which primarily describe the biological aspects of dying, does not directly answer the question on which the poem cited above ends, and a certain ignorance on even the medical causes of death cannot be denied. Still, the regular patterns and sudden changes as seen in mortality data do sometimes shed light on the complex backgrounds of death.

I.2.1 Administrative procedures and over-all results

In The Netherlands, a national registry of deaths has been kept, as part of the population register, since the early nineteenth century. In 1865 a law was issued which is still in force and which requires a medical certification of the cause of death, before permission for burial or cremation is given. National data on causes of death have been collected and published by the Central Bureau of Statistics since 1903.

The purpose of cause-of-death certification, apart from the recognition of unnatural forms of death for which a judicial

investigation is required, is the assignment of a so-called **"underlying cause of death"**. The underlying cause of death, also called the "primary cause of death", is defined as "the disease or injury that initiated the train of morbid events resulting in death, or the circumstances or violence that produced the fatal injury" [9].

In order to arrive at this underlying cause of death, the Dutch death certificate, which is a translation with minor modifications of the internationally agreed medical certificate of cause of death, has been arranged as follows (figure I.1). From an "immediate" cause of death, i.e. the disease, injury or complication which directly preceded death, the certifier has to make a backward reconstruction of the chain of events which originated in the underlying cause of death. Any other conditions which contributed to death, but do not have a causal relationship to the sequence mentioned under 1, should be mentioned under 2.

Although basically the certificates are similar, there are some subtle differences between the lay-out and phrasing of the Dutch death certificate and that of the internationally agreed upon certificate. On the Dutch certificate, the word "rechtstreeks" ("directly") under 1a. is placed in italics, suggesting that the immediate cause of death is more important than the underlying cause of death to be filled in under 1c. Also the word "bijkomstige" (adventitious) under 2. is not a correct translation of "other significant".

Coding of causes of death

Dutch death certificates are coded at the Central Bureau of Statistics, according to the "Rules for selection of cause of death for primary mortality tabulation" [9]. This is a set of rules which enable the coder to select the most plausible diagnostic entity present on the certificate for the assignment of the underlying cause of death code. The "general rule" is to select the condition entered under 1c., "unless it is highly improbable that this condition could have given rise to all the conditions entered above it". A Dutch study from 1963 showed that application of one or more specific rules for selection of the cause of death was necessary in ca. 20 % of all deaths, and that this percentage increased with the age of the deceased, suggesting an increase in ambiguity of cause-of-death certification with age [10].

Knowledge of these Rules for selection of the underlying cause of death is essential for a good understanding of cause-specific mortality rates. It is important to know, for example, that death during or after appendectomy, cholecystectomy, or another surgical procedure will be coded as due to Appendicitis, Cholecystitis, etc. if these conditions are reported on the certificate as having given rise to the surgical procedure.

Figure I.1 The Dutch death certificate, section D ("Natural death"), and the internationally agreed upon medical certificate of cause of death

D. NATUURLIJKE DOOD *(Voor niet nat. dood zie E; voor doodgeboren zie F)*		Duur tussen begin ziekte en overlijden (bij benadering):
1. a. Ziekte, welke *rechtstreeks* de dood ten gevolge had	1. a. ..... veroorzaakt door/gevolg van	.....
b. en c. Ziekten, welke hebben geleid tot de doodsoorzaak onder a. Bij vermelding van meerdere ziekten de aan het overlijden ten grondslag liggende het laatst opgeven *(zie toelichting)*	b. ..... veroorzaakt door/gevolg van	.....
	c.	.....
2. Bijkomstige, bij overlijden nog bestaande ziekten en bijzonderheden, welke tot de dood hebben bijgedragen, doch niet met de onder 1 genoemde ziekten in causaal verband staan	2.	

INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH

CAUSE OF DEATH		Approximate interval between onset and death
I		
*Disease or condition directly leading to death**	(*a*) . . . . . due to (or as a consequence of)	. . . . .
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(*b*) . . . . . due to (or as a consequence of)	. . . . .
	(*c*)	. . . . .
II		
Other significant conditions contributing to the death, but not related to the disease or condition causing it	. . . . .	. . . . .
	. . . . .	. . . . .

* This does not mean the mode of dying, e.g., heart failure, asthenia, etc. It means the disese, injury, or complication which caused death.

Lists of code-numbers and the corresponding nosological entities are provided, as are the Rules for selection of cause of death, by the **International Classification of Diseases (ICD)**. Since 1979 the ninth Revision is in force in The Netherlands [9]. Changes in the International Classification of Diseases have occurred approximately every ten years. These changes reflect scientific developments in medicine, as well as developments in the relative importance of specific health problems.

An example of the first is that Cerebrovascular disease was coded as a Disease of the nervous system and sense organs until the eighth Revision (in force since 1969 in The Netherlands), which was the first to classify it as a Disease of the circulatory system. An example of the second is that deaths from Traffic accidents, which were infrequent before modern means of transport, such as the automobile, came in common use, first were coded in a rubric called "smashing due to landslides, tramways, etc" ("verplettering door aardverschuiving, trams etc."). It was only in the fifth revision, in force in The Netherlands since 1941, that Traffic accidents were distinguished as a separate category.

Although the primary objective of the coding process is to assign a correct underlying cause-of-death code, some extra information is available on many certificates. This information is coded and tabulated as "secondary" causes of death. In The Netherlands, this is done on a limited scale, and results in an average number of coded entities per deceased of 1.5 (including the underlying cause of death) for both men and women [11]. In the United States, all diagnostic information present on the death certificate is coded in a systematic way [12]; this results in an average number of coded entities per deceased of 2.7 for white men and 2.8 for white women [13].

Over-all results

Table I.1 gives an impression of the over-all results of certification and coding of causes of death in The Netherlands. Mortality rates by **primary** (or underlying) cause are dominated by two ICD-chapters, Diseases of the circulatory system and Neoplasms. Together, these two groups of conditions account for appr. 70 % of Total mortality in both males and females. Although there is no reason to doubt the quantitative importance of these conditions as "true" underlying causes of death, some degree of overestimation may well be present in these percentages.

For Neoplasms, the percentage of all deaths receiving a code from this ICD-chapter as a secondary cause of death is very low (table I.1). This reflects the fact that patients with Neoplasms usually have short survival times, so that the chance that a Neoplasm is certified as "other significant condition" after the patient has died from another disease is relatively low. On the other hand, the Rules for selection of the underlying cause favour well-defined conditions such as Neoplasms at the expense of less clearly defined conditions, even if the Neoplasm has not been entered under 1c. of the certificate.

Table I.1 Assignment of "primary" and "secondary" causes of death by ICD-chapter, The Netherlands, 1984.

ICD-chapter		% of deaths receiving code from ICD-chapter as			
		Primary c. of d.		Secondary c. of d.	
		males	females	males	females
I	Infective/parasitic diseases	0.5	0.6	2.3	2.9
II	Neoplasms	29.8	25.2	2.6	1.6
III	Endocrine/nutritional/metabolic diseases	1.4	2.6	2.6	5.0
IV	Diseases of blood/blood-forming organs	0.2	0.4	0.4	0.6
V	Mental disorders	0.3	0.7	1.1	0.7
VI	Diseases nervous system/sense organs	1.6	1.6	1.4	1.3
VII	Diseases circulatory system	43.0	46.3	17.8	20.3
VIII	Diseases respiratory system	8.0	5.9	16.1	10.0
IX	Diseases digestive system	3.0	4.1	2.6	2.6
X	Diseases genito-urinary system	1.9	2.6	3.0	3.3
XI	Pregnancy/childbirth/puerperium	-	0.0	-	0.0
XII	Diseases skin/subcutaneous tissue	0.2	0.6	0.9	2.0
XIII	Diseases musc.skeletal syst./connect. tiss.	0.3	0.8	0.7	1.6
XIV	Congenital anomalies	0.7	0.6	0.2	0.2
XV	Certain causes of perinatal morbidity	0.5	0.4	0.4	0.3
XVI	Symptoms/ill-defined conditions	3.1	3.2	-	-
XVII	Accidents/poisonings/violence (E-code)	5.5	4.4	-	-
	Total	100.0	100.0	52.1	52.2

Note: The % of deaths receiving a secondary cause-of-death code, per ICD-chapter, may be slightly overestimated because each death may receive more than one secondary cause code from the same ICD-chapter.
Data from ref. 11.

For Diseases of the circulatory system it is the certification process which will tend to overestimate the importance of these conditions as causes of death. In cases of doubt, for example sudden death without prior history of disease, myocardial infarction will frequently be a convenient, not too implausible underlying cause of death.

Secondary cause-of-death codes are dominated by the ICD-chapters Diseases of the circulatory system and Diseases of the respiratory system. Together, these groups of conditions are coded in 30 % of all deaths and account for appr. 60 % of all secondary cause-of-death codes. Ischemic heart disease, Diseases of the lung circulation (i.e. cor pulmonale), and Heart failure are the most frequently coded among the Diseases of the circulatory system. In some cases,

these will be contributing causes ("other significant conditions, contributing to death"), in other cases immediate causes (sequelae of other conditions, "directly leading to death"). Chronic Obstructive Lung Disease and Pneumonia are the most frequently coded among the Diseases of the Respiratory system. Pneumonia, just like Septicemia (in chapter I, Infective and parasitic diseases), is an example of a frequent immediate cause.

It is worth noting that some of the smaller ICD-chapters are more frequently coded as a secondary cause of death than as a primary cause of death; this is the more remarkable given the low frequency of secondary cause-of-death coding in The Netherlands. If we assume that one death does not receive a code from the same ICD-chapter both as a primary and as a secondary cause of death, the sum of the percentages for primary and secondary causes of death gives an indication of the prevalence of different conditions (contributing to death) at death. Potentially, secondary causes of death could add valuable information on the presence, at the moment of dying, of conditions which are not likely to be selected as the underlying cause of death.

Unfortunately, the low frequency of coding and the lack of systematic "Rules for selection of secondary causes of death" at present seriously hamper the analysis and interpretation of these data in The Netherlands (cf. section X.4.1) [11].

I.2.2 The validity of cause-of-death statistics

There is not much direct evidence on the validity of cause-of-death statistics in The Netherlands. As stated in section I.1, a certain degree of misclassification is likely, if only because of the (necessarily) decentralized system of cause-of-death certification.

In general, the medical profession has a skeptical attitude towards the value of this information, partly because it is acutely aware of the fact that it may be quite difficult to complete the death certificate properly [14]. The certificate asks for certainty, but in practice it is sometimes very difficult to reach a firm conclusion on the true and only underlying cause of death. A study among a small number of Dutch general practitioners has shown that more frequently than reflected in national cause-of-death statistics they themselves prefer a code-number from the ICD-chapter "Symptoms and ill-defined conditions" [15].

The "production" of the underlying cause-of-death code involves three steps: diagnosis of the health problems of the patient; filling in a death certificate; and assignment of a code-number. In each of these steps an error may occur, leading to misclassification of the death for purposes of tabulation by underlying cause-of-death. Due to the fact that coding of death certificates is centralized and subject to quality assurance procedures in The Netherlands, this is probably not a major source of error. As a matter of fact, a study from the early 1960's showed that coding of death certificates in The

Netherlands compared favourably to that in other European countries [16].

Validation studies

In the literature, a large number of studies has been reported in which the validity of cause-of-death information was investigated (for a bibliography, see ref. 17). Two frequent types of study involve the comparison between death certificates and autopsy reports, and the comparison between death certificates and hospital records. Consideration must however be given to the fact that not every condition revealed at autopsy, or present on hospital records, is necessarily a true underlying cause of death.

In general, the concordance with diagnoses from other sources varies substantially between causes of death, and declines with age. For illustrative purposes the results of a small number of studies will be discussed.

Autopsy may reveal conditions which were not recognized ante mortem. One of the very few Dutch studies of the validity of cause-of-death information compared clinical diagnoses of cancer with autopsy findings. In 30 (4 %) out of 751 autopsies a cancer was found which had not been diagnosed clinically, and which was retrospectively considered to be the underlying cause of death [18].

Unfortunately, most autopsy series cover selected populations, precluding more general conclusions. An exception is a series of appr. 400 consecutive deaths in a department of internal medicine in Sweden, in which autopsy was performed in 96 % of the cases. In 30 % of the autopsied deaths the clinical diagnosis proved to be erroneous on a three-digit level of the ICD. Of these 30%, approximately half was a serious error, taking a death from one (sub)group of diseases to another. Fewer errors were discovered in patients below, than in patients above 70 years of age, and clinical diagnoses of Neoplasms were less frequently found to be erroneous than diagnoses of other conditions [19].

A comparison between death certificate information and **hospital record** information is less subject to selection bias, although not all patients die in a hospital. In a study of hospital discharge diagnoses and underlying causes of death in England it was found that for 39 % of the patients both diagnoses differed to such an extent, that they had to be coded to different subgroups of diseases. This disagreement may accurately reflect the actual situation (death may be due to another condition than the principal condition treated during hospital admission), but it can also be due to errors in one or both of the records. In a careful study of the causes of the discrepancies it was found that appr. 20 % of the death certificates were in error. Again, there were fewer errors in cases of malignant neoplasms than in other categories of disease, but age was not a factor here [20].

In a study of deaths among a cohort of Swedish twins, all below 70 years of age, death certificate information was compared with

information from all other records available, including hospital records, autopsy reports, information from general practitioners etc. Detection fractions (proportions of deaths with true underlying causes X which actually receive the code number for X) and confirmation fractions (the proportions of deaths coded as X which actually died from X) were determined, using a careful review of the other records as the standard. Both detection fractions and confirmation fractions were above 95 % for most forms of cancer, Ischemic heart disease, Cerebrovascular disease, Chronic Obstructive Pulmonary Disease, Accidents and Suicide. Lower detection and confirmation fractions were found for Diabetes mellitus (60 and 82 %), Other forms of heart disease (65 and 37 %), and Pneumonia (67 and 33 %) [21].

We will finally briefly discuss two pieces of evidence on the quality of certification of causes of death in The Netherlands: the frequency of autopsy; and the percentage of deaths coded in the ICD-chapter "Symptoms and ill-defined conditions".

Quality of cause-of-death information in The Netherlands: autopsy rates

The percentage of all deaths for which an autopsy was performed was 10.4 % in 1984 [22], and appr. 11 % in 1963 [10]. Although this suggests stable rates, the percentage of in-hospital deaths for which an autopsy was performed shows that rates have been rather dynamic in recent years. (Autopsies for deaths that have occurred outside hospital are rare.) In 1970, the percentage of in-hospital deaths for which an autopsy was performed was 25.5; this percentage rose to a maximum of 32.8 in 1977, and has since then started a gradual decline to 24.9% in 1983 [22]. This decline has also been observed elsewhere [23].

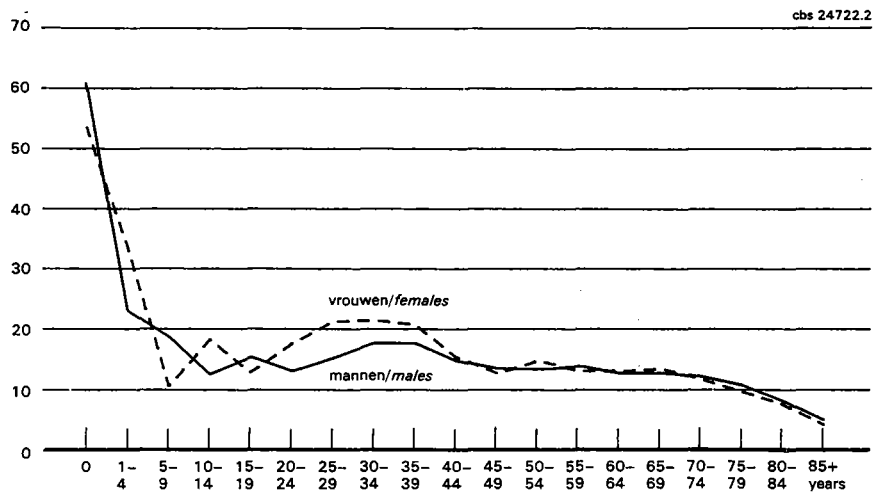
Figure I.2 gives the frequency of autopsy by age and sex in The Netherlands in 1984. Differences in the proportion of deaths for which an autopsy is performed, reflect both differences in uncertainty on the underlying cause of death, and differences in the wish to obtain more certainty. The lower frequency of autopsy in deaths among elderly people is probably not a reflection of more certainty, but of a lesser motivation to obtain certainty in doctor and family.

Quality of cause-of-death information in The Netherlands: "Symptoms and ill-defined conditions"

A crude indicator of the over-all success of the certification and coding process in assigning an underlying cause of death to the deceased, is provided by the percentage of deaths which receives a code for "Symptoms and ill-defined conditions".

This indicator first of all reflects the extensiveness of the information mentioned on the death certificate. The "Rules for selection of cause of death" state that, if the certificate suggests an underlying cause which is classifiable to "Symptoms and ill-defined conditions", but a condition classifiable to another category is

Figure I.2 Percentage of all deaths for which autopsy was performed, by age and sex, The Netherlands, 1984.



Reprinted from ref. 22

present (anywhere) on the certificate, this other condition should be selected as the underlying cause of death. (On the other hand, the coding office can influence the percentage of deaths for which there is insufficient information. In appr. 5 % of cases, the Dutch coding office directs queries to certifying doctors in order to ask for supplementary information [24].)

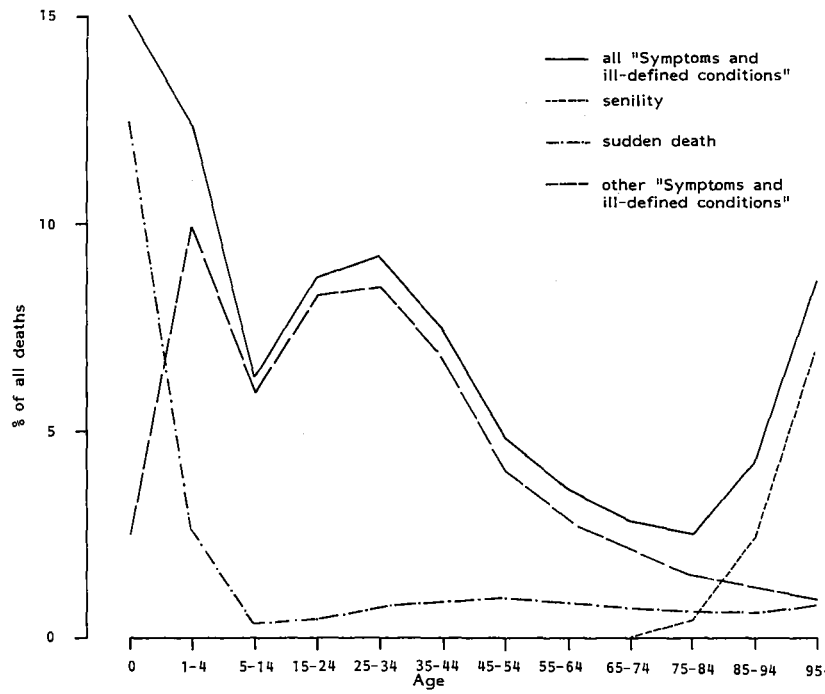
We will discern the following three subcategories of the ICD-chapter of "Symptoms and ill-defined conditions":

- "Senility without mention of psychosis" (i.e. without mention of dementia);
- "Sudden death" (in our analyses, this category excludes those "found dead, cause unknown");
- "Other ill-defined conditions", including symptoms, complications etc.

That these are quite different phenomena is apparent from figure I.3.

"Senility" is of course limited to older ages. Of deaths over 95 years of age, appr. 7% is classified as due to Senility. (Only

Figure I.3 Percentage of all deaths classified as due to "Symptoms and ill-defined conditions", by age, 1980-84.



appr. 1% of all deaths over age 95 is classified as due to Dementia, not shown in figure I.3.)

"Sudden death" has a high relative frequency in infants (Sudden Infant Death Syndrome or cot death). At higher ages, some deaths classified as "Sudden death" might in fact be due to Acute myocardial infarction or other cardiovascular calamities.

"Other ill-defined conditions" has a relative frequency between 5 and 10% at younger ages. After age 35, this category gradually declines in importance.

The highest frequencies of all "Symptoms and ill-defined conditions" together are found in the youngest age-groups. At first sight, the lower relative frequency of "Symptoms and ill-defined conditions" at higher ages (except 95+) seems to be at odds with the finding from many studies, cited above, that the validity of cause-

Table I.2 Development over time of the percentage of all deaths classified as due to "Symptoms and ill-defined conditions".

	Percentage of all deaths due to				
	Senility incl. dementia	Senility excl. dementia	Sudden death	Other ill-def. conditions	All "Symptoms and ill-def. conditions" [a]
1910	15.5	.	0.4	6.6	.
1920	7.2	.	0.5	5.0	.
1930	5.4	4.9	0.9	3.8	9.6
1940	6.4	5.3	2.1	1.5	8.9
1950	4.2	2.9	0.0	3.6	6.5
1960	1.9	1.5	0.7	1.3	3.5
1970	1.3	0.7	0.5	1.4	2.6
1980	1.0	0.8	0.8	3.1	4.7

Note: The cause-of-death categories presented in this table differ slightly in content from those used elsewhere in this thesis.

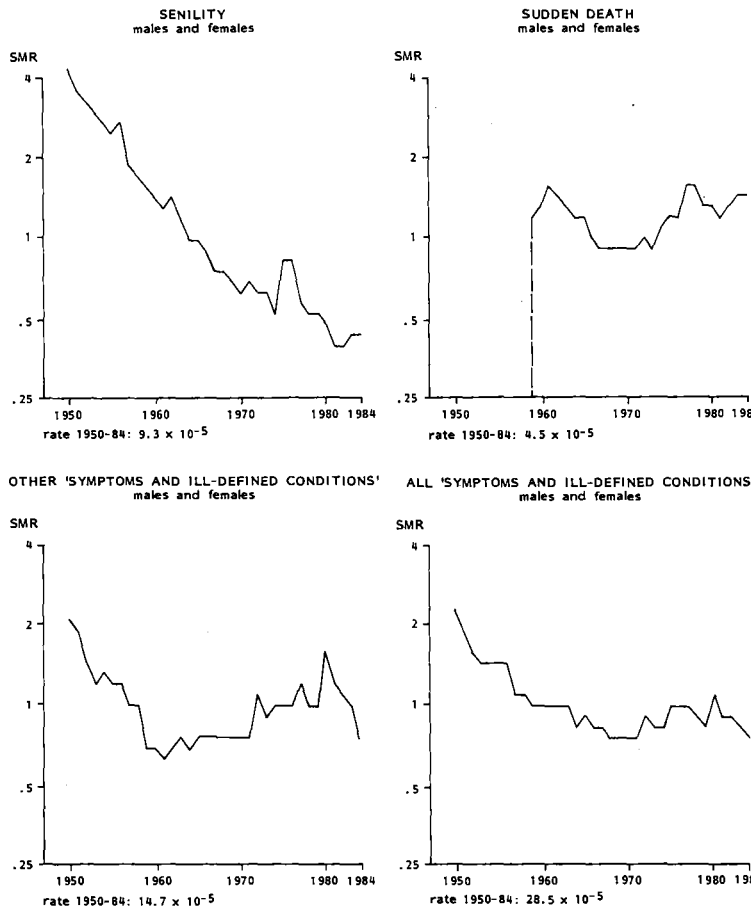
[a] Excluding dementia.

of-death information decreases with age. It may however simply reflect the fact that at higher ages more diagnostic information is available at the moment of death, so that some specific condition, whether relevant or not, can always be entered on the certificate.

The percentage of all deaths classified as due to Senility and Other symptoms and ill-defined conditions has rather drastically declined during this century (table I.2). In recent years, the decline of Other ill-defined conditions has slowed down and may even have reversed to a slight increase.

Figure I.4 shows this in more detail for the period 1950-1984. Standardized Mortality Ratios (SMRs) have been calculated in order to correct for changes in the age- and sex-composition of the population (see section I.6.3). For each cause of death, the average value for the complete period is 1.00. The category of "Sudden death" shows an erratic pattern, probably due to a change in the International Classification of Disease. In 1958 mortality due to Sudden death rose sharply, and a drop was registered for "Other ill-defined conditions". The latter category gradually increased in importance from 1960 to 1980, but may since then have been declining again.

Figure I.4 Trends in age-standardized mortality (SMRs) for "Symptoms and ill-defined conditions", 1950-84.



Note: The rates shown at the bottom of each graph are the average crude death rates (per person-year) for the entire period 1950-84.

I.2.3 The utility of mortality data

The value of routinely collected information on the health status of the population depends on a number of factors, which can be summarized under the following four headings:

1) Accessibility for analysis.
2) Coverage, with regard to
   - the population;
   - the range of health problems;
   - the range of consequences of health problems;
   - the time-period.
3) Availability of additional information, permitting a comparison between different time-units, geographical units, population subgroups, etc.
4) Measurement quality, i.e. a comparison between different "times, places, and persons" has sufficient
   - precision (absence of random error)
   - validity (absence of systematic error).

Compared with other sources of information, the **accessibility for analysis** of mortality data is rather good. National data on mortality by cause of death have been published since 1903 in a more or less standard format. On a more limited scale, regional and local data have also been published, whereas more detailed data can be obtained upon request. On the other hand, linkage with other routine data sources is difficult due to privacy protection rules.

"Coverage" is among the main assets of mortality data by cause of death. Mortality data cover the whole population, and all health problems which cause death, even if infrequently. Although death is only one consequence of health problems, it is a very important one. Furthermore, mortality statistics permit the analysis of long-term time trends.

Some **additional information** is available in mortality statistics, permitting an analysis of differences between time-units (e.g. calendar-years), geographical units (e.g. domiciliary region of the deceased), and population subgroups (e.g. by age, sex, and marital status). Unfortunately, socio-economic characteristics of the deceased are not registered in the Dutch mortality registry.

For most purposes, the crucial issue in **measurement quality** is that a comparison of cause-specific mortality between "times, places, and persons" is possible. The precision of such comparisons is sometimes insufficient in smaller causes of death. Possible threats to validity are differences in the probability of being registered, and differential misclassification of causes of death. These issues will be taken up in more detail in section I.6.1, whereas chapter II presents the results of an international study of differential misclassification of selected underlying causes of death.

I.3 Mortality and health policy

I.3.1 A historical note on the development of the study of mortality

The discovery of mortality as a phenomenon worthy of scientific and also political interest dates back to the seventeenth century. The application of quantitative methods to the study of mortality and other social problems was one of the most important scientific breakthroughs of that century. John Graunt's "Natural and political observations (...) upon the Bills of mortality" (1662) demonstrated the regularity of a number of mortality phenomena, for example the fact that from year to year certain causes of death formed a constant proportion of the total number of deaths. The first life tables also date from the second half of the seventeenth century (Christiaan Huygens, 1669; Edmund Halley, 1693) [25].

The further development of the study of mortality was closely related to the development of **health policy**. It was favoured by the fact, that it was increasingly recognized to be in the interest of the state to have the largest possible number of healthy, productive subjects [26]. Johann Peter Frank's "System einer vollständigen medicinischen Polizey" (1779) was one of the most clear expressions of this attitude. The concept of "medical police", i.e. the creation of a medical policy by governments and its implementation through administrative regulation, was based upon the recognition that there was a connection between problems of health and disease on the one hand, and the aim of augmenting the population on the other hand [27].

This political and administrative line of development was paralleled by a growth of interest among the medical profession for the relationship between health and environment. The French "Société Royale de Médecine" (1778) collected meteorological and disease data from all over France, as part of efforts to gain control over epidemics [28, 29]. In The Netherlands, a "Correspondentie-Sociëteit" of medical and other learned men did the same [30].

In the nineteenth century, the **"sanitary reformers"** built upon these early experiences, both in their application of quantitative methods and in their study of the relationship between environment and health. In the 1820's and 1830's, the "numerical method" had gained considerable popularity in the French medical profession, due to the works of Pinel, Louis, the Belgian Quetelet, and others. Statistical information gradually began to be collected.

This enabled Villermé to write his "Recherches statistiques sur la ville de Paris" (1828), "Tableau de l'état physique et moral des ouvriers" (1840), and many other works demonstrating the appalling state of health of the poor [31]. In England, the early public health movement culminated with Edwin Chadwick's "Report on the sanitary condition of the labouring population of Great Britain" (1842), William Farr's "Report on the mortality of cholera in England" (1852)

and other works of sanitary reformers [32, 33]. In all these reports, extensive use was made of mortality data. The Dutch counterpart of this movement, the "Hygiënisten", also used mortality data in their arguments for sanitary reform [34].

In the eighteenth and nineteenth centuries, the study of phenomena relating to health and disease often had a geographical focus. Survival of elements of the Hippocratic tradition in medicine have played an important role in this interest in **"medical geography"**. One of the Hippocratic writings ("On airs, waters, places") stated: "Whoever would study medicine aright must learn of the following subjects. First he must consider the effect of each of the seasons of the year and the differences between them. Secondly he must study the warm and the cold winds, both those which are common to every country and those peculiar to a particular locality. Lastly, the effect of water on the health must not be forgotten. Just as it varies in taste and when weighed, so does its effect on the body vary as well. When, therefore, a physician comes to a district previously unknown to him, he should consider both its situation and its aspect to the winds" [35].

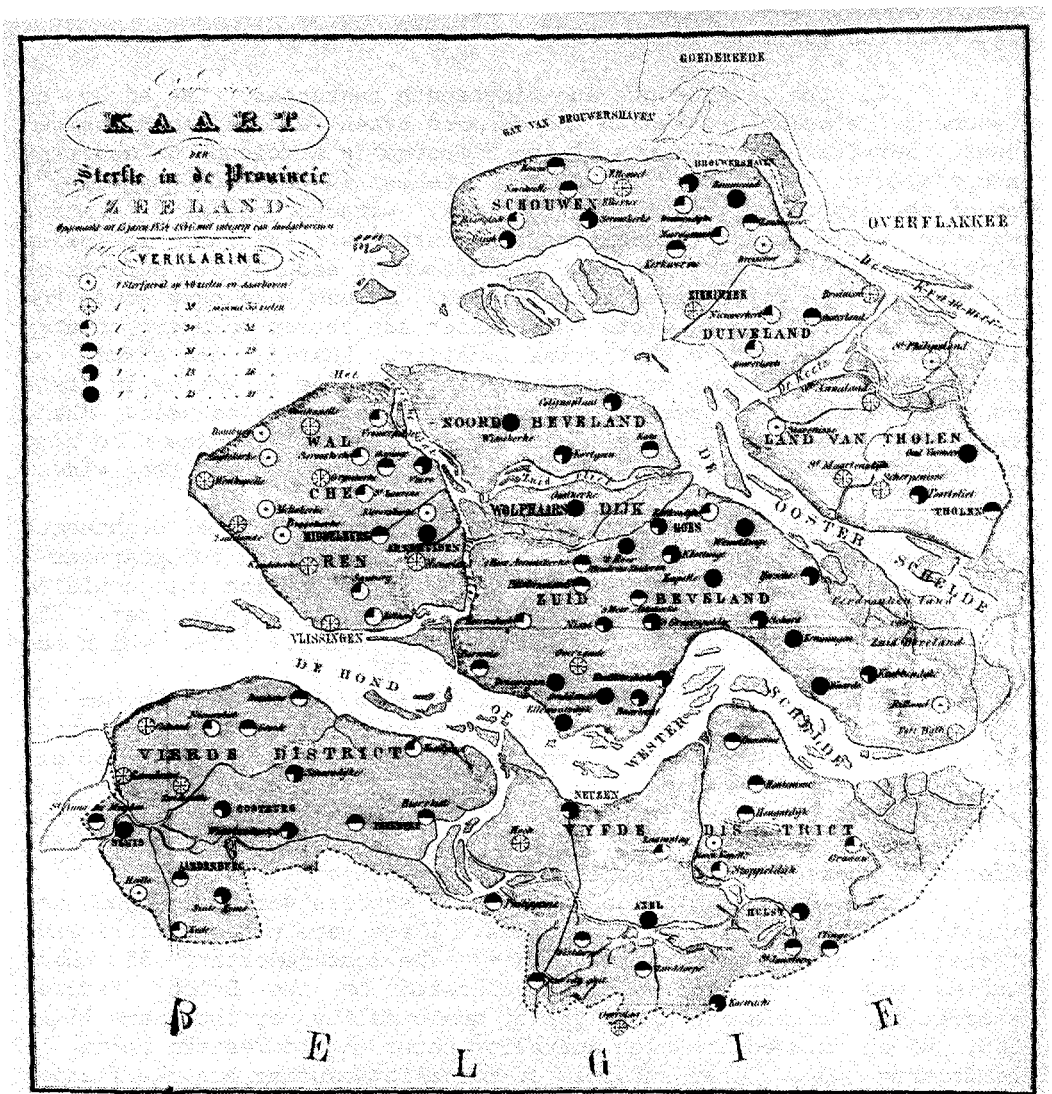
The main instrument of medical geography in the eighteenth and nineteenth centuries was the writing of "medical topographies", detailed descriptions of all aspects of a city or region that could be of relevance to the state of health of the population [e.g. ref. 36, 37]. These topographies followed a standard protocol [38], which had been prepared by the German Finke in 1795 [39].

The study of the city of Middelburg by Fokker and De Man of 1856 is a good example of a medical topography [37]. Characteristically, the study starts with a description of the physico-geographical aspects of the city's location and gives a detailed account of the lay-out of the city and the quality of its housing. Each description is followed by the authors' very tentative assessment of the possible effects of these characteristics on the population's health.

There was only a small number of studies which compared the situation in many different localities. These were mainly descriptive studies of differences in mortality. The most important of these studies was a mortality atlas published by the Dutch Medical Association, displaying mortality by municipality for the years 1841-1860, which showed the high mortality rates in the Western parts of the country [40]. Other examples of mortality mapping are the studies by Schick on mortality in Zuid-Holland [41], and the study by De Man on mortality in Zeeland [42], with its beautiful map (Figure I.5).

Attempts at explanation of these differences were again very provisional. A "geographical determinism" predominated, in which physico-geographical factors were thought to be the main determinants of observed differences. The high mortality rates in the Western provinces, for example, were frequently ascribed to their low altitude, brackish water and clay soil.

Figure I.5 Map of mortality in the province of Zeeland, 1834-1846



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I.3.2 Mortality, community diagnosis, and the circular principle

The use of data on mortality and causes of death for health policy purposes can be summarized under the heading "community diagnosis" [43, 44]: the description and analysis of the frequency and distribution of health problems in a population. Whereas a diagnosis of the health problems of an individual patient is intended to give suggestions for individual treatment, a community diagnosis may lead to suggestions for action on the part of health policy makers ("community medicine").

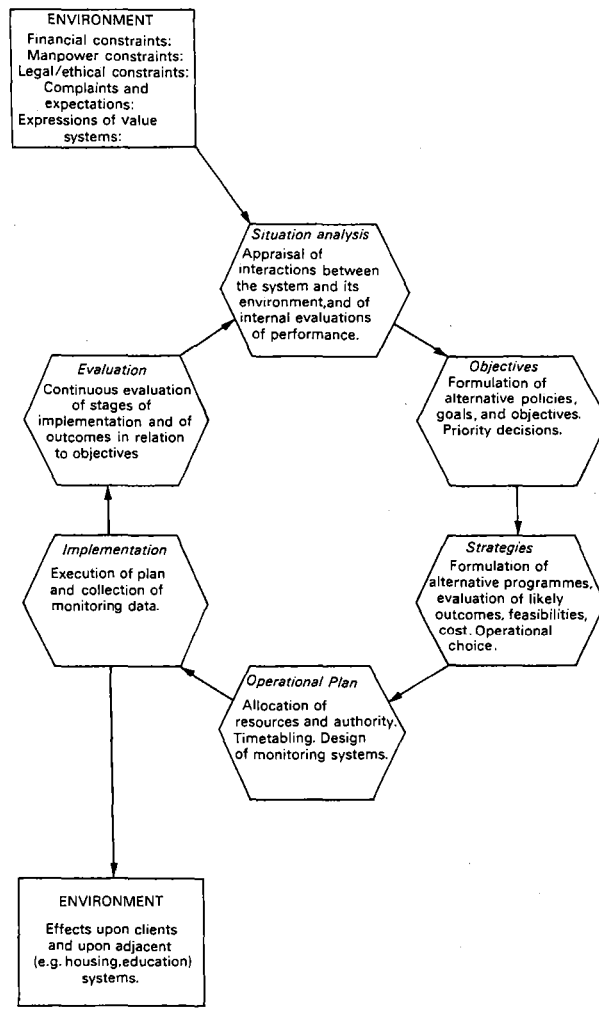
Although we know more on the origins of health problems than our predecessors of the seventeenth, eighteenth and nineteenth centuries, so that a twentieth century community diagnosis is likely to be more accurate, many effective actions have been taken in the past on the basis of completely wrong concepts. Most sanitary reformers, for example, were "anticontagionists", and believed that what we call "infectious diseases" were caused by filth and its foul vapours [33, 45].

An idealized representation of **health policy making** (or any other policy making process) is given in Figure I.6. Policy making is visualized here as a circular process, in which a series of steps is followed in a more or less systematic way. The process starts with the identification of a problem, based on a "situation analysis". In the phase of the formulation of "objectives", alternative policies are considered and priority decisions are taken. The third step involves the (ex ante) evaluation of alternative interventions, in the search for an appropriate "strategy". This strategy will have to be translated into an "operational plan", which specifies the details of the intervention, including time-tables, the allocation of resources etc. In the phase of "implementation" the plan is executed, and during and after the implementation an "evaluation" is carried out, to see whether the outcomes correspond to the objectives. The evaluation phase closes the circle, and may coincide with the situation analysis of a following cycle, if the original problem is not completely removed by the intervention [46].

Generally speaking, mortality analyses and other forms of community diagnosis may contribute to a situation analysis, or, if some kind of intervention to reduce mortality risks has been undertaken, to the evaluation of this intervention.

"Health policy" is a rather broad term, which is generally thought of as encompassing **"health care policy"**. In such a view, the health care system is one of the "instruments" of health policy. Chapter III presents the results of an attempt to see whether mortality analyses can also be useful in the framework of health care policy, by providing information on the "need" for health care services.

Figure I.6 The circular principle of (health) policy making: a planning cycle



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Most of this thesis, however, is concerned with the question whether mortality analyses can provide information which is useful in the evaluation of health care services, more specifically of "medical care".

I.3.3 A definition of medical care

The current use of the terms "health care" and "medical care" is rather confusing. A recent "Dictionary of epidemiology" [47] gives the following definition of "health care", which may serve as a first approximation: "Those services provided to individuals or communities by agents of the health services or professions, for the purpose of promoting, maintaining, monitoring or restoring health. Health care is broader than, and not limited to, medical care, which implies therapeutic action by or under the supervision of a physician".

Note the circularity of this definition. The intention of including the words "provided by (...) agents of the health services or professions" is probably to exclude environmental change, if undertaken by others (collective prevention), from the definition of health care. (There is also an entry in this dictionary for "health services", which gives a definition almost identical to that for health care, but the term medical care is replaced here by "personal health care".)

While probably everybody would agree that medical care is a more narrow concept than health care, the exact boundaries may be controversial. The definitions cited above suggest that medical care distinguishes itself by its objective (e.g. "therapeutic action"), its dominant provider (a physician), and its delivery in a "personal" encounter.

The part of the health care system which forms the focus of the analyses in this thesis, and which will be designated with the term medical care, contains a bit more than therapeutic actions on the part of physicians in a personal encounter with patients. We will use the following definition of medical care: **medical care is that part of the health care system where preventive, curative, and rehabilitative services are delivered in a personal encounter between a health care professional and a client.**

This definition includes some other objectives than treatment as well, and also includes more health care professionals than physicians only. Many actions that doctors take in their personal encounters with patients have preventive aims. Detection and treatment of hypertension is a good example. Note that vaccination and screening for Cervical cancer, which are provided by doctors in general practice and in hospital, but also by health care professionals working in public health services, are included in this definition of medical care.

I.4 The history of mortality and the role of medicine

I.4.1 The demographic transition

The population history of Europe was characterized by long cycles of growth and recession. There probably was a prolonged population rise between 1100 and 1350, another between 1450 and 1650, and a third after 1750 [48]. The first of these was followed by a particularly sharp recession, starting with the Black Death of 1348. Because the recession removed pressures, after some time the standard of living rose considerably [49], and the population increased again. Another recession, less severe than the first, started after 1650, partly due to climatic changes. The European population still increased, but at a relatively slow rate from appr. 100 million in 1650 to appr. 140 million in 1750. After 1750 a new rapid increase in population numbers occurred: the European population counted 190 million in 1800, 270 million in 1850, 400 million in 1900, and 600 million in 1950 [48].

The **cause of the rapid increase in population numbers after 1750** can either be an increased birth rate, or a decreased death rate. This has been the subject of intensive debate among historical demographers. Unfortunately, reliable national statistics on birth and death rates are only available since the beginning or middle of the nineteenth century for most countries (the second half of the eighteenth century for some Scandinavian countries). At the moment when national registration started, birth rates were already substantially higher than death rates in many European countries, leaving unanswered the question whether increasing fertility or declining mortality had caused the surplus of births over deaths.

Family reconstitution studies

That declining mortality rates were responsible is strongly suggested now by the results of family reconstitution studies and by the results of studies of selected populations, for which mortality rates happen to be known. The recent technique of family reconstitution studies intends to reconstruct "vital events" by the linkage of data on births (baptisms), marriages, and deaths (burials) available in parish registers. A synthesis of these studies [50] has led to the conclusion that trends in fertility did not show signs of an important increase in the eighteenth century. Trends in mortality, however, were probably declining. This is at least evident for Infant mortality, which was an important component of Total mortality in these days and which can be estimated relatively well from this type of study (table I.3).

Table I.3 Trends in infant mortality in the eighteenth century, estimated from family reconstitution studies.

	Deaths less than 1 year of age per 1000 live births	
	England	France
< 1750	187	252
1740-1790	161	213
1780-1820	122	195

Weighted averages of estimates obtained in family reconstitution studies.
Data from ref. 50.

Conclusions based on family reconstitution studies are supported by the results of studies of selected populations, like the British peerage [51] or the Knights of the Order of the Golden Fleece [52]. These studies, covering higher age-groups, have shown a decrease in death rates and a corresponding increase in survival starting with those born in the eighteenth century.

National registrations

Data from national registrations (figure I.7) also suggest that crude mortality rates were already declining before 1850. These data also show the importance of "mortality crises", years with exceptionally high mortality under the "Ancien régime". War, famine and/or epidemics were responsible. The Swedish data suggest that the amplitude of mortality fluctuations gradually diminished. The milder mortality crises of the mid-nineteenth century are due to epidemics of Cholera and other infectious diseases.

In The Netherlands, levels of mortality were generally higher than those in Sweden, England and France, and did not show a tendency to decline between 1840 (the first year for which national data were available) and ca. 1875. Infant mortality in The Netherlands, an important component of Total mortality in this period, even showed an increase between 1840 and ca. 1875 [53]. On the other hand, a reconstruction of Dutch mortality rates between 1800 and 1840, on the basis of data from a large part of the national territory, suggests that there was already some decline before 1840 [54], as there was in Sweden and France. Mortality decline in The Netherlands after 1875 may have been faster than that in Sweden, England and France (figure I.7).

Figure I.7 Crude mortality rates in the eighteenth, nineteenth and twentieth centuries: The Netherlands, Sweden, England, and France.

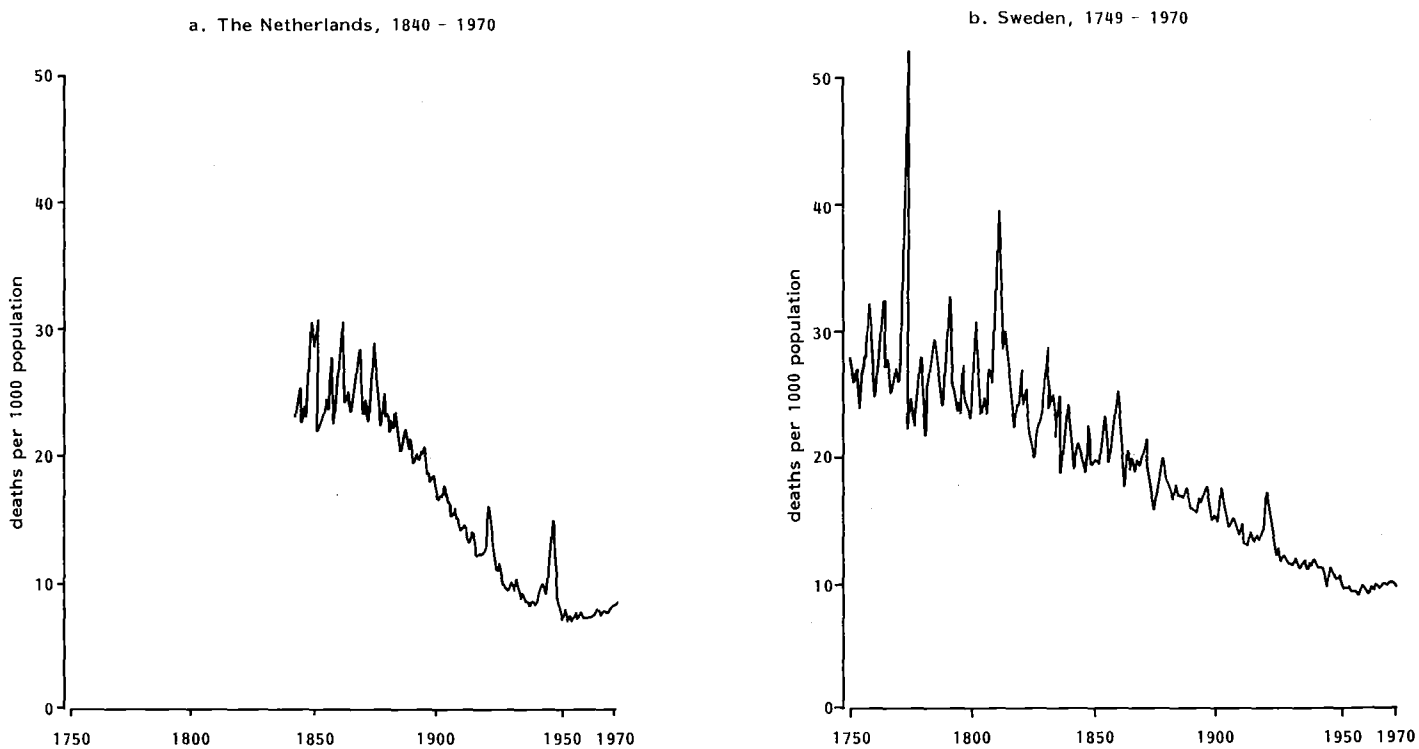
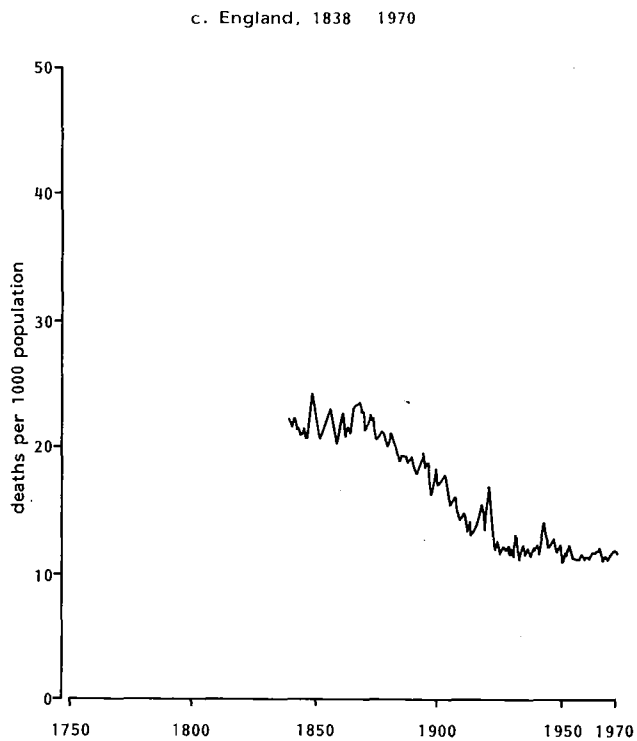
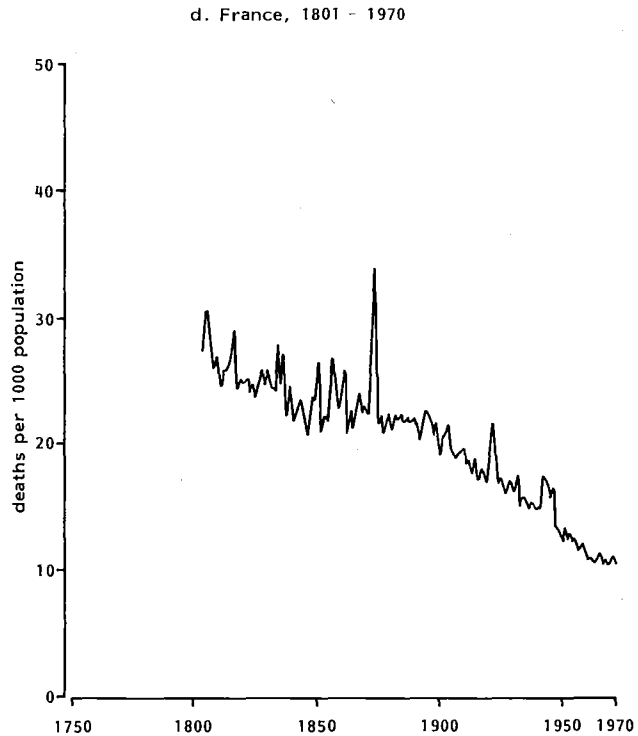


Figure I.7 (continued) Crude mortality rates in the eighteenth, nineteenth and twentieth centuries: The Netherlands, Sweden, England, and France.





Data from: ref. 56

These mortality declines mark the first phase of the **"demographic transition"**. During the demographic transition, a population evolves from a state with high mortality rates and high fertility rates to a state with low mortality rates and low fertility rates. Because fertility declines generally start later than mortality declines, a rapid growth of population numbers occurs [55]. In The Netherlands, fertility rates declined gradually since the late nineteenth century, but only started to approach the low mortality rates after rapid declines in the 1960's and 1970's.

Changes in life expectancy

The decline in mortality had important effects on average life expectancy at birth (table I.4). At the mortality rates prevailing in the period 1840/51 the average individual could expect to live less than 40 years. Life expectancy at birth has doubled between 1840/51 and 1980/84. Most of these gains were realized before 1950.

This is also evident from figure I.8, which shows survival curves by age since 1840/51. Low average life expectancy at birth since the nineteenth century was very much the result of low chances of survival in the first years of life. Dramatic changes occurred between 1840/41 and 1950/52, but the curves for the three most recent periods show rather small differences, especially for males. (Note that for males the 1950/52 and 1966/70 the lines cross twice. This is due to increasing mortality rates in certain age-groups in males between 1950/52 and 1966/70, cf. section I.4.2.)

The graphs also suggest a certain **"rectangularization"** of survival curves [58]. Not only has the curve for ages between 1 and 50 years nearly become horizontal, but the downward part of the curve for the periods 1950/52 and later is also considerably steeper than the curve for corresponding ages in earlier time-periods.

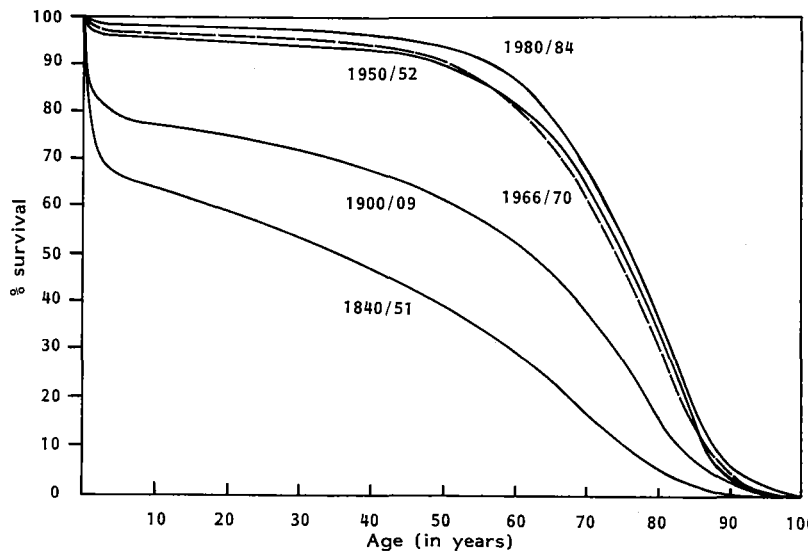
Table I.4 Evolution of average life expectancy at birth since the mid-nineteenth century, by sex, The Netherlands

	Life expectancy at birth in years	
	males	females
1840/51	36.2	38.5
1900/09	51.0	53.4
1950/52	70.6	72.9
1966/70	71.0	76.4
1980/84	72.8	79.4

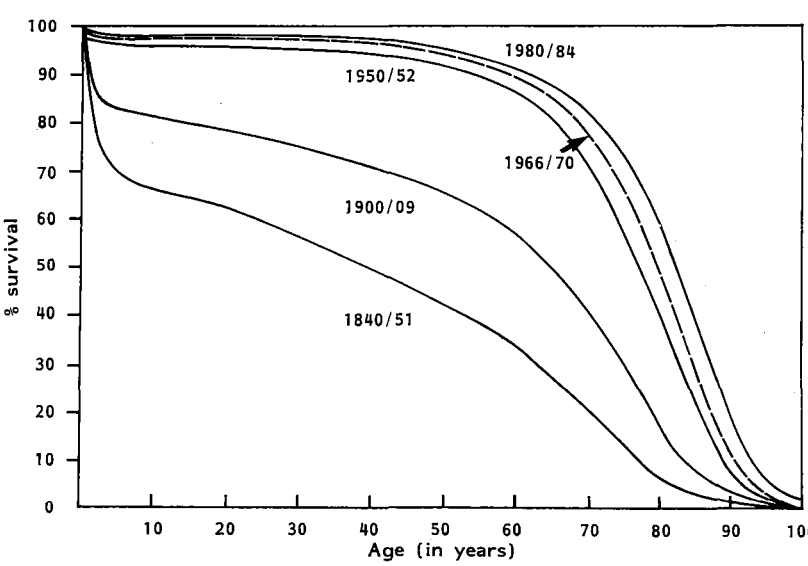
Data from: ref. 57

Figure I.8 Survival curves for successive time-periods since 1840/51, by sex, The Netherlands.

a. males



b. females



Data from ref. 57.

Table I.5 Death rates per million person-years, age-standardized, in broad groups of causes of death, England and Wales, 1848-54 and 1971.

	1848-54	1971	% reduction in Total mortality attributable to category
I. Conditions attributable to micro-organisms			
1. Airborne diseases	7259	619	40
2. Water- and food-borne diseases	3562	35	21
3. Other conditions	2144	60	13
Subtotal	12965	714	74
II. Conditions not attributable to micro-organisms	8891	4070	26
Total mortality, all causes	21856	5384	100

Data from ref. 59.

Cause-specific mortality changes

Information on causes of death in the eighteenth and nineteenth centuries is rather limited, and changes in classification make comparisons difficult. McKeown nevertheless succeeded in tracing developments in mortality for important causes of death since 1848 in England and Wales, the first year this information was available for England and Wales (table I.5) [59]. A similar analysis of changes in cause-specific mortality in the city of Amsterdam produced largely the same findings, possibly with the exception of Tuberculosis, which may have been less important for mortality decline than in England and Wales [60].

Conditions attributable to micro-organisms accounted for a large part of total mortality in 1848-54, and declined very fast as a cause of mortality between 1848-54 and 1971. The group of "air-borne diseases" includes such conditions as Tuberculosis, Bronchitis, pneumonia, and influenza, and diseases frequently occurring in children, such as Whooping cough, Diphtheria, Measles, and Scarlet fever. The group of "water- and food-borne diseases" includes Cholera, Dysentery, Typhoid, Typhus, unspecified Diarrhoea, etc. The group of other conditions in which micro-organisms are involved contains such conditions as "Convulsions" (occurring in children during fever episodes), Syphilis, Appendicitis, and Puerperal fever. It is clear from table I.5 that three-quarters of total mortality decline since the mid-nineteenth century can be attributed to a decline of infectious disease mortality.

I.4.2 Recent changes in mortality

The main causes of mortality in the period 1950-84 are completely different from those in the nineteenth century. As was evident from data presented in section I.2.1, the present mortality pattern is dominated by Diseases of the circulatory system and Neoplasms. Table I.6 presents the fifteen leading causes of death in The Netherlands in 1980-84 and 1950-54, for males and females separately.

Ischemic heart disease is the most important cause of death in **men** in 1980-84, and on its own accounts for almost one quarter of all deaths. Other important diseases of the circulatory system are Cerebrovascular disease, Other (non-rheumatic) heart disease, and Diseases of arteries (generalized atherosclerosis, aneurysms, arterial thrombosis). The most important cancers causing death in men are Cancer of the lung, Cancer of the prostate, Cancer of the stomach, and Cancer of the colon. Chronic Obstructive Pulmonary Disease and Influenza and pneumonia are the most important Diseases of the respiratory system.

Between 1950-54 and 1980-84 important changes in ranking occurred. Cancer of the lung and Cancer of the prostate increased in relative importance, and Cancer of the stomach decreased. Chronic Obstructive Pulmonary Disease increased, whereas Influenza and pneumonia decreased. Mortality due to Perinatal causes also decreased considerably in importance. (Please note that mortality due to the ICD-chapter Causes of perinatal morbidity, abbreviated here as "Perinatal causes", is not identical to "Perinatal mortality". The latter also includes still-births and first-week deaths due to other than "Perinatal causes", and excludes deaths older than 1 week!). Diseases of the circulatory system were already very important in 1950-54, but in later decades their share of Total mortality still increased considerably.

The mortality pattern of Dutch **women** is also dominated by Diseases of the circulatory system, but differs from that of men in a number of respects. Cerebrovascular disease is more, Ischemic heart disease is less important than in men. Cancer of the breast replaces Cancer of lung as the most important cancer.

Non-traffic accidents are also a more important cause of death in women. This is partly due to differences in the age-structure of the male and female populations. Mortality from Non-traffic accidents, which is largely due to accidental fall and hip fracture, is a cause of death of the (very) old; due to the higher life expectancy of women, the female population has a larger proportion of elderly. Another factor is the higher frequency of osteoporosis in women, and the resulting higher risk of hip fracture.

Since 1950-54 Ischemic heart disease climbed from the third to the first place in females. Other changes mirror those observed in males.

Table I.6 The fifteen leading causes of death, by sex, 1980-84 and 1950-54.

1980-84			1950-54	
Cause of death	% of all deaths	#	Cause of death	% of all deaths
		MALES		
Ischemic heart disease	23.7	1	Ischemic heart disease	13.0
Cancer of lung	11.4	2	Cerebrovascular disease	10.2
Cerebrovascular disease	8.1	3	Other heart disease [a]	9.0
Other heart disease [a]	7.6	4	Cancer of stomach	5.5
Chronic Obstr. Pulmon. Dis.	4.7	5	Influenza/pneumonia	4.4
Cancer of prostate	2.7	6	Perinatal causes [b]	3.9
Cancer of stomach	2.5	7	Cancer of lung	3.6
Diseases of arteries	2.4	8	Non-traffic accidents	3.1
Influenza/pneumonia	2.2	9	Traffic accidents	2.9
Traffic accidents	2.2	10	Diseases of arteries	2.6
Cancer of colon	1.9	11	Chronic Obstr. Pulmon. Dis.	2.6
Non-traffic accidents	1.7	12	Prostate hyperplasia	2.0
Suicide	1.5	13	Tuberculosis	1.8
Cancer of pancreas	1.3	14	Cancer of prostate	1.7
Cancer of bladder	1.1	15	Hypertensive disease	1.6
		FEMALES		
Ischemic heart disease	18.5	1	Cerebrovascular disease	14.1
Cerebrovascular disease	12.9	2	Other heart disease [a]	11.2
Other heart disease [a]	10.5	3	Ischemic heart disease	9.4
Cancer of breast	5.4	4	Influenza/pneumonia	4.9
Influenza/pneumonia	3.2	5	Cancer of stomach	4.2
Cancer of colon	2.8	6	Cancer of breast	3.7
Non-traffic accidents	2.3	7	Perinatal causes [b]	2.8
Diseases of arteries	1.9	8	Diseases of arteries	2.7
Cancer of stomach	1.8	9	Hypertensive disease	2.5
Chronic Obstr. Pulmon. Dis.	1.8	10	Diabetes mellitus	2.1
Diabetes mellitus	1.7	11	Non-traffic accidents	2.1
Cancer of ovary	1.6	12	Nephritis/nephrosis	1.8
Cancer of lung	1.5	13	Cancer of colon	1.8
Nephritis/nephrosis	1.4	14	Chronic Obstr. Pulmon. Dis.	1.8
Cancer of pancreas	1.4	15	Tuberculosis	1.6

Note: For ICD-code numbers, see Annex 1. Ill-defined and non-specified conditions have been excluded.

[a] Non-ischemic, non-rheumatic heart disease.

[b] Deaths, any age (excluding still-births), classified under chapter XV of the ICD.

Post-1950 time-trends for the leading causes of death

Changes in mortality rates for the leading causes of death, standardized for changes in the age-composition of the population, are shown in figure I.9. For men and women separately, Standardized Mortality Ratios (SMRs), all ages, were calculated with sex-specific standardrates derived from average mortality rates over the entire period 1950-1984. Because the SMRs have all been plotted on the same logarithmic scale, rates of change can be compared between causes of death, between the sexes, and over time.

Mortality from Ischemic heart disease has been increasing until the first half of the 1970's, and then started a gradual decrease, both in males and females. Other diseases of the circulatory system have shown more favourable trends. Cerebrovascular disease has declined gradually throughout the study-period, more in females than in males. Hypertensive disease (complications of hypertension not classifiable to Ischemic heart disease or Cerebrovascular disease) has declined rapidly.

Cancer of the stomach is the only quantitatively important cancer for which mortality has declined since 1950. Cancer of the lung has increased dramatically; the rate of increase seems to be decelerating in men after 1970, but it is accelerating in women. Cancer of the colon, prostate and breast all show slight mortality increases.

Mortality from Influenza and pneumonia has decreased since 1950; the apparent temporary increase just before 1970 is due to changes in coding (see section I.6.1). Deaths due to Perinatal causes have declined considerably. Mortality rates from Traffic accidents and Non-traffic accidents increased until the early 1970's, then started a rapid decrease. The peak in mortality from Non-traffic accidents in 1953 was caused by a flood disaster.

For all ages combined, **Total mortality** in males remained more or less stable between 1950 and 1970. Figure I.9 demonstrates that this is due to a mixture of decreasing mortality for some, increasing mortality for other conditions. Mortality increases are apparent especially for Ischemic heart diseases, Cancer of the lung, Chronic Obstructive Pulmonary Disease, and Traffic accidents. In the early 1970's a trend reversal occurred for Ischemic heart disease and Traffic accidents, and mortality increases for Cancer of the lung and Chronic Obstructive Pulmonary Disease slowed down.

The fact that Total mortality did not remain stable for females between 1950 and 1970, but decreased, is due to a number of factors. Ischemic heart disease, Cancer of the lung, Chronic Obstructive Pulmonary Disease, and Traffic accidents are less important and increased less in females. And some causes which declined even in this period, such as Cerebrovascular disease and Cancer of the stomach, are more important and/or declined faster in females.

Figure I.9 Trends in age-standardized mortality by cause of death and sex, The Netherlands, 1950-84.

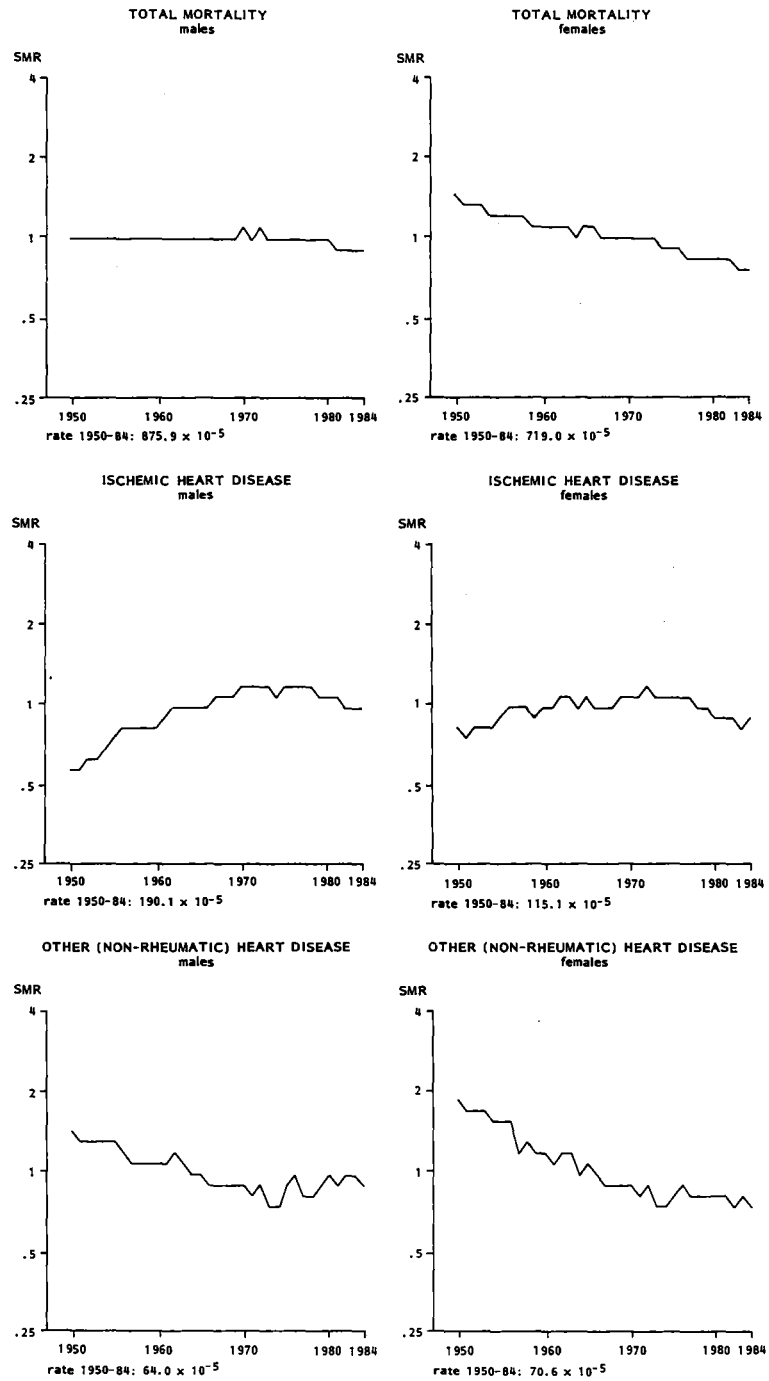


Figure I.9 (continued) Trends in age-standardized mortality by cause of death and sex, The Netherlands, 1950-84.

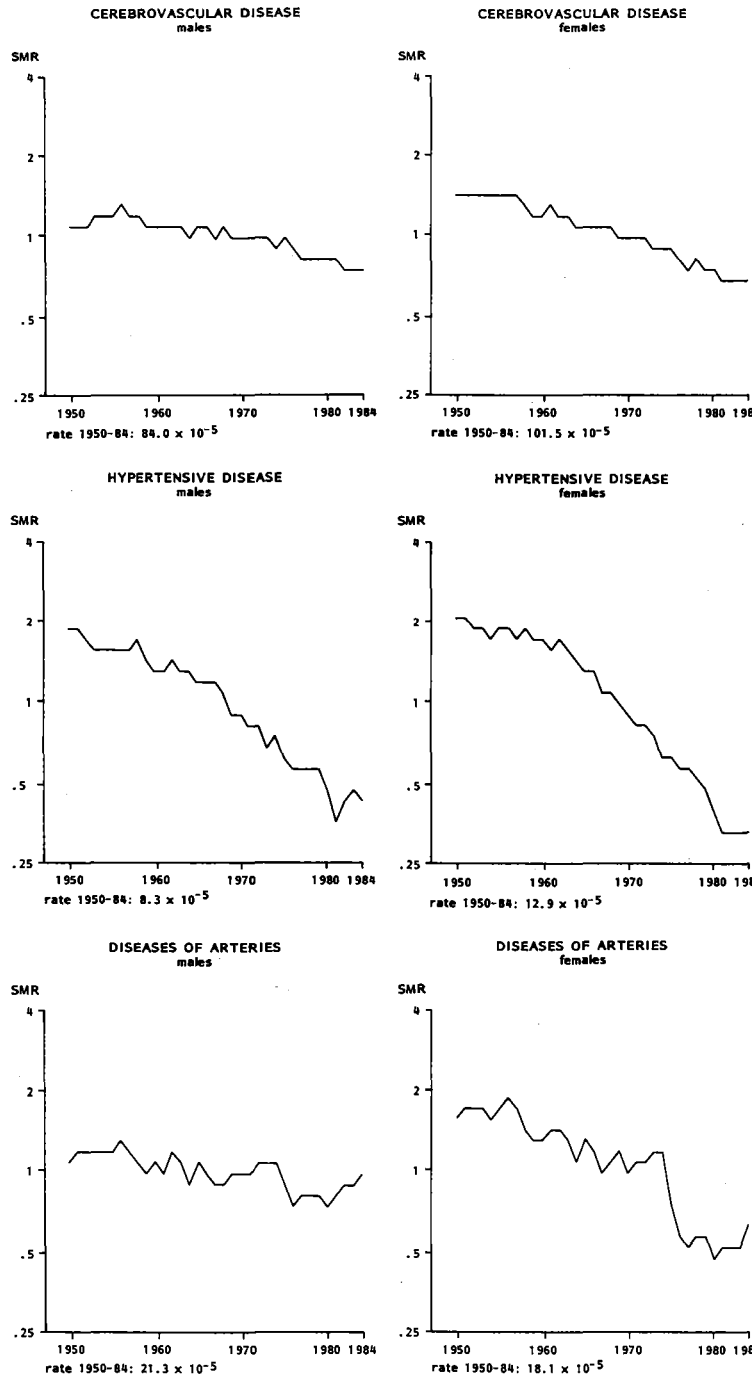


Figure I.9 (continued) Trends in age-standardized mortality by cause of death and sex, The Netherlands, 1950-84.

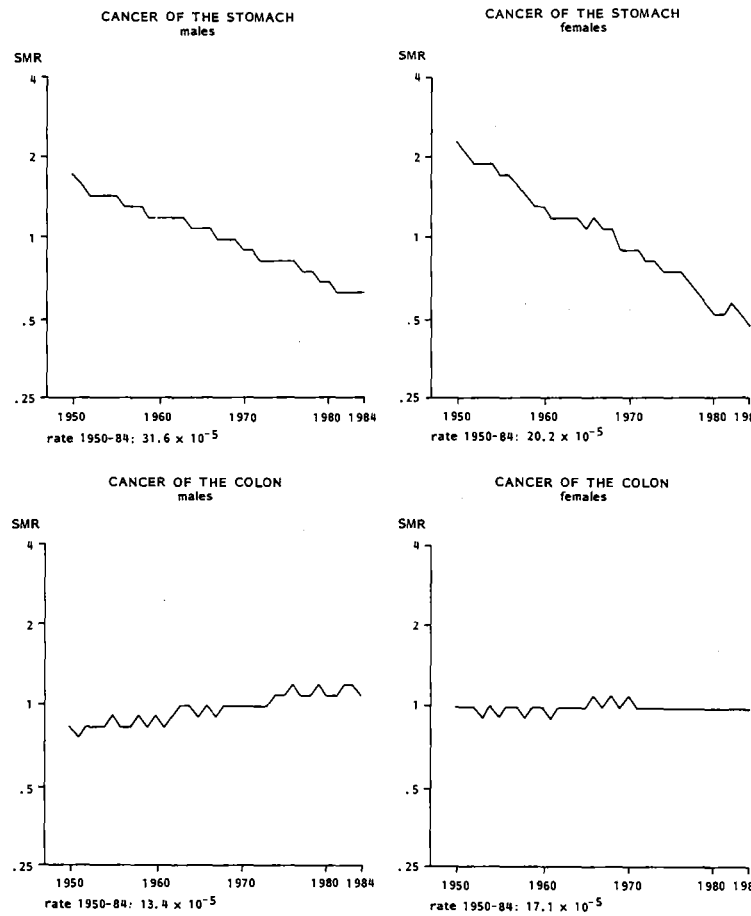


Figure I.9 (continued) Trends in age-standardized mortality by cause of death and sex, The Netherlands, 1950-84.

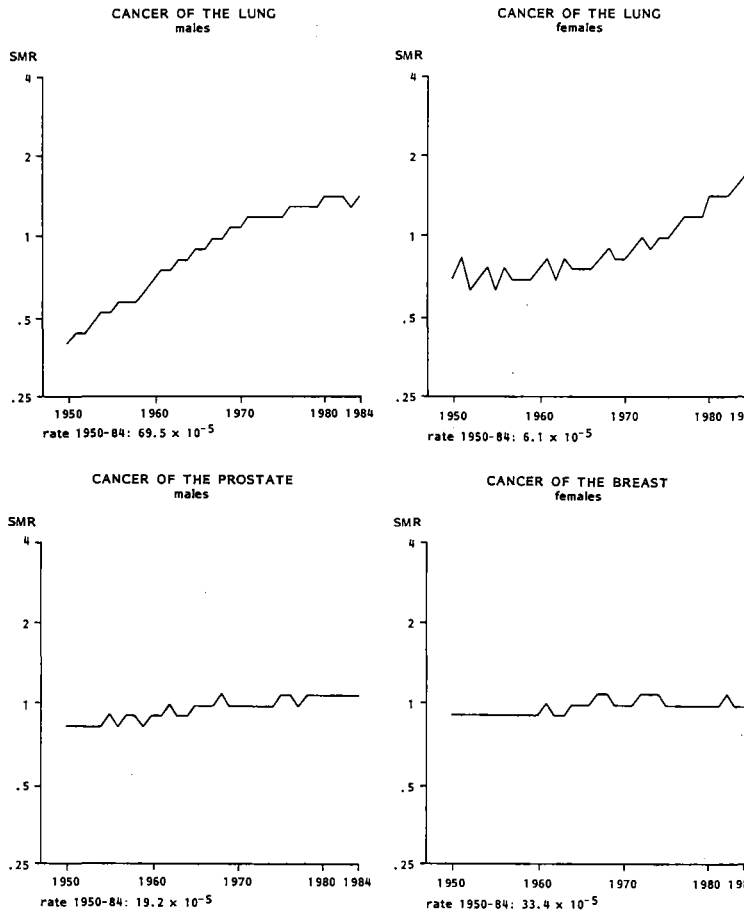


Figure I.9 (continued) Trends in age-standardized mortality by cause of death and sex, The Netherlands, 1950-84.

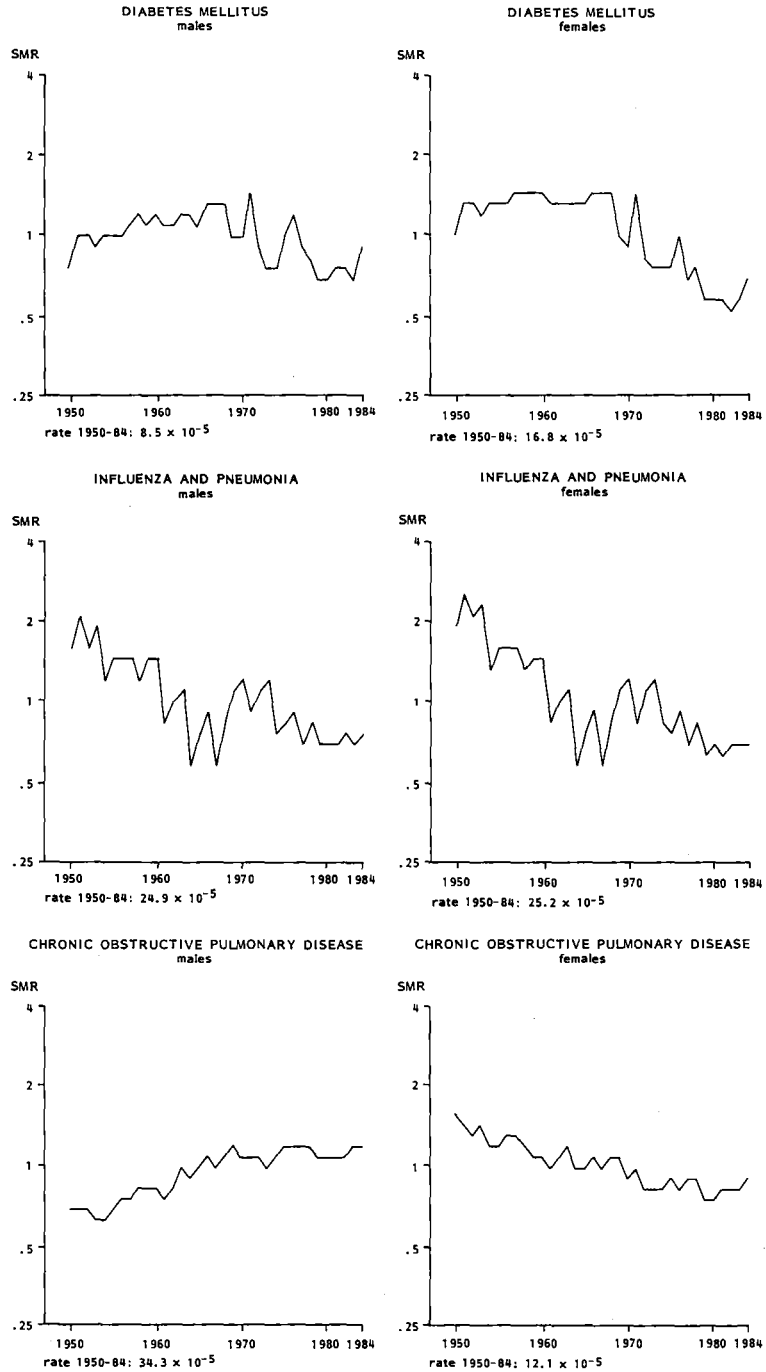
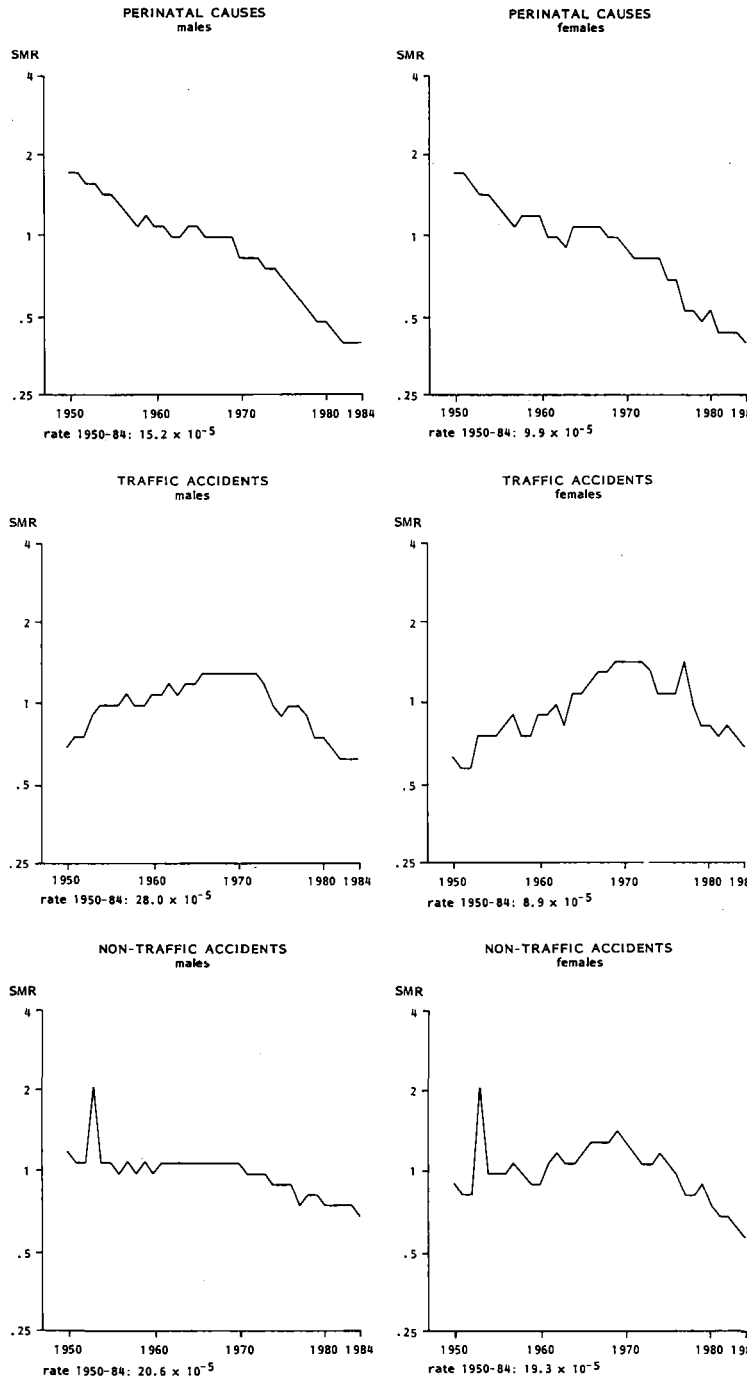


Figure I.9 (continued) Trends in age-standardized mortality by cause of death and sex, The Netherlands, 1950-84.



Less change after 1950 than before?

It has frequently been suggested that changes in mortality since 1950 have been much smaller than those in the period 1850-1950 (cf. section I.1). Although the changes in average life expectancy at birth and in crude mortality rates (section I.4.1) tend to support this view, a closer look at changes in age-specific mortality rates reveals that changes have in fact been not so small (see also ref. 61). Changes in average life expectancy at birth tend to "overestimate" the importance of changes in mortality rates at younger ages, because lives saved at younger ages add more years to life expectancy than lives saved at older ages.

Table I.7 shows both the changes in life expectancy and the changes in age-specific mortality rates, for selected ages. The period since 1950 has been divided into two parts, in order to allow for the effect of the trend reversals mentioned above. An **"absolute" measure of change** is used in this table: the difference between the value registered at the beginning of each period, and that registered at the end. Because the periods do not have the same lengths, the differences have been divided by the number of years passed.

Before 1950, especially between 1900/09 and 1950/52, the most impressive changes in mortality rates (per year) are registered in the 0-year age-group. This is also a period with rapid gains in life expectancy at birth. After 1950 the changes in mortality rates at age 0 become more modest, and changes in life expectancy also become less.

In men, mortality rates at ages 10, 20, 40 and 60 increased between 1950/52 and 1966/70, but declined again between 1966/70 and 1980/84. At younger ages, the recent declines are generally smaller than those registered before 1950, but at higher ages this is less true. In women, mortality declined at all ages during both parts of the post-1950 period. At age 80, the mortality declines have become larger and larger, and were even more important than those at age 0 after 1950.

With declining mortality rates it becomes increasingly difficult to achieve the same "absolute" changes in mortality. It may be more appropriate, therefore, to compare **proportional changes** in mortality. If the absolute changes (per year) are expressed as a percentage of their starting value, i.e. the mortality rate registered at the beginning of each period, a measure of "relative" change is obtained (table I.8). It appears that generally the relative declines were not smaller after 1950 than before, with the exception of changes in male mortality between 1950/52 and 1966/70, due to the "epidemics" of Ischemic heart disease and other causes of death.

Although gains in average life expectancy at birth have been small in comparison with earlier periods, age-specific mortality rates have thus declined considerably in recent years, and skepticism on our progress in the reduction of mortality is unwarranted.

Table I.7 "Absolute" changes in average life expectancy at birth and in mortality rates by age and sex, The Netherlands.

	"Absolute" changes (per year)						
	life expectancy at birth (in years)	mortality rate [a] (per 100.000) at age					
		0	10	20	40	60	80
males							
1840/51 - 1900/09	+0.2	- 86	-6	-11	-18	-22	- 40
1900/09 - 1950/52	+0.4	-245	-4	- 9	-10	-23	- 71
1950/52 - 1966/70	+0.0	- 72	+0	+ 1	+ 0	+22	- 40
1966/70 - 1980/84	+0.1	- 54	-2	- 2	- 4	-23	- 18
females							
1840/51 - 1900/09	+0.2	- 81	-6	- 8	-15	-15	- 35
1900/09 - 1950/52	+0.4	-209	-4	- 7	-11	-22	- 63
1950/52 - 1966/70	+0.2	- 57	-0	- 1	- 2	-14	-104
1966/70 - 1980/84	+0.2	- 40	-0	- 1	- 2	-11	-183

[a] In fact, this table uses the life table measure "mortality quotient".
Calculated from data in ref. 58.
See text for further explanation.

Table I.8 "Relative" or proportional changes in average life expectancy at birth and in mortality rates by age and sex, The Netherlands.

	Proportional changes (%, per year)						
	life expectancy at birth	mortality rate at age					
		0	10	20	40	60	80
males							
1840/51 - 1900/09	+0.7	-0.4	-1.1	-1.0	-1.0	-0.6	-0.2
1900/09 - 1950/52	+0.8	-1.7	-1.7	-1.8	-1.5	-0.9	-0.5
1950/52 - 1966/70	+0.0	-2.6	+0.2	+1.0	+0.2	+1.6	-0.4
1966/70 - 1980/84	+0.2	-3.4	-3.8	-1.5	-1.7	-1.3	-0.2
females							
1840/51 - 1900/09	+0.6	-0.5	-1.0	-0.9	-0.9	-0.5	-0.2
1900/09 - 1950/52	+0.8	-1.8	-1.8	-1.8	-1.6	-1.1	-0.5
1950/52 - 1966/70	+0.3	-2.7	-1.5	-1.8	-1.4	-1.3	-1.0
1966/70 - 1980/84	+0.3	-3.4	-1.7	-1.4	-1.7	-1.4	-2.2

Calculated from from the data in table I.7, and from life expectancy at birth c.q. mortality rate at beginning of each period.

I.4.3 The role of medicine

The most important event in the history of mortality of the last few centuries, is, of course, the enormous decline in infectious disease mortality (section I.4.1). McKeown has made an influential analysis of the possible causes for the decline in England and Wales, in which he considers three possible factors [3, 62]:

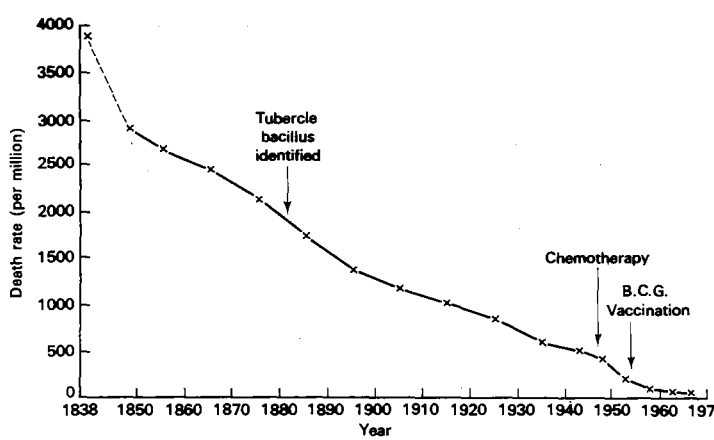
- "medical measures" of preventing and treating disease in the individual;
- a "spontaneous" change in the relation between infectious agent and human host;
- and improvements in the "environment".

We will follow his argument in some detail.

"Medical measures"

Medical measures, it is argued, can largely be discarded, because for most infectious diseases effective interventions were not available before the advent of the sulphonamides and antibiotics in the 1930's and 1940's. McKeown has published a large number of impressive graphs, in which it is shown that the decline of infectious disease mortality indeed had already largely occurred when these drugs became available. Figure I.10 presents the example of Respiratory tuberculosis. Approximately the same situation is present in e.g. Bronchitis, pneumonia and influenza, and Scarlet fever.

Figure I.10 Decline in mortality from respiratory tuberculosis (age-standardized), England and Wales.



Reprinted from: ref. 3.

According to McKeown, there was only a small number of exceptions, for example in Diphtheria where the introduction of anti-toxin in the late nineteenth century may have played an important role in the subsequent decline of mortality. Another exception he allows for is Syphilis, which, although it had already declined for other reasons, was still important as a cause of death when salvarsan became available early in the twentieth century.

For some infectious diseases, immunization was a more important breakthrough than antibiotics, but most forms of immunization were only introduced in England and Wales in the 1940's (Diphtheria) and 1950's (Whooping cough), or even later (Measles). McKeown does, however, recognize one important exception: Smallpox. Inoculation with infected material from Smallpox patients was practiced on a moderately large scale during the eighteenth century in England and Wales [63], and replaced by compulsory and more effective vaccination of infants during the nineteenth century.

The contribution of these preventive measures to the decline of Smallpox mortality is controversial. Some authors claim that Smallpox was a very important cause of death in the eighteenth and early nineteenth centuries, and that the decline of Smallpox incidence had an important side-effect in increasing resistance to other infections [64].

Recognizing that immunizations may have been more important in reducing morbidity than in reducing mortality, in a second edition of his book "The role of medicine" McKeown shows that notification rates for Poliomyelitis, Whooping cough, and Measles indeed declined much faster after their introduction.

Changes in host-agent interaction

A "spontaneous" change in the relationship between infectious agent and host is a second possible explanation for infectious disease mortality time trends. This possibility does not lend itself easily to empirical verification, but the apparently spontaneous rise and fall of a number of infectious diseases in the past have led to suggestions that changes in the virulence of micro-organisms and/or the resistance of the host do occur [65].

McNeill has made an interesting case for this mechanism in an attempt at explanation of the rise and fall of many infectious diseases. He claims that when new virulent micro-organisms enter a population which has not before been exposed to these agents, they start by killing off many people. Later, as the result of selection processes, milder strains displace those that killed their hosts too rapidly, and in addition the resistance of the population increases [66].

Most microbiologists would agree that a decreasing virulence of the streptococcus probably has played a major role in the decline of Scarlet fever mortality. McKeown states that this mechanism is unlikely to have been important for the decline of infectious disease mortality in general.

Changes in the "environment"

By exclusion, McKeown considers the third possibility, a favourable change in the environment, as the most plausible explanation for the decline of infectious disease mortality. Two changes could have had major effects: rising standards of living, particularly improved diet, and the hygienic measures introduced by the sanitary reformers. The latter measures date from about 1880, when improvements in water supplies and sewage disposal may have induced a decline in mortality from intestinal infections.

For **increased food production** during the eighteenth and nineteenth centuries there is only circumstantial evidence, based on estimates of land areas under cultivation, yields per acre, and amounts of imported and exported food. Of course, an increasing food production may also have been a consequence of the necessity to support larger population numbers, instead of the cause of the population increase. Nevertheless, there is some evidence that an "agricultural revolution" preceded the increase in population numbers, involving better organisation, new technologies (including new crops) and better transport. (In The Netherlands, a lowering of excise-duties on food-products caused an important extra increase in food consumption around 1860 [67].)

Evidence from the Third World indicates that nutritional status is indeed an important factor in the incidence and case fatality of infectious diseases, especially in infants and children [68]. The effect of better nutrition on mortality may have been important also in the case of Tuberculosis, one of the most important contributors to mortality decline in England and Wales. McKeown considers improved nutrition to be the single most important factor in the decline of infectious disease mortality.

McKeown's argument: a review

McKeown's analyses, and especially the summary of results presented in his 1976 book "The role of medicine: dream, mirage or nemesis", have exerted a powerful influence on attitudes towards medical care, both within and outside the medical profession. It had generally been assumed that medical measures have made an important contribution to the decline of mortality in the industrialized countries (see e.g. ref. 69). A detailed, but essentially simple analysis of the available information shows that other influences, especially changes of the environment, might have been more important.

In a discussion of these findings, it is important to distinguish between McKeown's interpretation of historical data and the possible conclusions that one might draw on the "role of medicine" at present and in the future.

McKeown's arguments against any important effects of medical measures on the decline of mortality in the past have the structure of a **syllogism**: - the decline in mortality since the eighteenth century can be attributed to a decline of infectious disease mortality; - no

effective medical interventions were available against infectious diseases before the middle of the twentieth century; - thus, most of the decline in mortality cannot be attributed to the introduction of effective medical interventions.

The first part of the syllogism is largely beyond dispute. Although some critics have pointed to the unreliability of historical cause-of-death information [70], it is generally agreed that diseases in which micro-organisms were involved dominated the mortality pattern of the eighteenth and nineteenth centuries, and were responsible for most of the mortality decline since then.

On the second part of the syllogism more disagreement is possible. Some disagreement on the effect of compulsory vaccination against Smallpox was already mentioned above. Older historians have argued that the rapid growth of hospitals in the eighteenth century contributed to the decline of mortality [69], but it is not unlikely that hospitalization, surgery, and institutional midwifery did in fact more harm than good [63]. Although McKeown may have been a little too rigorous for some infectious diseases, for example for Whooping cough, where immunization may have been in widespread use earlier than he believed [71], the analysis is in fact quite robust against such "fallibility in detail" [72].

Whether McKeown is right in believing that better nutrition was the main factor in mortality decline is beyond the scope of this thesis. As stated above, the evidence is largely circumstantial, and there is no quantitative precision in the effect estimates. On a more general level, however, it can be safely stated that **"ecological"** factors have been the dominant influence on the mortality decline of the eighteenth, nineteenth and early twentieth centuries. The exact contribution of more specific factors is unknown, and apart from better nutrition and sanitation (of water supplies and sewage disposal), declining fertility [73], better and more spacious housing [74], and many other factors.

Interestingly, the increase in the frequency of certain other ("Western") diseases, which occurred during or after the decline in infectious diseases, can also be viewed in terms of changes in the ecosystem. Changes in food-habits may be responsible for the rise in Hypertension, Diabetes mellitus, Ischemic heart disease, Colorectal cancer and other diseases; changes in fertility to the rise in Breast cancer; etc. [75].

Finally, it is important to note that at least some of the "environmental" changes which caused the decline of infectious disease mortality, were the results of **conscious efforts** to reduce health risks, and that these efforts were based on knowledge gained by the medical profession in its study of the determinants of disease (cf. section I.3.1).

The potential importance of conscious, as opposed to more spontaneous, environmental change is also suggested by the results of

two cross-sectional analyses of the relationship between life expectancy at birth and per capital national income, one for 1930 and one for 1960. The data available for this analysis covered a large number of countries from all over the world. At both moments in time, a higher national income went together with a higher life expectancy, but in 1960 a given level of the national income was associated with a substantially higher life expectancy than in 1930 (national income for 1930 expressed in 1960 values). This was true over the complete range of national income values, and suggests that other factors than those associated with economic progress were at work too in lowering mortality rates. For the less developed countries public health efforts directed against a number of infectious and parasitic diseases, such as Smallpox, Cholera and Malaria, may have played an important role, independent of that of economic change [76].

Wider implications

McKeown drew a number of more far-reaching conclusions from his historical analyses which appear to be less robust. McKeown has repeatedly argued that the historical evidence suggests that today's health problems are also more likely to be controlled by removing their causes (i.e. by changing the environment) than by intervening in disease mechanisms (i.e. by medical care for those that are already sick). However, from the fact that environmental change has made a larger contribution to mortality decline in the past than medical intervention, it does not necessarily follow that environmental change is a more effective means of intervention under all circumstances.

In some less developed populations, for example Navajo indians in the United States [2] and Eskimos in Greenland [77], the introduction of effective tuberculosis treatment had a much greater impact, because it came at a time when environmental changes had not yet been substantial, and because mortality rates from this disease were still as high as those in European countries in the nineteenth century.

In fact, a **universal comparison of the effectiveness of environmental change and medical measures** is not possible with McKeown's historical data. "Environmental measures were tested when mortality was high, antibiotics when mortality was low; environmental measures were tested alone, antibiotics against a background of environmental change. (...) English archers at Agincourt did better than English riflemen on the Somme, and it does not follow that archers have greater military potential" [72].

One could further argue that the comparison between the changes induced by the introduction of antibiotics and immunization, and the changes that occurred in a very long period of time before that, does injustice to and belittles the advances of medical care. **For contemporary patients, only contemporary effects count.** "To have witnessed the change in outlook that modern chemotherapy brought for an individual patient with tuberculosis has been a thrilling and

unforgettable experience. McKeown has, unfortunately, experienced this only by inspection of the mortality slope. (...) What was the point in even calculating the effect of specific anti-tuberculous therapy on the number of deaths due to tuberculosis since 1848, when the first effective drug came into use a century later?" [70]

McKeown's brief treatment of the actual effects of these drugs, in which he shows enlargements of the "tail" of the mortality curves for Tuberculosis and Pneumonia, which suggest important changes in mortality trend at the moment of introduction of antibiotics [3], is rather unsatisfactory.

The main problem with which we are left after reading McKeown is, that the effect of medical care on mortality in the second half of this century remains essentially unknown. Mortality developments after 1950 have been quite dynamic, and a comprehensive analysis of possible changes induced by improvements in medical care is simply not available. The analyses in chapters IV, V and VI are attempts to fill parts of this gap.

I.5 The geography of mortality and medical care

I.5.1 International differences in mortality

As shown in section I.4.1, the average **life expectancy at birth** in The Netherlands in 1980-84 was 72.8 years for males, and 79.4 years for females, thus approximately 76 years for both sexes combined. These life expectancy values are among the highest in the world. An average life expectancy at birth of more than 70 years is only found in Europe (excluding the USSR, where life expectancy was exactly 70.0 years in 1980-84), North America, Australia, New Zealand, and Japan (figure I.11), and in a small number of countries in other world regions, such as Israel, Costa Rica, Chili and Taiwan.

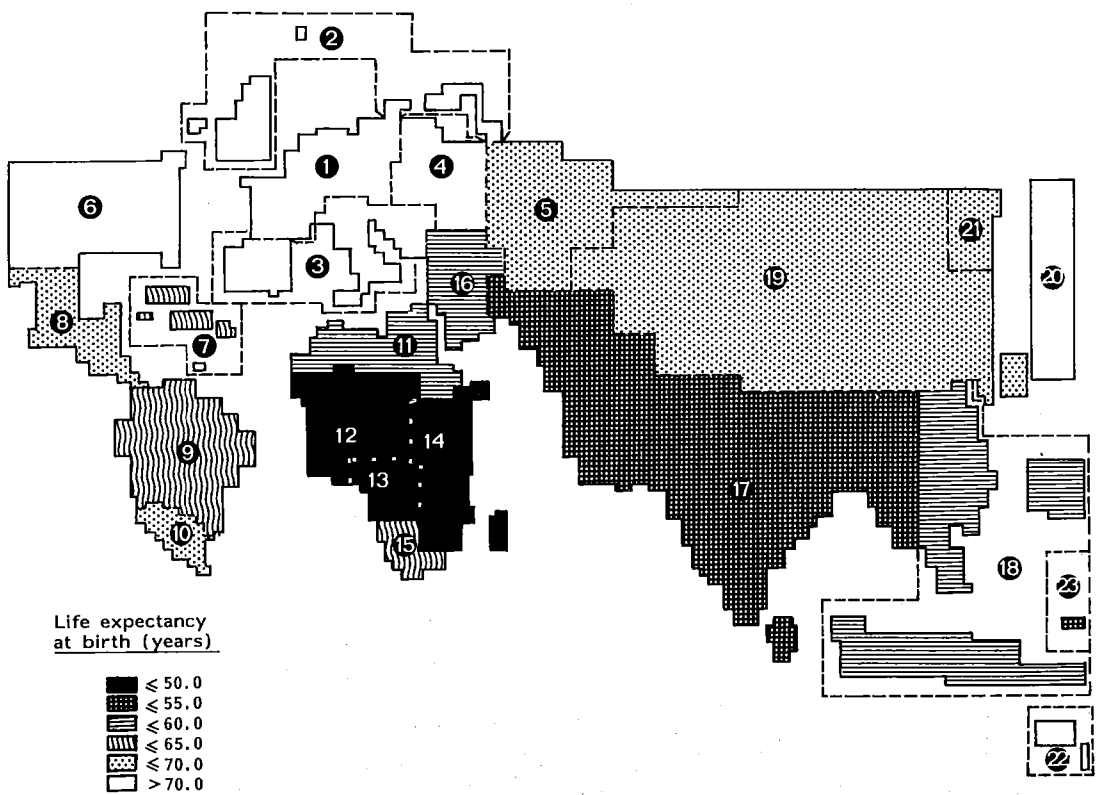
In certain parts of Africa, life expectancy was still below 50 years: 47.0 years in Middle Africa, 48.5 years in Western Africa, and 49.2 years in Eastern Africa. These values are similar to those for The Netherlands in 1890-1899. The region containing India and neighbouring countries, Middle South Asia, had an average life expectancy of 51.2 years (a value comparable to that calculated for The Netherlands in 1900-1909).

These differences in life expectancy between different regions of the world reflect the fact that many Third World countries are probably only at the beginning of a "demographic transition". Increases in life expectancy in the Third World have started in the twentieth century, for some countries only after World War II, but have been rather rapid in the last decades. The rate of increase has sometimes even exceeded that registered in European countries in a similar phase of the demographic transition [55].

Of the regions distinguished in figure I.11, China had the largest increase in life expectancy since 1960-64: 14.8 years were added in 20 years time. It rose from 55.0 to 69.8 years, values reached by The Netherlands in the early 1910's and the late 1940's respectively, which represents a period of appr. 35 years. The explosive growth of population numbers in the Third World has largely been caused by these mortality reductions, which were not paralleled by fertility reductions.

Mortality rates in The Netherlands are not only low by world standards, they also rate among the lowest of the industrialized countries (table I.9). Only Switzerland, Japan, Iceland, Sweden, Norway and Greece(!) had lower age-standardized death rates in the early 1980's than The Netherlands. The relatively low over-all mortality rates in The Netherlands are due to lower than average standardized death rates for three of the four largest cause-of-death groups: Diseases of the circulatory system, Diseases of the respiratory system, and Accidents, poisonings and violence (External causes). Dutch mortality rates are relatively high, however, for Malignant neoplasms.

Figure I.11 Demographic base map showing average life expectancy at birth in different regions of the world, both sexes combined, 1980-84.



Data from: ref. 78

Table I.9 Age-standardized death rates per 100.000 person-years [a], both sexes, in a number of industrialized countries, 1982 (or year nearest to 1982 for which data were published).

	All causes	Circulatory diseases	Malignant neoplasms	Respiratory diseases	External causes
Switzerland [4, b]	712	314	195	34	68
Japan	720	306	163	63	48
Iceland [3]	750	361	188	67	64
Sweden	789	422	172	51	53
Norway	795	376	181	63	58
Greece	797	352	159	49	47
The Netherlands	**798**	**351**	**222**	**52**	**41**
Australia [3]	821	414	192	58	50
Canada	825	385	202	58	59
USA	842	407	193	53	62
France	842	286	206	53	84
Italy [1]	870	402	198	63	49
Denmark	880	398	226	59	67
Finland [3]	913	476	187	69	76
New Zealand [3]	923	442	214	104	53
England/Wales	930	442	215	135	36
West-Germany	931	450	210	53	62
Belgium	946	402	231	64	76
Portugal	980	421	152	65	78
Austria	983	495	209	49	86
Scotland [3]	1044	519	238	116	52
Ireland [3]	1073	544	214	146	49
Yugoslavia	1102	580	161	62	68
Poland [3]	1138	578	205	58	77
Bulgaria	1142	654	149	91	62
Romania	1211	724	143	147	70
Czechoslovakia [3]	1243	674	235	101	81
Hungary	1277	682	244	69	113

[a] Directly standardized, European standard population.

[b] In 1984, the age-standardized death rate, all causes, was 699 in Japan (and 784 in The Netherlands).

[1] 1981 [3] 1983 [4] 1984.

Data from ref. 78.

Dutch over-all mortality rates are also substantially lower than those of its immediate neighbours: West-Germany, Belgium and, across the North Sea, England and Wales. These three countries have higher death rates for Diseases of the circulatory system and Diseases of the respiratory system (with extremely high rates in England and Wales). Death rates for Malignant neoplasms are approximately the same. With regard to Accidents, poisonings and violence England and Wales is the only country with lower death rates than The Netherlands. The highest over-all mortality rates of the industrialized countries are found in Eastern Europe. High rates for Diseases of the circulatory system are the main factor.

Mortality from Malignant neoplasms has less variation at the international level than any of the other groups of causes of death mentioned in table I.9. The variation coefficient of mortality from Malignant neoplasms is only 14 %, whereas it is 25 % for mortality due to Diseases of the circulatory system, 41 % for Diseases of the respiratory system, and 25 % for Accidents, poisonings and violence. This may be due to greater internal heterogeneity of the cause-of-death group Malignant neoplasms (and averaging out of more outspoken patterns of variation for specific cancers), or to more uniform certification and coding of cancer, or to both.

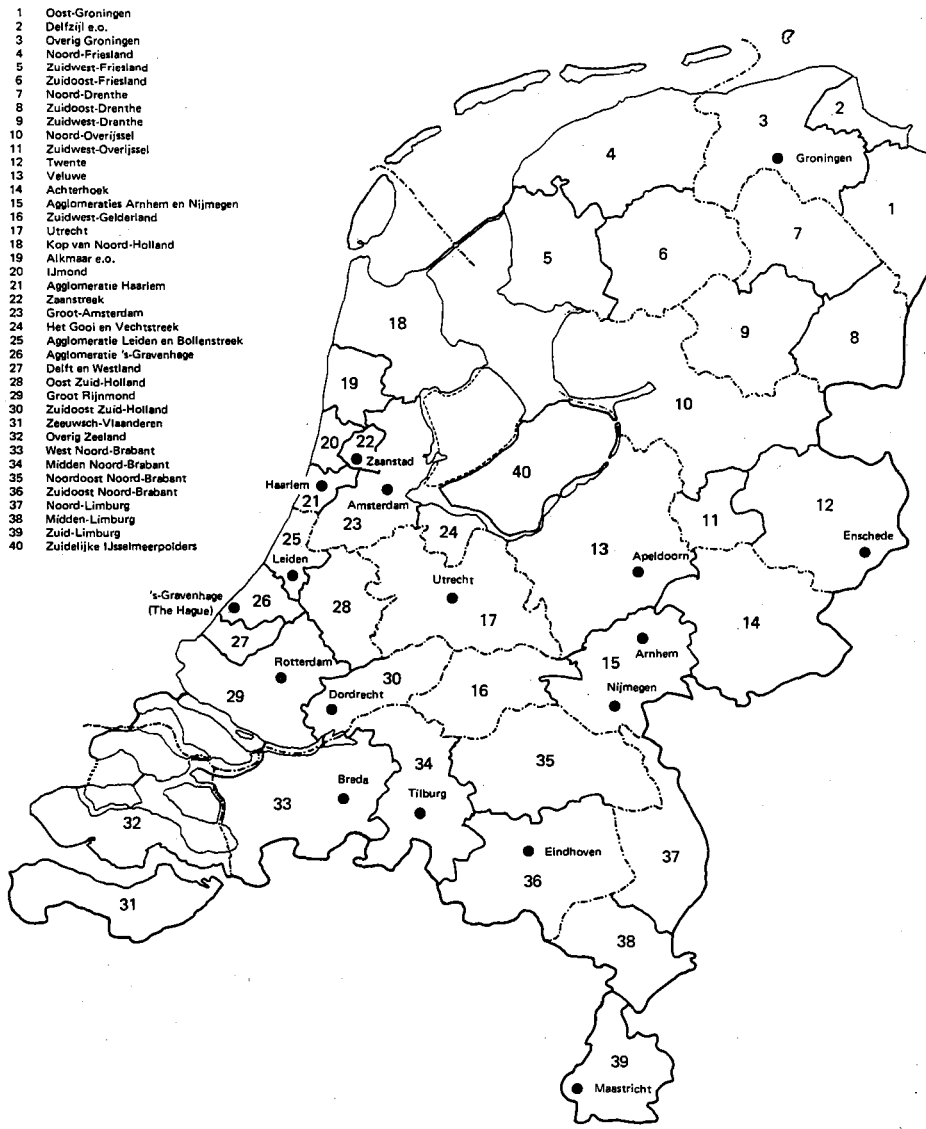
I.5.2 Regional mortality differences within The Netherlands

A note on the level of analysis

Within The Netherlands mortality rates differ between geographical areas. The level of analysis which has been chosen in most of the regional analyses to be reported in this thesis is that of the so-called COROP-regions (figure I.12). Exceptions are chapters III and VII, where provinces have been used, and chapter VIII, where COROP-regions have been amalgamated to 28 larger regions. COROP-regions have been created for statistical purposes, without any relationship to existing levels of administration, except that all COROP-regions fit within provincial boundaries.

Although a few regions are rather small for mortality analysis (cf. chapter VIII), from a point of view of statistical power the 40 COROP-regions seem a good compromise between the level of provinces (n = 11 during the study-period), and the level of e.g Economic-geographic regions (n = 129) or Nodal regions (n = 80), all in use for presentation of statistical information. COROP-regions have been formed according to a "nodal" classification principle, i.e. COROP-regions have been formed around towns acting as primary or secondary regional centres. Frequently these towns will also act as centres for health service provision, so that COROP-regions are expected to have a certain discriminatory power with regard to differences in medical care, especially hospital care.

Figure I.12 COROP-regions.



Regional variation in Total mortality, 1950-84

Regional differences in Total mortality in 1950-54, 1960-64, 1970-74 and 1980-84, standardized for differences in age- and sex-composition of the population are mapped in figure I.13. The Standardized Mortality Ratios (SMR's) have been calculated with the national mortality rates by age and sex of the same time-period as standardrates. Although some minor differences in regional pattern between males and females exist, we will ignore these for presentational purposes.

An important feature of regional mortality patterns in The Netherlands in **1980-84** is the contiguous area of relatively high mortality in the south-east (parts of the province of Gelderland, and all regions in Noord-Brabant and Limburg). Other areas with relatively high mortality are Twente, Kop van Noord-Holland, and Groot-Amsterdam. A belt of relatively low mortality stretches from the north-east into the middle and western parts of the country. The south-west, i.e. the province of Zeeland, is also characterized by low Total mortality rates.

The differences are not particularly large: the region with highest mortality, Zuid-Limburg, has an SMR of 1.09 (mortality rates are 9% above the national average), followed by Noord-Limburg with an SMR of 1.07. The region with lowest mortality, Zuidelijke IJsselmeerpolders, has an SMR of .85, followed by Overig Zeeland with an SMR of .90.

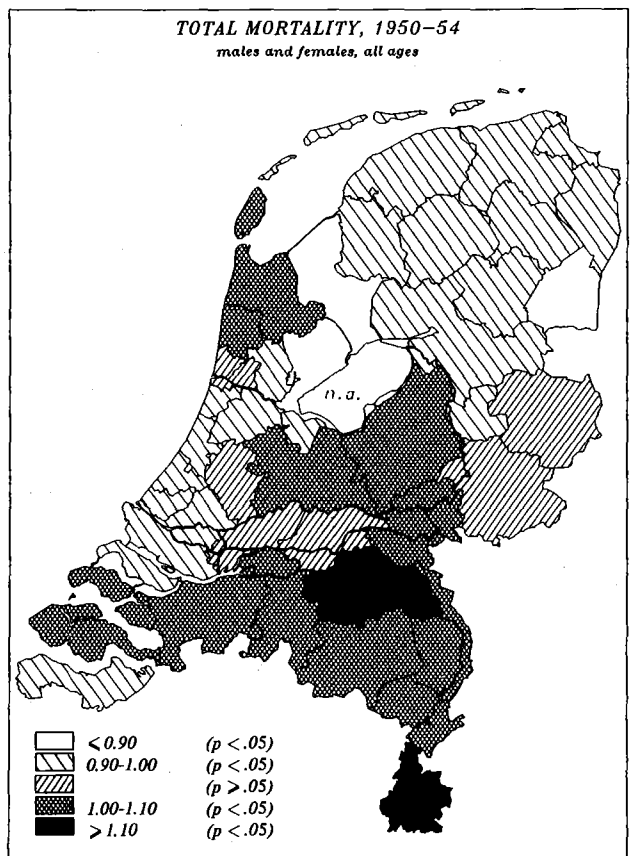
Since 1950-54 the mortality pattern has changed in a number of respects, although differences in SMR's are mostly small. A number of regions in the middle part of the country, Utrecht and Veluwe, improved their positions from statistically significantly above the national level to statistically significantly below. (The temporarily high mortality rates in Overig Zeeland in 1950-54 were caused by the flood disaster of 1953.) The mortality rate in Groot-Amsterdam, which held a favourable position in the early 1950's, is now slightly but statistically significantly above the national level. A general trend towards more unfavourable positions is also present in the north. The range of variation in 1950-54 was not so much different from that in 1980-84: the lowest SMR in 1950-54 was .90 (Zuidoost-Drenthe), the highest 1.15 (Zuid-Limburg).

Regional mortality by cause of death

As might have been expected from the dynamic evolution of cause-specific mortality over time (section I.4.2), regional cause-specific mortality patterns have also changed considerably between 1950-54 and 1980-84. We will summarize these changes in a statistical way, and then illustrate them with some maps. Finally, we will present a few maps showing recent mortality patterns for selected causes of death.

Table I.10 gives a crude impression of regional mortality patterns for the causes of death which were among the ten largest in either 1980-84 or 1950-54. Correlations between mortality (SMR's) and two variables indicating geographical position ("NORTH", or latitude, and "EAST", or longitude) are given. A positive correlation between

Figure I.13 Regional variation in age-standardized mortality (SMR's), all causes, 1950-54, 1960-64, 1970-74 and 1980-84.



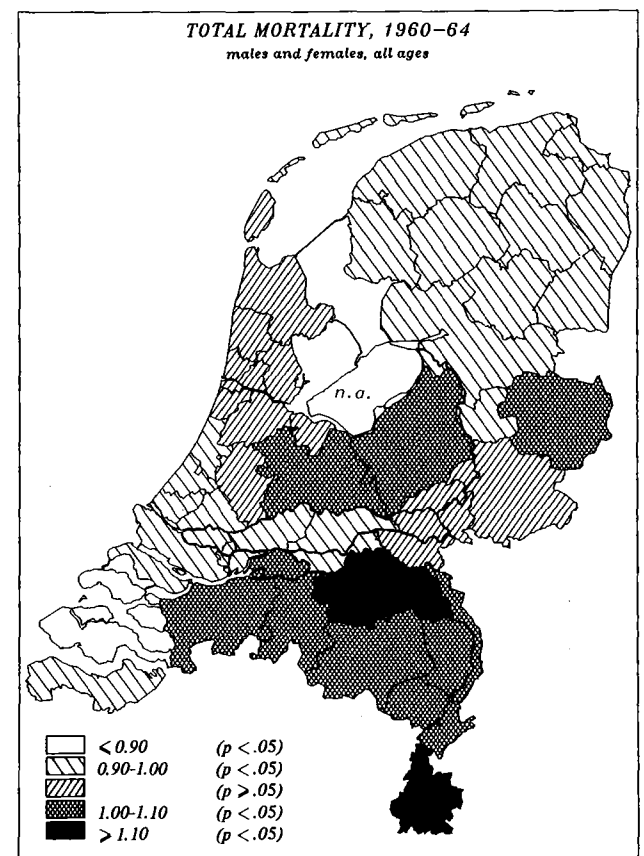
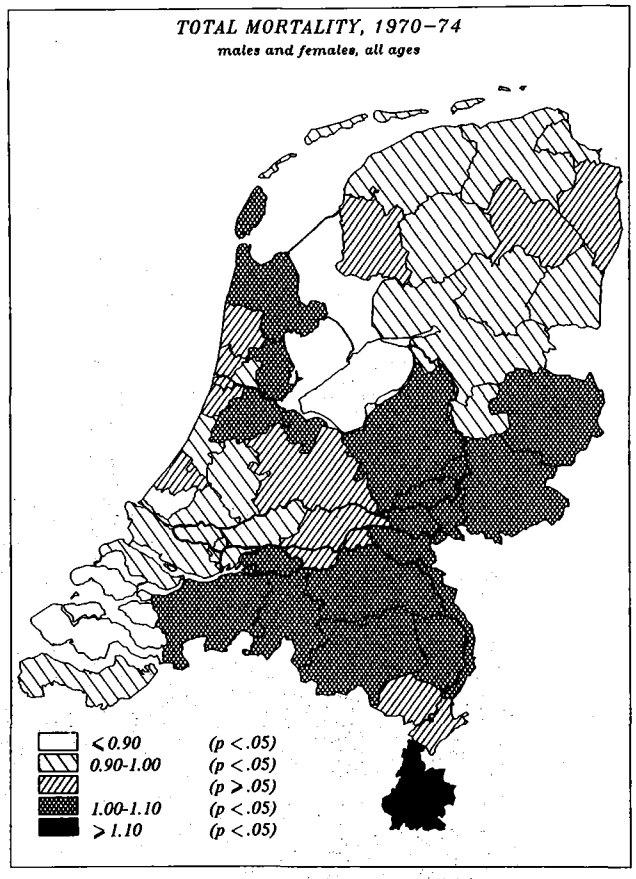


Figure I.13 (continued) Regional variation in age-standardized mortality (SMR's), all causes, 1950-54, 1960-64, 1970-74 and 1980-84.



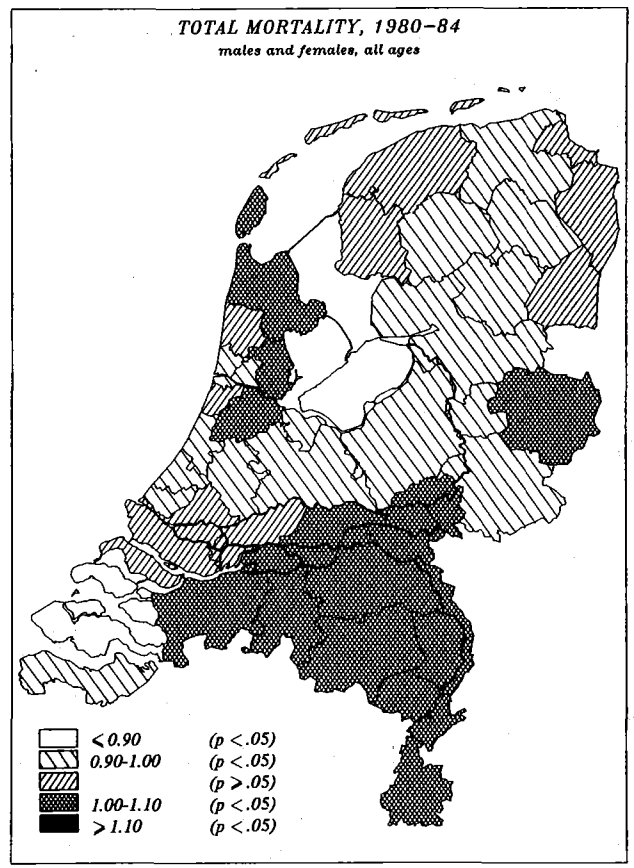


Table I.10 Correlations [a] between age-standardized mortality by cause of death and two variables indicating geographic position, 1980-84 and 1950-54.

	1980-84		1950-54	
	NORTH	EAST	NORTH	EAST
Ischemic heart disease	-.02	.55*	-.13	-.45*
Other heart disease [b]	-.20	-.03	-.48*	.06
Cerebrovascular disease	-.25	.18	-.42*	-.38*
Hypertensive disease	.13	.10	-.47*	-.43*
Diseaseses of arteries	-.57*	-.32*	-.09	.06
Cancer of stomach	.05	.07	-.00	.20
Cancer of colon	-.05	.24	.31*	-.23
Cancer of lung	-.54*	-.36*	-.23	-.53*
Cancer of breast	.16	-.18	.11	-.55*
Cancer of prostate	.55*	-.20	.19	-.37
Diabetes mellitus	-.05	.35*	-.68*	-.34*
Influenza/pneumonia	-.16	-.14	-.42*	.32*
Chronic Obstr. Pulmon. Dis.	-.34*	.20	-.04	.66*
Perinatal mortality [c]	-.07	.16	-.21	.55*
Traffic accidents	.14	.51*	.04	.32*
Non-traffic accidents	.19	.02	.32*	.03
Total mortality	-.34*	.20	-.69*	-.21

NORTH = latitude, EAST = longitude.
Significance levels (two-sided test): * $p < .05$.
[a] Product-moment correlations, unweighted (n=39).
[b] Non-ischemic, non-rheumatic heart disease.
[c] Still-births plus first week deaths per 1000 births.

mortality and "NORTH" means that mortality is generally higher in more northerly regions; a positive correlation with "EAST" that there is a gradient of mortality from west to east, with higher mortality in the east.

The last row of table I.10 shows the results for Total mortality. In 1980-84 Total mortality had a modest negative correlation with NORTH, indicating that mortality rates were generally higher in the south (cf. figure I.13). In 1950-54 the correlation between Total mortality and NORTH was more negative, probably due to lower mortality in the north-east. In 1980-84, most of the specific causes of death (10 out of 16) also had negative correlations with NORTH, and even more so in 1950-54.

In 1980-84 mortality from **Ischemic heart disease** had a rather strong west-east gradient. Between 1950-54 and 1980-84, the mortality gradient for Ischemic heart disease seems to have reversed: in 1950-54, mortality generally was higher in the west. Many other changes are apparent too, e.g. for Perinatal mortality and Chronic Obstructive Pulmonary Disease, where the strong west-east gradient of 1950-54 was lost.

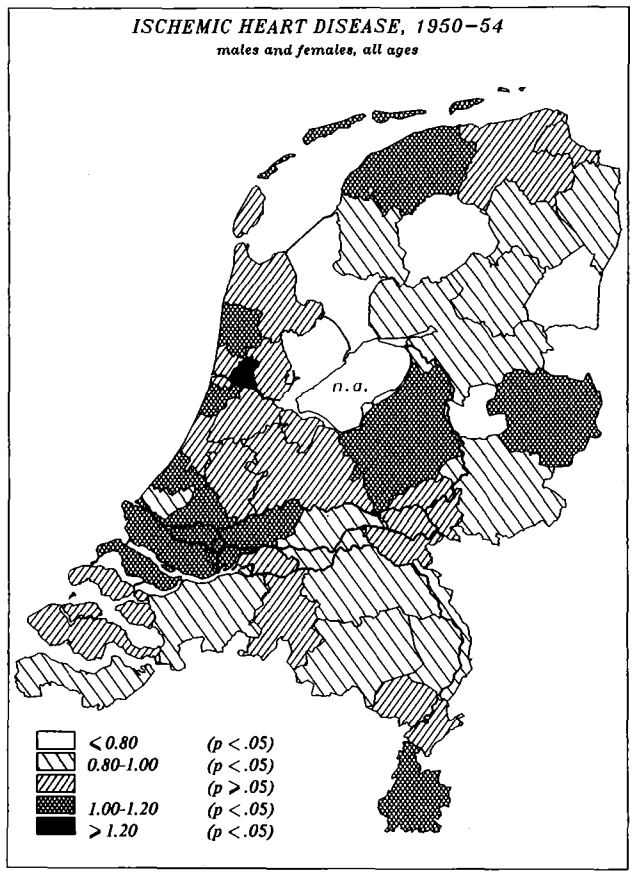
Figure I.14 illustrates the change in the regional pattern of Ischemic heart disease mortality. In 1980-84 mortality from Ischemic heart disease indeed had an important west-east gradient. Only some eastern regions have SMR's of 1.20 or more: Oost-Groningen, Midden-Limburg, and Zuid-Limburg. In 1950-54 areas with high mortality were also found in the west. Only two (industrialized) regions situated in the east, Zuid-Limburg and Twente, already had high mortality from Ischemic heart disease in 1950-54.

Different forms of cancer sometimes have completely different patterns of regional variation (figure I.15). Cancer of the stomach is a disease of rural and peripherally situated regions, both in 1950-54 and in 1980-84. Differences in mortality are particularly large for this condition. In Overig Zeeland, a region otherwise characterized by low mortality rates in 1980-84, the SMR for Cancer of the stomach is 1.61.

In 1950-54 Mortality from Cancer of the lung had a strong east-west gradient, with higher mortality in the highly urbanized regions in the western part of the country (table I.10). In 1980-84 higher than average mortality from Cancer of the lung has also spread into the south-east (figure I.15).

In 1980-84 mortality from Traffic accidents is low in the highly urbanized western part of the country, and is very high in parts of the north, the east and the south-east (figure I.16). Differences are quite large, several regions attaining SMRs of 1.40 or higher (Zuidoost-Drenthe, Achterhoek, and Noordoost-Noord-Brabant).

Figure I.14 Regional variation in age-standardized mortality from Ischemic heart disease (SMR's), 1950-54, 1960-64, 1970-74 and 1980-84.



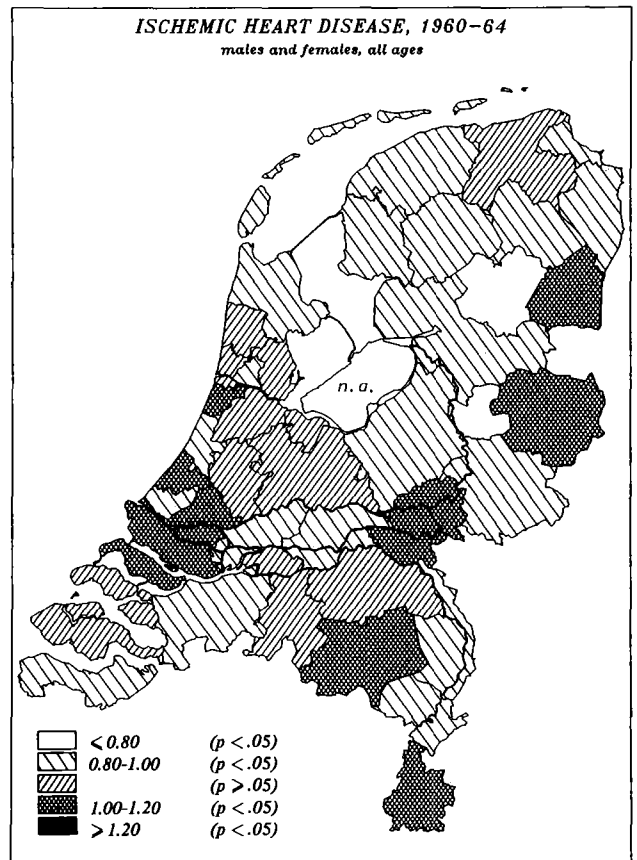
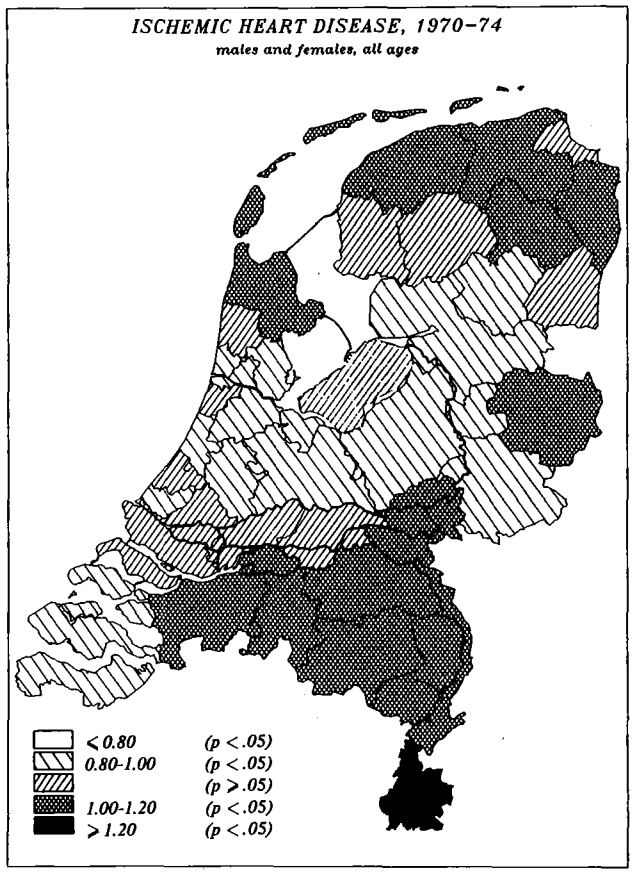


Figure I.14 (continued) Regional variation in age-standardized mortality from Ischemic heart disease (SMR's), 1950-54, 1960-64, 1970-74 and 1980-84.



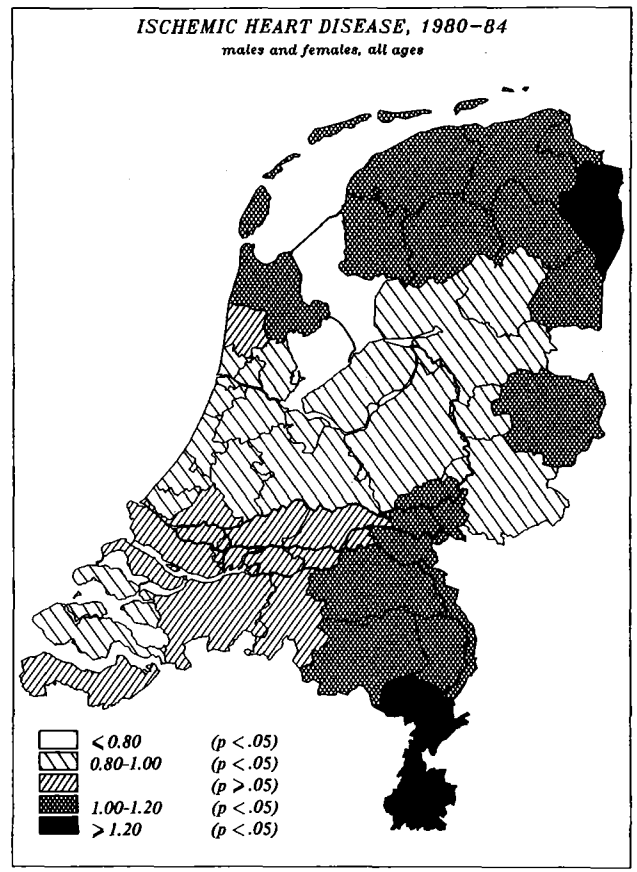
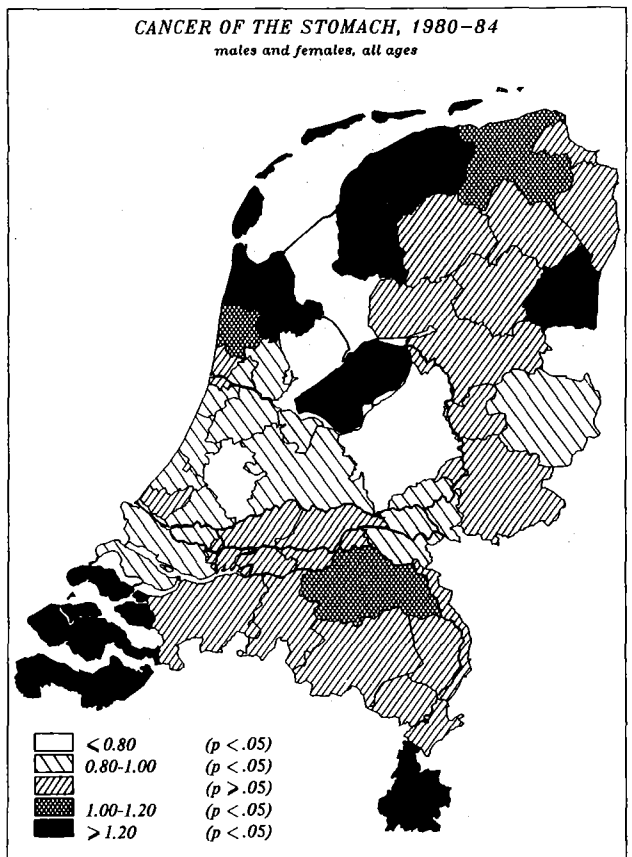


Figure I.15 Regional variation in age-standardized mortality from a number of cancers (SMR's), 1980-84.



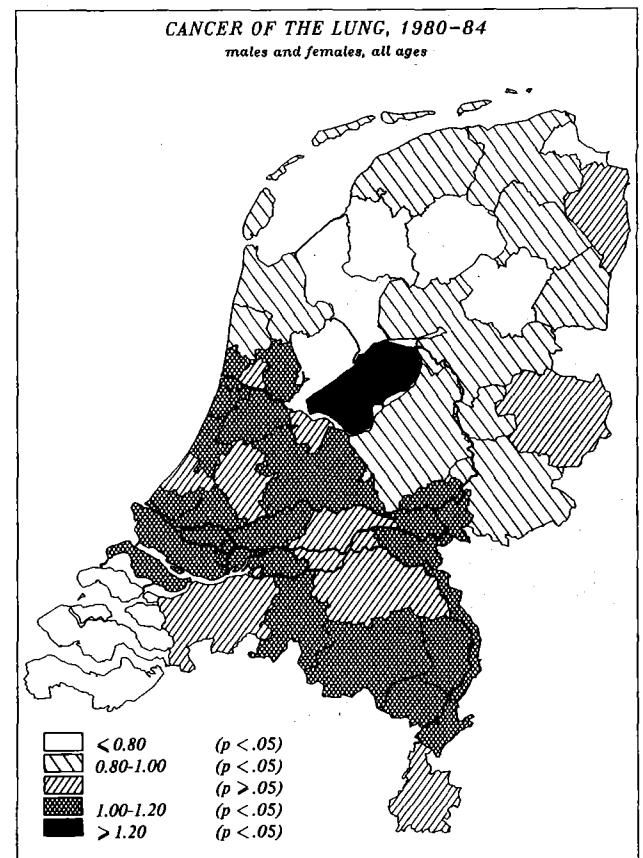
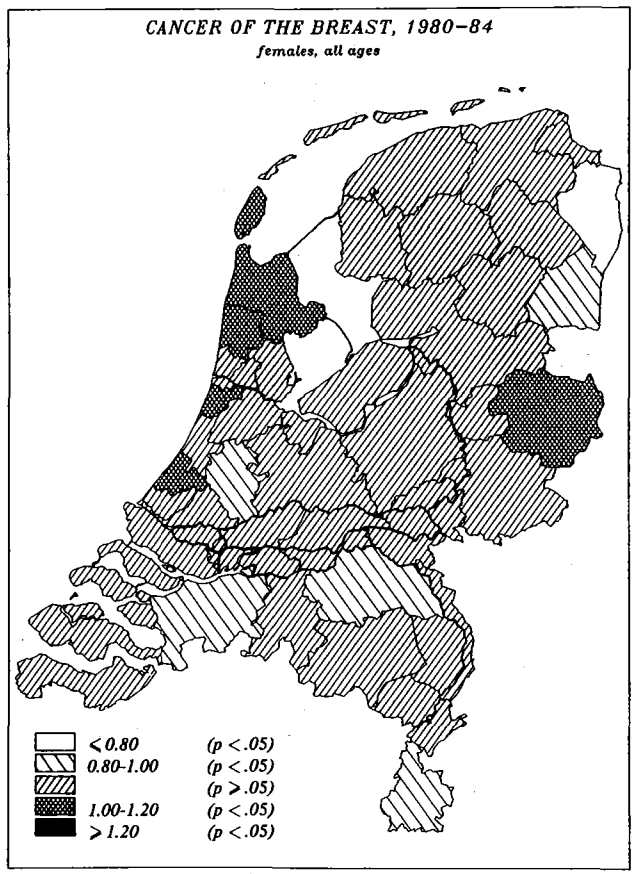


Figure I.15 (continued) Regional variation in age-standardized mortality from a number of cancers (SMR's), 1980-84.



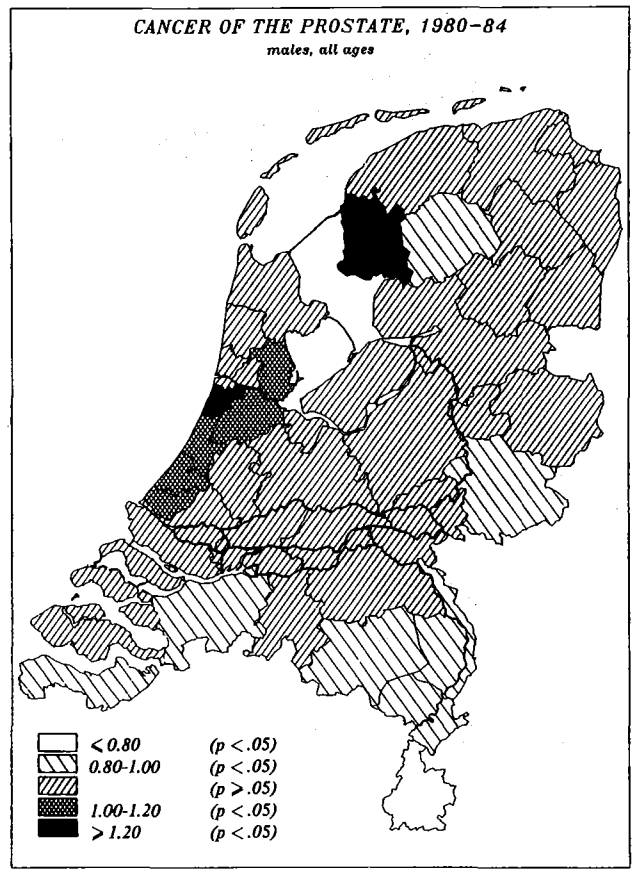
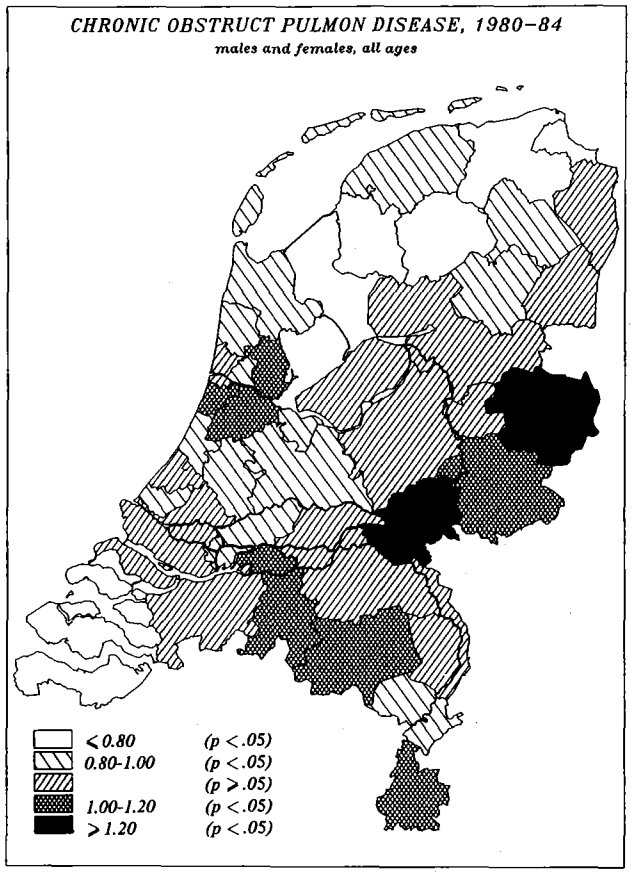
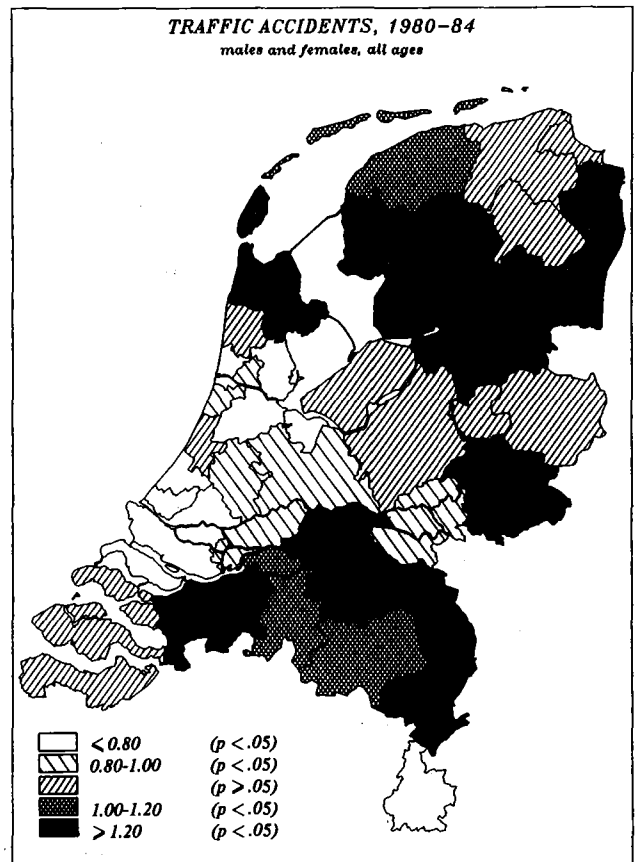


Figure I.16 Regional variation in age-standardized mortality from Chronic Obstructive Pulmonary Disease and Traffic accidents (SMR's), 1980-84.





I.5.3 Geographical variation in effectiveness of medical care?

"Medical geography"

Regional variation in mortality by cause of death has been a favourite subject for studies in "medical geography". Two broad subareas of this field of research may be distinguished: the study of the geography of health problems, and the study of the geography of health care [79, 80]. The first subarea has a long history, which has briefly been mentioned in section I.3.1, but the second subarea is of more recent origin.

If compared to the situation in a number of other countries, the study of regional mortality variations has not been flourishing in recent years in The Netherlands, and the same applies to medical geography in general [81, 82]. The publication of an "Atlas of cancer mortality", covering data from the period 1969-1978 [83], has not led to many attempts at explanation of the observed differences. There has only been a small number of studies of regional variation in mortality recently [84-87].

The studies reported in chapters VII, VIII and IX of this thesis concern regional variation in mortality from selected conditions in The Netherlands (and some other countries), and thus naturally fall in the first, or "classical", branch of medical geography. The focus, however, is on the relationship with medical care, and they may thus perhaps also be classified as studies of the geography of health care.

Regional mortality difference and the supply of medical care: literature review

As an introduction to these studies, we will briefly review some earlier work on the relationship between mortality and medical care at the regional level. These studies have led to conflicting results, mirrorring those of studies of international mortality differences and medical care [88].

In a large number of studies associations between supply of medical care and Total mortality rates were found to be not statistically significant and inconsistent (e.g. refs. 89-91). Although some degree of control for potential confounding factors, such as sociodemographic variables, was achieved in these studies, the design is generally crude.

It is only in a small number of studies that a more elaborate attempt was made to investigate the contribution of differences in medical care to the explanation of regional mortality differences. Two important studies analysed the effect of differences in medical care on perinatal mortality in **England and Wales** at the end of the 1960's [92] and in the mid-1970's [93]. In the first study, it was found that the proportion of low-birthweight infants and the birthweight-specific perinatal mortality rate were closely related to a number of sociodemographic variables. Measures of the "input" of medical care were only available on a limited scale, but specific in

character (proportions of institutional confinements in different birthweight groups), and did only explain a very small part of the variance [92].

In the second study, a large number of variables describing levels of supply and utilization of medical care was available, many of them specifically related to obstetrics and neonatal care. Variations in these characteristics showed little evidence of an effect on either the proportion of low birthweights or the birthweight-standardized perinatal mortality rate [93].

These findings contrast with the results from a number of studies concerning regional variation in mortality in the **United States**, in which the impact of differences in supply and/or use of medical care on mortality rates was investigated using econometric models [94-96]. The association between state neonatal mortality rates, corrected for differences in birthweight and socio-economic conditions, and "accessible specialist physician density" (number of obstetrician-gynecologists per 1000 births, multiplied by the proportion of hospital-born infants) was found to be negative and statistically significant in 1968 [94].

In another U.S. study of variation in mortality by state, the elasticity of the age-adjusted death rate with respect to the supply of medical services (a "production function" combining the supply of physicians, paramedical personnel, capital and drugs) was statistically significantly negative, although some other variables were far more important than medical care [95].

A recent and comprehensive analysis of age- and cause-specific mortality rates by U.S county group in 1970 found that a higher utilization of medical care was statistically significantly associated with lower mortality rates. After controlling for other factors, such as income, education, marital status, work experience, cigarette consumption, and an indicator of the prevalence of disability, greater use of medical care was associated with lower mortality in almost all age-/sex-/race-groups. In a comparison between cardiovascular diseases, cancer, and external causes, it was found that the largest estimated effect was on mortality from cardiovascular diseases [96].

Small-area variations in medical procedures

Associations between such "structural" characteristics as the supply of medical care and mortality, if any, need further explanation in the form of more specific mechanisms. One will have to suppose that the structural characteristic has an effect on the frequency, quality, or other aspect of specific medical procedures. That mortality is not insensitive to structural differences in medical care is evident from studies of the relationship between surgical volume and mortality: for many forms of surgery, postoperative mortality is lower in hospitals where that type of surgery is more frequently performed, suggesting the existence of scale effects [97, 98]. On the regional level, we know that regional variation in the frequency of certain medical

interventions can be quite large, and that this variation is related to the supply of medical care. This has best been documented for common **surgical procedures** [99, 100].

A large number of studies has highlighted the existence of variations in the frequency of certain procedures among small areas in the United States. The total rate of surgery differs as much as two-fold between areas, and the variation in specific procedures, such as tonsillectomy, hysterectomy, and prostatectomy is even much larger. While the total rate of surgery is closely related to the supply of hospital beds and physicians in the area, the wide variations in individual procedures are probably to a large extent due to differences in the style of medical practice of local physicians [99].

These small-area variations in the use of common surgical procedures are not limited to the United States, but have also been documented in other countries. Although average rates of surgery differ between the United States, England and Norway, the rank order of variability of individual procedures was remarkably similar: tonsillectomy, hemorrhoidectomy, hysterectomy and prostatectomy varied more from area to area than did appendectomy, abdominal hernia repair, or cholecystectomy. The degrees of controversy and uncertainty concerning the indications for these procedures appear to be similar among clinicians in all three countries [100]. Although there is no direct evidence, it is generally considered to be highly unlikely that such large variations in the frequency of surgical procedures can be explained by differences in the incidence or prevalence of underlying conditions [101].

Geographical variation in the rate of surgical procedures is better documented than that in other medical interventions, but there is no reason to suppose that the latter is less. A large degree of variation in the frequency of medical procedures is bound to cause variation in **effectiveness** of medical care. In the literature on small area variations in surgical procedures there has been much speculation on the possibility of associated differences in mortality. An excessively high rate of surgery might lead to more surgical deaths, simply due to the risks of operation. Although some associations between high rates of appendectomy and high rates of mortality from Appendicitis have been claimed, for example for West-Germany [102], the issue has not been resolved [103]. It is difficult to reach firm conclusions in this type of study, because high mortality rates might also indicate a high need for surgery.

Nevertheless, the existence of regional differences in the frequency of specific medical interventions shows that regional variation in effectiveness of medical care is not impossible, to say the least. The studies reported in chapters VII, VIII and IX are intended to contribute with new material to this question.

I.6 Methodological notes on the explanation of time trends and regional differences in mortality

Time trends and regional differences in mortality can be due to a number of factors, which can be summarized under three general headings (cf. ref. 104):

1) artefact
2) selection
3) causation.

I.6.1 Artefact

Mortality rates by cause of death are based on a numerator (numbers of deaths, by underlying cause of death code), and a denominator (number of person-years at risk). Changes over time, or regional differences in the process of data collection may cause artificial changes or differences in mortality rates by cause of death. In The Netherlands, the denominator can be derived from the population register, which has substantial advantages over the use of data from periodic censuses, and consequently presents practically no problems in mortality analyses.

Underregistration of Perinatal mortality

The registration of numbers of deaths can also be considered to be complete for all practical purposes. Perinatal mortality is the only important exception. Perinatal mortality is defined as the number of still-births and first-week deaths, divided by the sum of the number of still-births and live-births. In The Netherlands, current rules specify that only still-births after more than 28 weeks of gestation have to be certified; no such restriction applies to deaths within the first week among those having vital signs at birth.

A substantial degree of underregistration of perinatal deaths is likely. A recent study from Amsterdam showed that 14% of perinatal deaths occurring in hospitals had not been reported. Underregistration was more frequent for still-births and first-week deaths among children with very low birth weights (< 1000 g) and/or low gestational age (< 28 weeks), and for deaths within 24 hours (this i.e. treated as a still-birth of less than 28 weeks gestation, these difficulties are avoided [105].

Although Amsterdam does not have a particularly good record for the correct application of certification rules (vide infra), some degree of underregistration is probably present everywhere in The Netherlands. If the degree of underregistration has changed over time, or is different between regions, time trends and geographical differences in Perinatal mortality could be biased.

Changes in registration criteria for Perinatal mortality

The analysis of time trends of Perinatal mortality is complicated by another problem: a change in the rules for registration of (deaths among) live-born infants. In the period 1950-1963, live-born infants with a gestational age of less than 28 weeks, dying before certification, were not included in national birth and Perinatal mortality counts. Fortunately, the original data were preserved by the Central Bureau of Statistics, and could be included in our analyses of Perinatal mortality.

Changes over time in coding of causes of death

For other age-groups, information on the cause of death is more liable to bias. The decennial revisions of the International Classification of Diseases (ICD) are a major source of concern in analyses of mortality time trends by cause of death. The changes caused by these revisions can be complicated and even irremediable.

To bridge each of the recent revisions, the USA coding office has double-coded large numbers of death certificates, both according to the old and according to the new revision [106-108]. From the results "comparability ratios" have been calculated, indicating the degree of correspondence between a certain subgroup of diseases under the old revision and its most nearly comparable counterpart in the new revision. Large changes have been demonstrated by these studies, necessitating complicated exchanges between subgroups of three- and four-digit ICD-codes. Guided by these publications, and by an inspection for possible breaks in mortality time trends at the moment of introduction of a new ICD-revision, we composed the cause-of-death groups used in the analyses of the following chapters (see Annex 1 for the ICD-codes of these cause-of-death groups). Two examples are given as an illustration of the complicated exchanges which were sometimes necessary.

Influenza and pneumonia are coded as part of the ICD-chapter Diseases of the respiratory system in ICD-editions 8 and 9, in force from 1969-1978 and from 1979 onwards respectively. In ICD-revisions 6 and 7, however, Pneumonia of the newborn was coded with a number from the ICD-chapter Certain causes of perinatal morbidity. The "comparability ratio" of Influenza and pneumonia according to ICD-edition 8, as compared to ICD-edition 7 was calculated as 1.04, indicating that the new category contained 4% more deaths than the old one. This was mainly due to the transfer of Pneumonia of the newborn [107].

In our category of Influenza and pneumonia, Pneumonia of the newborn is included throughout the period studied (see table 1 of Annex 1). Despite these precautions, the time trend for mortality due to Influenza and pneumonia shows a break coinciding with the transition from ICD-edition 7 to ICD-edition 8, which is due to a sudden rise in mortality within a four-digit category.

Ischemic heart disease is an example of the necessity of more complicated exchanges. The comparability ratio of Ischemic heart

disease according to ICD-edition 8, relative to the most nearly comparable category Arteriosclerotic heart disease of ICD-edition 7, was 1.15. This was due to a transfer from a number of ICD-7 categories, the most important of which was Other myocardial degeneration with arteriosclerosis, which at first formed part of Other heart diseases (422.1) [107]. This ICD-7 (and -6) code-number was therefore included in our category Ischemic heart disease.

Between ICD-editions 8 and 9 again important changes took place. The comparability ratio of Ischemic heart disease according to ICD-edition 9, relative to the same category in ICD-edition 8, was 0.88. This was due in great part to the separation of Cardiovascular disease, unspecified (ICD-9 429.2), from Ischemic heart disease as defined in ICD-edition 8 [108]. Consequently, we retained this ICD-9 code-number in our category Ischaemic heart disease.

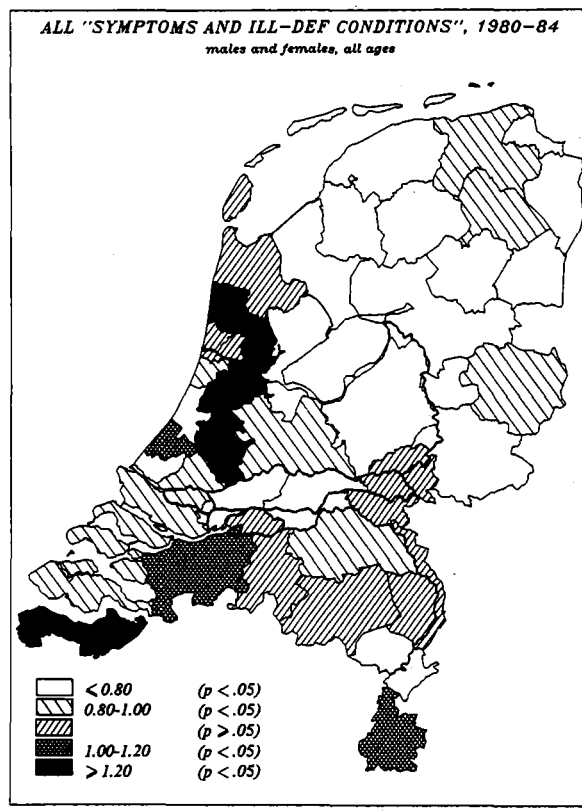
Not all problems could be solved. Mortality from Asthma, for example, shows important breaks between ICD-editions 7 and 8, and between ICD-editions 8 and 9, which could only be "repaired" by adding Asthma to other Chronic Obstructive Lung Diseases. This precluded a separate analysis of this condition, which is a pity from the point of view of medical care effectiveness.

Regional differences in cause-of-death certification

Regional differences in recording practices may also induce artificial differences in mortality by cause of death. The main issue here is the possibility of geographical variation in diagnostic procedures and death certification practices. The fact that physicians tend to settle not far from the university where they obtained their degree [109], suggests that systematic differences of this kind are possible. (In some countries, e.g. in Belgium, coding of death certificates is decentralized, and coding differences may explain some of the observed mortality patterns by cause of death. In The Netherlands, there is only one, national, coding office.).

Research into the possible effects of regional variation in diagnostic and certification practices on observed mortality differences is very scarce. In two studies of the regional variation of Cerebrovascular disease mortality, in which death certificate information was compared with the clinical records, it was concluded that there was no evidence that differences in diagnosis or certification could account for the observed variation in mortality rates [110, 111]. In a study in which written case histories were distributed to doctors in different British regions, who then completed death certificates on the basis of the available information, no significant differences in certification were found [112].

Figure I.17 Regional variation in age-standardized mortality from "Symptoms and ill-defined conditions" (SMRs), 1980-84.



Nevertheless, figure I.17 does suggest at least some differences in certification of causes of death between regions in The Netherlands. Several regions have age-standardized mortality rates more than 20% above the national average for the cause-of-death category "Symptoms and ill-defined conditions" (cf. section I.2.2). The Standardized Mortality Ratio (SMR) for Alkmaar is 1.28, for Groot-Amsterdam 1.99, for Oost-Zuid-Holland 1.31, and for Zeeuws-Vlaanderen 2.16. The percentage of all deaths classified in this category is 7.1 in Groot-Amsterdam, and 8.0 in Zeeuws-Vlaanderen, whereas the average for all regions (except the 4 mentioned above) is 3.1.

The high rates in Groot-Amsterdam are due to the fact that coding by the Central Bureau of Statistics is hampered by inadequacies in notification. More frequently than elsewhere, no death certificate reaches the Central Bureau of Statistics, or the death certificate is filled out very incompletely or even not at all. If the name of the certifying doctor is also lacking on the certificate, it is impossible

certifying doctor is also lacking on the certificate, it is impossible to obtain supplementary information (Van der Vlist, personal communication, august 1987). The high rates in Zeeuws-Vlaanderen may be due to the fact that many patients receive hospital care in Belgium, which may cause administrative problems in obtaining information on the cause of death.

If all causes of death have an approximately equal chance of contributing to the excess of "Symptoms and ill-defined conditions", all cause-specific SMR's of Groot-Amsterdam are underestimated with appr. 0.04 (7.1 - 3.1 = 4.0), and those of Zeeuws-Vlaanderen with appr. 0.05 (8.0 - 3.1 = 4.9). This appears to be a rather minor problem in view of the observed range of SMR-values for these regions, and is not likely to bias associations between mortality and other regional characteristics.

I.6.2 Selection

Selection on the basis of health-related mobility is another possible explanation of time trends or regional differences in mortality. If the health status of individuals (c.q. their risk of dying) acts as a selection criterion with regard to movement into and out of the aggregate units which are being compared, a difference in average health status between these groups arises.

Health-related selection has been shown to contribute to differences in mortality between socio-economic groups, upward social mobility being associated with better health [113]; between marital status groups, getting married being associated with better health [114]; and between emigrants and those that stayed behind [115, 116].

Whether health-related selection may be of influence on regional mortality patterns is an issue which has been largely neglected. Migration between regions usually forms systematic patterns for longer periods of time. On the average, those who migrate over longer distances are likely to be more healthy than those who do not. (Short-distance migration may more frequently be an effect of ill-health, for example in the case of admission to a nursing home.) Regions with sustained net emigration or immigration might thus differ in mortality solely as an effect of population flows.

In a study from England and Wales it was found that those who had migrated between regions in the 5 years before the census had considerably lower SMR's than the national average. This effect was most pronounced in the first years after migration, which is consistent with regional migrants excluding people whose ill health prevented them moving. Those migrating from the north and west to the south and east had lower SMR's than those who stayed behind (but those who migrated from the south and east to the north and west had higher mortality than those who stayed behind !). Because of the low level of interregional migration, however, health-related mobility does not make a noticeable contribution to observed mortality patterns between

regions in England and Wales (high mortality in the north and west, low mortality in the south and east) [117].

In The Netherlands, the population of the newly formed region of Zuidelijke IJsselmeer Polders has increased from little more than 10.000 to more than 100.000 from 1969 to 1984. The complete population thus consists of recent (interregional) immigrants. This is probably one of the factors explaining the rather low mortality rates in this region (cf. section I.5.2).

I.6.3 Causation

Whereas an explanation of the "selection" type emphasizes an effect of health on the aggregate unit to which one belongs, a "causal" explanation specifies an effect of a characteristic of the unit on the health of its members. The issue of confounding here becomes important. Any other factor which is associated with both mortality and the characteristic of interest can act as a confounder.

In a study of infectious disease mortality in two time-periods, one before the introduction of antibiotics and another thereafter, any factor which is associated with mortality and happens to be present more in one of the two subperiods, will act as a confounder of the relationship between infectious disease mortality and antibiotics. If mortality rates of regions with a different level of supply of medical care are compared, any other factor, influencing mortality, which in its geographic distribution happens to be associated with medical care supply will bias the effect estimate. Multiple regression analysis can be used to correct for the influence of possible confounding factors.

Standardization of mortality rates

One potential confounder, age (and sex), is often removed in the descriptive phase of a mortality study through standardization. In many of the analyses reported in this thesis, the Standardized Mortality Ratio (SMR) has been employed. The SMR is the ratio of the observed number of deaths, and the number of deaths that would have been expected if the mortality rates by age (and sex) of a certain "standard" population had applied in the "index" population. Just as every other summary measure of differences in mortality rates, the calculation of an SMR assumes that the ratio of mortality rates is the same for all age-(and sex-)groups [118].

The calculation of an SMR is a form of "indirect" standardization; in "direct" standardization, the age-specific mortality rates of the index population are applied to the age-(and sex-)structure of a standard population. There has been much debate on the appropriateness of direct vs. indirect standardization, but in practice, the direct and indirect methods mostly give largely identical results [119]. An important advantage of the SMR is that it has a smaller standard error, because the observed number of deaths,

for all ages combined, of an index population is less subject to chance fluctuation than a series of age-specific mortality rates, which may be based on rather small numbers [120].

Some of the analyses to be reported in the next chapters make use of a more flexible approach to removing the influence of differences in age- and sex-structure between populations: loglinear regression analysis (see method sections of chapters IV, VI and IX).

I.6.4 "Ecological analysis"

The search for causal explanations of mortality differences over time and across geographical units is complicated by the fact that the analyses deal with aggregate units. Associations between mortality rates and other characteristics of aggregate units are not necessarily identical with associations at the individual level. Figure I.18 provides a diagrammatic representation of the general form that an explanation of mortality differences at the aggregate level might take.

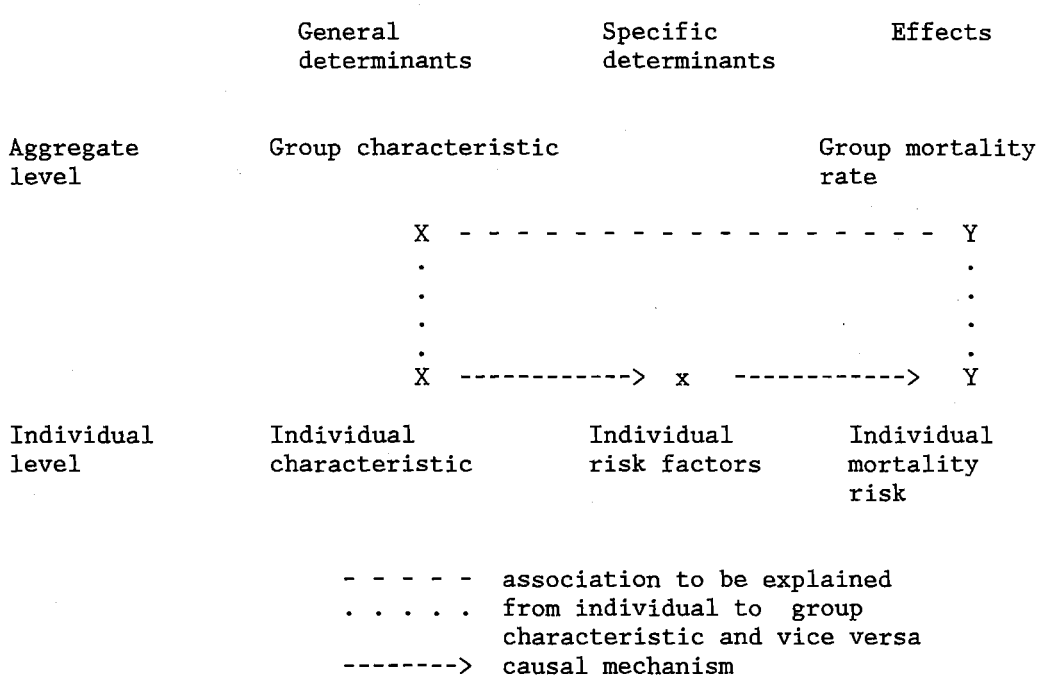
It also visualises that fact that studies of possible explanations of time trends and regional differences in mortality frequently use independent variables of a rather general nature, such as the supply of medical care or socio-economic status. Any association between such a general characteristic and mortality requires further explanation in the form of more specific causal mechanisms. Is the effect on incidence or case fatality? Which attributes of the characteristic under study cause the effect on mortality?

A "group characteristic", for example the hospital bed density of a region, can only affect mortality rates through: - an effect on the accessibility of hospital care for the individual ("individual characteristic"); - an effect of accessibility on the probability of a correct application of efficacious medical procedures in the case the individual falls ill ("individual risk factor", more appropriately "individual protection factor" in this example); - and an effect of medical procedures on the risk of dying from the disease ("individual mortality risk"). It is the aggregate of these individual mortality risks that we are measuring in conventional mortality analyses.

"Ecological fallacy"

Empirical studies which involve the group as the unit of analysis, are frequently called "ecological" studies in sociology and epidemiology (note that in section I.4.3 the term "ecology" was used in a different sense). The primary analytic feature of ecological studies is that we do not know the joint distribution of the study factor(s) and disease (i.e. mortality risk) within each unit of analysis. This study design is therefore sometimes called an "incomplete" design, and is generally regarded as inferior for inferring individual level relationships, due to the problem of "ecological fallacy" [121].

Figure I.18 Schematic representation of the general structure of causal explanations of mortality differences at aggregate level.



In the studies reported in the next chapters, however, the aggregate level of analysis is not a surrogate for the individual level of analysis. The studies aim at inferring the effect of medical care on mortality at population level. As in all studies of the effectiveness of medical care, aggregate effects are the focus of analysis, and the assessment of discrepancies between effects at individual and aggregate level are an integral part of evaluation efforts.

The cause of discrepancies between individual and aggregate associations was first systematically discussed by Robinson, who showed that the effect of aggregation on correlation coefficients generally is to exaggerate them. The correlation between two phenomena is generally higher at aggregate level than it is at individual level, due to the averaging out of individual variations [122].

Regression coefficients, although less subject to change across different levels of analysis, will however also differ if the "ecological" variable (the average value of the individual characteristic for an entire aggregate unit) measures a different "underlying construct" than the same variable does at the individual level [123, 124].

This situation may arise, for example, when the aggregate effect of a characteristic is different from that of the same characteristic on individuals, due to so-called "structural" effects. A not too hypothetical example could be a structural effect of unemployment. The effect of unemployment as evaluated at an aggregate level, e.g. by a comparison of neighbourhoods, may differ from that found in studies of individuals, if high average unemployment rates have collective effects on these neighbourhoods. The effect of unemployment on health may be greater in neighbourhoods with a higher average rate of unemployment, due to the disrupting effects of such a high rate on the community. The "group characteristic" of the average unemployment rate then measures something else (or more) than the corresponding "individual characteristic".

If one is interested in individual level relationships, the study of aggregate associations between unemployment and e.g. mortality rates would be subject to "ecological fallacy", i.c. "positive ecological bias", causing overestimation of the effect of unemployment on health. If one is interested in the effect of unemployment on communities, there is no bias.

Structural effects may also be important in the explanation of aggregate associations between the level of supply of medical care and mortality (section X.3.2).

I.6.5 Further problems in the explanation of differences in mortality at an aggregate level [125]

1) The effects of changing scale [126]

The theory of the "ecological fallacy" states that aggregate level

relationships are not necessarily identical to individual level relationships. This can be generalized to apply to studies at different levels of aggregation.

The scale at which the analysis of geographical variation takes place can exert a strong influence on the results. In general, variables have less variance at larger levels of aggregation; this is because extremes are averaged out. The reduction of between-group variance with higher levels of aggregation is likely not to be the same for all variables of interest. More specifically, in a geographical analysis the grouping will frequently not be based on different levels of the dependent variable (mortality), but on different levels of one or more of the independent variables (such as socio-economic characteristics). Between-group variance in mortality (and other variables which are not related to the grouping) will decrease with higher levels of aggregation; between-group variance in the independent variables on which the grouping took place may remain the same or decrease less rapidly.

These scale effects may be critical to the interpretation of research results. A higher level of aggregation will tend to inflate correlation coefficients between mortality and independent variables on which the grouping took place (although regression coefficients should be roughly comparable between levels). On the other hand, aggregation may result in a reduction of the variance of other independent variables of interest, and in a certain dilution of the effect. Consequently, the association between mortality and these other variables may never reach statistical significance.

2) Spatial autocorrelation and other simple patterns of geographical variation [127, 128]

Most statistical analyses of the association between mortality and other characteristics at the level of geographical units assume that each unit provides an independent estimate of the dependent variable, mortality. The geographical areas often are, however, far from independent, as a result of their proximity. If it is possible to explain this non-independence in terms of covariates which are also spatially correlated, no problem arises, but mostly the similarity of contiguous areas cannot be fully accounted for by known covariates. The error term in multiple regression models will be spatially correlated, and failure to allow for this may result in overestimates of the significance of relationships.

A frequent specific form of spatial autocorrelation is the existence of linear (or non-linear) gradients of mortality across geographical space. The existence of such a gradient, for example a simple pattern of increasing mortality from north to south, will induce spatial autocorrelation, and treating separate regions as independent units may be misleading (cf. chapter VIII).

3) Multicollinearity

Independent variables tend to be more highly correlated with each

other at an aggregate level than they are at the individual level. The resulting "multicollinearity" makes it difficult to isolate the effects of separate variables on mortality, especially when the number of aggregate units is small.

4) Latency and mobility

Frequently there is a considerable time-lag between exposure to a harmful (or protective) agent and the emergence of disease, let alone the moment of dying. The current distribution of mortality thus reflects the distribution of causative factors at an earlier moment in time.

Although time-lags, if known, can be incorporated in the analysis, complications may still arise from the fact that migration occurs. The exposure to mortality risks of people dying in a certain area has not only occurred earlier in time, but may also partially have occurred elsewhere. Apart from migration, mobility in general will tend to reduce associations between mortality and other regional characteristics. Mortality from Traffic accidents, for example, may partially have occurred outside the domiciliary region of the deceased. Use of health care services in neighbouring regions may compensate for any deficiencies in the region where the patient actually lives.

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II Certification and coding of two underlying causes of death in The Netherlands and other countries of the European Community

II.1 Introduction

The interpretation of mortality statistics by cause of death is usually complicated by uncertainties about possible biases arising from differences in certification and coding of causes of death. Data are reported from two studies which were attempts to obtain detailed information on certification and coding practices for a selection of causes of death in countries of the European Community. The method employed consisted of the distribution of sets of case histories to samples of doctors in the participating countries, who filled in death certificates for these cases. The certificates were subsequently coded by national coding offices and a World Health Organization (WHO) reference center.

In order to understand what is being measured in this type of study it is necessary briefly to recall that the production of the numerical code representing the so-called "underlying cause of death" involves three steps: the diagnostic process; completion of a death certificate; and coding of the statements on the death certificate, according to the rules and classifications provided by the International Classification of Diseases (ICD) [1]. In each of these steps, an error can take a patient with a (true) underlying cause of death "X" to a code number representing another cause of death. Conversely, patients with other (true) underlying causes of death can erroneously receive the codenumber for "X". This is illustrated in table II.1.

Table II.1 Schematic representation of possible relationships between "true" underlying causes of death and observed underlying-cause-of-death codes.

		Underlying-cause-of-death code	
		Diagnosis X	All other
True underlying cause of death	Diagnosis X	a	b
	All other	c	d

$$\text{Detection fraction} = \frac{a}{a+b} \qquad \text{Confirmation fraction} = \frac{a}{a+c}$$

The schematic representation in table II.1 suggests two simple measures for the validity of an observed number of deaths from cause "X":

- the "detection fraction": the proportion of deaths with a true underlying cause of death X which actually receives the code number for X;
- the "confirmation fraction": the proportion of deaths receiving the code number for X which actually died from X.

Although both detection and confirmation fractions should ideally be 100%, for epidemiological purposes it is generally sufficient that there are no important differences in detection and confirmation fractions between the "times, places and persons" that are being compared. Studies in which sets of case histories are used are, essentially, an attempt to estimate (differences in) detection fractions in so far as these are determined by the second and third steps mentioned above (certification and coding, respectively).

Some of the results from the two European Community studies on death certification and coding have already been published [2,3], concentrating on the overall pattern of differences. This pattern, which will be briefly summarized here, raised important questions on the exact nature and the relative contribution of differences in certification and coding practices. A detailed analysis of the frequency of specific errors in certification, and of the contribution of certification and coding differences is presented for The Netherlands.

II.2 Methods

In both studies, of which the first was carried out in 1981 and the

second in 1983/84, sets of 10 case histories were sent to (different) samples of doctors in the then 8 member countries (excluding Luxembourg) of the European Community. In most countries, including The Netherlands, names of doctors were extracted from random samples of death certificates received by national coding offices in a given month. In France and Italy, many certificates were unsigned or names were illegible and untraceable from the central offices. In Italy, therefore, a random sample of certifying doctors was obtained from regional registry offices stratified by town size. In France, it was possible to obtain a list of doctors from a single region, to eliminate doctors unlikely to complete certificates and to draw a random sample from the remainder. In Germany, data protection policies operate which prevent access to death certificates. German doctors were therefore selected from registers of practising physicians in the Berlin (West) region only. The German sample of the first study included general practitioners and internists but excluded physicians in hospitals; the sample of the second study consisted of hospital internists.

Although more case histories were sent out, it is with a limited number of mutually comparable case histories that this article is concerned (table II.2). The other case histories were descriptions of a variety of other conditions of which the results cannot easily be summarized. The 6 case histories selected from the first study all concern a death from Chronic Obstructive Pulmonary Disease (COPD) - treated here as one diagnostic entity, although the ICD distinguishes between chronic bronchitis, emphysema, and asthma. The 5 case histories selected from the second study all concern a death from a specific form of cancer. Numbers 1 to 4 were rather straightforward; number 5 required a choice between 2 causes of death (of which a specific form of cancer was the right one).

The type of information presented in these case histories was the diagnostic information which would normally be available to hospital doctors or general practitioners certifying the death of a patient in their practice. Each doctor was asked to complete a death certificate, as used in his/her own country, as if certifying an actual death. An incentive of (the equivalent of) £ 20 was offered.

Reasonable response rates were obtained (table II.3). The objective was to obtain approximately 50 doctors in each country. Response percentages were between 60% and 92% in the first study (excluding West-Germany), and between 56% and 86% in the second study. For The Netherlands, response percentages were 67% and 65%, respectively.

Completed certificates were sent for coding at national (in some countries: regional) coding offices, which treated the certificates according to practices in force at the time of the study. Finally, English translations of all certificates were sent to a World Health Organisation reference centre (which happened to be the English Office of Population Censuses and Surveys (OPCS)) for coding according to uniform criteria.

Table II.2 Case histories used for further analysis.

Study	Case history:	Intended 3-digit ICD-9 codes
I. 1.	Chronic Obstructive Pulmonary Disease, dies during acute infection	One of: 490-493,496
2.	Chronic Obstructive Pulmonary Disease, progressieve dyspnoea	One of: 490-493,496
3.	Chronic Obstructive Pulmonary Disease, dies during pneumonia	One of: 490-493,496
4.	Chronic Obstructive Pulmonary Disease, dies during acute severe dyspnoea	One of: 490-493,496
5.	Chronic Obstructive Pulmonary Disease, progressive dyspnoea	One of: 490-493,496
6.	Chronic Obstructive Pulmonary Disease, cor pulmonale	One of: 490-493,496
II. 1.	Bladder cancer, dies during pneumonia	188
2.	Stomach cancer, dies during pneumonia	151
3.	Cancer of cervix uteri, dies in cachexia	180
4.	Malignant melanoma, dies during pneumonia	172
5.	Pleural mesothelioma, dies after pulmonary embolism	163

Table II.3 Response percentages.

Study	Den-mark	W-Ger-many	Engl./ Wales	Ire-land	Nether-lands	Bel-gium	France	Italy	All
I Complete re-plies (n)	69	20	61	53	48	50	45	50	396
Response (%)	92	25	85	66	67	63	60	63	65
II Complete re-plies (n)	50	39	50	63	51	50	53	50	406
Response (%)	83	71	74	63	65	86	56	70	70

Table II.4 Estimates of detection fractions (x100%) for Chronic Obstructive Pulmonary Disease and a group of 5 specific cancers.

Study	Den-mark	W-Ger-many	Engl./ Wales	Ire-land	Nether-lands	Bel-gium	France	Italy	All
I COPD	90	90	86	92	91	72	85	60	83
(idem, after reference center coding)	(85)	(88)	(86)	(91)	(84)	(85)	(69)	(63)	(82)
II 5 cancers	85	90	80	74	94	83	84	82	83
(idem, after reference center coding)	(76)	(83)	(79)	(79)	(85)	(84)	(78)	(87)	(81)

Note: For definition of detection fractions see table II.1; for codes used in determining detection fractions see table II.2.
Some of the material on which this table is based has been published in another form by Kelson and Heller [2] and Kelson and Farebrother [3].

II.3 Results

After certification and coding by national coding offices, on average 83% of all cases received a correct underlying-cause-of-death code, both in the first and in the second study (table II.4). There were, however, important differences between countries. In the first study, the degree of variation between countries was larger than in the second study. Italy and Belgium had distinctly lower than average detection fractions in the first study. Reference center coding improved the detection fractions of Belgium and, although to a lesser extent, Italy, which suggests that the differences are completely (Belgium) or partly (Italy) explained by differences in coding. Ireland had a lower-than-average detection fraction in the second study, which improved only slightly after reference center coding.

An interesting finding in both the first and the second study was that reference center coding reduced the detection fractions for Denmark, West-Germany, The Netherlands and France (table II.4). This suggests that certification practices are less reliable than the resulting national codes suggest, and that strict adherence to the rules for selection of the underlying cause of death by the reference center more clearly exposes the errors in certification.

Table II.5 Errors on death certificates, The Netherlands, first study (6 cases of COPD)

Type of error (according to doctors' entry)	All certificates		Certificates receiving "intended" code from national coding office	Certificates receiving "intended" code from reference center
	n	(%)	n	n
False diagnosis in part I	21	(7)	7	3
Only symptoms, complications etc. in part I and II	13	(5)	6	1
Correct diagnosis in part II	13	(5)	12	4
Correct diagnosis in part I, but false sequence*	12	(4)	12	11
No error: correct diagnosis in part I, correct sequence	228	(79)	225	221
Total number of certificates	287+	(100)	225	221

Note: For "intended" codes, see table II.2.

* Not corrected by stating the interval between onset and death.

\+ One certificate was returned empty.

In order to gain more insight into these overall results, we classified the Dutch certificates according to the most serious certification error occurring on it. The Dutch death certificate is a translation, with minor modifications, of the internationally agreed medical certificate of cause of death [1]. Part I contains the sequence of events going back from the "direct cause of death" under 1a to the "underlying cause of death" under 1c. Part II should contain other conditions contributing to death which are not causally related to the underlying cause of death.

The types of error considered for counting were, in order of diminishing seriousness:

- a false diagnosis in part I of the certificate; examples of this were "lung fibrosis" instead of COPD and "lung cancer" instead of mesothelioma;
- no diagnosis is mentioned on the certificate, only signs and symptoms or complications; examples of this were "cor pulmonale" without mention of the underlying COPD, and "pneumonia" without mention of the underlying cancer;
- the correct diagnosis is on the certificate but in part II, "not causally related"; a frequent example of this in the first study

Table II.6 Errors on death certificates, The Netherlands, second study (5 different cases of cancer)

Type of error (according to doctors' entry)	All certificates		Certificates receiving "intended" code from national coding office	Certificates receiving "intended" code from reference center
	n	(%)	n	n
False diagnosis in part I	3	(1)	1	0
Only symptoms, complications etc. in part I and II	3	(1)	0	0
Correct diagnosis in part II	37	(14)	27	26
Correct diagnosis in part I, but false sequence*	9	(4)	9	7
No error: correct diagnosis in part I, correct sequence	203	(80)	202	183
All certificates	255	(100)	239	216

Note: For "intended" codes, see table II.2.

* Not corrected by stating the interval between onset and death.

was "pneumonia" in part I and COPD in part II;

- the correct diagnosis is in part I but in a wrong sequence, not corrected by stating the interval between onset and death; an example of this was "cancer of the cervix" "due to cachexia".

While the first of these four types of error is clearly an error of diagnosis, the other three will more often be errors of certification (arising when completing the death certificate).

In both studies, about 20% of Dutch certificates showed one of these errors (tables II.5 and II.6). In the first study (table II.5) "a false diagnosis in part I" was more frequent than each of the errors of certification sensu stricto, but added together these were present on not less than 14% of the certificates. Remarkably, many certificates, although in error, received an "intended" (i.e. corresponding to the case histories) underlying-cause-of-death code from the national coding office. Part of this "correction" resulted from application of WHO coding rules, as is evident from the fact that reference center coding also assigned an "intended" code to some of these certificates, especially in cases of a false sequence in part I. Another part of this "correction", however, must be the result of

strictly national coding practices. These coding practices apparently involve a lot of (re-)interpretation of the statements on the death certificate.

In the second study (table II.6), by far the most frequent type of error was "correct diagnosis in part II". This was about as often corrected by the national coding office as by the reference center. Now some discrepancies occurred for certificates which had been placed (by the authors) in the category "no error". These discrepancies were largely due to the fact that certificates for case history no. 5, stating "malignant mesothelioma" without mention of the site, were coded by the reference center as "malignant neoplasm, site unspecified", and by the Dutch coding office as "malignant neoplasm of the pleura". This again is evidence of the interpretative efforts of the Dutch coding office.

II.4 Discussion

A recent bibliography of cause-of death validation studies published between 1958 and 1980 [4] reveals that the use of sets of case histories to study differences in certification practices is relatively infrequent. Only one study employing this method was published during this period [5], studying differences in certification of certain causes of death between the United States, the United Kingdom, and Norway. Another study from the same period studied international differences in coding by supplying sets of completed certificates to national coding offices [6]. In 1982 the results of a study employing case histories were published [7], investigating regional differences in certification practices within England and Wales.

The studies reported here were unique in the fact that certification and coding practices were studied at the same time. The studies mentioned above either studied differences in certification between countries [5] or differences in coding [6].

It is evident from our studies that certification and coding practices should preferably be studied in combination. Some differences in certification will be compensated for in the process of coding. The fairly high Dutch detection fractions found for two (groups of) underlying causes of death result from reasonable performance in certification and a coding process adapted to the frequency of some certification errors. Nevertheless, the over-all results, after national coding, suggest that differences in certification and coding could in some cases be an important determinant of international mortality differences by cause of death.

The main limitation of case history studies is that it is very difficult to ensure external validity. Neither choice and content of the case histories nor respondents' behaviour are necessarily representative of "real life". Nevertheless, the studies reported here

have indirectly demonstrated a certain degree of external validity. Some of the discrepancies between countries found in the first study have been shown to correspond to observed mortality patterns [2], and the discrepancies found with the case history of cancer of the cervix in the second study have been shown to correspond to some observed mortality differences for this condition [3].

The frequency of certain certification errors found in our detailed analysis of the Dutch material could give some clues for improvement. The frequency of a correct diagnosis in part II of the certificate instead of in part I suggests that some doctors in The Netherlands do not quite understand the meaning of the phrase: "other significant conditions contributing to the death, but not related to the disease or condition causing it" (which has a rather tortuous Dutch translation). Clarifying the objectives of this part of the certificate seems necessary.

In the meantime, further international standardization of coding practices would not necessarily improve the validity of Dutch cause of death statistics.

II.5 Summary

Differences in certification and coding of causes of death between countries of the European Community were studied by sending sets of case histories to samples of certifying physicians. Completed certificates were coded by national coding offices and by a WHO reference center. Detection fractions ranged from 60 to 92% in a first study (concerning cases of Chronic Obstructive Pulmonary Disease) and from 80 to 94% in a second study (concerning cases of cancer).

A detailed analysis of the findings for The Netherlands, which performed very well in both studies, reveals a substantial frequency of errors in certification (as opposed to errors in diagnosis). Comparison of national and reference center coding suggests that the Dutch coding process is to a certain extent adapted to the frequency of these certification errors, leading to deviations from WHO coding rules. It is concluded that certification and coding practices should be studied together, and that further international standardization of coding practices will not necessarily improve the validity of national cause of death statistics.

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Members of the Working Party: Belgium: M. Kornitzer, Y.C. Yernault; Denmark: J. Mosbech, J. Mosbech; France: R. Pariente, F. Neukirch; Germany: D. Borgers, H. Huckauf; Ireland: G. Dean, E. Shelley; Italy: A. Marinoni, G. Casali, M. Grassi; The Netherlands: J.P. Mackenbach, W.M.J. van Duyne; United Kingdom: W.W. Holland (chairman), R.F. Heller, M.C. Kelson, M. Farebrother, J. Goldschmidt.

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III Health care policy and regional epidemiology

– international comparisons and a case-study from The Netherlands

III.1 Introduction

In The Netherlands, as in many other countries, the uncontrolled expansion of the health care sector during the 1960's gave rise to growing state intervention [1,2]. Extensive legislative efforts in the 1970's produced several acts, including the important Health Care Services Act [3]. This Act (to be built into a largely analogous but wider Health Care and Social Services Act in the 1980's) specifies the increased responsibilities of the national, regional ("provincial") and local (municipal) authorities vis-à-vis the health care system.

The existence of regional and local levels of health care policy is not a uniquely Dutch phenomenon. On the regional level, England has its Regional Health Authorities and Scotland its Health Boards, whereas in Denmark, Norway and Sweden "amtskommunene", "fylkeskommunene" and "landstinge" respectively have responsibilities for the health care sector.

The emergence of these levels of health care policy raises two important questions:

- which criteria should be used for the allocation of financial, material and manpower resources to administrative units?
- which criteria should be used for the development and evaluation of regional and local health care policy?

As the goals of health care provision are related to the health status of the population, it is only logical that several countries have witnessed attempts to introduce measures of the health status of the population into both resource allocation formulas and procedures for developing and evaluating regional health care policy. We will discuss these attempts in section III.3 of this paper, after a specification of the epidemiological information that could be relevant in these contexts (section III.2). The Netherlands are trying to keep up with the developments in neighboring countries with a number

of studies, recently performed or still in progress [4-7]. The results of one of these studies, focussing on the question of allocation of finance to regions, will be presented in section III.4. As a result of these and other epidemiologically inspired studies there is an increasing awareness among health care policy-makers that the health status of the population is influenced by many other factors than health care alone. In The Netherlands, as well as in other countries, this has led to some propaganda for "health planning" instead of "health care planning", involving other policy areas than health care policy alone [8, 9]. For the sake of simplicity, however, this paper concentrates on health care policy.

III.2 Epidemiological information for the planning and evaluation of health care services

III.2.1 "Need"

A specification of the type of information that could be relevant for the planning of health care services necessarily begins with a short elaboration on the concept of "need" for health care services, a classic example of health care terminology not settled in its meaning [10]. In Bradshaw's taxonomy [11] a distinction has been made between, among other things, "normative need", defined by some authority, and "felt need", perceived by the individual who is supposed to have the need. One form of normative need is "professionally defined need", and it is here that epidemiology could make a valuable contribution.

An appropriate use of measures of need requires a functional perspective of health care [12, 13]. For the four basic functions of health care, the planning of services could be related to the following measures of (professionally defined) need:
- primary and secondary prevention: the incidence and prevalence of risk factors and early stages of disease;
- medical treatment: the incidence and prevalence of disease;
- (physical and social) rehabilitation: the incidence and prevalence of disabilities and handicaps (in the sense of the International Classification of Impairments, Disabilities and Handicaps (ICIDH)) ;
- (boarding and nursing) care: the incidence and prevalence of restrictions in Activities of Daily Living (ADL).

Usually, consideration of measures of need serves a policy of "equal access" to services. The distribution principle of equal access is popular in welfare states, because, to a large extent, it avoids having to judge the effectiveness of services [14]. The amount and nature of resources to be spent per unit of need (or "need equivalent" in the terminology of Donabedian [15]) is then simply equal to the "usual" amount of the "usual resources. This procedure does not in itself guarantee equality of result, in the sense of an equal distri-

bution of some kind of outcome measure, e.g. mortality, across the population. Some authors therefore argue that one should consider the effectiveness of services in assigning need equivalents [16, 17].

III.2.2 "Outcome"

In the evaluation of health care services outcome measures play an important role. What has been said about need also applies to "outcome", if we use this term in its ordinary sense of "final consequence": death, disease, disability/handicap, discomfort, dissatisfaction [18-20]. There is again a distinction between professionally defined outcomes (death, disease, disability) and the analogues of felt need (discomfort, dissatisfaction), with professionally defined outcomes more the domain of epidemiologists.

Again, each function of health care has its own set of relevant outcome measures:

- primary and secondary prevention: the incidence of preventable conditions;
- medical treatment: the duration of treatable disease; the incidence of avoidable consequences of disease (e.g. a more severe stage of the disease, disability, mortality);
- (physical and social) rehabilitation: the duration of modifiable disabilities/handicaps; the incidence of avoidable consequences of disabilities/handicaps (e.g. permanent handicaps in the field of work or Activities of Daily Living);
- (boarding and nursing) care: the incidence of avoidable consequences of ADL-restrictions (e.g. decubitus ulcers, inadequate food intake).

Interestingly, then, a need for medical treatment could be an outcome of prevention, a need for care could be an outcome of medical treatment, and so forth.

III.2.3 Necessary disaggregation

With a variation on Lind and Wiseman's dimensions of priority setting [21], there are at least three important dimensions for the measurement of needs and outcomes: type of health problem, e.g. disease group (HP); population subgroup (POP); geographical subunit (GEO). Without a split-up of measures of need and outcome into recognizable health problems it is very difficult to decide upon need equivalents or to look for deficiencies in the health care system. Ideally, the dimensions of population subgroup (age, sex, marital status, some indicator of socio-economic status, ethnic group) and geographical subunit (regions, subunits of regions) should be combined with the dimension of health problem (POPxHP and GEOxHP; table III.1).

Table III.1 Availability of information on mortality, hospital admissions, disability benefits and health interview responses by "provincie" in The Netherlands, according to three dimensions of disaggregation

	Mortality	Hospital admissions	Disability benefits	Health interview survey
HP	+	+	+	(+)
POPxHP	± [a]	- [b]	- [b]	(+)
GEOxHP	+	+	+	(+)

HP = according to health problem; POP = according to population subgroups;
GEO = according to geographical subunits within "provincies".
( ) Small number problems.
[a] Only age, sex, marital status, nationality.
[b] Only age, sex.

III.3 Some British and Scandinavian examples of the use of regional epidemiological information for health care policy

III.3.1 Using regional epidemiological information in resource allocation formulas

The most widely discussed example of the use of regional epidemiological information for resource allocation purposes is the formula for the allocation of finance to regional, district and area health authorities in England as developed by the Resource Allocation Working Party (RAWP)[22]. This so-called RAWP-formula is a serious attempt to base the geographical distribution of financial resources available for the National Health Service on the distribution of need in the population, instead of on historical patterns of supply. "Equal access" is the distribution principle. Apart from a number of demographic characteristics (size of the population, composition by age, sex and marital status), the formula employs Standardized Mortality Ratios (SMRs) by cause of death as measures ("proxies") of differences in "morbidity" between regional populations. Mortality data by cause of death are generally considered to be the most promising source of information available [22-24], as will be illustrated in more detail for the Dutch situation in section II.4.2.

The need equivalent assigned to these measures of need is the "usual" amount of the "usual" resources. For instance, if the regional SMR for a given disease category is 1.10, presumably indicating a 10% higher incidence or prevalence in this region as compared to the national population, the region receives 10% more funds from

the national budget currently spent on this disease category.

The RAWP-formula has served as a source of inspiration for several other countries, both inside and outside the United Kingdom. Scotland [25], Wales [26], Northern Ireland [27], New Zealand [28] and New South Wales (Australia) [29] developed analogous formulas, though all substituting condition-specific mortality by Total mortality. Norway's formulas for the allocation of revenues from the social insurance system (covering health care expenditure) to regions and municipalities also employ standardized mortality (all causes) as a measure of need [30, 31].

Although the principle for assigning need equivalents in these countries is essentially the same as in England, table III.2 shows some cracks in the reasoning. The table mentions the approximate "weights" assigned to standardized mortality data in the different formulas. A weight of 100% corresponds to the English position explained above. In Scotland the weights are smaller, though still considerable, due to the fact that the use of SMRs is limited to mortality and health care expenditure in the age groups 0-64 years. In Norway the weights are smaller still, due to a completely different structure of the formula. In New South Wales the weight assigned to the SMRs for the allocation of resources for in-patient hospital services is bigger than in England, because the budget includes the psychiatric hospitals.

Table III.2 "Weights" assigned to standardized mortality data in formulas for the allocation of financial resources to regions.

	In-patient hospital services [a]	Out- and day-patient hospital services [a]	Community health services
England	100	100	100
Scotland	ca 65	ca 82	ca 78
Wales	100	100	100
Northern Ireland	100	100	100
New Zealand	100	100	100
New South Wales	> 100 [b]	> 100 [b]	100
Norway	ca 7	n.a.	ca 5

[a] Excluding obstetrics and hospitals for mentally ill and mentally handicapped.
[b] Including obstetrics and hospitals for mentally ill.
Data from refs. [22] and [25-31].

The publication and adoption of the RAWP-formula, both in 1976, have given rise to a lot of criticism, especially concerning its use of mortality data. Earlier in this paper, mortality data were introduced as possible outcome measures for a specific function of health care, but in RAWP- and related formulas mortality data are used as general measures of need. This conceptual leap is valid only if regional mortality differences reflect differences in incidence or prevalence over a wide range of conditions (i.e. if case fatality differences are small in comparison with incidence and prevalence differences) and of their consequences in terms of e.g disabilities/ handicaps. Many critics of the RAWP-formula have expressed doubts about the identification of mortality with morbidity [32-38]. A general conclusion from the debate, which has been reviewed elsewhere [39], would be that the use of mortality data in this formula is based on insufficiently validated assumptions.

III.3.2 Using epidemiological information for regional health care policy

Although RAWP meant its formula to be used for the allocation of the regional budget to (the since abolished areas and) districts too, this has been criticized on both statistical [40, 41] and philosophical grounds [42, 43]. As one critic wrote: "At lower levels of population aggregation real resource considerations operate too powerfully for abstract formulae to exert much influence. (...) National uniformity as a desirable aim in itself must be abandoned and the development of different methods of health care by different health authorities be encouraged" [43]. A fresh consideration of measures of need and outcome at this level, in the light of regional circumstances, seems necessary. Again, mortality data have been tried first. In the United Kingdom, a number of causes of death has been selected as potential outcome indicators for use at the regional level [44]. The possibilities and limitations of this study of "avoidable mortality" are now being investigated. This includes the development of a framework for studying the causes of regional differences in avoidable mortality [45].

A Swedish group studied the availability of regional epidemiological information [24], and decided to start with a "regional mortality display", indicating areas for further action or study. The same group has recently published a number of guidelines for regional mortality analyses [46]. The results of these studies are intended to be used for developing regional health policy, not merely regional health care policy.

III.4 A Dutch case-study

III.4.1 The Dutch "provincie" and the health care system

The Dutch "provincie" is an administrative layer between the municipal and national authorities, covering populations ranging from 350.000 to 3.100.000 people. A predecessor of the Health Care Services Act, the Hospital Services Act, already charged the provincial authorities with certain responsibilities for the health care system, viz. the task of drawing up 4-year-plans for the hospital services (acute general hospitals, specialized hospitals, nursing homes, psychiatric hospitals, institutions for the mentally handicapped). The Health Care Services Act now extends this plan-making activity to all levels of administration and the whole health care sector. The following distribution of responsibilities is envisaged: the national authorities will draw up a plan for a limited number of services with national importance, the provincial authorities for the hospital services, and the municipal authorities for first echelon services (family practitioners, midwives, district nurses etc.) and public health services.

The distribution of the nationally available resources across provinces will be regulated by a number of central guidelines. These guidelines regarding the use of financial, material and manpower resources will act as constraints on the planning activities by provinces. The Ministry of Welfare, Public Health and Culture has expressed the wish that these guidelines will reflect the need for health care services. (The distribution of resources within provinces will be dealt with in the provincial plans, which will form the basis for granting licences (necessary to build or run a service) and certifications (necessary to receive funds from public services)).

The intention to use measures of need can at least in part be realized by using demographic information (size and composition of the population served) and relating this to the volume of services (as in the commonly used bed/population ratios), but this was felt as being insufficient.

III.4.2 What use could be made of routinely collected epidemiological information?

In The Netherlands, there are four general sources from which data can be made available at the regional (i.e. provincial) level: mortality statistics; hospital admission statistics; disability benefit statistics, based on a registration of new cases eligible for (long-term) disability benefits; the Health Interview Survey, conducted in a yearly sample (n=ca.10.000) of the non-institutionalized population. Unfortunately, there is no national cancer registry in The Netherlands, whereas one other potentially important form of information, short-term sickness benefits, cannot be made available on the pro-

vincial level because place of residence is unrecorded. Apart from these general sources, there is a small number of sources more limited in scope (e.g. notifications of infectious diseases, traffic accidents) which this paper does not consider.

Table III.1 summarizes the availability of information from the aforementioned four general sources. Apart from the lack of information for specific population subgroups there are other important problems. As indicated in table III.1, the small number of respondents in the Health Interview Survey renders an analysis by health problem difficult, even at the provincial level. Disability benefit statistics suffer from the problem that the size and composition of the population-at-risk (those insured) are not exactly known, and that labour market conditions exert a powerful influence on disability benefit rates. Hospital statistics strongly reflect existing health care supply. Our conclusion, in line with the British and Scandinavian experience, was, that mortality data by cause of death are a relatively promising source of regional epidemiological information for health care policy purposes.

In view of the doubts surrounding their interpretation (see section III.3) we decided to limit the use of mortality data to disease groups displaying a certain degree of correspondence between mortality on the one hand, and hospital admissions and incidence of cases eligible for disability benefits on the other hand. A correspondence in the pattern of provincial differences between mortality and one or both of the other measures will be interpreted as evidence for the conclusion that mortality differences do reflect incidence or prevalence differences, a prerequisite for the use of mortality data as measures of need.

III.4.3 Provincial differences in disease-specific mortality, hospital admissions and disability benefits

The disability benefit data were restricted to males, because the female population at risk for this type of work disability is only a small part of the total female population. For males and females separately we selected diagnoses for which, on the national level, at least 250 deaths, hospital admissions or new disability cases respectively had been registered in the two years 1977 and 1978. Standardized Mortality Ratios were calculated with national age-specific rates as the standard. For the sake of convenience, we will use the terms Standardized Mortality Ratios (SMRs), Standardized Hospitalization Ratios (SHRs) and Standardized Disability Incidence Ratios (SDIRs). We calculated Spearman rankorder correlations between SMRs and SHRs (males and females separately) and between SMRs and SDIRs (males only).

Provincial SMRs, SHRs and SDIRs for all causes combined are presented in table III.3. The southwestern province of Zeeland appears to occupy a favorable position in all the data, for males as well as for females. The southern provinces of Noord-Brabant and Limburg occupy unfavorable positions. For the other provinces the pattern is not very consistent, especially for the northern province of Groningen, which has low total SHRs, low to average SMRs, and very high SDIRs.

Table III.3 Standardized Mortality Ratios (SMRs), Standardized Hospitalization Ratios (SHRs) and Standardized Disability Incidence Ratios (SDIRs), all causes, by "provincie" and sex (1977/1978 combined).

	SMR (males)	SMR (females)	SHR (males)	SHR (females)	SDIR (males)
Groningen	0.98	0.98	0.83*	0.85*	1.36*
Friesland	0.95*	0.99	0.90*	0.95*	1.04*
Drenthe	0.94*	0.98	0.83*	0.88*	1.22*
Overijssel	0.99	1.02	0.93*	0.95*	1.06*
Gelderland	1.00	1.02*	1.00	1.00	1.03*
Utrecht	1.00	0.99	1.05*	1.05*	1.02*
Noord-Holland	1.00	0.97*	1.04*	1.05*	1.03*
Zuid-Holland	0.99	0.97*	0.96*	0.96*	0.74*
Zeeland	0.88*	0.92*	0.95*	0.94*	0.73*
Noord-Brabant	1.04*	1.08*	1.10*	1.04*	1.04*
Limburg	1.11*	1.09*	1.11*	1.11*	1.44*
Chi-square	205.31	172.45	8119.05	6245.52	6816.85

* $p < .05$

Table III.4 Diagnosis-specific rank order correlations between Standardized Mortality Ratios (SMRs) and Standardized Hospitalization Ratios (SHRs), and between SMRs and Standardized Disability Incidence Ratios (SDIRs).

ICD-chapter		Diagnosis	ICD-8	SMRs vs SHRs males	SMRs vs SHRs females	SMRs vs SDIRs males
II	1.	Stomach cancer	151	0.82*	0.78*	-
	2.	Intestinal cancer	152-153	0.58*	(0.52)	0.13
	3.	Rectum cancer	154	(0.10)	(0.52)	-
	4.	Cancer respiratory organs	160-163	0.42	0.84*	-0.44
	5.	Breast cancer	174	-	0.41	-
	6.	Cervix uteri cancer	180	n.a.	0.60*	n.a.
	7.	Prostate cancer	185	(0.23)	n.a.	-
	8.	Bladder cancer	188	0.51	(0.07)	-
	9.	Leukemia	204-207	0.35	(0.12)	-
III	10.	Diabetes mellitus	250	(0.53)	0.44	(-0.10)
IV	11.	Paralysis agitans	342	(0.60)*	0.24	(0.32)
VII	12.	Hypertension	400-404	(-0.05)	0.26	(-0.07)
	13.	Ischemic heart disease	410-414	0.13	-0.12	0.84*
	14.	Symptomatic heart disease	427	0.79*	0.81*	0.23
	15.	Cerebrovascular disease	430-438	0.71*	0.49	0.05
	16.	Arteriosclerosis	440	0.75*	0.58*	0.62*
	17.	Arterial embolism/thrombosis	444	(0.67)*	0.66*	-
	18.	Pulmon. embolism/infarction	450	0.32	0.42	-
	19.	Phlebitis/thromb./embolism	451-453	(0.14)	(0.66)*	(0.51)
VIII	20.	Pneumonia and influenza	470-474, 480-486	0.68*	0.59*	-
	21.	Chronic obstr. pulm. dis.	490-493	0.79*	0.13	0.08
IX	22.	Ulcer of stomach/duodenum	531-533	(0.05)	(0.60)*	(0.30)
	23.	Liver cirrhosis	571	(0.40)	(0.61)*	(0.70)*
	24.	Cholelithiasis/-cystitis	574-575	0.30	(-0.16)	-
X	25.	Nephritis/nephrosis	580-584	(-0.06)	(0.10)	(-0.17)
	26.	Infection of kidney/bladder	590-595	(-0.05)	(-0.41)	-
	27.	Hyperplasia of prostate	600	(-0.03)	n.a.	-
XVII	28.	Fracture of verebral column and trunk	N805-809	0.51	(0.21)	0.14
	29.	Fracture of neck of femur	N820	(0.85)*	0.73*	(0.43)
	30.	Intracranial injury	N850-854	0.20	-0.23	0.42
All causes			all	0.86*	0.45	0.18

* Rank order correlation coefficient significantly different from 0 ($p < .05$)

\- Number of deaths, hospital admissions or new cases of disability benefits < 250 (1977+1978)

( ) No statistically significant provincial differences (Chi-square test, $p > 0.05$) for one or both of the data

Rankorder correlations between SMRs and SHRs and between SMRs and SDIRs, for the selected conditions, are presented in table III.4. As could be expected on the basis of the patterns for total SMRs, SHRs and SDIRs, correspondence between SMRs and SHRs is generally better than that between SMRs and SDIRs. The correspondence between SMRs and SHRs is, however, not simply a matter of one underlying pattern. The positive correlations between mortality and hospital admissions for Stomach cancer (no. 1 in table III.4), for instance, are the result of a pattern completely different from the one seen in Total mortality and hospital admissions. Here, Groningen, Friesland and Zeeland have the highest rates (cf. table III.3).

Although there is some correspondence between SMRs and SHRs, there are also important exceptions. For both males and females there is a conspicuous lack of agreement between mortality and hospital admissions for Ischemic heart disease (no. 13 in table III.4). Inspection of the individual SMRs and SHRs (not shown in the tables) suggests that the main reason is that the high SMRs for Ischemic heart disease observed in Groningen for both males and females are not matched by high SHRs.

III.5 Discussion

Correspondence between mortality by cause of death and two other routinely available, equally doubtful indicators of morbidity is not a very powerful test of the validity of mortality as an indicator for regional morbidity differences. Nevertheless, a general identification of regional mortality with morbidity or need for a range of health problems, as assumed in RAWP- and related formulas, does require some support, and that certainly is not what this study provides. For example the lack of correspondence between mortality and hospital admissions for Ischemic heart disease could be due to a number of factors. The hospital data could be biased by differences in certification of diagnostic information but so could the mortality data (for a bibliography on the validity of cause of death information see ref. 47). There could be differences in admission policy, leading to a larger number of patients being treated outside hospital in Groningen, but also case fatality for this condition could be greater in Groningen.

In view of these findings, and the uncertainties expressed in the literature, we conclude that in the context of the formal allocation of resources to administrative units, confidence in mortality data by cause of death as indicators of morbidity is not enough to assign weights comparable to those used in RAWP- and related formulas [4, 5]. If one does want to allow for higher or lower total mortality in certain regions, in addition to differences in size and composition of the population, a more judicious procedure would be to

analyse case by case to check whether a higher or lower mortality for the two or three largest cause-of-death groups can be found back in health care consumption patterns, and to take the proportions of these groups of conditions in different health care sectors as weights in an allocation formula. On the other hand, in the context of developing and evaluating regional health care policy, where a more flexible approach is possible, mortality data by cause of death can be very useful by providing a focus on population health status and a starting point for further studies. Expressed more formally, mortality data will be useful in a stage of hypothesis formation, implying that other more powerful studies will follow to test and refine the hypotheses [48]. This will almost automatically broaden the scope from health care policy to health policy.

III.6 Epilogue

Throughout this paper, we have tried to specify information requirements from the health care policy viewpoint. Available information on the health status of regional populations offers only modest perspectives for a need- and outcome-based health care policy. It is, however, equally important to specify policy requirements from an epidemiological viewpoint. Two requirements are obvious when one wishes to focus health care policy on population health status:
- the interpretation of regional epidemiological information requires intensive study (cf. the frameworks for regional mortality analysis developed in the United Kingdom [45] and Sweden [46]). This can only be realized if epidemiological expertise is at the disposition of the relevant authorities;
- if the results of these studies are to be useful, the scope of possible actions open to the authority in question should not be very limited. As shown in section III.2.2, a careful consideration of measures of need and outcome always involves more than one link in the chain of health care utilization. The restriction of the responsibilities of the provincial authorities in The Netherlands to hospital services is thus an important structural limitation to the development of an epidemiological approach towards regional health care policy.

III.7 Summary

In a number of countries, regional levels of administration have assumed responsibilities for the health care sector. This paper presents a specification of epidemiological information that could be relevant for health care policy towards and within regions, as well as

a review of a number of British and Scandinavian attempts at using routinely available mortality data for these purposes. A Dutch case-study is then presented. To determine whether regional mortality data by cause of death can be used as indicators of need for health care, and consequently be used as criteria for the allocation of financial resources, the correspondence between provincial disease-specific mortality, hospital admissions and new cases of disability benefits was analyzed. The findings were not convincing: for a number of diseases a reasonable correspondence between mortality and hospital admissions could be shown; for other conditions however, especially Ischemic heart disease, none at all. It is concluded that:
- in the context of the formal allocation of health care resources to administrative units, a strong confidence in mortality data by cause of death is unwarranted;
- in a (broader) context of developing and evaluating regional health care policy mortality data by cause of death can be useful for providing a focus on population health status and a starting point for further studies.

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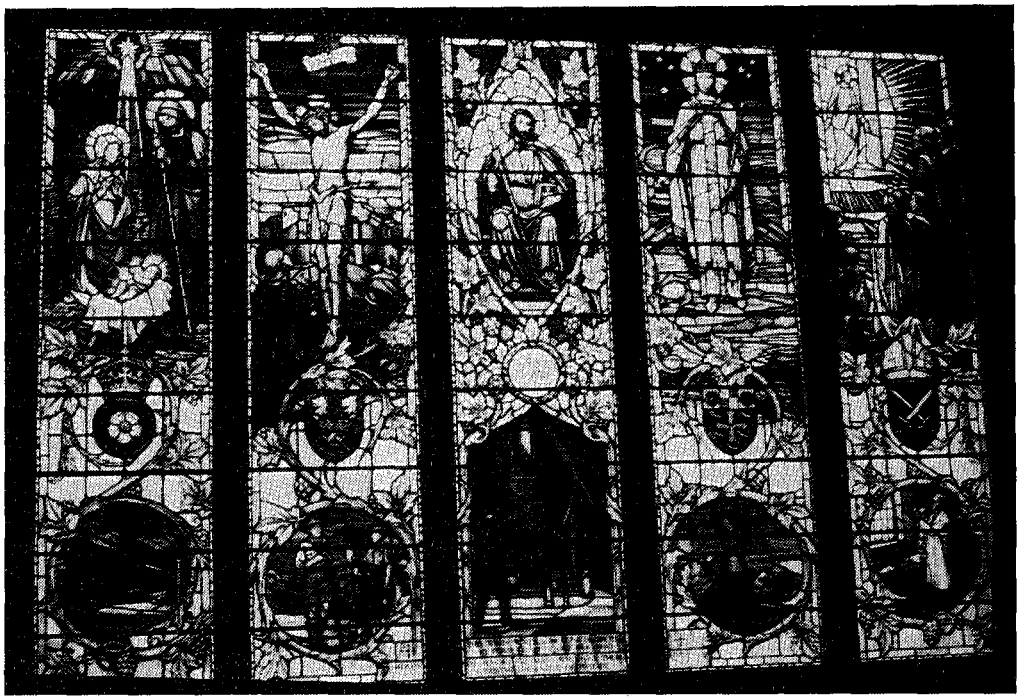


Stained glass window in St. James's Church (Sussex Gardens, London). A commemorative text tells us that "This window, replacing one destroyed by home-blast in October 1940, holds in memory the many who gave their lives during the battle of Britain". In the lower right hand corner Alexander Fleming is shown at work in his laboratory, which was located in the vicinity of this church.

The photograph was kindly made available by the Reverend Mr. D. Perkin.

IV Secular trends of infectious disease mortality in The Netherlands, 1911-1978

– quantitative estimates of changes coinciding with the introduction of antibiotics

IV.1 Introduction

A large part of the decline of infectious disease mortality occurred before the introduction of efficacious drugs: the sulphonamides, just before World War II, and penicillin and a number of other antimicrobial drugs, just after World War II [1,2]. Nevertheless, visual inspection of mortality curves does suggest a certain impact of the first antibiotics (we will omit the bothersome "and chemotherapeutics") on mortality from Puerperal fever, Pneumonia, Syphilis and Tuberculosis in England and Wales [1].

A linear regression analysis on crude mortality rates in Sweden led the authors to conclude that, after the introduction of the first antibiotics, mortality rates declined faster for Septicemia, Syphilis and Non-meningococcal Meningitis, but not for 10 other infectious diseases, including Puerperal fever, Pneumonia and Tuberculosis [3]. The method of analysis employed in this study was, however, rather crude. Mortality rates were not standardized for age and sex, and used in the regression analysis without a logarithmic transformation.

The study reported here is an analysis of secular trends of infectious disease mortality in The Netherlands, meant to provide quantitative estimates for changes coinciding with the introduction of antibiotics. Our "design" can be described as a "simple interrupted time series design" [4], in which a number of observations on mortality from infectious diseases before the introduction of antibiotics, serve as a baseline against which "signs of interruption" are to be detected. The main limitation of this design is, of course, the absence of a control group. No otherwise comparable populations without the benefit of antibiotics are available.

Table IV.1 shows the causes of death for which an effect of the introduction of antibiotics could be expected.

Table IV.1 Causes of death included in the analysis.

Cause of death	Deaths 1911-1978	Idem, as % of total mortality
Puerperal fever	5538	0.1
Scarlet fever	4001	0.1
Rheumatic fever	5946	0.1
Erysipelas	6791	0.1
Septicemia	17349	0.3
Meningoccoccal meningitis	3839	0.1
Non-meningococcal meningitis	21742	0.4
Acute bronchitis	22067	0.4
Pneumonia	331032	5.5
Otitis media	6312	0.1
Upper respiratory infections	10938	0.2
Influenza	97746	1.6
Measles	21145	0.4
Pyelonephritis	16802	0.3
Cystitis	4590	0.1
Skin infections	10165	0.2
Osteomyelitis	3614	0.1
Syphilis	21999	0.4
Tuberculosis	279181	4.7
Bacillary dysentery	2791	0.0
Typhoid fever	6832	0.1
All other diseases	5064713	84.9
Total mortality	5965133	100

Table IV.2 The first antibiotics: amounts delivered to hospitals in The Hague, The Netherlands, 1946-1958

	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	1957	1958
Penicillin (10^9 i.U.)	1	9	14	39	46	52	68	86	90	100	109	106	114
Streptomycin (kg)		2	10	13	18	26	26	33	50	47	45	49	56
PAS (kg)			6	400	540	570	490	460	480	430	483	417	472
Chloramphenicol (kg)				1	2	11	18	14	21	25	34	50	58
Tetracyclin (kg)				0	3	3	5	11	13	12	14	17	16

Data from annual reports Apotheek Haagse Ziekenhuizen, The Hague, The Netherlands.

Influenza and Measles are included in the analysis because death mainly occurs from bacterial superinfections; this may also apply to some other respiratory infections. "All other diseases" are included for comparison: changes resembling effects of antibiotics are expected not to be present for this category.

Sulphanilamide was first used in The Netherlands in 1936, penicillin in 1944 (but supplies were very limited until 1947 [5, 6]), streptomycin in 1947 and chloramphenicol in 1949. A central registration of drug sales did not exist in The Netherlands in these years, but information is available on amounts of antibiotics delivered to hospitals in The Hague (table IV.2).

Apart from PAS (used in the treatment of Tuberculosis) all drugs show gradual increases in the amounts delivered, suggesting slow diffusion. As the data apply to one of the more highly developed parts of the country, another number of years has to be added to allow for diffusion into more backward regions.

Two types of effect on infectious disease mortality will therefore be considered:
- a sharp reduction of mortality, approximately coincident with the moment of introduction of antibiotics, showing as a change in level or intercept in a regression analysis;
- a longer lasting (acceleration of) mortality decline, in the period between introduction and large scale application of antibiotics, showing as a change in trend or slope in a regression analysis.

Further improvements of the efficacy of antibiotics and indirect effects on incidence (due to treatment of otherwise infective cases, as in Syphilis and Tuberculosis, activating a "positive feedback loop" [7,8]) will tend to reinforce the second type of effect.

IV.2 Sources of data

Numbers of deaths by underlying cause, calendar year (1911-1978), age-group and sex were extracted from the yearly publications of the Dutch Central Bureau of Statistics (CBS) [9]. Cause-of-death codes were carefully selected so as to minimize the effect of changes in the International Classification of Diseases (ICD) [see Annex 1 for code-numbers]. Inspection of the numbers of deaths for the so-formed causes did not reveal important breaks between ICD-revisions. Changes in classification by age made it necessary to use ten-year age-groups (<1, 1-4, 5-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+). Population numbers, by age-group and sex, were available from other CBS-publications [10]. Approximate person-years at risk for a given calendar-year were calculated by averaging the population numbers of the 31st of December of the current and the previous year.

IV.3 Methods

For a first impression, the mortality data were standardized for changes in age- and sex-structure of the population by calculating Standardized Mortality Ratios (SMRs) [11]. Average mortality rates by age and sex for the entire period 1911-1978 were used as standardrates.

Inspection of SMR time trends was followed by loglinear regression analysis [12], in which the observed number of deaths (Y) was related to the explanatory variables person-years at risk, age-group and sex, and calendar year as follows:

$$E(y_i) = N_i e^{(\alpha_i + \beta X)}$$

where
- $E(y)$ = expected number of deaths
- N = person-years at risk
- e = base of natural logarithm
- α, β = parameters to be estimated
- X = calendar-year
- i = subscript denoting age-group and sex

β is the slope of the regression line of the natural logarithm of mortality density vs. calendar year, and thus represents the trend of mortality with time. α is the intercept of this regression line. The effect of assigning different values of α to different age- and sex-groups i is that β is not sensitive to changes in the age- and sex-structure of the population; β is assumed to have the same value for all age- and sex-groups.

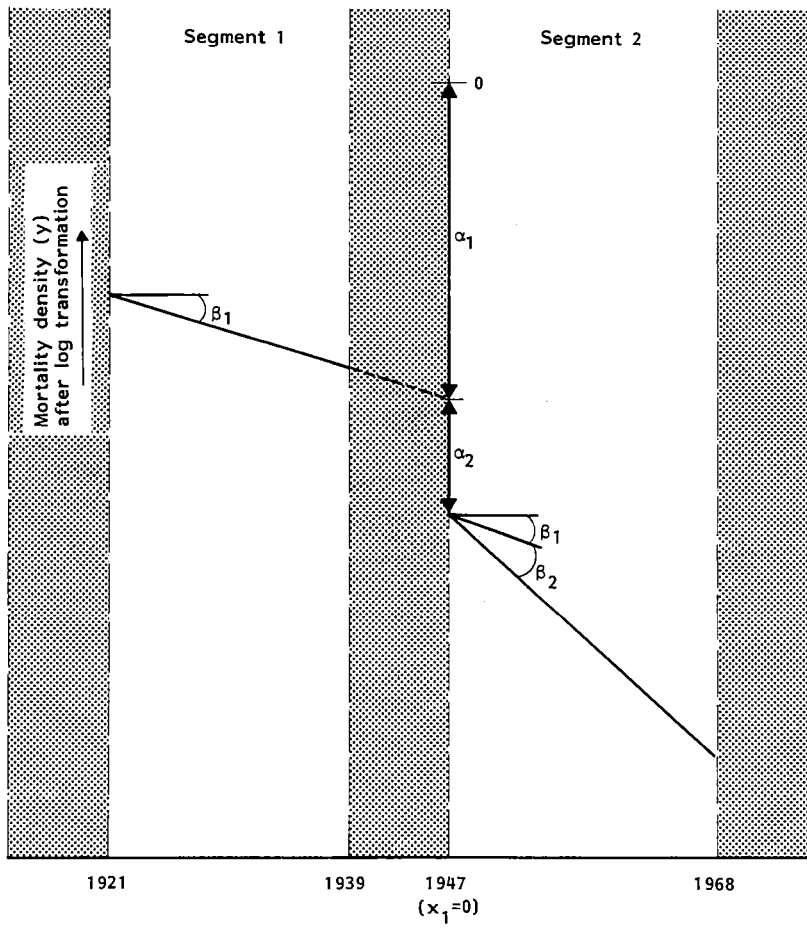
On the basis of this basic model we constructed a number of "segmented regression models" [13] in which a first segment covered the years before the introduction of antibiotics, and a second segment a period of approximately the same length thereafter. The first and second segments connected in 1947. The years before 1921 were excluded because of the effect of World War I. We ignored the observed values for 1940-1946 because of the effect of World War II, and assumed that in the absence of World War II mortality would have continued the trend of 1921-1939 (figure IV.1).

The computations were performed with the GLIM computer package, specifying a Poisson regression model [14]. A sequence of 4 models was fitted:

1) no change between segments 1 and 2 ($\alpha_2 = 0$, $\beta_2 = 0$);
2) a change in intercept in 1947, but no change in slope ($\beta_2 = 0$);
3) a change in slope in 1947, but no change in intercept ($\alpha_2 = 0$);
4) a change in intercept and a change in slope in 1947.

Because differences in scaled deviance between models showed that the addition of α_2 and that of β_2 were highly statistically significant (p

Figure IV.1 Schematic representation of the segmented regression model.



Formal structure:

$$E(y_i) = N_i e^{[\alpha_{1i} + \beta_1 X_1 + (\alpha_2 + \beta_2 X_1)X_2]}$$

where
- α_1 = intercept for segment 1
- β_1 = slope for segment 1
- α_2 = change in intercept between segments 1 and 2
- β_2 = difference in slopes between segments 1 and 2
- X_1 = calendar-year - 1947
- X_2 = dummy variable (1 if calendar-year > 1946, 0 if calendar-year < 1947)

For E(y), N and i see text.

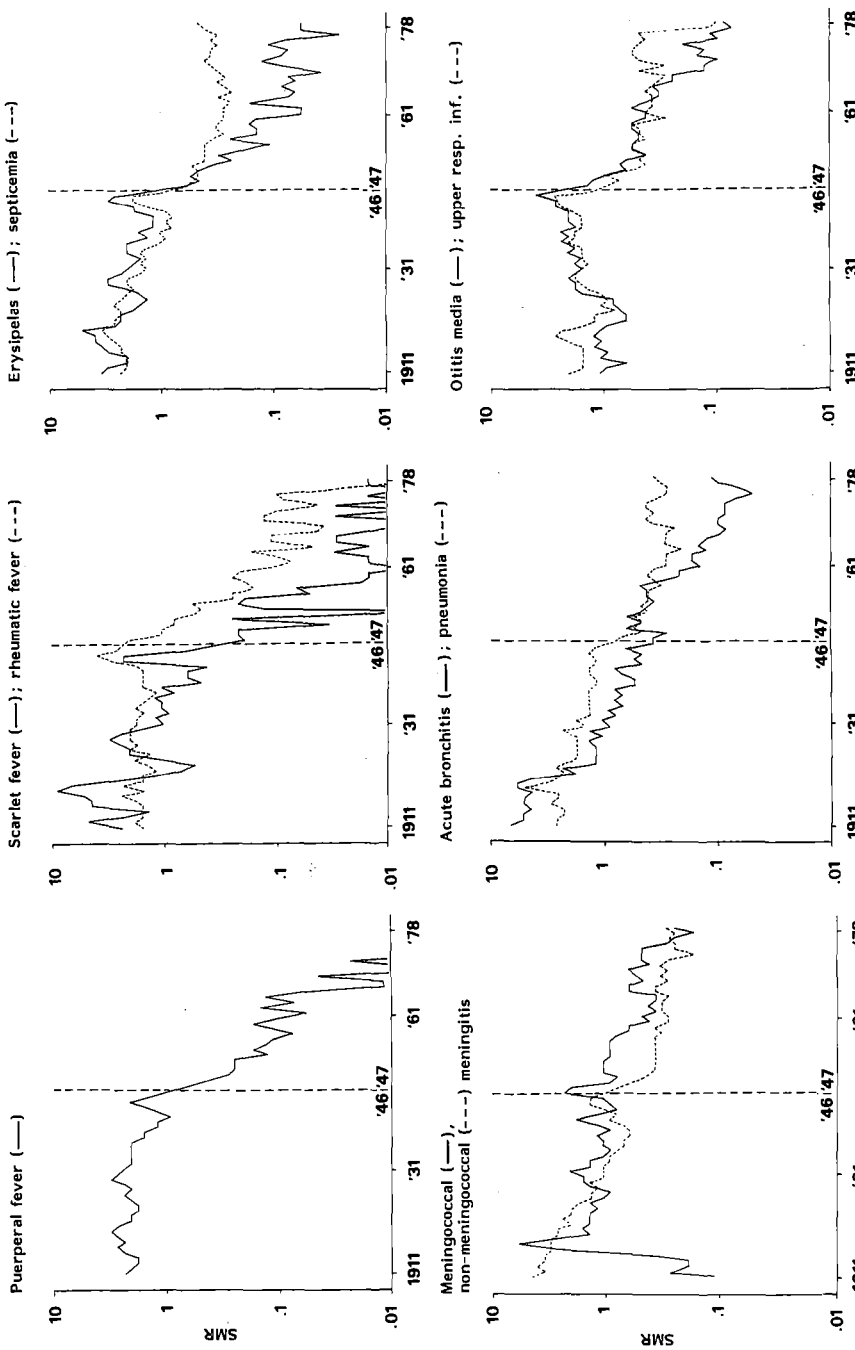
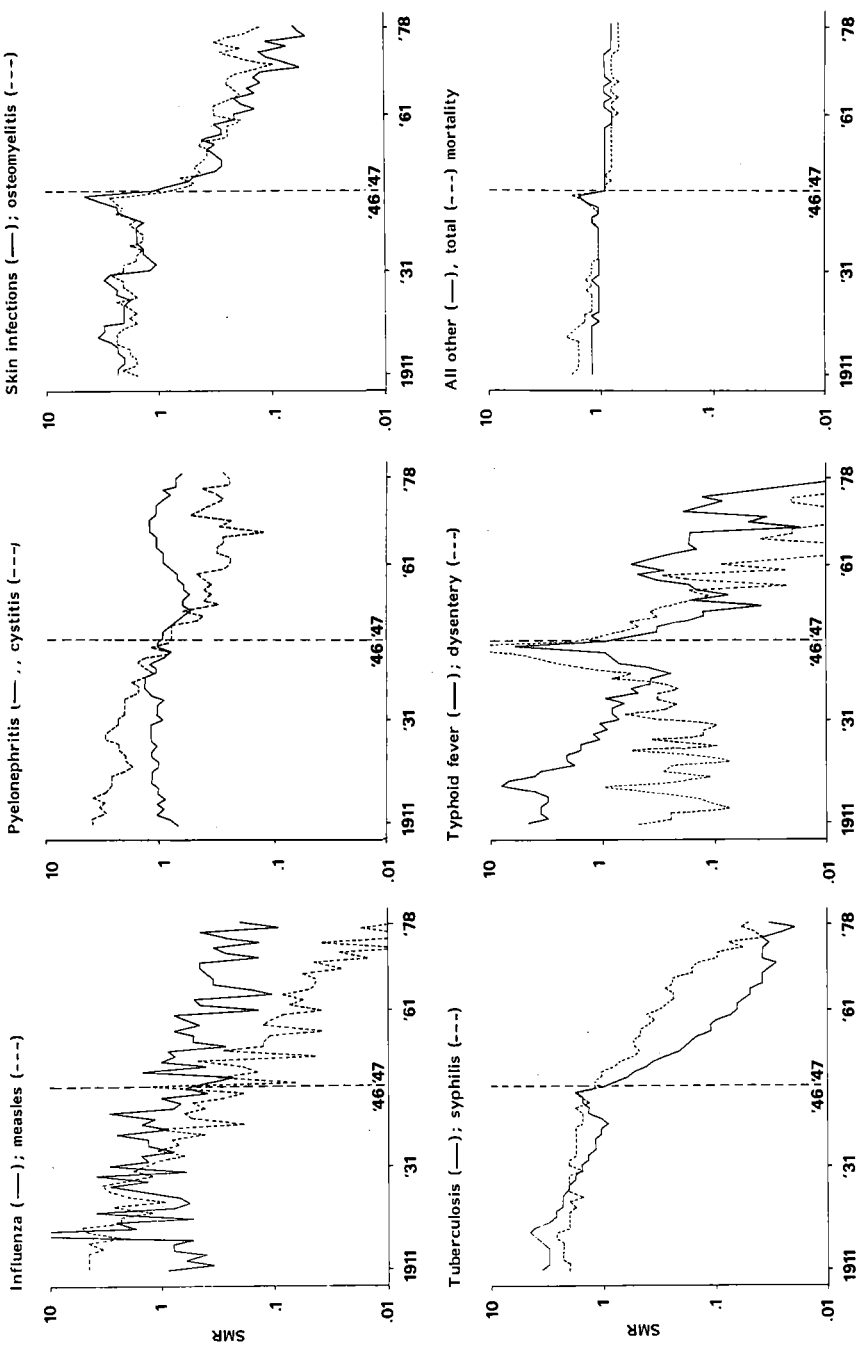


Figure IV.2 Time trends of age- and sex-standardized mortality (SMRs) from infectious diseases in The Netherlands, 1911 - 1978.

Figure IV.2 (continued) Time trends of age- and sex-standardized mortality (SMRs) from infectious diseases in The Netherlands, 1911 - 1978.



< 0.001) in almost all cases, we will uniformly report parameter estimates obtained with model 4.

This regression analysis assumes a linear relationship between log mortality density and calendar-year within the two time-periods. A formal test for linearity, based upon the Wald-Wolfowitz "runs test" [15], showed that some systematic deviations did occur. Deviations from linearity were highly statistically significant ($p < .001$) in Pyelonephritis, which was therefore excluded from the analysis. Deviations for some other diseases, although statistically significant ($p < .05$), were relatively minor on visual inspection, and these were therefore retained in the analysis.

IV.4 Results

Mortality time trends for 21 infectious diseases, age- and sex-standardized and semi-logarithmically plotted, are presented in figure IV.2. For most infectious diseases there is a general downward trend in mortality since 1911, temporarily interrupted by the effects of World War I and, even more so, of World War II.

For some diseases a sharp reduction in mortality, to a level lower than that immediately before World War II, may have taken place in the late 1940's: Erysipelas, Pneumonia, Otitis media, Upper respiratory infections, Skin infections, Osteomyelitis are examples. For a number of other diseases, however, mortality levels in the second half of the 1940s are higher than those in the years before World War II, e.g. for Meningococcal and Non-meningococcal meningitis and for Tuberculosis.

If mortality trends before and after World War II are compared, an accelerated or fresh mortality decline seems to be present in the second period for e.g. Puerperal fever (possibly even starting before 1940, with the introduction of the sulphonamides?), Scarlet fever, Rheumatic fever, Erysipelas, Otitis media, Upper respiratory infections, Influenza, Tuberculosis, Syphilis, and Bacillary dysentery.

The results of the regression analysis are presented in table IV.3. The downward trend of mortality before the introduction of antibiotics is reflected in the generally negative values for β_1. The estimates for changes in level in 1947 are mostly negative, implying the expected sharp reductions of mortality after World War II. In "All other diseases" there is also a drop in mortality, but this is much smaller. As was already observed in the SMR plots (figure IV.2), the change in level is sometimes positive (Meningococcal and Non-meningococcal meningitis; Acute bronchitis; Tuberculosis; Bacillary dysentery; Typhoid fever). Inspection of figure IV.2 suggests that, with the exception of Acute bronchitis, late effects of World War II may be involved.

Table IV.3 Estimates and standard errors of changes in mortality level and changes in mortality trend in 1947

	Trend 1921-1939		Change in level		Change in trend	
	β_1	s.e.	α_2	s.e.	β_2	s.e.
Puerperal fever	- .01	.003	-1.37	.104	- .11	.011
Scarlet fever	- .03	.005	-1.33	.171	- .11	.019
Rheumatic fever	- .00	.004	- .03	.081	- .18	.008
Erysipelas	- .02	.003	- .98	.091	- .10	.008
Septicemia	- .06	.002	- .10	.056	.02	.004
Meningococcal meningitis	- .01	.005	.27	.108	- .05	.007
Non-meningococcal meningitis	- .08	.002	.53	.056	.04	.004
Acute bronchitis	- .07	.003	.68	.060	- .02	.004
Pneumonia	- .04	.001	- .41	.013	- .01	.001
Otitis media	.05	.004	-1.26	.076	- .13	.006
Upper respiratory infections	.03	.003	-1.22	.064	- .08	.005
Influenza	- .01	.001	- .60	.021	- .04	.001
Measles	- .08	.002	- .37	.067	- .01	.006
Cystitis	- .04	.003	- .50	.081	- .02	.006
Skin infections	- .03	.003	- .75	.073	- .04	.006
Osteomyelitis	- .01	.005	-1.00	.117	- .04	.009
Syphilis	- .01	.002	- .40	.042	- .08	.003
Tuberculosis	- .06	.001	.24	.015	- .12	.002
Bacillary dysentery	.05	.014	.40	.247	- .26	.021
Typhoid fever	- .11	.005	.62	.123	.09	.008
All other diseases	- .01	.000	- .04	.003	.01	.000
Total mortality	- .02	.000	- .05	.003	.01	.000

The estimates for changes in trend are also mostly negative (and statistically significantly so in 16 infectious diseases), implying faster mortality decline after 1947. It is important to note that the pre-war decline in mortality from "All other diseases" did not accelerate, but instead slowed down after 1947.

The estimated values for α_2 and β_2 are not small. For example, a value for α_2 of -.41, as in the case of Pneumonia, implies a reduction of mortality to a level of exp(-.41) = .66 times the level expected on the basis of the mortality experience of 1921-1939. Values for β_2 (if not too large, say > -.10 and < .10), multiplied by 100, are approximately equal to the difference in per cent per annum mortality decline before and after 1947. Thus, in the case of Syphilis, where mortality decreased 1 % per annum in 1921-1939 (100 x β_1), the rate of decline accelerated with 8 % (100 x β_2) to 9 % per annum after 1947.

IV.5 Discussion

Whether or not the introduction of the first antibiotics has had a notable impact on infectious disease mortality is one of the classical questions of epidemiology. Most analyses of this question have been of an informal nature. In the formal analysis presented here two types of change in secular trends of mortality, roughly coinciding with the introduction of antibiotics, were measured. The results show that these changes were present in a wider range of infectious diseases than was known so far. Differences between infectious diseases may be due to a number of factors, including differences in effectiveness of antibiotics.

In order to obtain quantitative estimates for these changes it was necessary to make a number of assumptions. One of these (linearity of log mortality density vs. time within the two subperiods) was already shortly discussed in the Methods section. Some diseases included in table IV.3 had statistically significant deviations from linearity, for example Tuberculosis and Syphilis. Within the second subperiod, the curve of log SMR vs. time is concave for Tuberculosis, and convex for Syphilis (figure IV.2). Although a different model might have produced slightly different estimates, a comparison between table IV.3 and figure IV.2 suggests that these and other deviations from linearity are not likely to invalidate the global picture.

A second assumption, necessary because observed values for 1940-1946 were ignored, was that without World War II mortality would have continued the trend of 1921-1939. Actually, World War II deflected mortality trends to such an extent that, for some diseases, mortality in 1947 was higher than in 1939 (figure IV.2). Possible explanations are that living conditions (food and housing) were still

precarious, and that sanitation efforts were not yet at pre-war levels. Observed changes in level of mortality in 1947 thus combine the late effects of World War II and the sharp mortality reductions that may have accompanied the introduction of antibiotics. Although observed changes in trend are less sensitive to violations of this assumption, underestimating a change in level may cause overestimation of a change in trend, and vice versa. For most infectious diseases both changes in level and changes in trend are however negative, so that it is difficult to escape the conclusion that some real changes in mortality occurred.

A third assumption was absence of interactions between β_1, α_2, and β_2, on the one hand, and age and sex, on the other hand. Calculations with a model in which β_1, α_2, and β_2 were made age- and sex-specific, just as α_1, show that differences between age- and sex-groups are frequently statistically significant and of a relevant magnitude. The estimates presented in table IV.3 must thus be thought of as crude weighted averages of the different mortality experiences of separate age- and sex-groups. Inspection of age- and sex-specific estimates suggested that the most important pattern is that of increasing (less negative) values for the three parameters with age, sometimes excepting the very young (< 10 years). For presentation purposes, we collapsed this model into a version in which β_1, α_2 and β_2 were estimated for three broad age-groups: 0-9, 10-59 and 60+ years. Results are presented for the two largest infectious diseases, Pneumonia and Tuberculosis, in table IV.4.

Table IV.4 Age-specific estimates of β_1, α_2 and β_2 for Pneumonia, Tuberculosis, All other diseases, and Total mortality.

	β_1 (s.e.)			α_2 (s.e.)			β_2 (s.e.)		
	0-9	10-59	60+	0-9	10-59	60+	0-9	10-59	60+
Pneumonia	-.06	-.04	-.03	-.29	-.87	-.41	-.01	-.04	-.02
	(.001)	(.001)	(.001)	(.025)	(.035)	(.017)	(.002)	(.003)	(.001)
Tuberculosis	-.08	-.06	-.04	.23	.21	.52	-.25	-.16	-.08
	(.002)	(.001)	(.002)	(.050)	(.018)	(.034)	(.010)	(.002)	(.003)
All other diseases	-.03	-.01	-.00	.13	-.08	-.09	-.00	.01	.00
	(.000)	(.000)	(.000)	(.010)	(.007)	(.004)	(.001)	(.000)	(.000)
Total mortality	-.04	-.02	-.01	.08	-.10	-.11	.00	.01	.00
	(.000)	(.000)	(.000)	(.008)	(.006)	(.004)	(.001)	(.000)	(.000)

Although the observed changes in mortality are roughly coincident with the introduction of antibiotics, a causal relationship is not necessarily implied. At least two other explanations should be considered: changes in the rate of improvement of a number of material circumstances, and changes in the intensity and effectiveness of public health programmes. The decline of infectious disease mortality since the 18th and 19th centuries has generally been ascribed to changes in material circumstances. McKeown, for example, has argued that increases in food supplies led to a decrease in incidence and case fatality of infectious diseases [16]. A favourable change in the rates of improvement of any of these material circumstances could act as a confounder of the relationship between antibiotics and infectious disease mortality trends. A favourable change in the rate of economic development certainly took place in The Netherlands. This is evident from the development of mean income levels, which increased slowly in The Netherlands from Hfl. 2805 in 1921 to Hfl. 2875 in 1939 (expressed in 1975 values). During the period 1948-1969 mean income levels increased rapidly from Hfl. 4300 to Hfl. 8907 [17]. On the other hand, longterm developments in availability of food (milk, meat) and fertility and crowding do not show accelerations after World War II [17].

Another alternative explanation for the changes in mortality trend could be a change in intensity or effectiveness of public health programmes (not involving the use of antibiotics). Immunization does not have to be considered, as no diseases are included in the analysis against which immunization was instituted in The Netherlands on a large scale before 1968. The only disease for which a significant change in public health programmes (not only involving the use of antiobiotics) took place is Tuberculosis. Pasteurization of milk was introduced in 1940, reducing the incidence of Non-respiratory tuberculosis [7,18]. Mass radiography was introduced in 1949, and the combined effects of early detection and effective treatment may have caused a considerable acceleration of the decline in Tuberculosis incidence [19]. Nevertheless, in the late 1940's and the early 1950's mortality from Tuberculosis declined much faster than incidence, in The Netherlands as well as in many other countries [20].

The fact that mortality from "All other diseases" does not show an important reduction in level of mortality in 1947, and its trend, if anything, changes in the opposite direction, strongly suggests that the changes described in this paper have a cause that is specific to the infectious diseases. Although the exact contribution of antibiotics to these changes cannot be assessed, it may well have been substantial. Antibiotics have come late in the history of infectious diseases, but could well have been the miracle-drugs which contemporary reports claimed them to be.

IV.6 Summary

Secular trends of mortality from 21 infectious diseases in The Netherlands were studied by inspection of age/sex-standardized mortality curves and by loglinear regression analysis. An attempt was made to obtain quantitative estimates for changes coinciding with the introduction of antibiotics. Two possible types of effect were considered: a sharp reduction of mortality at the moment of the introduction of antibiotics, and a longer lasting (acceleration of) mortality decline after the introduction.

Changes resembling the first type of effect were possibly present for many infectious diseases, but were difficult to measure exactly, due to late effects on mortality of World War II. Changes resembling the second type of effect were present in 16 infectious diseases and were sometimes quite large. For example, estimated differences in per cent per annum mortality change were 10% or larger for Puerperal fever, Scarlet fever, Rheumatic fever, Erysipelas, Otitis media, Tuberculosis, and Bacillary dysentery. No acceleration of mortality decline after the introduction of antibiotics was present in mortality from "All other diseases".

Although the exact contribution of antibiotics to the observed changes cannot be inferred from this time trend analysis, the quantitative estimates of the changes show that even a partial contribution would represent a substantial effect of antibiotics on mortality from infectious diseases in The Netherlands.

Acknowledgement

The data of table IV.2 were kindly made available by Mr Ruijtenbeek, Apotheek Haagse Ziekenhuizen, The Hague.

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V Improvements in cancer survival rates since the 1950's

V.1 Introduction

Whether progress in the treatment of cancer patients has led to an improvement in the chance of survival has often been the subject of heated discussion [1-5]. On the one hand, there have been great developments in the treatment of cancer patients since World War II. The systematic use of radiotherapy since the 1950's and the introduction and use of combination chemotherapy, especially since the 1960's, are regarded as important breakthroughs. It is clear from the results of clinical trials that improvements in survival rates have been achieved for Hodgkin's disease since the 1960's [6] and for Cancer of the testis since the 1970's [7] and also for a number of cancers that are especially found in children [8]. Significant progress was made with Wilm's tumour (a cancer of the kidney in children) as early as the 1950's [9] while progress with Acute lymphocytic leukemia followed in the 1970's [8].

On the other hand, from the large number of clinical trials it is extremely difficult to form a clear picture of the extent to which the survival rates at population level of these and other cancer patients have in fact improved. Two types of factor are of importance here. In the first place the reports of different trials often cannot be properly compared with each other [10]. Differences in the selection of patients, in previous treatment, in therapy used, in definitions and measurements of the stage of disease and response to treatment, in completeness of follow-up and in methods of reporting, make it difficult to construct a systematic review of trial results from which it would be possible to ascertain, for example, trends in survival rates.

In the second place, it is not justifiable to simply use trial results to make generalisations about the effect in the total population. These research projects are only concerned with treated

patients (patients who for one reason or another do not get treated are thus overlooked) and in many cases the research is carried out in leading clinics (which are not necessarily representative of the current treatment situation).

It is thus important to have information about survival rates that apply to all cancer patients in the population and that can be monitored over a long period. The most suitable source of such information is a cancer registry in which not only the occurrence but also the length of survival of cancer patients is recorded. Here a review will be given of the improvements in survival rates that have been observed in cancer registries in the United States, Norway and Finland. The questions are:

- are there notable improvements in survival rates?
- are there notable international differences in the observed improvements in survival and the resulting survival rates?
- how should the observed improvements in survival be interpreted?

V.2 Data

In a number of cancer registries not only is the date of diagnosis or first treatment of cancer patients recorded, but also the date of death, which makes it possible to get an impression of chance and length of survival. Although the date of death is now recorded by a large number of registries in many countries [11], only a few registries have been in existence long enough to enable an analysis of survival trends since the 1950's. The best-known registry is in the United States but those in Norway and Finland are also important. (The cancer registry in Denmark also has recorded date of death since the 1940's but the most recent published survival data concern patients who were diagnosed in the period 1959-1962 [12]. In Great Britain published survival statistics are limited in scope and only cover a short period [13].)

In the United States there are several regionally-operating cancer registries. The survival data from a number of these registries have been collected, analysed and published by the so-called "End Results Section" of the National Cancer Institute. This led to a series of 5 reports, the most recent having been published in 1976 [14]. Data about patients diagnosed in the period 1950-1954 will be used as reference values. The most recent patient group that has been incorporated in this programme was diagnosed in the years 1970-1973. Information concerning these patients has recently been published [15].

In the meantime, the End Results programme has been incorporated into a wider Surveillance, Epidemiology and End Results (SEER) programme, of which the data are however not completely comparable with those in the End Results programme, due to a different selection

of cancer registries. Survival data have also been published from the SEER programme [16]; they refer to patients diagnosed in the period 1973-1982. Only data concerning white patients will be used here.

Norway has had a national cancer registry since 1952. The earliest published survival data concern patients diagnosed in the period 1953-1957 [17], the most recent are for patients diagnosed in the years 1972-1975 [18].

There has been a national cancer registry in Finland since 1953. The earliest survival data concern patients from 1953-1959; the most recent are for patients from 1967-1974. These data have mostly only been published in graphical form [19], but were kindly supplied in tabular form by the author (Hakulinen, personal communication, 1985).

Although there was information for more categories of cancer, data available for all three countries concerned 30 types of cancer in males and 32 types in females. In some cases it was necessary to combine smaller categories, in which case weighted averages were calculated.

It is not possible to deal with the registration procedures in detail here. However, in comparing changes in survival between the three countries it is important to know that:

- in all three countries only invasive cancer is registered, thus carcinoma in situ is excluded;
- in the analysis of survival data patients in whom cancer is only identified at autopsy or first recorded on a death certificate are excluded;
- the cancer registries which provided data for analysis in the American End Results programme are partly population-based and partly hospital-based, while the Norwegian and Finnish registries are both population-based and cover the whole country;
- in Norway and Finland the methods for registration and follow-up are practically identical: the definitions and criteria for classification are regularly discussed in joint meetings [20] and both countries use linkage between cancer registry and death registration through personal identification numbers since the 1960's.

V.3 The Relative Survival Rate

Survival of cancer patients is usually expressed in terms of a Relative Survival Rate (RSR). The RSR is the quotient of:

- the proportion of patients that are still alive after a given period;
- the proportion that would still have been alive after that period if **in that calendar-period** the death rate for the group had been the same as for the total population **in the same age and sex groups.**

Both numerator and denominator are calculated using actuarial methods;

the quotient is usually multiplied by 100 so that the RSR is expressed as a percentage. If the RSR equals 100%, the probability of survival of patients is equal to that for the total population. If the RSR is less than 100%, the mortality of cancer patients is higher. A RSR of, for example, 60% can be interpreted as: there is a 60% chance that after the chosen period of time the patients have not died **from the cancer**. Conversely, the value of (100 - RSR), in the example 40%, can be interpreted as the chance of dying from the cancer within the chosen period of time.

The chosen period of time is usually 5 years. Here too, 5-year survival rates will be used. Only sometimes can the RSR after 5 years be taken as a measure of the probability of complete recovery. Even after the fifth year mortality rates for cancer patients are generally higher than those for the total population. This is apparent from published survival rates after 10 and 15 years. The mortality rates for Cancer of the breast and prostate remain higher for an even longer period. Nevertheless, an improvement in 5-year survival rates will in general be accompanied by an increase in the percentage of patients that escape death from that cancer altogether.

Although the denominator of the Relative Survival Rate makes allowance for the age of cancer patients in calculating "expected" survival, a comparison of Relative Survival Rates from different time-periods or different countries requires further correction for possible differences in age distribution. The reason for this is that older patients have lower Relative Survival Rates than younger patients. Unfortunately, it is not possible to carry out this correction with published data. The effect of this omission on survival trends will generally be that, due to aging of the population and an associated increase in the average age of cancer patients, improvements in survival will be underestimated.

We are concerned here with **changes** in the survival rates of cancer patients. There are various ways of expressing these changes which do not necessarily lead to the same interpretation. Calculating the difference between RSR's for two calendar-periods ($RSR_2 - RSR_1$) is one obvious method. This depicts the improvement in an "absolute" sense; a difference of 20% means that 20% more patients out of the group have not died from their cancer during the first 5 years. In addition, improvements in a "relative" sense can be shown, either as a percentage of the original survival rates ($[RSR_2 - RSR_1] / RSR_1$), or as a percentage of the original case fatality rates ($[RSR_2 - RSR_1] / [100 - RSR_1]$).

This last figure makes allowance for the fact that the higher the survival rates already are, the more difficult it may be to achieve further improvement. For those types of cancer for which the survival rates were already relatively high at the beginning of the period studied (for example, in the United States the RSR for Cancer of the uterus had then already reached 72%), it may therefore be of interest to express the improvement as a percentage of the 5-year case fatality rate in the first period. In the United States the RSR for

Cancer of the uterus increased to 81%, an "absolute" improvement of 9%. but a "relative" change of 9/(100-72) = 32%. As the two methods of calculation do not give the same rank order for the degree of improvement, the results from both methods will be presented.

V.4 Results

If the data for all types of cancer for which comparison was possible (30 for males and 32 for females) are taken together, it is apparent that in the United States, in Norway and in Finland 5-year survival rates have on average improved both for men and for women (table V.1). The high positive correlations between the survival rates for separate types of cancer show that there was a reasonable correspondence between the three countries at both the beginning and the end of the period studied (table V.2).

There are, however, also important differences. The survival rate of registered cancer patients at the beginning of the 1950's was clearly higher in the United States than in Norway and Finland (table V.1). It seems that as a result of great improvements Norway has reduced that difference; it is difficult to express a judgement about Finland as the last period for which figures are available (1967-1974) is on average earlier than the corresponding period for the United States or Norway. Furthermore, there is not a particularly close correspondence between the trends in survival rates for different forms of cancer (table V.2).

Figures V.1 and V.2 show the degree of improvement for the 9 types of cancer (approximately a quarter of the total number of 35 cancers studied) for which, on average, the greatest improvements were found in these three countries. When the improvement is expressed as the difference between the two Relative Survival Rates (thus as the "absolute" difference) the rank order is (figure V.1): Hodgkin's disease, Cancer of the prostate, Malignant melanoma, Cancer of the thyroid, bone, testis, kidney, cervix and colon. For Cancer of the testis, for example, the proportion not dying in the first 5 years is between 10 and 20% higher in the most recent period than in the 1950's.

When the improvement is expressed as a percentage of the original case fatality rate (figure V.2) the rank order changes considerably: now Cancer of the thyroid is first and Cancer of the uterus suddenly appears near the top of the list. For some forms of cancer the improvements are certainly striking. Note that there is sometimes a considerable difference between the three countries; for Hodgkin's disease, for example, there is a considerably larger improvement in the United States, and for Cancer of the thyroid there is a considerably larger improvement in Norway.

Table V.1 Averages and standard deviations for 5-year survival rates and for changes in 5-year survival rates (30 types for males and 32 for females) in the United States, Norway and Finland.

		RSR_1 (*)		RSR_2 (**)		$RSR_2 - RSR_1$ (***)		$(RSR_2 - RSR_1)/(100 - RSR_1)$ (***)	
		av.	(s.d.)	av.	(s.d.)	av.	(s.d.)	av.	(s.d.)
USA	m	35	(24)	42	(25)	7	(9)	11	(19)
	f	39	(24)	45	(24)	7	(8)	11	(16)
Norway	m	31	(23)	40	(25)	10	(10)	16	(25)
	f	32	(23)	43	(26)	11	(10)	20	(29)
Finland	m	31	(22)	38	(23)	7	(7)	12	(14)
	f	34	(22)	42	(23)	8	(6)	12	(11)

* Relative Survival Rates (in %) for patients diagnosed in 1950-1954 (USA), 1953-1957 (Norway) and 1953-1959 (Finland).

** Relative Survival Rates (in %) for patients diagnosed in 1970-1973 (USA), 1972-1975 (Norway) and 1967-1974 (Finland).

*** See text for an explanation of these measures of changes in survival.

Table V.2 Product moment correlation coefficients of 5-year survival rates and changes in 5-year survival rates for cancer (30 types for males and 32 for females) in the United States, Norway and Finland.

		RSR_1 (*)	RSR_2 (**)	$RSR_2 - RSR_1$ (***)
USA vs. Norway	m	.92	.93	.34
	f	.90	.92	.15
USA vs. Finland	m	.90	.90	.62
	f	.94	.92	.40
Finland vs. Norway	m	.92	.92	.14
	f	.92	.94	-.11

*, **, *** See footnotes to table V.1.

Figure V.1 Changes in 5-year survival rates for 9 types of cancer showing the greatest improvement, United States, Norway and Finland (RSR_2 - RSR_1, in %, see footnotes to table V.1).

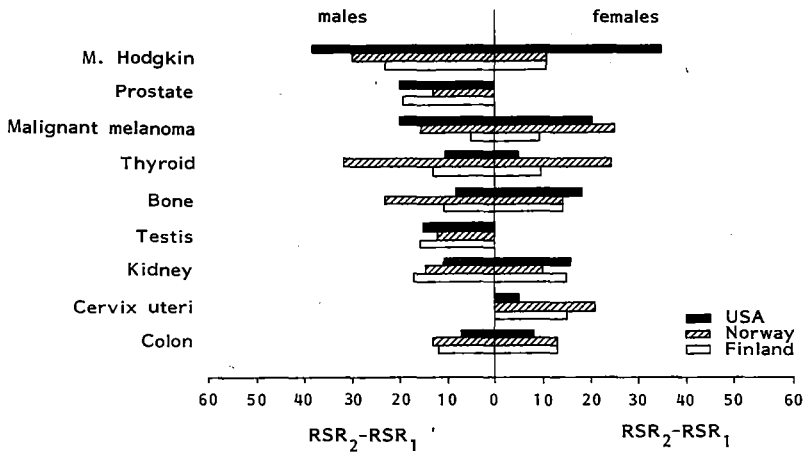
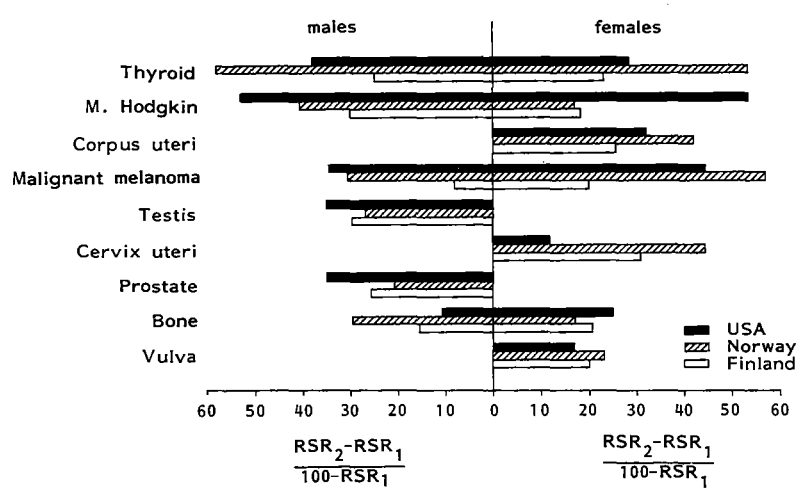


Figure V.2 Changes in 5-year survival rates, expressed as a percentage of the original case fatality rate, for 9 types of cancer showing the greatest improvement, United States, Norway and Finland ($[RSR_2 - RSR_1]/[100 - RSR_1]$, in %, see footnotes to table V.1).



From figure V.3 it is apparent that the relatively favourable developments with Hodgkin's disease in the U.S.A. have led to a higher survival rate among patients diagnosed at the beginning of the 1970's. The relatively favourable development for Cancer of the thyroid in Norway would appear to be a catching up with developments elsewhere.

With American and Finnish data it is possible to make a separate study of improvements in the survival rates of child and adolescent cancer patients (table V.3). In addition to significant improvements in Hodgkin's disease we also find considerable improvements in Cancer of the kidney (i.e. Wilm's tumour) and, at least in the United States, Leukemia (i.e. Acute lymphocytic leukemia). The fact that this most recent improvement was not yet evident in Finland could indicate that there was a delay in introducing breakthroughs in therapy in that country.

For the most recent period, i.e. cancer patients diagnosed after 1973 (U.S.A.), 1974 (Finland) and 1975 (Norway), only American data are available [16]. As these data (from the SEER programme) are not exactly comparable with those from earlier periods, analysis of trends should as far as possible be carried out within that new programme. For this purpose the data have been divided into two periods, 1973-1976 and 1977-1982. It must be added that, at the time of publication, the follow-up for the most recent period was inevitably incomplete. No hopeful 'new' improvements in survival can be seen for adults. For children there is a continuation of the favourable trends in Hodgkin's disease, Wilm's tumour and especially Acute lymphocytic leukemia, and also a hopeful new development in Acute granulocytic leukemia and Non-Hodgkin's lymphomas. It will be another few years before it is possible to draw firm conclusions on these recent trends.

Figure V.3 Recent 5-year survival rates for types of cancer in which great improvements have been observed since the 1950's, United States, Norway and Finland (RSR_2, in %, see footnotes to table V.1).

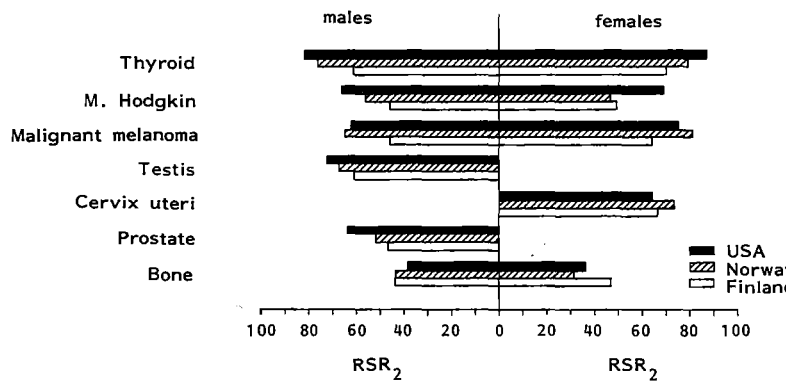


Table V.3 Changes in 5-year survival rates for young cancer patients in the United States and Finland.

	$RSR_2 - RSR_1$								
	Testis	Kidney	Eye	Brain	Bone	Connective tissue	Non-Hodgkin's lymphoma	Hodgkin's disease	Leukemia
USA (m + f)	9	23	-1	10	0	-19	0	34	26
Finland (m + f)	0	30	32	15	-8	-3	15	33	1

* RSR_1 in this case is for patients (under 15 or under 25 years old) diagnosed in 1950-1959 (USA) and 1953-1959 (Finland). RSR_2 is for patients diagnosed in 1967-1973 (USA) and 1967-1974 (Finland).

V.5 Discussion

Improvements in the survival of cancer patients seem to be a fairly general phenomenon. It is striking that the types of cancer for which very considerable improvements were shown in clinical trials of new forms of treatment (Hodgkin's disease, Cancer of the testis, Wilm's tumour and Acute lymphocytic leukemia), do not stand out conspicuously from types of cancer for which improvements were much less evident, such as Cancer of the thyroid and Cancer of the prostate. This in itself makes it clear that the observed improvements in survival must be interpreted with great caution.

In the introduction (section V.1) it has already been mentioned that these improvements are the subject of much discussion. The questions that have arisen can be summarised as follows:

- are the observed improvements **real** or only apparent?
- in as far as the improvements are real, are they due to improvements in **therapy** or to other factors?

As far as the first question is concerned, various situations are imaginable in which one might observe an improvement in survival rates for cancer patients, without there being any real favourable development in the course of the illness (i.e. only an "apparent" improvement). The most important situations in which this can happen are [4, 5, 21]:

1) Earlier diagnosis, so that the length of time between diagnosis and death (= the observed length of survival) increases, without there being any real change in the length of time between the start of the illness and death (= the real length of survival). This is known as "lead time bias".

2) Extension of the registered categories by the addition of relatively benign forms of the same cancer:

a. due to the detection of previously undiscovered cases that take a relatively favourable course.

b. due to changes in the criteria for diagnosis and registration, whereby types that were not previously regarded as malignant (i.e. invasive), are later classified as such.

It is extremely likely that many types of cancer are now diagnosed earlier on average than during past decades; the general increase in diagnostic possibilities and efforts must have led to earlier diagnosis. Moreover, for a few types of cancer (cervix, breast) there have been special campaigns aimed at earlier diagnosis. It is difficult to quantify the effect that this has had on the observed improvements in survival. This would only be possible if the method of staging had remained the same, and this is probably not the case [15]. Furthermore, the efforts made to find metastases and the ability to do so have also increased in the course of years; it has recently been demonstrated that this can flatter recent, stage-specific survival rates [22].

Table V.4 Changes in the percentage of patients for whom stage of disease at registration was recorded as "localised", United States.

	Percentage "localised" 1970-1973 minus percentage "localised" 1950-1954	
	males	females
Colon	+ 2	+ 1
Cervix uteri		- 8
Corpus uteri		+ 9
Vulva		0
Prostate	+ 13	
Testis	- 9	
Kidney	0	+ 1
Malignant melanoma	+ 16	+ 18
Thyroid	+ 6	- 3
Bone	+ 1	- 19
Hodgkin's disease	n.a.	n.a.

n.a. = not applicable

The best source of information about changes in stage-distribution at registration are the American data. The published Norwegian data are not sufficiently detailed for this purpose, while in Finland the percentage of patients for whom the stage of illness was recorded as "unknown" at registration greatly increased between 1953-1959 and 1967-1974, which renders further analysis rather difficult. Table V.4 shows the changes in the percentage of patients for whom the stage of illness was recorded as "localised" at registration in the United States, for those types of cancer presented in figures V.1 and V.2. The average percentage (for all types of cancer for which data were available) has remained more or less the same. However, for some types of cancer it has greatly increased, despite the greater efforts and improved methods for tracing metastases. This strongly suggests earlier diagnosis, which may thus have been a relevant factor in the observed improvements in the 5-year surival rates, in particular for Cancer of the thyroid, Cancer of the prostate, Malignant melanoma and Cancer of the uterus.

If we accept at least some of the improvements as "real", the second question is whether these improvements can be ascribed to changes in therapy. It is conceivable that (real) improvements in the survival of cancer patients occur without an improvement in treatment, due to an increase in the "resistance" of the "host" or due to a

decline in the malignancy of the disease. There are conjectures about the latter for a few types of cancer for which incidence has changed considerably:

- The incidence of Malignant melanoma of the skin has greatly increased in white populations, partly due to an increase in the exposure to sunlight. This increase in incidence has possibly been accompanied by a reduction in the degree of malignancy [23].
- The incidence of Cancer of the uterus has increased in many countries, to some extent in association with the increase in the use of oestrogens for treating postmenopausal complaints. These "new" cases may be less malignant [24].
- The incidence of Cancer of the thyroid has also greatly increased, partly due to therapeutic radiation treatment of the neck area (including the thymus). This increase has been greatest for the histological type papillary carcinoma, for which the survival rates are relatively favourable [25].

In the final analysis, it is impossible to determine the reason for observed improvements in survival rates by using information from the registries alone. We can only say that for a few types of cancer where clinical trials have shown that a clear advance has been made, improvements are also found in survival rates estimated on the basis of data from cancer registries. For some other forms of cancer it is true that significant improvements in survival rates have been observed, but the extent to which these are due to progress in therapy is uncertain.

The problems associated with interpretation of the data, however, do not affect the importance of maintaining a cancer registry in which the survival of cancer patients is recorded. Such registries make it possible to examine to what extent and how quickly a breakthrough in treatment for a given type of cancer actually benefits patients in the general population. Some of the differences that are observed between the three countries (especially for Hodgkin's disease and Leukemia in children), for example, indicate that there has probably been a delay of at least several years between the U.S.A. on the one hand and Norway and Finland on the other.

Table V.5 shows, by way of illustration, how the above-mentioned breakthroughs are reflected in Dutch cause-specific mortality statistics. Changes in mortality are, however, the result of changes in survival **and** incidence and are thus a poor substitute for survival statistics. For a short time in the 1950's the survival of cancer patients in The Netherlands was registered, under the auspices of the Central Cancer Registry [26]. Survival data have so far not been recorded in the SOOZ cancer registry in the Eindhoven region. It is important that in The Netherlands information concerning the survival of cancer patients is collected. A (preferably but not necessarily nationwide) cancer registry which records information about factors affecting prognosis (histology, stage, treatment) **and** the date of death, could meet this need.

Table V.5 Percentage change in mortality [a] from certain types of cancer in The Netherlands since the 1950's (males).

	All ages			Below 30 years		
	'59/'63 vs. '50/'53	'69/'73 vs. '59/'63	'79/'83 vs. '69/'73	'59/'63 vs. '50/53	'69/'73 vs. '59/'63	'79/'83 vs. '69/'73
Testis	+ 5	- 14	- 48	+ 5	- 1	- 54
Kidney	+ 57	+ 20	+ 29	- 15	- 40	- 39
Hodgkin's disease	+ 7	- 24	- 37	- 8	- 43	- 57
Leukemia	+ 35	+ 1	+ 6	+ 21	- 30	- 25
All cancers	+ 13	+ 15	+ 8	+ 7	- 11	- 25

[a] Indirectly standardized for changes in the age structure of the population.

V.6 Summary

The extent to which five-year cancer survival rates have improved since the 1950's is studied using information from cancer registries in the United States, Norway and Finland. In these three countries there has, on the whole, been a modest improvement in five-year survival rates. For some types of cancer, including Hodgkin's disease, Cancer of the prostate, Malignant melanoma, Cancer of the thyroid, bone and testis, there has been a more pronounced improvement. If the improvements are expressed as a percentage of the original case fatality rate clear improvements are also seen in Cancer of uterus and cervix. Further great improvements are seen for Cancer of the kidney (Wilm's tumour) and Leukemia (Acute lymphocytic leukemia) in children.

Some of these improvements can probably be explained by improvements in treatment (Hodgkin's disease, Cancer of the testis, Wilm's tumour and Acute lymphocytic leukemia). In other cases it is possible that other factors also play an important role. Trends in these three countries are certainly not identical. This is all the more reason for setting up a registry of cancer and cancer survival in The Netherlands.

Acknowledgements

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VI Post-1950 mortality trends and medical care

– gains in life expectancy due to declines in mortality from conditions amenable to medical intervention

VI.1 Introduction

Measured on a time-scale of centuries, medical care has probably had only a modest impact on the development of mortality in industrialized countries, as the work of the medical and demographic historian Thomas McKeown has clearly shown [1]. Unfortunately, a comprehensive analysis of mortality changes in the last 40 years, with the objective of assessing the impact of medical care innovations, is not available. It is evident from, for example, successive editions of textbooks of medicine [2], that there has been quite a number of remarkable innovations since the 1920's. Not all of these have received due attention from McKeown, if only because his analysis ends in 1971.

The publication by Rutstein et al. of lists of "unnecessary untimely mortality" [3] has provided a basis for an analysis of medical care impacts on recent trends in mortality. Rutstein's "Working Group on Preventable and Manageable Diseases" listed a number of conditions in which death can be avoided by adequate preventive or therapeutic intervention. Most of these conditions have only become preventable and/or manageable due to the remarkable innovations since the 1920's.

Recently, two studies have shown mortality declines for a subset of this group of diseases in six countries since 1950 [4], and in Finland since 1969 [5]. The study reported in this paper is an attempt to assess the post-1950 mortality impact of medical care innovations in The Netherlands. We analysed mortality trends for a selection of conditions which was intended to cover all innovations, for which the evidence on favourable incidence or case fatality effects is relatively undisputed. This selection is presented in table VI.1. Medical care was defined as "the application of biomedical knowledge through a personal service system" [6] or that part of the health care system where preventive, curative and rehabilitative

Table VI.1 Causes of death which have become amenable to medical care, by type of innovation.

	Innovation [a]	Cause of death [b]
Group I	Specific medical therapies (1922, 1927, 1945)	Diseases of the thyroid; Diabetes mellitus (< 25 years); Pernicious anemia; Other anemias
Group II	Improvements in surgery/ anesthesia (ca. 1930?)	Peptic ulcer; Appendicitis; Cholelithiasis/ -cystitis; Abdominal hernia; Ileus without hernia; Benign prostatic hyperplasia
Group III	Improvements in antenatal and perinatal care (ca. 1930?)	Maternal causes: compl. of pregnancy, delivery, puerperium; Perinatal causes: diseases of mother, birth injury, hemolytic disease, other
Group IV	Chemotherapeutics (1936) and antibiotics (1947)	Tuberculosis; Pneumonia/influenza; Septicemia; Infections of the urinary system; Other infectious diseases [c]
Group V	Surgical repair of congen. anomalies (ca. 1950)	Congenital digestive anomalies; Congenital cardiovascular anomalies
Group VI	Prophylaxis (ca. 1950) and heart valve surgery (ca. 1965)	Rheumatic heart disease
Group VII	Mass vacination (1953)	Diphtheria/whooping cough/tetanus/poliomyelitis
Group VIII	Hemodialysis (ca. 1960)	Nephritis and nephrosis
Group IX	Hypertension detection and treatment (ca. 1960)	Hypertensive disease; Cerebrovascular disease
Group X	Improvements in cancer treatment (a.o. combination chemotherapy (ca. 1970))	Cancer of lip and skin; Cancer of kidney (< 15 years); Morbus Hodgkin; Cancer of testis; Leukemia (< 15 years)
Group XI	Mass screening (1976)	Cancer of cervix uteri

[a] With approximate year(s) of introduction for general use in The Netherlands.

[b] For causes of death which have been underlined, there is evidence of "spontaneous" incidence trends during the study-period. These trends were all downward, except for Ileus without hernia, Infections of the urinary system, Cancer of lip and skin, and Cancer of testis (see text).

[c] This category includes: a number of specific bacterial infections; viral diseases commonly occurring in children; Syphilis; Infections of the central nervous system other than Poliomyelitis; Bacterial endocarditis; Infections of the respiratory system other than Pneumonia/influenza; Infections of the skin; Infections of the locomotor system.

services are delivered in a personal encounter between a health care professional and a client [section I.3.3]; mass vaccination and mass screening were included.

Although based on Rutstein et al.'s lists of "unnecessary untimely mortality", our selection of conditions is not completely the same. We omitted conditions for which effective intervention mainly takes place outside the medical care system (many forms of primary prevention) and conditions for which very small numbers of deaths were recorded even in 1950. We further omitted some conditions which have high survival rates and thus may have seemed "manageable" to Rutstein et al., but for which we were not able to find convincing evidence of significantly increasing effectiveness of medical care (as in the case of Cancer of the thyroid). We added a small number of conditions not mentioned by Rutstein et al., but for which evidence on increased effectiveness of medical care is available: Congenital digestive anomalies [7], Nephritis and nephrosis [8-11], and Cancer of the testis [12, 13]. [An annotated bibliography covering all diseases mentioned in table VI.1 is added as Annex 2 to this thesis.]

In most cases there was no clear evidence that incidence or case fatality effects were limited to certain age groups. Exceptions are Diabetes mellitus [14] (improved survival in the young only, where death was mainly due to diabetic coma), Cancer of the kidney [15] (more effective treatment of Wilm's tumour only, which occurs mainly in children) and Leukemia [16, 17] (more effective treatment of Acute lymphocytic leukemia, which also occurs primarily in the young).

Although some innovations were introduced before 1950 (such as insulin (1922), sulphonamides (1936) and penicillin (1947)), complete diffusion throughout the relevant patient population probably required some time, and was only possible after improvements in accessibility of medical care in the 1940's and 1950's [18]. Another reason for including conditions for which the increase in effectiveness of medical care started before 1950 is, that the treatment of many conditions benefitted from gradual and multiple improvements over a protracted time period. A clear example of this is provided by improvements in surgery and anesthesia, which, although starting with the introduction of intravenous fluid therapy around 1930, form a continuum till the present day [19-21]. Another example would be Diabetes mellitus: data from the Joslin clinic for diabetic patients show that survival of younger patients was still improving in the 1950's [14], although insulin then had already been available for 30 years.

The effect of some innovations would be expected earlier in the study-period than the effect of others. In groups I, IV, and VII, one would roughly expect the largest effect in the first half of the period. In groups VIII, IX, X and XI, on the other hand, one would expect the largest effect in the second half of the period. For this reason, we divided the period 1950-1984 into two parts, and compared mortality trends of the first subperiod with those of the second.

As indicated in table VI.1 there is evidence of "spontaneous" (i.e. not related to increased effectiveness of medical care)

incidence trends during the study period for many of the selected conditions. These trends were mostly downward, although incidence increases have probably occurred for Ileus without mention of hernia [22], Infections of the urinary system [23], Cancer of lip and skin [24], and Cancer of testis [25]. Important examples of conditions with incidence declines are Tuberculosis and some other diseases of infectious origin (where improved living conditions have reduced incidence [26, 27]), Maternal and Perinatal mortality (where the declining birth-rate has reduced the proportion of high-risk pregnancies [28, 29]), and Cerebrovascular disease (where mortality and probably incidence has declined for unknown reasons since the 1940's [30, 31]). Mortality changes for the selected conditions can therefore not simply be interpreted as an estimate of the effect of medical care; for an unbiased estimate, the effect of spontaneous incidence declines would have to be subtracted.

VI.2 Data and methods

Numbers of deaths by calendar year (1950-1984), age (0, 1-4, 5-14,.....85-94, 95+), sex, and cause of death (categories mentioned in table 1, translated into the appropriate code numbers of revisions 6, 7, 8 and 9 of the International Classification of Diseases (ICD)) were extracted from a computerized file supplied by the Dutch Central Bureau of Statistics.

Population numbers for the 31st of December of each calendar-year, by age and sex, were extracted from published and unpublished sources based on the Dutch population register. Approximate person-years at risk for the deaths occurring in a given calendar-year were calculated by averaging the population numbers for the 31st of December of the current and the previous year.

Perinatal mortality is represented in our data by deaths due to "diseases of the newborn period" (chapter XV of the ICD), regardless of age at death and excluding still-births. This is not the usual measure of Perinatal mortality (still-births + all first-week deaths), but it assures consistency within our data set, and facilitates an analysis of constituent parts of Total mortality (from which still-births are usually excluded).

In a loglinear regression analysis observed numbers of deaths (Y) were related to the explanatory variables person-years at risk, age and calendar-year. Parameters were estimated for males and females separately. We specified the following regression equation:

$$E(y_i) = N_i e^{(\alpha_i + \beta X)}$$

where
$E(y)$ = expected number of deaths
N = person-years at risk
e = base of the natural logarithm
X = calendar-year
α, β = parameters to be estimated
i = subscript denoting age-group

β is the parameter of interest. Technically speaking, it is the slope of the regression line of the natural logarithm of mortality density vs. time. If β is small (say, $-.10 < \beta < .10$), 100 times the value of β is approximately equal to the percent change in mortality density per annum. An estimated value for β of, for example, -.02 thus indicates 2% mortality decline per annum. α is the intercept of the regression line, and takes on different values in different age-groups i. The effect of including α_i is that the trend parameter (β) is not influenced by changes in age-composition of the population.

β was estimated separately for the subperiods 1950-1968 and 1969-1984; the regression lines of the two subperiods are not necessarily connected, as the model permitted a change in level between 1968 and 1969. The division between the two parts of the period was chosen as 1968/1969 in order to coincide with the change between ICD-revisions 7 and 8.

The computations were performed with the GLIM computer package, specifying a Poisson regression model [32]. In a Poisson regression model, the differences between the observed (Y) and the predicted (y) values of the dependent variable are evaluated in terms of the probability under a Poisson distribution of a value of Y being equal to y. The GLIM package calculates maximum likelihood estimates for the regression parameters by using an iteratively reweighted least squares procedure.

VI.3 Results

The predominant impression from table VI.2, in which the results from the loglinear regression analysis are presented, is that mortality declined for almost all selected conditions, both in the first and in the second subperiod and both for males and females.

VI.3.1 First subperiod

Very large mortality declines ($\beta < -.10$) were found for Pernicious anemia; Maternal mortality due to complications of delivery; Tuberculosis; and Diphtheria/whooping cough/tetanus/poliomyelitis.

Pernicious anemia is the only condition from group I (specific medical therapies introduced before 1950) with convincing mortali-

Table VI.2 Changes in mortality: results of loglinear regression analysis [a].

	Cause of death	Trend parameter estimate (β) 1950-1968 males	1950-1968 females	1969-1984 males	1969-1984 females
Group I	Diseases of the thyroid	-.00	-.01*	-.08*	-.07*
	Diabetes mellitus (< 25 years)	-.02	-.04*	-.07*	-.08*
	Pernicious anemia	-.09*	-.12*	-.13*	-.11*
	Other anemias	.00	-.02*	-.01	-.01
Group II	Peptic ulcer	-.03*	-.01*	-.05*	-.02*
	Appendicitis	-.05*	-.06*	-.10*	-.10*
	Cholelithiasis/-cystitis	-.00	-.04*	-.03*	-.06*
	Abdominal hernia	-.01*	-.01	-.05*	-.06*
	Ileus without hernia	-.02*	-.01*	-.01	.00
	Benign prostatic hyperplasia	-.04*	n.a.	-.09*	n.a.
Group III	Maternal: compl. pregnancy [b]	n.a.	-.08*(-.08*)	n.a.	-.10*(-.06*)
	Maternal: compl. delivery [b]	n.a.	-.11*(-.10*)	n.a.	-.13*(-.08*)
	Maternal: compl. puerperium [b]	n.a.	-.06*(-.06*)	n.a.	-.07*(-.03)
	Perinatal: diseases of mother	-.00	-.00	-.14*	-.12*
	Perinatal: birth injury	-.05*	-.05*	-.09*	-.08*
	Perinatal: hemolytic disease	-.06*	-.03*	-.20*	-.21*
	Perinatal: other	-.02*	-.02*	-.05*	-.05*
Group IV	Tuberculosis	-.15*	-.19*	-.02*	-.03*
	Pneumonia/influenza	-.06*	-.07*	-.04*	-.04*
	Septicemia	-.04*	-.04*	.06*	.05*
	Infections urinary system	.04*	.03*	-.07*	-.07*
	Other infectious diseases	-.06*	-.07*	-.05*	-.04*
Group V	Congenital digestive anomalies	-.03*	-.02*	-.09*	-.06*
	Congenital cardiovasc. anomalies	.00	-.00	-.04*	-.06*
Group VI	Rheumatic heart disease	-.02*	-.03*	-.04*	-.02*
Group VII	Diphth./whoop. cough/tet./polio	-.23*	-.25*	-.07*	.02
Group VIII	Nephritis and nephrosis	-.03*	-.06*	.01*	.01*
Group IX	Hypertensive disease	-.03*	-.03*	-.06*	-.08*
	Cerebrovascular disease	-.01*	-.02*	-.02*	-.03*
Group X	Cancer of lip and skin	-.05*	-.06*	-.01*	-.03*
	Cancer of kidney (< 15 years)	-.01	-.00	-.07*	-.08*
	Morbus Hodgkin	.00	-.01*	-.04*	-.05*
	Cancer of testis	-.00	n.a.	-.06*	n.a.
	Leukemia (< 15 years)	.01*	.00	-.04*	-.06*
Group XI	Cancer of cervix uteri	n.a.	-.01*	n.a.	-.04*
	All other causes	.01*	-.01*	-.00*	-.02*
	Total mortality	.00	-.02*	-.01*	-.02*

* β statistically significantly different from 0 (two-sided test; p< .05).

[a] For definitions of groups, see table VI.1.

[b] Values between parentheses have been obtained with a model in which the number of births was substituted for person-years at risk (N).

ty declines during the first subperiod. Mortality due to Diseases of the thyroid and Diabetes mellitus declined more during the second period, which is not what one would expect if the mortality declines were related to the medical care innovations mentioned in table VI.1. It is interesting to note that during the first subperiod the steep declines of Maternal mortality due to complications of delivery are parallelled by relatively favourable trends in Perinatal mortality due to birth injury. This suggests that great progress was being made in obstetric care. Not only Tuberculosis, but also most other infectious diseases show their most pronounced mortality declines during the first subperiod. This is what one would expect given the time of introduction of antibiotics. The extremely steep mortality declines in group VII suggest that mass vaccination had a tremendous effect on Diphtheria/whooping cough/tetanus/poliomyelitis in a very short period of time.

VI.3.2 Second subperiod

For many of the selected conditions mortality declines accelerate after 1968. This applies not only to most of the conditions in group IX (hypertension detection and treatment), group X (combination chemotherapy), and group XI (mass screening for cervical cancer), but also to those in group II (improvements in surgery and anesthesia), group III (improvements in antenatal and perinatal care - but the acceleration in maternal mortality decline appears to be due to fertility trends), and group V (surgical repair of congenital anomalies).

A very impressive acceleration is visible in the decline of Perinatal mortality due to hemolytic disease (anti-D-immunoglobulin was introduced around 1970). Some of the other accelerations also coincide with known "accelerations" in the effectiveness of medical care, as in the case of Congenital cardiovascular anomalies, Hypertensive and Cerebrovascular disease and a number of cancers. Cancer of lip and skin is the only condition in group X for which mortality declined considerably before 1969. This is consistent with the fact that effective treatment methods were available relatively early. Mortality from Cancer of the cervix declined faster in the second period, but apart from screening efforts this may also reflect a greater frequency of hysterectomy.

The absence of an acceleration of mortality decline in Nephritis and nephrosis (mortality even increased in the second subperiod) suggests that hemodialysis did not have an appreciable mortality impact in The Netherlands. Since hemodialysis was not available on a large scale before 1970, the mortality decline for this condition during the first subperiod must be due to other factors (a changing relationship between the human race and the streptococcus [27]?).

Mortality from the digestive and urogenital conditions of group II also declined more after 1968. There are important differences between males and females for Peptic ulcer (female mortality

declined less) and Cholelithiasis and -cystitis (male mortality declined less). These differences, which can hardly be explained by differences in effectiveness of medical care, could be due to differential incidence developments [33, 34]. Ileus without mention of hernia did not show significant mortality declines; this could be due to an increase in incidence, following from a greater prevalence of operation-induced intraperitoneal adhesions [22].

VI.3.3 Effects on life expectancy

Although the analysis by cause of death presented in table VI.2 gives a comprehensive and detailed view of mortality trends in the Netherlands since 1950, it does not provide us with a summary measure of the overall impact of mortality changes. The contributions of these conditions to the over-all mortality level in the early 1950's differed widely. By far the largest cause of death in our selection is Cerebrovascular disease (accounting for more than 10% of Total mortality). Pernicious anemia, as an example of one of the smaller causes, accounted for less than .1%.

A summary measure of the impact of changes in mortality from the conditions in our selection is the effect on life expectancy at birth (table VI.3). Life expectancy at birth for Dutch males was 70.85 years in 1950-54, and increased by almost 2 years to 72.76 years in 1980-84. If mortality for the conditions analysed in this paper had remained at 1950-54 levels, life expectancy at birth for males in 1980-84 would have been 69.80 years. (There has been an increase in mortality from some other causes, e.g. Lung cancer, Ischemic heart disease, Motor vehicle accidents.) The difference between the latter figure and the actual life expectancy at birth in 1980-84, 2.96 years, is a measure of the impact of reductions in mortality from the selected conditions on life expectancy of Dutch males. As table VI.3 shows, conditions in group IV (infectious diseases) made the largest contribution.

Life expectancy at birth of Dutch females was 73.32 years in 1950-54, and increased by almost 6 years to 79.18 years in 1980-84. Without the reductions in mortality from conditions which have become amenable to medical intervention life expectancy in 1980-84 would have been 75.23 years. The contribution of these reductions to life expectancy of Dutch females can thus be calculated as 79.18 - 75.23 = 3.95 years. The difference with the corresponding figure for males can almost entirely be explained by the greater contribution of Hypertensive disease and Cerebrovascular disease (Group IX), which are more important causes of death **and** declined faster in females (cf. table VI.2).

Table VI.3 The effects of mortality reductions for the selected conditions on life expectancy at birth (1950/54 - 1980/84)[a].

	Life expectancy gains (in years) [b]					
	Group II	Group III	Group IV	Group IX	Other groups	All selected conditions
males	0.36	0.72	0.94	0.43	0.58	2.96 [c]
females	0.25	0.63	1.13	1.32	0.80	3.95 [c]

[a] For definitions of groups, see table VI.1.

[b] Gains have been measured as the difference between life expectancy at birth calculated with 1980/84 mortality rates and life expectancy at birth calculated with 1950/54 mortality rates for the selected group(s) of conditions and 1980/84 mortality rates for all other conditions.

[c] The life expectancy gain due to reductions in mortality from all selected conditions is not equal to the sum of the effects of mortality reductions for separate groups of conditions.

VI.4 Discussion

Post-1950 reductions in mortality from conditions which have to some extent become preventable and/or manageable with adequate medical care, have contributed appreciably to the life expectancy increases observed in the same period.

As stated in the introduction, mortality decline from these conditions cannot be attributed solely to medical care innovations. There is evidence of "spontaneous" incidence declines in more than half of these conditions (cf. table VI.1). As a matter of fact, some of the results provide some indirect support for the view that spontaneous trends also played an important role: - differences between males and females, as in the case of Peptic ulcer, Cholelithiasis and -cystitis, and Cerebrovascular disease; - the occurrence of mortality declines before an effect of medical care innovations could reasonably be expected, as in the case of Hypertensive disease, Cerebrovascular disease, Nephritis and nephrosis, and Cancer of the cervix; - and the occurrence of mortality declines later than was expected on the basis of a priori knowledge of medical care innovations, as in the case of Diseases of the thyroid and Diabetes mellitus.

Unfortunately there are no registrations of morbidity in The Netherlands which cover so wide a range of conditions, and which date back as far as 1950. The only source of information which can be used for comparison with our mortality data is the national registration of hospital admissions. Although this registration started in the early 1960's, its coverage of Dutch hospital patients is considered to be

sufficient only since about 1971. Table VI.4 compares trends in mortality since 1971 with trends in hospital admissions. Because of important changes in obstetric care and a corresponding increase in the proportion of hospital deliveries, group III (Maternal and Perinatal causes) was omitted from this comparison; because of very small numbers Diphteria/whooping cough/tetanus/poliomyelitis was also excluded.

The frequency of hospital admissions declined for a substantial number of the selected conditions, suggesting that incidence declines did play an important role in the mortality changes observed in the second subperiod. (Also, some anomalous mortality observations could well be related to incidence increases (Other anemias) or to differences in incidence decrease between males and females (Peptic ulcer, Cholelithiasis and -cystitis).)

In some cases (Tuberculosis, Rheumatic heart disease, Hypertensive disease, Cancer of cervix uteri) incidence declines could have been induced by medical care interventions, but in other cases they should probably be interpreted as "spontaneous".

On the other hand, mortality rates declined faster than hospital admission rates, even if one takes into account a general increase in the rate of hospitalization, showing as an augmentation of over-all age-standardized hospital admission rates of 12% (males) and 8% (females). This is generally true for groups I (!), II, V, IX and X. Hospital admission rates for some of these conditions even increased, while mortality decreased, e.g. for Cerebrovascular disease. This suggests that case fatality changes did also play an important role in the second subperiod.

The occurrence of "spontaneous" incidence declines implies that the calculated gains in life expectancy overestimate the impact of medical care to an essentially unknown extent. This may however be compensated to a certain degree by the fact that we included only those conditions for which the evidence on medical care effects is relatively undisputed. Like Rutstein et al. we excluded, for example, important causes of death such as Ischemic heart disease and Breast cancer, where evidence on medical care effects [35, 36] is more controversial.

As McKeown has shown, the contribution of medical care to the impressive decline in mortality since the 18th and 19th centuries has probably been small in comparison with that of other influences. Since 1950 increases in life expectancy have become less impressive, especially for males; nevertheless, gains in life expectancy were 2 and 6 years for Dutch males and females respectively. Reductions in mortality from conditions which have become amenable to medical intervention have contributed appreciably to these gains in life expectancy. Although it is difficult to disentangle the various influences on mortality from these conditions, this observation shows that the post-1950 mortality impact of medical care could well have been substantial.

Table VI.4 Mortality and hospital admission rates 1981/83, expressed as a proportion of the rates in 1971/73 [a]

	Condition	Mortality		Hospital admissions	
		males	females	males	females
Group I	Diseases of the thyroid	0.49*	0.54*	0.77*	0.78*
	Diabetes mellitus (< 25 years)	0.43	0.43	1.14*	0.92*
	Pernicious anemia	0.39*	0.28*	0.70*	0.70*
	Other anemias	0.90	0.84	1.60*	1.26*
Group II	Peptic ulcer	0.59*	0.80*	0.47*	0.75*
	Appendicitis	0.33*	0.38*	0.74*	0.70*
	Cholelithiasis and -cystitis	0.73*	0.51*	0.89*	0.68*
	Abdominal hernia	0.66*	0.56*	0.88*	0.86*
	Ileus without hernia	0.90	0.99	1.41*	1.42*
	Benign prostatic hyperplasia	0.39*	n.a.	1.23*	n.a.
Group IV	Tuberculosis	0.74*	0.68*	0.55*	0.65*
	Pneumonia/influenza	0.66*	0.62*	0.97*	0.93*
	Septicemia	1.61*	1.57*	1.11	1.05
	Infections of the urinary system	0.51*	0.44*	0.67*	0.69*
Group V	Congenital digestive anomalies	0.42*	0.48*	1.09*	1.10*
	Congenital cardiovascular anomalies	0.71*	0.56*	0.90*	0.93*
Group V	Rheumatic heart disease	0.72*	0.78*	0.47*	0.71*
Group VIII	Nephritis and nephrosis	1.14*	1.22*	1.02	1.02
Group IX	Hypertensive disease	0.55*	0.41*	0.73*	0.71*
	Cerebrovascular disease	0.78*	0.71*	1.49*	1.33*
Group X	Cancer of lip and skin	0.86	0.68	1.40*	1.42*
	Cancer of kidney (< 14 years))	0.58	0.29*	1.17	0.82
	Morbus Hodgkin	0.62*	0.62*	0.88*	0.94
	Cancer of testis	0.47*	n.a.	2.02*	n.a.
	Leukemia (< 14 years)	0.64*	0.49*	0.93	1.14*
Group XI	Cancer of cervix uteri	n.a.	0.64*	n.a.	0.53*
	Over-all mortality/hospital admissions	0.91*	0.80*	1.12*	1.08*

* Value significantly different from 1 (two-sided test; $p < .05$).

[a] Indirectly standardized for changes in age-composition of the population.

VI.5 Summary

In order to assess the impact of medical care innovations on post-1950 mortality in The Netherlands, we analysed trends in mortality from a selection of conditions suggested by Rutstein et al.'s lists of "unnecessary untimely mortality". This selection covers 11 types of innovation, and includes 35 conditions which have become amenable to medical care.

Loglinear regression analysis shows that for most of these conditions mortality declined during each of two subperiods (1950-1968; 1969-1984). Mortality decline accelerated in the second subperiod for many conditions. Reductions in mortality from these conditions between 1950/54 and 1980/84 added 2.96 years and 3.95 years to life expectancy at birth of Dutch males and Dutch females respectively.

Both a priori evidence and a comparison with changes in hospital admission rates between 1971/73 and 1981/83 indicate that these mortality reductions are due in some extent to "spontaneous" incidence declines. Although the exact contribution of medical care innovations to these changes in mortality cannot be determined, the impact of medical care on post-1950 mortality in The Netherlands could well have been substantial.

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VII Medical care and regional mortality differences within the countries of the European Community

VII.1 Introduction

Regional mortality differences within countries are a universal and intriguing phenomenon. Many questions can be asked about their explanation, of which the question to what extent these differences reflect differences in medical care has a special relevance. If it were to be shown that differences in supply, accessibility or effectiveness of medical care give rise to differences in mortality, there would be a clear case for action on the part of health care providers and policy makers. The literature on this subject does not, however, provide us with a clear answer to this question.

In a large number of studies regional differences in total (all-cause) mortality have been related to differences in the total (all-conditions) supply of medical care. These studies generally found weak and inconsistent relationships. For example, Valkonen and Notkola examined the contribution of physician density to the explanation of regional all-cause mortality differences within Finland, Sweden and Norway, controlling for the percentage of urban population and housing density [1]. This contribution, measured as an increment in the variance explained, was small. Negative regression coefficients were expected, as a higher level of medical care supply should be associated with a lower level of mortality, but the study found positive as well as negative signs for the regression coeffients. Auster et al. studied the relationship between medical care expenditures and variations in total mortality across states in the USA, controlling for a large number of confounding variables [2]. Their findings were in agreement with the expectation of a negative relationship, but the contribution of the medical care variables was small as compared to that of other variables.

Whereas these studies considered mortality from all causes of death it is for certain causes of death only that medical interven-

tion can effectively reduce mortality risks. More convincing results can perhaps be expected from the analysis of regional patterns of mortality from such causes. For example, in his study on the relationship between medical care use and mortality from cardiovascular diseases, cancer and "external" causes for county groups in the USA, Hadley found a negative relationship for the cardiovascular diseases only [3]. This was considered to lend support to the conclusion that the relationship between medical care supply and all-cause mortality was causal, as cardiovascular diseases are probably more amenable to medical intervention than cancer and external causes.

Other examples are two studies from England and Wales on the relationship between Perinatal mortality and medical care variables at the area and local authority level [4, 5]. Both studies controlled for a large number of confounding variables, including birth-weight. Knox et al. considered condition-specific medical care supply variables as the number of hospital beds for pediatrics and for obstretrics, special baby-care units, and hospital and home nurses [5]. Nonetheless, both studies found a very low proportion of variance explained and inconsistent signs of regression coefficients. On the other hand, from a rigorous analysis of mortality in the states of the USA during the 1960's, it was concluded that neonatal mortality and medical care were indeed negatively related [6].

The present study represents a new attempt to establish a relationship between the level of medical care supply and regional differences in cause-specific mortality. It derives its focus from a new approach in which a series of causes of death amenable to medical intervention are selected for further analysis.

VII.2 A new line of research: causes of death amenable to medical intervention

A systematic approach to the study of the relationship between medical care and cause-specific mortality would require a comprehensive list of causes of death amenable to medical intervention. The lists of diseases that have been published by Rutstein et al., for which mortality is considered to be largely avoidable given appropriate medical intervention, could serve as a basis for such an exercise [7].

A first attempt along these lines, using a selection from Rutstein's lists, showed large differences between Area Health Authorities in England and Wales for such diseases as Tuberculosis, Hodgkin's disease and Appendicitis, all in principle amenable to medical intervention [8]. These differences could only in part be explained by a number of social indicators or available measures of morbidity, suggesting that at least part of the variation might be related to differences in medical care [9].

Following these publications from England and Wales, a

European Working Group was formed which, in the framework of a European Community (EC)-sponsored "Concerted Action Project", collected and analysed data on regional differences in mortality from a comparable set of conditions within the participating countries. These countries are: Belgium, Luxembourg, The Federal Republic of Germany, Denmark, France, Greece, Italy, Ireland, The Netherlands, Northern Ireland, England and Wales, and Scotland; the countries of Spain and Portugal, which were not yet EC member countries when the working group was formed, have not been included. Results will shortly be published in the "EC Atlas on Avoidable Mortality, 1974-1978" [10]. For some countries, descriptive studies on the same material have already been published [11, 12, 13].

Table VII.1 presents the selection of causes of death for which mortality data have been analysed in the Atlas. Tuberculosis is a manageable disease since the introduction of tuberculostatic drugs; preventive efforts, both within the health care system (mass screening, chemoprophylaxis in contacts) and outside this system (pasteurization of milk), have also played a role in the reduction of Tuberculosis mortality since World War II. Mortality from Cervical cancer can to some extent be prevented by mass screening. Hodgkin's Disease is one of the few cancers for which an effective treatment has been developed in recent years. Chronic rheumatic heart disease can be prevented by penicillin treatment of Streptococcus infections, and can be treated by heart valve surgery or heart valve replacement. Respiratory diseases among children are mostly infectious in origin, and can be treated with antibiotics. Asthma, if treated carefully with the drugs which have become available, need not, in most cases, lead to premature death. Appendicitis, Abdominal hernia, and Cholelithiasis and cholecystitis are conditions which can be treated effectively by surgery, the safety of which has itself increased. Deaths due to Hypertensive and cerebrovascular disease can to some extent be prevented nowadays by early detection and treatment of hypertension. The risk of Maternal and Perinatal mortality has been reduced by improvements in antenatal and perinatal care. Medical interventions were considered to be most effective in selected age groups, mentioned in table VII.1.

As the Atlas does not only contain data on mortality from the above-mentioned conditions, but also contains information on the supply of medical care and on socio-economic conditions, it presents an interesting opportunity to explore the relationship between mortality and medical care a little further. In this paper we will address the following questions:

Do these different causes of death have a common pattern of regional variation within each country of the European Community? If these selected causes of death have high, positive intercorrelations, a common relationship with medical care would be suggested. For example, a common regional pattern for Appendicitis, Abdominal hernia, and Cholelithiasis and -cystitis would strongly suggest that similar aspects of basic surgical care underlie the regional mortality

Table VII.1 Causes of death selected for analysis, with age-groups, ICD code numbers and crude death rates for the EC as a whole (per 100,000 person-years, 1974-1978).

Cause of death		Age-group	ICD code numbers (8th revision)	Crude death rate
TUB	Tuberculosis	5-64	010-019	1.63
CERV	Cancer of cervix uteri [a]	15-64	180	2.01
HODG	Hodgkin's disease	5-64	201	1.00
CRHD	Chronic rheumatic heart disease	5-44	393-398	0.61
RESP	All respiratory diseases	1-14	460-519	0.65
ASTH	Asthma	5-44	493	0.29
APPX	Appendicitis	5-64	540-543	0.28
HERN	Abdominal hernia	5-64	550-553	0.28
CHOL	Cholelithiasis and -cystitis	5-64	574-575	0.66
HYP	Hypertensive and cerebrovascular disease	35-64	400-404, 430-438	18.21
MAT	Maternal mortality	all	630-678	0.21 [b]
PERI	Perinatal mortality	< 1 week	all	18.82 [b]
ALL	Total mortality, all causes	all	all	1076.25

[a] For regional mortality analyses within France, Greece and Italy this category has been replaced by a category including both Cancer of the cervix and Cancer of the body of the uterus (ICD code 182), because mortality from Cancer of the uterus in these countries contains a considerable proportion of deaths from Cancer of the cervix [14].

[b] Number of deaths per 1000 live- and still-births; data were not available for Greece.

distributions. Similarly, common medical care relationships would be possible if high positive correlations between Asthma and Respiratory diseases among children, and between Maternal and Perinatal mortality were to be found.

- To what extent can regional differences in condition-specific mortality be explained by differences in the level of medical care supply ? We would expect that medical care variables succeed to explain more of the variation in mortality from the selected causes than in all-cause mortality. We further expect to find negative relationships. As it may be anticipated that for many conditions some of the regional variation in mortality can be explained by socio-economic indicators [15], these will be used as control variables.

The available information allows us to examine whether similar answers are obtained for different countries. We expect to find more substantial relationships between mortality and medical care supply in countries with a low general level of supply and/or large

Table VII.2 Number and mean population size of administrative areas used in the analysis, by country.

	Number of areas	Mean Population Size, 1974-1978 (thousands)
Belgium	9	1090
Luxembourg	1	359
West-Germany	11	5603
Denmark [a]	15	338
France	95	554
Greece	10	922
Italy	89	631
Ireland	8	404
The Netherlands	11	1250
Northern Ireland	1	1538
England and Wales	98	505
Scotland	12	434
Total	360	745

[a] Bornholms County in Denmark was excluded from our analysis because of its very small population size.

regional differences in the amount of medical care supply.

Our primary interest is in within-country mortality differences, and not in between-country differences. We will nevertheless without much comment also present the results of a cross-national analysis because between-country differences have been the subject of some earlier studies [16]. Such analyses are, however, severely handicapped by data problems (see next section).

VII.3 Data

Table VII.2 shows that there is a considerable variation in the number of areas distinguished within each country. No data are given on within-country differences for Luxembourg and Northern Ireland, while data are available for a large number of areas in the case of France,

Italy, and England and Wales. The fourth large country, West Germany, could only provide data for a few, disproportionally large areas (the federal states).

For each area the Atlas gives information on the level of mortality from twelve selected causes of death and on the Total (all-cause) mortality level. Only deaths in the selected age-ranges are considered; Total mortality applies to all ages. The mortality data are for 1974-1978, except for France (1973-1977). For the relevant age-ranges, Standardized Mortality Ratios (SMR's) have been calculated by using two different sets of standardrates: one set for the whole EC and another for each individual country. The between-country analysis is based on SMR's calculated from the first set of standardrates, while the within-country analyses use the SMR's from the second set. The within-country SMR's were tested to see (a) whether for the country as a whole the degree of heterogeneity between different areas is greater than could be expected to occur by chance alone [17], and (b) for each area, whether the mortality level is significantly higher than the national level (one-sided test)[18].

Maternal mortality is expressed as the number of deaths per 1000 live- and still-births, and Perinatal mortality is expressed as the number of still-births and first-week deaths per 1000 live- and still-births. The same significance tests were carried out for these two causes of death.

The outcomes of the significance tests are given in table VII.3 for each cause of death. For a number of causes there are few countries with significant heterogeneity among regions; also, few of these regions have mortality levels significantly above the national level. Most of these causes have low mortality rates (see table VII.1). Significant heterogeneity in almost all countries is only found for Tuberculosis, Cervical cancer, Chronic rheumatic heart disease, Hypertensive and cerebrovascular disease, and Perinatal mortality.

Information on the three available measures of medical care supply is given in table VII.4. A substantial variation in the amount of medical care supply is found within France and Greece. The situation in Greece is particularly interesting for our analysis because the uneven distribution of medical care supply is combined here with a low over-all level of supply.

Data on the following three indicators of socio-economic conditions were available: the percentage of households with a fixed shower or bath, the average number of persons per room, and the number of private cars per 100 population. For England and Wales these have been substituted by the following socio-economic measures: the percentage of households with basis amenities, the percentage of households renting accomodation, and the percentage of households with cars. No socio-economic indicators were available on a regional level for Ireland.

Table VII.3 Number of EC countries with significant regional heterogeneity of mortality, and number of regions with mortality rates significantly above the national level, by cause of death, 1974-1978 [a,b].

Cause of death	Number of countries signif. heterogen. (n = 10)	Number of regions signif. higher (n = 358)
Tuberculosis	10	65
Cancer of cervix uteri	8	68
Hodgkin's disease	4	35
Chronic rheumatic heart disease	7	57
All respiratory diseases among children	5	45
Asthma	5	33
Appendicitis	3	33
Abdominal hernia	5	39
Cholelithiasis and -cystitis	4	39
Hypertensive and cerebrovascular disease	10	113
Maternal mortality	4	38
Perinatal mortality	10	97
Total mortality, all causes	10	145

[a] Significance level is 95%.

[b] Countries excluded are: Luxembourg and Northern Ireland.

Table VII.4 Mean and coefficient of regional variation (c.v., in %) of medical care variables [a], by country, appr. 1974-1978.

	GPS		BED		CONS	
	mean	c.v.	mean	c.v.	mean	c.v.
Belgium	102	23	4.9	22	86	43
W. Germany	45	14	8.6	24	44	23
Denmark	49	6	6.0	36	28	37
France	86	33	6.0	26	47	57
Greece	[b]		3.7	46	[b]	
Italy	87	28 [c]	7.8	20 [c]	17	22 [c]
Ireland	47	11	5.1	27	22	39
Netherlands	37	8	5.2	16	51	32
England/Wales	44	11 [c]	3.8	38	20	13
Scotland	60	16	4.3	25	27	55
EC [d]	60	43	5.8	21	42	60

[a] Definitions of the variables:
GPS - number of general practitioners per 100,000 population
BED - number of acute hospital beds per 1000 population
CONS - number of consultants per 100,000 population

[b] The number of general practitioners and consultants in small areas in Greece was only available for both together; mean = 60, c.v. = 85.

[c] Data were only available for larger areas, and we had to assume that the values applied to all regions within such a larger area.

[d] Means and coefficients of variation were calculated from national data. Greece (for GPS and CONS), Luxembourg (for CONS), and Northern Ireland (all variables) were excluded because of incompatible or missing data.

It is quite likely that there are considerable differences in registration criteria and procedures between countries. For example, the differences in medical care supply between countries, as suggested by table VII.4, could in part be due to international differences in the definition of a general practitioner, an acute hospital bed, or a consultant. Similarly, it has been shown that EC countries differ in certification and coding of causes of death [19]. Such differences are an important obstacle to between-country analyses of the relationship between medical care supply and mortality.

VII.4 Methods

We will look for a common pattern of regional variation of mortality from the selected causes of death in two ways. Firstly, factor analysis (principal components analysis, without rotation) will be carried out in order to examine whether there is a first factor which indeed represents a common regional pattern for most causes of death. Secondly, Spearman rank order correlations will be calculated for specific combinations of causes of death that were expected to show particularly strong covariations (see section VII.2).

The question on the relationship between mortality and medical care supply will be examined by a forward stepping, multiple regression procedure, during which the three socio-economic variables are forced to enter before the three medical care variables.

All analyses were carried out for each country separately. In addition, the results of a transnational analysis, using national data, will be presented too. The calculations were performed with the BMDP computer package. SMR's were used as input without any transformations.

Because of lack of data, no analyses could be made of regional mortality differences within Luxembourg and Northern Ireland. The regression analysis has not been carried out for Ireland because no socio-economic data were available.

VII.5 Regional covariation among the selected causes of death

Table VII.5 presents the results of the factor (principal components) analysis of regional variation in mortality from the selected causes. For each country, it gives the loading of each separate cause of death on the first factor. The variance explained by this factor ranges from 19 per cent in France to 44 per cent in Greece. For most countries, the loadings are clearly positive for most of the selected conditions (a higher score on the first factor goes together with higher cause-specific mortality). This means that this first factor represents a common regional pattern underlying most of the selected causes of death.

It is important, however, also to note the exceptions. Hodgkin's disease rather frequently has negative loadings on the first factor. Also, the "composition" of the first factor varies among countries. In most countries, for example, including the larger countries France and England and Wales, Tuberculosis is an important component of the first factor. In some countries, however, not at all, e.g. in Italy.

Table VII.5 Loading of each cause of death [a] on the first unrotated factor, by country, 1974-1978.

	TUB	CERV	HODG	CRHD	RESP	ASTH	APPX	HERN	CHOL	HYP	MAT	PERI
Belgium	1.0	.5	.2	.5	-.5	.8	.7	.8	.8	.6	.7	.2
W. Germany	.6	.1	.7	.8	-.7	.2	-.0	.8	.8	.8	.5	.5
Denmark	.8	.3	-.1	.6	-.4	.0	.1	.3	.1	.9	.5	-.1
France	.7	.5	-.0	.2	.0	.5	.3	.3	.2	.8	.1	.5
Greece	.9	-.6	-.6	.6	.9	.2	-.5	.2	.7	.9	n.a.	
Italy	-.0	.5	-.4	.9	.8	.0	.5	.6	.5	.5	.6	.8
Ireland	-.0	.5	-1.0	.1	.7	.7	-.2	.4	.5	.8	-.7	.1
Netherlands	-.2	-.6	-.7	.7	.6	-.4	.7	-.3	.4	.9	-.6	.8
England/Wales	.6	.7	.2	.8	.3	.2	.5	.2	.3	.9	.1	.8
Scotland	.7	-.3	.7	.7	-.1	-.1	.6	.8	-.2	.7	.8	.9
EC [b]	.7	-.7	.8	.8	.8	.4	.1	.7	.3	.6	-.1	.9

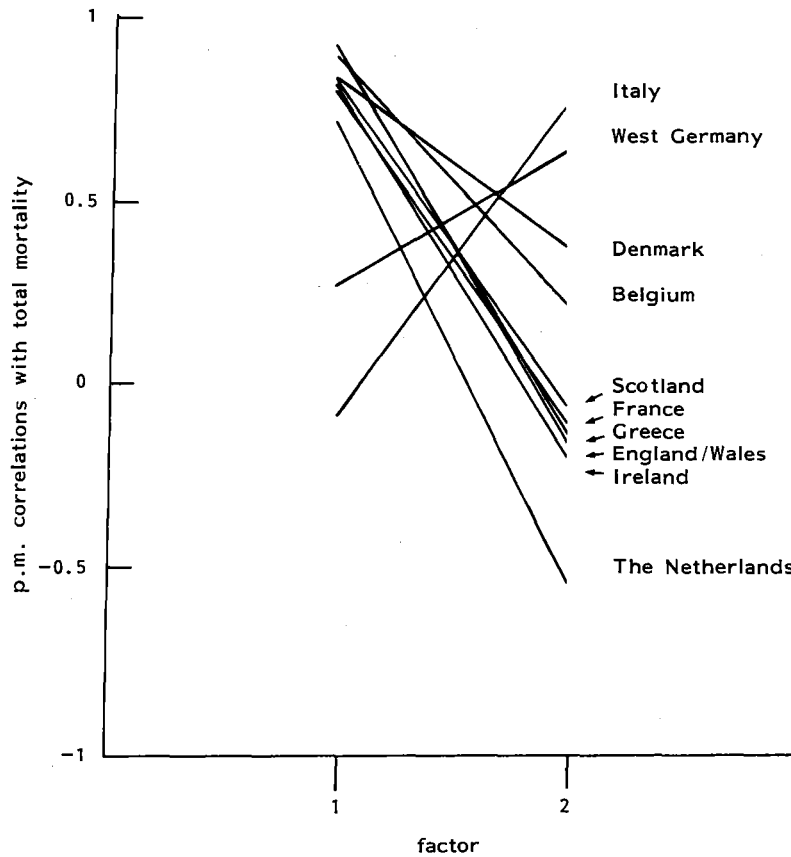
[a] For abbreviations, see table VII.1.

[b] Results of factor analysis on national data. Greece was excluded because of missing data.

The correlation between the first and second factor and Total mortality, all causes, is presented in figure VII.1. In most countries, the exceptions being West-Germany and Italy, the correlation is high for the first factor. In these cases, the common pattern of "avoidable" mortality appears to be determined by factors which are associated geographically with the factors that underlie the regional variation in Total mortality. These factors may even be the same. (Part of the correlation between the first factor and Total mortality might, of course, be due to the fact that the selected causes of death are included in Total mortality, but the proportion of all deaths that can be attributed to the selected causes in the selected age-groups, excluding perinatal deaths, is low: 2.4% for the EC as a whole.)

The situation in West-Germany and Italy, where the first factor is not strongly associated with the all-cause mortality level but where the second factor is, can be described as follows. The findings for Italy are explained by the fact that the well-known north-south contrast is different for mortality from the selected causes than it is for Total mortality. The regions south of Naples have high scores on the first factor (i.e. high mortality from the selected causes) but have low Total mortality rates, while areas in the northern part of Italy have low scores on the first factor but high Total mortality rates.

Figure VII.1 Product moment correlations between the first and second factors and Total mortality, all causes, by country, 1974-78



Note: For each country, the figure shows the line which connects the two points representing the correlation of the first and the second factor with Total mortality.

The situation in West-Germany is less clear and seems to be determined by the mortality pattern of two urban federal states. The first, Hamburg, scores low on the first factor (i.e. Hamburg in general has low "avoidable" mortality) while its Total mortality is not very different from the national level. The second, Berlin, has both a high Total mortality level and a very high score on the second factor.

Table VII.6 Rank order correlation coefficients between specific combinations of causes of death, and mean values of all correlations between these causes and other selected causes, by country, 1974-1978 [b].

	APPX vs. HERN	APPX vs. CHOL	HERN vs. CHOL	A,H,C vs. other	RESP vs. ASTH	R,A vs. other	PERI vs. MAT	P,M vs. other
France	.05	.14	.09	.08	.05	.10	.17	.07
Italy	.29	.11	.19	.16	.14	.12	.44	.20
England/Wales	.14	.13	.21	.16	.23	.13	.07	.15
EC [b]	.27	.34	.39	.20	.45	.19	.07	.34

[a] For abbreviations, see table VII.1; A,H,C = APPX, CHOL, HERN; R,A = RESP, ASTH; P,M = PERI, MAT.

[b] Correlations calculated from national data. Greece was excluded because of missing data.

The results of the analysis of intercorrelations among specific causes of death will be presented for three large countries only: France, Italy, and England and Wales (table VII.6). For the smaller countries, the same results are obtained. Rank order correlations "within" combinations of specific causes of death are compared with the arithmetic mean of their correlations with the other "avoidable" causes of death. Relatively high correlations within each combination would suggest specific medical care effects that are common to the causes making up the combination. Such situations are, however, not found, with the exception perhaps of Perinatal and Maternal mortality in Italy.

VII.6 Relationship with medical care supply variables

Table VII.7 gives a short summary of the results of the regression analysis. For some of the selected causes of death (all causes for which there was significant regional heterogeneity in most countries, cf. table VII.3) and for Total mortality, table VII.7 presents the signs of the regression coefficients for each medical care variable, estimated with a model containing all socio-economic and medical care variables. Negative coefficients were expected, implying lower mortality in regions with a larger supply of medical care.

Table VII.7 Signs [a] of the regression coefficients of medical care variables [b], controlling for socio-economic variables, by country and cause of death [c], 1974-78.

	TUB			CERV			CRHD			HYP			PERI			ALL		
	G	B	C	G	B	C	G	B	C	G	B	C	G	B	C	G	B	C
Belgium	+	-	+	+	+	-	-	▬	-	+	-	+	-	-	-	+	-	-
W.Germany	-	+	+	-	-	+	-	-	+	-	+	+	-	+	-	-	+	+
Denmark	-	-	+	+	+	-	-	-	+	-	+	+	-	-	+	-	+	-
France	-	+		-	+	-	+	+	-	-	+	-	+	-	▬	▬	+	+
Greece	+	▬		-	+		+	+		+	-		n.a.			+	▬	
Italy	▬	-	-	-	▬	+	-	-	-	▬	-	-	+	+	-	▬	-	-
Netherlands	+	-	+	-	+	+	-	+	+	-	-	+	+	-	-	+	-	-
England/Wales	-	+	+	▬	+	▬	-	-	-	▬	-	▬	▬	-	-	▬	+	-
Scotland	+	-	+	-	-	-	+	+	-	+	+	▬	+	+	-	+	-	-
EC [d]	+	-		-		-	+	+		+	-		+		+	+	-	

[a] A sign of the regression coefficient is denoted by '▬' if the one-sided test that it is less than zero is significant ($p < 0.05$). When no sign is given the variable has not been entered into the regression because the tolerance level was exceeded.

[b] The variables are represented by the following characters:
G - number of general practitioners per 100,000 population
B - number of acute hospital beds per 1000 population
C - number of consultants per 100,000 population
In the case of Greece 'G' stands for the number of general practitioners and consultants together.

[c] For abbreviations, see table VII.1.

[d] Calculated on the basis of national data. Luxembourg, Greece, Ireland, Northern Ireland, and England and Wales were excluded because of incompatible or missing data.

The general pattern suggests that the coefficients assume positive and negative values in a random way. Not surprisingly, the coefficients only very rarely attain statistical significance in the countries with a small number of regions. In Italy and England and Wales, but not in France, the coefficients are slightly more often negative than positive. Unexpectedly, a negative association (statistically significant) with general practitioner density is also found for Total mortality in France, Italy, and England and Wales.

Table VII.8 Percentage of variance in SMR's explained by medical care variables only (MC), by socio-economic variables only (SE), and by both medical care and socio-economic variables (MC + SE), by cause of death [a] and country, 1974-1978.

	TUB			CERV			CRHD			HYP			PERI			ALL		
	MC	SE	MC+SE	MC	SE	MC+SE	MC	SE	MC+SE	MC	SE	MC+SE	MC	SE	MC+SE	MC	SE	MC+SE
France	6	49	50	5	10	12	16	8	23	17	41	46	11	30	35	12	61	64
Italy	21	6	26	19	19	27	47	76	77	26	9	26	55	70	76	29	10	35
England/W.	29	57	60	28	32	50	11	36	39	16	58	67	16	35	49	26	77	83

[a] For abbreviations, see table VII.1.

Table VII.8 gives the percentage of variance explained by medical care variables only (MC), by socio-economic variables only (SE), and by both medical care and socio-economic variables (MC+SE). The difference between SE and MC+SE gives the additional percentage of variance explained by medical care variables after entering socio-economic variables. We only present the results for France, Italy and England and Wales. The number of regions is small in other countries, so that when six independent variables are entered into the regression, the percentage of variance explained will be artificially high.

It appears that the contribution of medical care variables to the explanation of regional mortality differences is quite modest, both without control for confounding variables and when measured as the additional percentage of variance explained after entering socio-economic variables. Without control for confounding variables, the percentage of variance explained by medical care variables is relatively high for Chronic Rheumatic Heart Disease and Perinatal mortality in Italy. After entering socio-economic variables, however, the extra contribution of medical care variables is small. There is no systematic difference in the contribution of medical care variables between the selected causes of death and Total mortality.

The contribution of socio-economic variables to the explanation of regional mortality differences is sometimes considerable. Generally, better socio-economic conditions are associated, as expected, with a lower level of mortality, both from the selected causes and from all causes together. It is interesting to see that socio-economic variables can account for a large part of the variance in Total mortality in France and England and Wales, but not in Italy. This points again at the peculiar regional pattern of Total mortality in Italy that was already mentioned in section VII.5.

VII.7 Discussion

With this paper we aim at contributing to the debate on the relationship between medical care and regional differences in mortality. We are aware of the fact that mortality covers only one objective of medical care, but it is an important and relatively "hard" criterion. Our analyses of the relationship between medical care and mortality differ from previous studies in two respects:
- we analysed mortality from a number of carefully chosen conditions, known to be amenable to medical intervention;
- we made parallel analyses of the situation in a number of countries which are known to have different levels and degrees of variation in medical care supply.

The results show that, although a common pattern of regional mortality for the selected conditions can to a certain extent be distinguished, this pattern generally resembles the pattern of regional variation in Total mortality. More specific intercorrelations, e.g. between causes of death which refer to broadly the same type of medical care, were not found. This suggests that the pattern of regional variation for these causes is not determined by a common medical care factor.

The results further show that levels of medical care supply generally add little to the explanation of regional differences in mortality from the selected conditions. This also applies to countries like France and Greece, where regional variation in medical care supply is substantial. The relationships found are seldom statistically significant, and are not very consistent. No important differences with Total mortality have been observed.

Before coming to any conclusions, one preliminary question should be whether these results could be explained by deficiencies in the data or in the analysis. Our mortality data certainly have a number of weaknesses:

- Small numbers of deaths: mortality from conditions amenable to medical intervention is generally low, which leads to a rather important role of chance fluctuations, for example evident from the less consistent loading of smaller causes of death in the factor analysis. This is inherent to the approach, but it is theoretically possible that important relationships between mortality from one of the smaller conditions and levels of medical care supply exist, which are obscured by the "noise" present in the data.

- Misclassification of deaths: cause-specific mortality data potentially suffer from misclassification, as both certification of the cause of death (by doctors) and coding of death certificates (by coding officers) are subject to error. Even if one assumes these misclassifications to be nondifferential (cf. ref. 20), there will be a bias toward the null, i.e. measures of medical care supply effects will be underestimated [21].

- Aggregate level: the area level chosen for the presentation of mortality data in the Atlas conceals a certain amount of medical care supply variation present at lower levels of aggregation, which might have a stronger relationship with mortality levels. The information for West-Germany is particularly handicapped by its level of aggregation, but in principle the same problem applies to all countries.

A feature of our analysis which might also have obscured some of the relationship, if any, between medical care supply and mortality is that we considered socio-economic variables to be confounding variables, and consequently controlled for socio-economic variations in the regression analysis. Socio-economic conditions and the level of medical care supply are often correlated [22]. For most countries of the EC we found high correlations (smaller than -0.7 or larger than +0.7) between socio-economic variables and medical care variables, most of them indicating an inverse relationship (better socio-economic conditions, more medical care). Such multicollinearity renders estimates of regression coefficients unstable.

Although the results from the regression analysis may in part be explained by features of the data or the analysis, we tend to believe that in most EC countries regional differences in mortality from selected conditions do not to any serious extent reflect inequalities in the level of medical care supply. Levels of medical care supply within EC countries are probably above a minimum level necessary for effective modification of case fatality, and any real shortages in medical care supply are probably readily compensated for by cross-regional patient flows. Mortality differences are then much more the result of variations in other factors.

This is not to say, however, that any relationship between regional mortality and medical care factors is necessarily non-existant. The way in which the available level of supply is organised, made to conform to quality standards, and made accessible to the population is probably more important in the prevention of "avoidable" deaths than the level of supply itself. The low correlation which was found between mortality from Cholelithiasis and -cystitis, Appendicitis, and Abdominal hernia may perhaps be interpreted as an indication that the relevant medical care factors are much more subtle than originally expected.

An important next step might therefore be to examine whether more subtle, condition-specific indicators of the quality and accessibility of medical care at the regional level can be developed and used in aggregate level analyses. As it is highly improbable that these indicators will be comparable across countries further studies should be done within individual countries. At this moment, such studies are in progress in England and Wales, Belgium, The Netherlands, and France.

Another, at least as promising line of research would be to leave the realm of aggregate data studies and to investigate indivi-

dual deaths in an attempt to identify deficiencies in the availability, uptake, and effectiveness of medical services. There is an important tradition for this type of study in the field of Maternal and Perinatal mortality, where confidential enquiries have been used to obtain detailed information on the care received by the deceased [23, 24]. This approach is probably also feasible for other causes of death. Local "avoidable factors" in medical services may be found to have a substantial impact on the incidence of deaths from these causes. One of the main uses of the data of the Atlas of Avoidable Mortality would then be the identification of "hot spots" of avoidable mortality, where further investigation promises high rewards [25].

VII.8 Summary

This paper addresses the question whether regional mortality differences within developed countries reflect differences in supply of medical care. It adds two new elements to previous studies on this subject: its focus is on mortality from selected conditions, considered to be amenable to medical intervention, and it makes parallel analyses for ten EC countries. The results show that levels of medical care supply contribute little to the explanation of regional differences in mortality from the selected conditions. It is concluded that if regional differences in mortality from these conditions are related to medical care, other factors than the level of supply are probably involved.

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VIII Regional differences in mortality from conditions amenable to medical intervention in The Netherlands

– a comparison of 4 time-periods

VIII.1 Introduction

Monitoring the effectiveness of medical care services at population level is not the easiest task of health care policy makers. This activity requires the availability of outcome indicators that are precise and valid, and that are easy to collect. Unfortunately, there is no abundance of such indicators [1].

An English research group, building upon the work of Rutstein et al [2], has proposed to use data on mortality from conditions which are considered to be largely amenable to medical intervention [3]. Important geographical variation in mortality from such conditions has been demonstrated, both in England and Wales [3] and in other countries of the European Community [4]. The important question now is, whether these mortality differences indeed reflect differences in medical care outcome, and, if so, to which aspects of medical care delivery these outcome differences can be traced.

Two approaches to obtain an answer to this question have been distinguished: studies of the association between mortality, medical care characteristics, and potential confounding factors at an aggregate level, and in-depth studies of medical care and other factors in individual deaths from such causes [5]. The latter approach, while probably being the most informative, presents many practical and methodological difficulties, and has not yet yielded any published results.

The former approach however, being more feasible, has already produced some empirical findings. In England and Wales, it was found that regional variation in morbidity, estimated from hospital admissions, notifications of infectious diseases, and cancer registry data, could only partly explain regional variation in mortality from conditions amenable to medical intervention [6]. In another study, negative associations were found between mortality from such "avoida-

ble" causes and some indicators of the level of resource provision (i.e. a higher level of provision was associated with a lower level of mortality, as expected). It was noted that a correction for socio-economic differences would probably reduce the associations, as medical care supply and socio-economic conditions are strongly correlated in England and Wales [7]. In Belgium, positive associations were found between mortality from the selected conditions and the level of medical care supply, after controlling for socio-economic conditions [8]. From France, weak negative associations, after controlling for socio-economic factors, have been reported [9]. In a comprehensive analysis of the relationship between medical care supply and mortality from these conditions in all countries of the European Community, we found associations to be generally weak and inconsistent [Chapter VII].

Mortality from conditions which have become amenable to medical intervention has generally decreased in the past decades [10, 11; Chapter VI]. For each of these conditions, mortality decline in part reflects the introduction and diffusion of (a number of) innovations in the medical care system. This suggests that associations between mortality levels and medical care supply characteristics at regional level could well be time-dependent in the following way:
- before a given cause of death becomes amenable to medical intervention, regional mortality levels are not associated with medical care supply characteristics;
- during introduction and diffusion of the innovation(s) an association may emerge between regional mortality levels and one or more medical care supply characteristics if the latter determine the degree of application of the intervention at that particular moment in time;
- after general diffusion, the association disappears again, due to the "law of diminishing returns" (a similar difference in degree of application produces a smaller difference in the level of mortality), and due to the fact that the prevailing degree of regional variation in medical care supply is not likely to bring about large enough differences in effort.

The analysis reported in this paper is an attempt to introduce this time dimension into the study of regional differences in mortality from "amenable" causes in The Netherlands. A presentation of the association with medical care supply characteristics in the early 1980's will be followed by an analysis of its evolution over time since the early 1950's.

VIII.2 Data

For four time-periods (1950-54, 1960-64, 1970-74, 1980-84) numbers of deaths, by age (0, 1-4, 5-14,.....85-94, 95+), sex, region, and cause of death were extracted from a large computerfile supplied by the Dutch Central Bureau of Statistics. Population numbers, by age, sex,

Table VIII.1 Causes of death selected for analysis, grouped according to time of introduction of effective medical interventions within the study period (1950-1984).

Group	Cause of death	Age-limits	Total number of deaths	
			1950-54	1980-84
I	Influenza and pneumonia	0-74	8973	2233
"Early"	Tuberculosis	0-74	5867	429
	Other infectious diseases [a]	0-74	4967	1162
II	Peptic ulcer	0-74	2197	901
"Early/	Three "surgical" conditions [b]	0-74	3646	1055
late"	Prostate hyperplasia	0-74	1365	194
	Perinatal mortality [c]	< 1 week	37898	9089
	Rheumatic heart disease	0-74	3905	2563
III	Congenital heart disease	0-74	2584	1453
"Late"	Cerebrovascular disease	0-74	21959	18492
	Hypertensive disease	0-74	4528	1618
	Cancer of cervix uteri	0-74	1443	1190
	Cancer at younger ages	0-34	3758	3069
IV	Total mortality, all causes	0-74	240504	277536

[a] Specific bacterial infections; viral diseases commonly occurring in children; Syphilis; Infections of central nervous system; Bacterial endocarditis; Infections of respiratory system other than Influenza and pneumonia; Infections of skin; Infections of locomotor system.
[b] Appendicitis; Cholelithiasis/-cystitis; Abdominal hernia.
[c] Still-births plus first-week deaths.

and region, were available from several sources based on the Dutch population register.

Although the mortality-file permits a larger number of regions to be distinguished, we amalgamated small contiguous regions so as to obtain a minimum population size of approximately 200.000 throughout the period 1950-84. The resulting number of regions was 28, with a minimum population size of 184.000 in 1950 and 225.000 in 1980, and with a median population size of 293.000 in 1950 and 477.000 in 1980.

The causes of death included in the analysis reported in this paper are presented in table VIII.1. International Classification of Disease (ICD)-codes [12] for the four revisions in force during the period 1950-1984 were selected to achieve maximum correspondence be-

tween revisions. National trends in mortality from each of the so-formed causes did not show important breaks between revisions, which suggests that the nosological content of these causes has not changed to a degree invalidating comparison over time. Age-limits were applied because avoidability of death and quality of cause-of-death certification become increasingly questionable with age.

The causes of death presented in table VIII.1 form a selection from a larger number of conditions which can be considered amenable to medical intervention (cf. ref. [2]). The analysis was restricted to those causes for which the number of deaths was reasonably large during most of the study-period, and for which mortality has declined in The Netherlands during (parts of) the period 1950-1984 [Chapter VI, in which selected references are given too]. In order to reach sufficient numbers of deaths, some smaller causes were grouped together (a number of "Other infectious diseases", 3 "Surgical" conditions, and all Cancers in children and young adults, a large proportion of which has become manageable with the advances against Morbus Hodgkin, Leukemia, Cancer of the testis, &cetera [13]).

The resulting selection of diseases has been ordered in table VIII.1 according to the moment of introduction of medical care innovations. Chemotherapeutics and antibiotics, important in the reduction of infectious disease mortality, were introduced before 1950. Although some effective interventions were available before 1950 for group II, important improvements and further significant innovations took place during the study-period. Effective medical interventions for Congenital heart disease, Cerebrovascular and Hypertensive disease, Cancer of cervix uteri and Cancer at younger ages only became available late in the study-period.

The number of variables available for "explanation" of regional mortality patterns (table VIII.2) is rather restricted, due to the fact that statistical information on a regional level has become more extensive only in recent years. Four medical care supply characteristics (two on the general level of supply, and two indicators of the level of technology in hospital care) were available for the whole study-period. Three sociodemographic characteristics could be used to control for possible confounding: average income (as an indicator of socio-economic conditions), net immigration (which may indicate another aspect of socio-economic development, and perhaps also selection processes) and urbanisation (as an indicator of ways of living). The fertility rate (number of births per 1000 females 15-49 years), not mentioned in table VIII.2, will be used as an additional control variable in the analysis of Perinatal mortality.

It is clear from table VIII.2 that general practitioner density has decreased since 1950-54, and that hospital bed density has increased, whereas there has been a sharp reduction in the percentage of regional hospital beds located in small hospitals. The coefficient of variation of general practitioner density has decreased substantially, which indicates increasing geographic homogeneity. Average

Table VIII.2 The medical care supply characteristics and sociodemographic variables used in the analysis.

	Variable	1950-54 Mean	1950-54 Coeff. of variation	1980-84 Mean	1980-84 Coeff. of variation
GP	Number of general practitioners (per 10.000 population)	4.48	26	3.81	7
BED	Number of hospital beds (per 1000 population)	3.94	28	4.57	25
UNIV	Percentage of regional hospital beds located in university hospitals	7.14	255	7.33	217
SMALL	Percentage of regional hospital beds located in small hospitals (i.c. with less than 200 beds)	46.34	69	12.07	105
INC	Mean income per capita (in 1000 guilders)	1.16	16	12.27	11
MIGRA	Crude immigration rate (per 1000 population)	-2.66	0.45 [a]	0.17	0.33 [a]
URB	Degree of urbanisation [b]	25.20	108	28.15	78

[a] Standard deviation instead of coefficient of variation.

[b] Calculated as (0.5 * A) + B, where A and B are the percentage of population living in cities with 50,000 - 100,000 and more than 100,000 inhabitants respectively.

income has of course increased (not corrected for inflation), but geographical heterogeneity has decreased.

Intercorrelations between medical care and other independent variables were generally of a modest magnitude. In 1950-54 the only product-moment correlation > .50 or < -.50 was between the percentage of beds in small hospitals (SMALL) and degree of urbanization (URB) (-.57). In 1980-84 the only larger correlation was between hospital bed density (BED) and average income (INC) (.50).

VIII.3 Methods

For each cause of death (except Perinatal mortality) and for each of the 4 periods, regional Standardized Mortality Ratios (SMR's) were calculated using national age- and sex-specific mortality rates of the

same period as the standard. Regional Perinatal mortality rates (still-births and first-week deaths, per 1000 births) were expressed as a percentage of the national rate for the same period. For each cause of death and each period an over-all chi-square-test on heterogeneity between regions was carried out [14].

In the regression analyses, the (natural) logarithm of the SMR (ln SMR) was used as the dependent variable, so that, for example, an SMR of .50 is treated as having the same distance to 1.00 as an SMR of 2.00. In order to minimize the influence of chance fluctuations, regions were weighted according to the reciprocal of the variance of their SMR's, under the assumption that for these, mostly small, causes of death the variance of the error term in the regression is dominated by sampling variation [15]. The variance of ln SMR is equal to the reciprocal of the observed number of deaths [16]. The calculations were carried out with the BMDP-package.

Spatial patterns, either of disease or of explanatory variables, often exhibit a simple gradient structure; e.g. in The Netherlands there is a north-south gradient of mortality which can be followed through Belgium into Northern France [17]. Such mortality gradients probably reflect (otherwise unobservable) environmental, social or cultural factors, i.e. not medical care. The a priori probability of two geographic gradients being non-orthogonal is high, so that a significant association between e.g. medical care supply and mortality might exist solely because of similar gradients [15].

Variables describing geographic mortality gradients can thus be treated as potential confounders. Two series of multiple regression analyses were therefore carried out. In a first series only the independent variables mentioned in table VIII.2 were entered. In a second series we added a set of variables which permit the measurement of geographic gradients in mortality: longitude, latitude, the squared values of longitude and latitude, and the cross-product. The parameter estimates obtained with the regression model of the first series were quite robust against the addition of variables describing geographic gradients, so that we will only report the results of the more parsimonious model.

VIII.4 Results

Regional variation in mortality from the selected causes is mostly much larger than could be expected to occur by chance alone (table VIII.3). Cancer in children/young adults, where geographic heterogeneity never reached conventional levels of statistical significance, is the exception. This is not a small number problem (cf. table VIII.1), but appears to be due to a lack of variation. As was to be expected, the coefficient of variation in general is larger with smaller numbers of deaths (compare tables VIII.1 and VIII.4). On the

Table VIII.3 Regional variation in mortality from the selected causes: coefficient of variation of SMRs and significance level according to chi-square-test for heterogeneity between regions.

		Coefficient of variation/ significance level			
		1950-54	1960-64	1970-74	1980-84
I	Influenza and pneumonia	21 / ***	19 / ***	20 / ***	16 / ***
	Tuberculosis	23 / ***	40 / ***	25 /	37 / ***
	Other infectious diseases	10 / **	12 / *	16 / **	16 / **
II	Peptic ulcer	22 / ***	23 / ***	14 /	28 / **
	Three "surgical" conditions	18 / ***	20 / ***	18 / ***	26 / ***
	Prostate hyperplasia	23 / ***	24 / **	31 / **	44 /
	Perinatal mortality	9 / ***	8 / ***	8 / ***	8 / ***
	Rheumatic heart disease	20 / ***	15 / ***	17 / ***	18 / ***
III	Congenital heart disesae	19 / **	13 / **	15 / *	19 / *
	Cerebrovascular disease	9 / ***	12 / ***	10 / ***	10 / ***
	Hypertensive disease	17 / ***	25 / ***	20 / ***	15 / *
	Cancer of cervix uteri	23 / ***	21 / ***	15 / *	20 / ***
	Cancer at younger ages	12 /	13 /	11 /	15 /
IV	Total mortality, all causes	6 / ***	6 / ***	5 / ***	5 / ***

Significance levels: blank $p \geq .05$; * $p < .05$; ** $p < .01$; *** $p < .001$

other hand, Other infectious diseases, "Surgical" conditions, and Cancer of cervix uteri, being about equal in size in 1980-84, have differing degrees of regional variation, with "Surgical" conditions clearly in top.

In the course of time, most of the causes of death have decreased in size. The accompanying increase in the relative importance of chance fluctuations will tend to inflate the coefficient of variation. It is remarkable, therefore, that in some of these causes the coefficient of variation has decreased or remained stable instead, as in Influenza and pneumonia, Perinatal mortality, and Hypertensive disease. This suggests increasing geographic homogeneity of mortality from these causes.

Table VIII.4 Correlation of mortality with medical care supply characteristics, 1980-1984.

		Product moment correlations [a]			
		GP	BED	UNIV	SMALL
I	Influenza and pneumonia	.13	.10	-.00	-.07
	Tuberculosis	.00	.30	-.11	-.13
	Other infectious diseases	-.07	.22	-.03	-.22
II	Peptic ulcer	.13	-.02	.09	.17
	Three "surgical" conditions	-.20	-.26	-.53*	.35+
	Perinatal mortality	.20	.05	-.28	-.16
	Rheumatic heart disease	-.45*	-.04	.06	-.05
III	Congenital heart disease	.16	-.06	-.32+	.09
	Cerebrovascular disease	-.21	-.14	-.26	-.31
	Hypertensive disease	.06	.25	-.25	.34+
	Cancer of cervix uteri	.18	.11	.04	.28
IV	Total mortality, all causes	.09	.01	.07	-.26

Significance levels (two-sided test): + $p < .10$; * $p < .05$.
[a] Unweighted correlations (n = 28).

Table VIII.4 gives a first impression of the association between mortality and medical care supply characteristics in 1980-84, excluding causes for which no statistically significant geographic heterogeneity was found. The number of significant correlations is very small. The overall pattern is not very consistent, although all correlations attaining some degree of statistical significance are in the expected direction: negative for general practitioner density (GP) and percentage of regional hospital beds located in university hospitals (UNIV), positive for percentage of regional hospital beds located in small hospitals (SMALL).

Table VIII.5 Regression of mortality on medical care supply characteristics, controlling for sociodemographic variables, 1980-1984 [a].

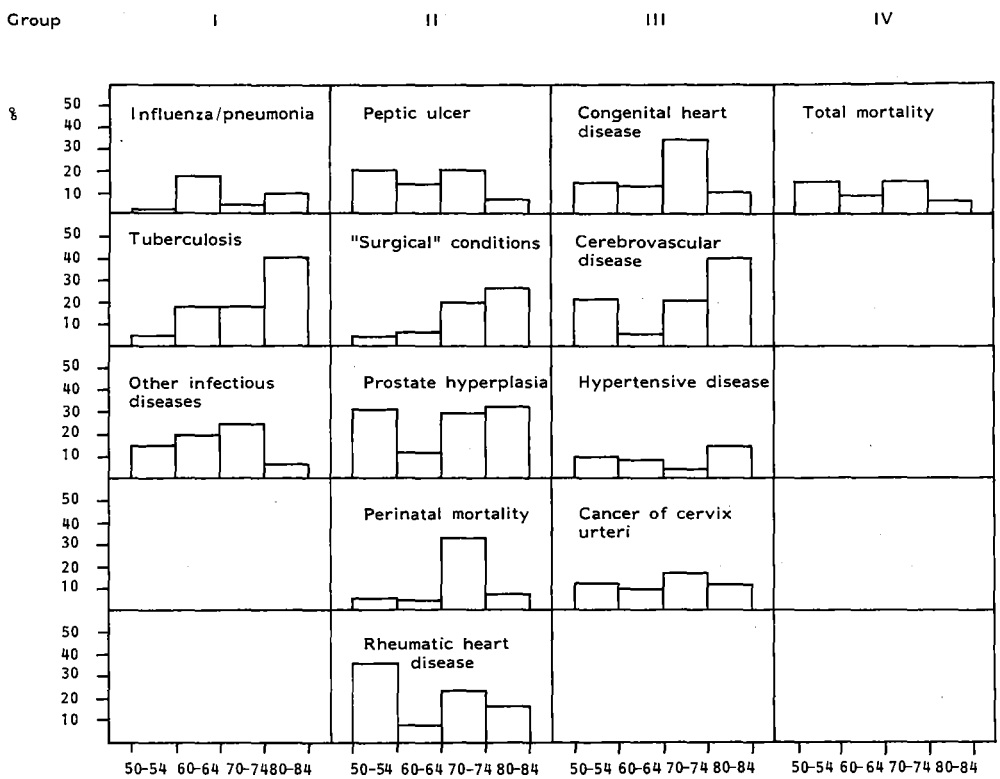
		Regression coefficient			
		GP	BED	UNIV	SMALL
I	Influenza and pneumonia	.177	.011	-.0027	-.0011
	Tuberculosis	-.103	.253*	-.0076	-.0076
	Other infectious diseases	-.092	.023	-.0020	-.0023
II	Peptic ulcer	.224	-.004	.	.0028
	Three "surgical" conditions	-.151	.012	-.0087*	.0048
	Perinatal mortality	.045	-.017	-.0014	.0003
	Rheumatic heart disease	-.337+	.063	.0008	.0019
III	Congenital heart disease	-.036	-.003	-.0047	-.0018
	Cerebrovascular disease	-.037	.017	-.0040*	-.0042*
	Hypertensive disease	-.080	.025	-.0027	.0043
	Cancer of cervix uteri	.132	-.029	.0001	.0049
IV	Total mortality, all causes	.005	.006	-.0005	-.0010

Significance levels (two-sided test): + $p < .10$; * $p < .05$.

[a] Multiple regression model containing four medical care variables and three sociodemographic variables. Dependent variable is ln SMR, weighted with the observed number of deaths. When no value is mentioned in the table, the variable has not been entered into the regression model because the tolerance level was exceeded.

Multiple regression analysis produces a slightly different picture of the associations between mortality and medical care supply characteristics in 1980-84 (Table VIII.5). The number of statistically significant associations is again very small. Some of these are in the expected direction, but others are not, e.g. between mortality from Tuberculosis and hospital bed density (positive), and between Cerebrovascular disease mortality and % beds in small hospitals (negative).

Figure VIII.1 Additional percentage of variance explained by medical care supply characteristics, after controlling for sociodemographic variables.



In order to investigate whether the associations between mortality from the selected causes and medical care supply characteristics are time-dependent, the results of regression analyses for each of the 4 time-periods were compared. For each cause of death figure VIII.1 shows the (additional) percentage of variance explained by the four medical care supply variables, after controlling for sociodemographic variables. We expect relatively important contributions of medical care variables in 1950-54 and 1960-64 for group I, and in 1970-74 and 1980-84 for group III. For group II, it is more difficult to specify such a hypothesis.

The findings show that the associations are indeed time-dependent, but that the timing of changes only partly conforms to our expectations. In group I, medical care variables contribute little in 1950-54, and a bit more in 1960-64. The largest contribution is for Tuberculosis in 1980-84.

In group III, the contribution of medical care supply characteristics to the explanation of regional mortality patterns is relatively small in 1950-54 and 1960-64 for all diseases, except for Cerebrovascular disease. An important association emerges in 1970-74 for Congenital heart disease. For Cerebrovascular disease the contribution of medical care variables increases towards the end of the study-period.

In group II, changes in the association with medical care variables can be seen for several diseases. For "Surgical" conditions the additional percentage of variance explained is larger in 1970-74 and 1980-84. For Prostate hyperplasia the contribution is relatively large in 1950-54, then decreases, and finally increases again. For Perinatal mortality, a larger contribution of medical care supply characteristics emerges temporarily in 1970-74.

For Total mortality the additional percentage of variance explained by medical care variables after controlling for sociodemographic factors is uniformly small.

Table VIII.6 presents parameter estimates for those combinations of time-periods and causes of death that were characterized by relatively high additional percentages of variance explained ($\geq$ 20%) by medical care variables. General practitioner density has many statistically significant associations with mortality, but many of these are not in the expected direction. The negative associations between the percentage of regional hospital beds located in university hospitals are in line with our expectations.

Table VIII.6 Regression of mortality on medical care supply characteristics, controlling for sociodemographic variables, for a few selected causes of death and time-periods [a].

		Regression coefficient			
		GP	BED	UNIV	SMALL
I	Tuberculosis (1980-84)	-.103	.253*	-.0076	-.0076
	Other infectious diseases (1960-64)	.039+	.020	-.0005	-.0008
	Other infectious diseases (1970-74)	.250*	.007	-.0019	-.0007
II	Peptic Ulcer (1950-54)	.034	.064	.0015	.0037*
	Peptic Ulcer (1970-74)	-.045	.048	-.0037+	-.0008
	"Surgical" conditions (1970-74)	.038	.069	-.0034	.0039+
	"Surgical" conditions (1980-84)	-.151	.012	-.0087*	.0048
	Prostate hyperplasia (1950-54)	.046	.151*	-.0008	.0024
	Prostate hyperplasia (1970-74)	.464*	.006	.	.0029
	Prostate hyperplasia (1980-84)	-.700*	-.037	-.0061	.0058
	Perinatal mortality (1970-74)	.134*	-.004	-.0026*	-.0004
	Rheumatic heart disease (1950-54)	-.100*	-.039	.0031	-.0024
	Rheumatic heart disease (1970-74)	-.288*	.064	-.0010	.0002
III	Congenital heart disease (1970-74)	.022*	.010	-.0018	-.0006
	Cerebrovascular disease (1950-54)	.097	.016	.0005	-.0012
	Cerebrovascular disease (1970-74)	-.087	.027	-.0020+	-.0006
	Cerebrovascular disease (1980-84)	-.037	.017	-.0040*	-.0042*

Significance levels (two-sided test): + $p < .10$; * $p < .05$.
[a] See note a, table VIII.5.

VIII.5 Discussion

In The Netherlands, as in many other countries, important geographical variation in mortality from conditions amenable to medical intervention exists. For a recent time-period (1980-84) associations with a number of simple medical care supply characteristics were shown to be weak and inconsistent - a finding analogous to that of other studies.

Meaningful associations were, however, not totally absent. The presence of a university hospital appears to be associated with lower mortality levels for "Surgical" conditions and Cerebrovascular disease. Further study is necessary to reveal whether or not this is a spurious association, occurring by chance (multiple significance testing as in tables VIII.4 and VIII.5 is likely to produce a small number of statistically significant coefficients, even in the absence of any real associations), or due to insufficient control of confounding variables.

A comparison of regression results over time shows, that the percentage of variance in regional mortality levels which can be "explained" by medical care supply variables is rather time-dependent. Associations emerge and disappear, and although the timing of these changes is not very different from what one would expect on an a priori basis, the exact nature of the associations is sometimes puzzling. A larger number of general practitioners per 10.000 population (which is equivalent to smaller average list-size of general practitioners) repeatedly was associated with higher mortality from conditions amenable to medical intervention. Again this could be a spurious association, but it could also indicate that improvements in medical care reach the average patient with these conditions later in regions where a larger proportion of patient care is being delivered by general practitioners.

In the regression analyses the sociodemographic variables were treated as possible confounders, suggesting that associations between these variables and mortality are not to be viewed as effects of variations in medical care delivery. This is not necessarily true. Part of the effects of average income and degree of urbanisation on mortality might arise from differences in other aspects of medical care delivery than were reflected in the four measures of medical care supply used in this study. Unfortunately, it is very difficult to separate the contribution of different mechanisms without more detailed information.

The question, whether geographic variation in mortality from conditions amenable to medical intervention reflects differences in medical care outcome, and, if so, to which aspects of medical care delivery these outcome differences can be traced, is only partly answered by this study.

The absence of a clear pattern of associations between medical care supply characteristics and mortality from these

conditions does not invalidate the latter as indicators of medical care outcome. Mortality could be determined by more specific aspects of medical care delivery, that are not strongly associated with the 4 crude variables available in this study.

On the other hand, our findings on the relationship between mortality and the supply of medical care suggest that, within the prevailing range of variation, differences in supply do not have serious effects on at least one outcome indicator, mortality. Whether this is a comforting or a disturbing thought is difficult to say.

VIII.6 Summary

In The Netherlands, as in many other countries, important geographical variation in mortality from conditions amenable to medical intervention exists. Associations with a number of simple medical care supply characteristics (general practitioner density, hospital bed density, and percentage of regional hospital beds located in university and small hospitals, respectively), are generally weak and inconsistent, both before and after controlling for possible confounders.

One of the possible reasons for this lack of consistency, viz. time-dependency of the relationship between medical care supply and mortality from these causes, was explored. A comparison of associations in 4 time-periods (1950-54, 1960-64, 1970-74 and 1980-84) shows that the percentage of variance in regional mortality levels which can be "explained" by the medical care supply variables, has changed over time.

Although patterns of change are not very different from what one would expect on the basis of the time of introduction of medical care innovations, the exact nature of the associations is puzzling. Apart from some expected negative associations between mortality and the presence of university hospitals, a few unexpected positive associations are found with general practitioner density.

Possible explanations for these findings are discussed, and it is concluded that further study is necessary to reveal the causes of a higher or lower mortality level for conditions considered to be amenable to medical intervention.

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IX Regional differences in decline of mortality from selected conditions, The Netherlands, 1969-1984

IX.1 Introduction

After a period of rather stable all-cause mortality rates, a decline set in at the end of the 1960's or the beginning of the 1970's in many industrialized countries. A reversal from an increasing to a decreasing mortality trend for Ischemic heart disease was among the main contributors to this event [1]. Other conditions have contributed as well, either through acceleration of an already apparent decline, such as in Cerebrovascular disease [2] and Perinatal mortality [3], or through the onset of new declines, as seen in certain smaller cancers [4].

Although very few would disagree that improvements in medical care did have some effect, there is no consensus on their exact contribution, and other factors certainly also played an important role. The trend reversal for Ischemic heart disease, the most widely discussed of the favourable cause-specific mortality changes, is generally ascribed to a combination of changes in life-style and medical care [5]. The contribution of medical care to mortality decline may have been relatively large for causes of death which are now considered to be amenable to medical intervention, like Cerebrovascular disease, Perinatal and Maternal mortality, some "surgical" conditions (such as Appendicitis), Hodgkin's disease, Cancer of the cervix etc. [6, 7].

The study reported here analysed regional variation in decline of mortality from a number of conditions for The Netherlands. A description of regional differences in mortality improvement was thought to provide useful information for health policy makers, because it identifies regions where progress is unsatisfactory. The analyses addressed the following questions:

- Did regions within The Netherlands differ in their rate of mortality decline for a number of important conditions during the period 1969-

1984?
- What patterns are formed by these differences, and how do regional differences in mortality decline relate to differences in mortality level?
- With which of a number of available socio-demographic or health care characteristics are these differences in mortality decline associated?

IX.2 Data and methods

Numbers of deaths, by age (< 1 week, 1-52 weeks, 1-4, 5-14,.....85-94, 95+ years), sex, calendar-year (1969-1984), region, and cause of death were available from a large computerfile supplied by the Dutch Central Bureau of Statistics. Numbers of still-births (necessary for the calculation of Perinatal mortality) were also obtained from the Central Bureau of Statistics. Mid-year population numbers, by age, sex, calendar-year and region were available from various sources based upon the Dutch population register.

39 regions were distinguished, with a median population size of 235.000 in 1969 and 303.000 in 1984. These so-called COROP-regions have been created for statistical purposes only, and represent geographical areas serviced by one or more larger cities. Region no. 40 (Zuidelijke IJsselmeer Polders), land which was recently claimed from the waters of the former Zuiderzee, was omitted because its population was increasing rapidly during the study-period (from 14.000 in 1969 to 116.000 in 1984).

Loglinear regression analysis was used to obtain estimates for regional mortality levels and trends, controlling for differences in (changes of) the size and age/sex-composition of the population. For computational reasons we first estimated national mortality levels, by age-group and sex, and national mortality trends. Then regional departures from national mortality levels and trends were estimated. For each region a regression equation was fitted to the observed number of deaths which had the following formal structure:

$$E(y_{ij}) = N_{ij} e^{\alpha_i + \alpha' + (\beta+\beta')X}$$

in which:

- $E(y)$ = absolute number of deaths in a region as expected under the model
- N = person-years at risk in a region
- e = base of the natural logarithm
- X = calendar-year
- α = national mortality level, fixed
- α' = regional departure from national mortality level, to be estimated

β = national mortality trend, fixed
β' = regional departure from national mortality trend, to be estimated
i = subscript denoting age/sex-group
j = subscript denoting calendar-year

In the case of Perinatal mortality, person-years at risk were replaced by the number of births. The model assumes that national mortality trends and regional departures from national levels and trends are the same, on a logarithmic scale, for all age/sex-groups (i.e. that there is no interaction between age/sex and calendar-year or region). The calculations were performed with the GLIM-package, specifying a Poisson regression model [8]. The GLIM-package produces maximum likelihood estimates using an iteratively reweighted least squares procedure.

Differences in scaled deviance (SD) between this model and a model not containing β' (but including α') were used to assess the statistical significance of β', by comparison with a chi-square-distribution with one degree of freedom [8]. Fitting these models to the observed values for each region r produces a series of differences in scaled deviance (dSD_r), the summation of which ($\Sigma_r dSD_r$) gives a test-statistic for the statistical significance of over-all geographical heterogeneity of mortality trends (chi-square-distribution, 38 degrees of freedom).

The causes of death selected for analysis are presented in table IX.1. Apart from Total mortality (all causes) we selected a number of important contributors to mortality decline in The Netherlands in the period 1969-1984. Perinatal mortality, Cerebrovascular disease and a global category of conditions which are frequently considered to be amenable to medical intervention are included, because an earlier analysis had shown that mortality decline for these conditions has contributed appreciably to trends in Total mortality in The Netherlands [Chapter VI] as it has in other countries [6, 7]. Stomach cancer is included because it is the only larger cancer for which mortality declined in the study-period [9]. After earlier sharp increases, mortality from Ischemic heart disease has been declining in The Netherlands since 1972 [10]. Mortality from Traffic accidents has shown a trend reversal comparable to that of Ischemic heart disease in The Netherlands [11], coinciding with the introduction of a number of preventive measures. International Classification of Disease (ICD)-code numbers for each of these conditions were carefully chosen so as to minimize the effects of the introduction of the 9th Revision in 1979. Inspection of mortality trends did not reveal important breaks between 1978 and 1979.

We exclude deaths at ages 75 and over, in order to reduce possible age/sex-interactions (mortality generally declined less in the very old) and because the validity of cause-of-death certification becomes increasingly questionable at higher ages. Mortality from

Table IX.1 Causes of death selected for analysis.

Cause of death	Age-range	National deaths 1969-84	National trend (% per annum mortality change) 1969-84 [a]
Perinatal mortality [b]	< 1 week	43877	- 4.9
Cerebrovascular disease	0-74	67666	- 3.2
"Amenable" selection [c]	0-74	185743	- 4.5
Cancer of the stomach	0-74	24188	- 3.6
Ischemic heart disease	0-74	210175	- 1.4
Traffic accidents	0-74	36721	- 5.8
Total mortality	0-74	922220	- 1.6

[a] Calculated as $100(\beta)$.
[b] Still-births plus first-week deaths.
[c] A selection of causes of death considered to be amenable to medical intervention [6, 7, 13]: Tuberculosis; Influenza and pneumonia; a number of other infectious diseases; Perinatal and Maternal mortality; Rheumatic heart disease; Appendicitis; Cholelithiasis and -cystitis; Abdominal hernia; Cerebrovascular disease; Hypertensive disease; Hodgkin's disease; Cancer of the cervix uteri.

the selected causes declined considerably in the age-group below 75 years during the study-period, as indicated by the last column of table XI.1. Total mortality also declined, although less than most of the selected conditions (except Ischemic heart disease).

IX.3 Results

Table IX.2 shows that the rate of mortality decline differed between regions in The Netherlands for most of the selected conditions. Overall regional heterogeneity of mortality trends is statistically significant for Perinatal mortality, Cerebrovascular disease, the "Amenable" selection, and Ischemic heart disease, as well as for Total mortality. For Cancer of the stomach and Traffic accidents, however, the regional variation in mortality decline is what could be expected to occur by chance alone.

A truncated range of variation is given by the last two columns of table IX.2, which present the 10th and 90th percentile values for the regional rates of mortality decline (in per cent per annum, calculated as $100(\beta + \beta')$). For e.g. Perinatal mortality, four-

Table IX.2 Geographic heterogeneity of cause-specific mortality trends, 39 Dutch regions, 1969-1984.

Cause of death	Significance tests		Truncated range of variation of regional trends (% per annum mortality change)[a]	
	Over-all test [b]	No. regions different ($p < .05$)	10th percentile	90th percentile
Perinatal mortality	71.9**	3	- 3.7	- 6.1
Cerebrovascular disease	60.1*	4	- 2.4	- 4.2
"Amenable" selection	76.3***	6	- 3.8	- 5.5
Cancer of the stomach	39.7	1	- 2.7	- 5.0
Ischemic heart disease	114.0***	12	- 0.6	- 1.9
Traffic accidents	52.4	4	- 4.4	- 7.0
Total mortality	124.7***	11	- 1.3	- 2.0

[a] Calculated as $100(\beta + \beta')$.

[b] $\Sigma_r dSD_r$, comparing the full model with an otherwise identical model not containing β'; significance levels (chi-square distribution, 38 degrees of freedom): * $p < .05$; ** $p < .01$; *** $p < .001$.

fifths of all regions thus have mortality declines between 3.7 and 6.1 % per annum. On the whole, the range of variation appears to be considerable.

On the other hand, for each of the selected conditions no region had a steady level of mortality (0 % decline), or a mortality increase; Total mortality also declined in all regions.

For Perinatal mortality, Cerebrovascular disease, Ischemic heart disease and Total mortality, patterns of regional variation are illustrated graphically in figure IX.1. To facilitate comparisons, figure IX.1 shows both the (long-term) regional departures from the national mortality level (α') and the regional departures from the national mortality trend (β'). Dark shading implies higher mortality levels (α' positive) and less rapid mortality decline (β' positive).

Average levels of Perinatal mortality over the entire period 1969-1984 were elevated in certain areas in the north, east and south of the country. It is only for a small number of regions that the trend of Perinatal mortality differed statistically significantly ($p < .05$) from the national trend, but areas of faster and slower decline tend to cluster together, suggesting a systematic pattern of variation. Mortality declined faster in some areas in the north, east and

Figure IX.1 Regional departures from national mortality levels and trends, 1969-84.

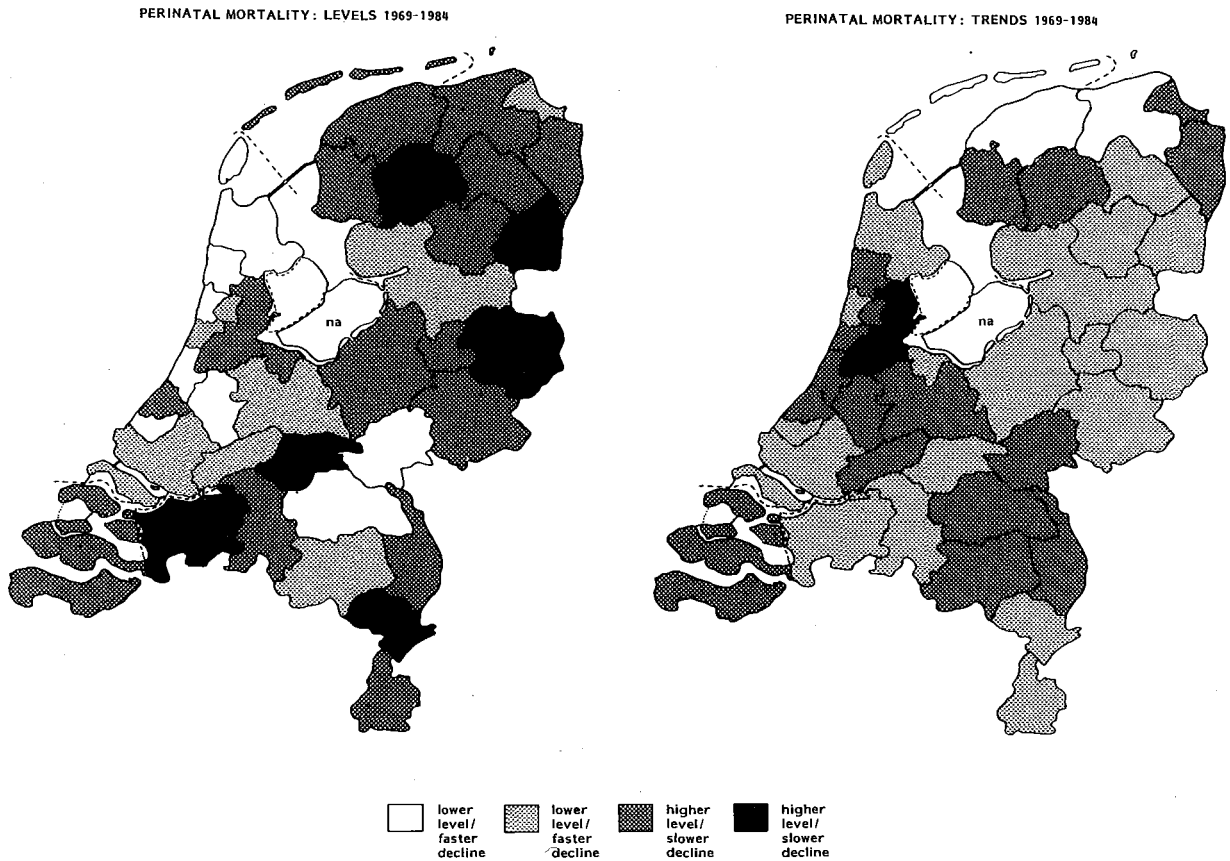


Figure IX.1 (continued) Regional departures from national mortality levels and trends, 1969-84.

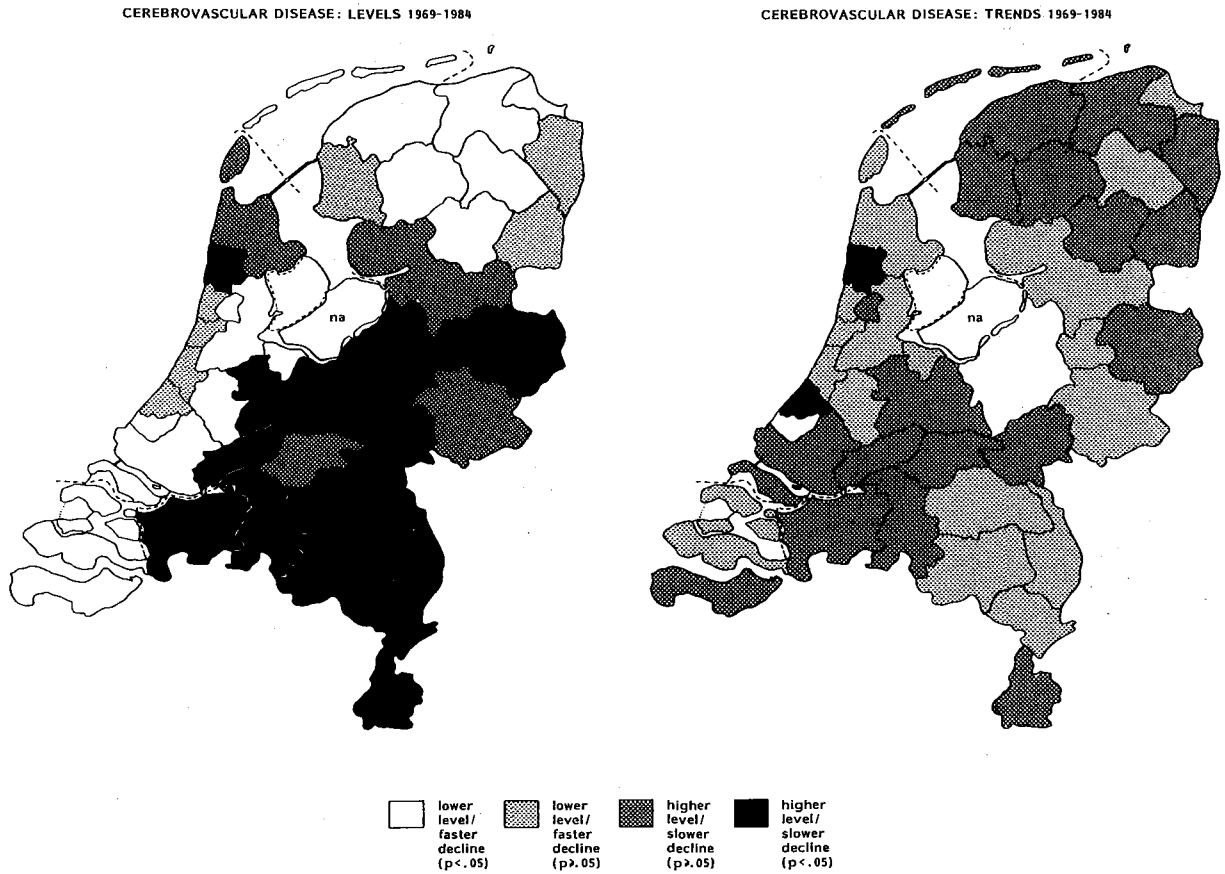


Figure IX.1 (continued) Regional departures from national mortality levels and trends, 1969-84.

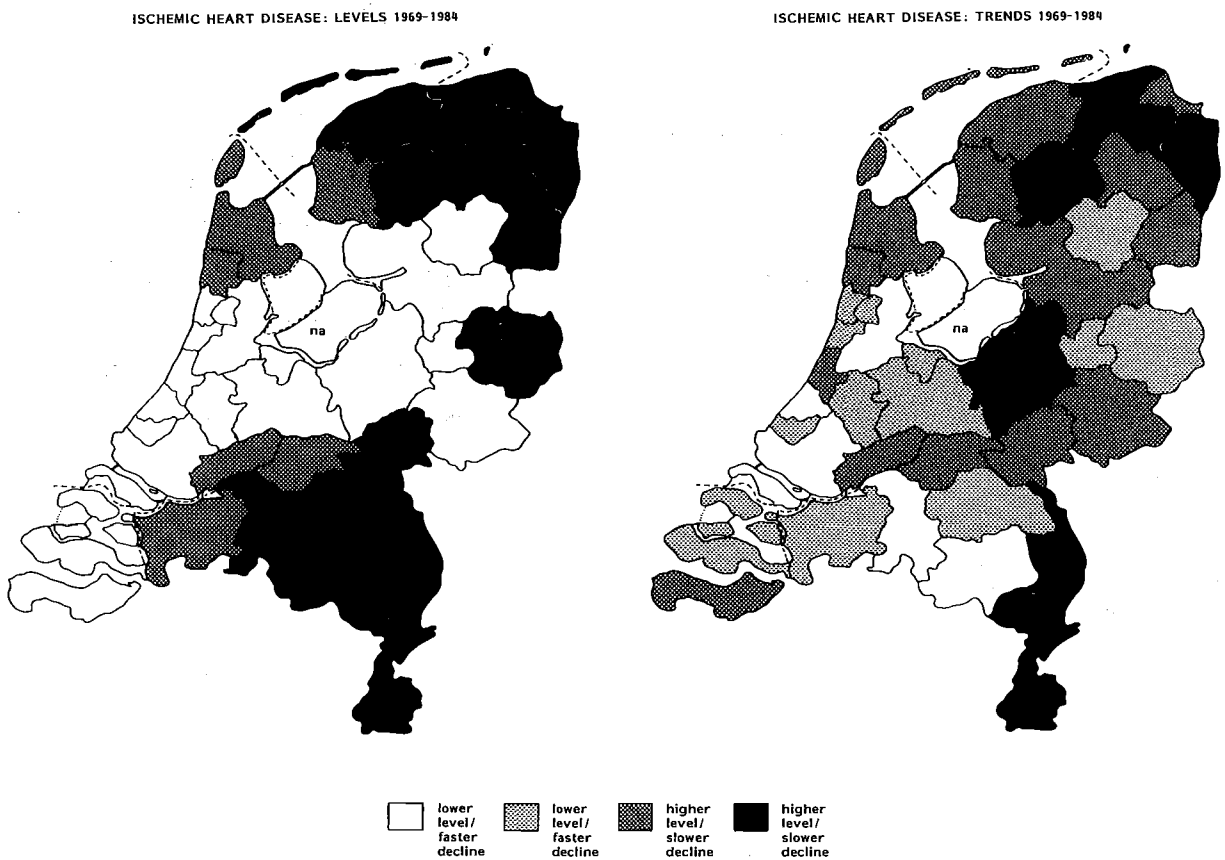
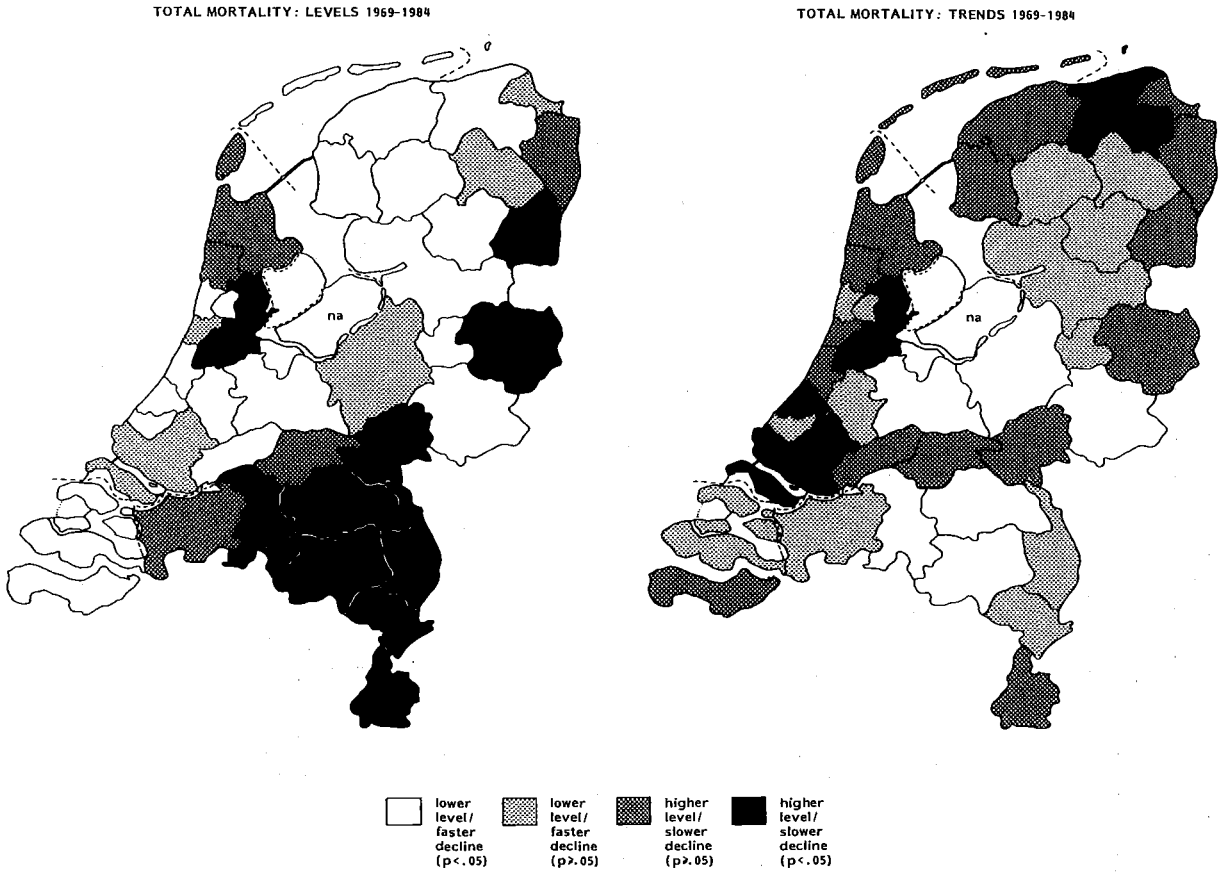


Figure IX.1 (continued) Regional departures from national mortality levels and trends, 1969-84.



south. Note that the region of Greater Amsterdam, which is the only region shaded black in the trend map (mortality decline slower than the national average, $p < .05$), did also have an unfavourable over-all level of Perinatal mortality.

Low levels of Cerebrovascular disease mortality can be found in a belt stretching from the north-east to the south-west of The Netherlands, and high levels in a large contiguous area in the south-east. Trends in mortality form a rather different pattern.

Although average mortality levels for Ischemic heart disease were also high in the south-east, there are some important differences with the pattern for Cerebrovascular disease: Ischemic heart disease mortality was also high in a large contiguous area in the north-east. Mortality decline has been fastest in the highly urbanized western parts of the country, as well as in some areas in the south. The north-east and south-east have had the least favourable trends.

One of the important features of the pattern of decline for Total mortality is that the decline was slower in the western regions containing the three largest cities, Amsterdam, Rotterdam and The Hague. In contrast to this, declines for Ischemic heart disease were faster in these regions.

A comparison between average levels and trends is important from a monitoring perspective: regions with both a higher average level and a more unfavourable trend clearly warrant attention. This comparison may, however, not give an accurate impression of tendencies of convergence or divergence. The average mortality level over the entire period 1969-1984 is partly determined by the trend of mortality over the same period: faster decline results in a lower average level of mortality. We therefore calculated correlations between the mortality trend and the mortality level in 1969 (as estimated with the parameter values obtained in the regression analysis)(table IX.3).

For Perinatal mortality, the correlation between the 1969-84 mortality trend and the 1969 mortality level is negative. Mortality declined faster in regions with a higher starting level, suggesting a certain convergence. For the other conditions, the correlation is positive, especially for Ischemic heart disease. For Ischemic heart disease mortality declined faster in those regions where the starting level was already lower, indicating a divergence of mortality levels.

Table IX.3 Correlations between regional departures from national mortality trends (β') and mortality levels in 1969.

Cause of death	Product-moment correlations [a] with mortality level 1969 [b]
Perinatal mortality	-.28
Cerebrovascular disease	.20
"Amenable" selection	.26
Ischemic heart disease	.45
Total mortality	.12

Note: Positive values for correlation coefficients imply less mortality decline in regions with a higher level of mortality in 1969.

[a] Weighted product-moment correlations (each pair of observations was weighted by 1/variance (β'); the variance is given as a result of the regression analysis).

[b] Value calculated for X = 0 using the estimated regression parameters.

In an exploratory search for covariates of regional trends in mortality we calculated correlation coefficients between the regional departures from the national mortality trend (β') and a number of variables, measured at the beginning of the study-period (table IX.4). We chose the following variables, which were hypothesized to be determinants of the uptake of innovations of whatever kind: the percentage of hospital beds located in university hospitals (UNIV), the percentage of population living in larger cities (URB), the distance in kilometers from the nearest city in the 'Randstad' (the cultural and economic centre of the country, located in an urbanized belt stretching between Amsterdam, The Hague, Rotterdam and Utrecht) (PERIF), and average income per inhabitant (INC).

Table IX.4 Correlations between regional departures from national mortality trends (β') and selected regional characteristics, ca.1970

Cause of death	Product-moment correlations [a] with [c]			
	UNIV	URB	PERIF	INC
Perinatal mortality	.18	.28	-.51	.44
Cerebrovascular disease	-.11	.16	.15	.00
"Amenable" selection	-.07	.40	-.15	.20
Ischemic heart disease	-.06	-.55	.63	-.48
Total mortality	.50	.53	-.05	.42

Note: Positive values for correlation coefficients imply less mortality decline in regions with a higher level of the other variable.

[a] See note a, table IX.3.

[b] UNIV: % of regional hospital beds located in university hospitals
URB: % of regional population living in larger cities
PERIF: distance in kilometers to the nearest city in the 'Randstad'
INC: average income per inhabitant.

These variables are of course intercorrelated, but some differences in the association with regional mortality decline do emerge (table IX.4). For Perinatal mortality, the "Amenable" selection, and for Total mortality, mortality in general declined less, contrary to what one might expect, in regions with a high degree of urbanization, a central location, and/or a high average income in ca. 1970. Note that Perinatal mortality, Cerebrovascular disease, and the "Amenable" selection did not decline faster in regions with a university hospital. These findings suggest that faster mortality decline for these conditions is not due to faster diffusion of new medical technologies.

Mortality from Ischemic heart disease declined faster in urbanized, centrally located, high income areas. There is, again, no association with the presence of a university hospital. This suggests that faster mortality decline is related to faster diffusion of new life-styles.

Table IX.5 Correlations between regional departures from national mortality trends (β') and changes in the level of possible mortality determinants.

	Product-moment correlations [a] with average yearly change (ca. 1970 - ca. 1980) in [b]:				
	BED	GP	INC	EDUC	UNEMP
Perinatal mortality	.00	-.02	-.12	-.31	.30
Cerebrovascular disease	-.20	.19	-.26	-.28	-.18
"Amenable" selection	-.08	.22	-.33	-.40	-.06
Ischemic heart disease	-.25	-.06	.17	.45	-.19
Total mortality	.05	-.05	-.65	-.21	.07

Note: Positive values for correlation coefficients imply less mortality decline in regions with a larger increase in the other variable.

[a] See note a, table IX.3.

[b] BED: number of hospital beds per 1000 population
GP: number of general practitioners per 1000 population
INC: average income per inhabitant
EDUC: % of population having attained more than first-level education
UNEMP: % of working population temporarily without work.

An alternative way of looking for covariates of differences in mortality trend is to investigate the association between changes in mortality and changes in possible determinants of mortality. Table IX.5, which provides correlations between changes in mortality and the supply of medical care, as well as between changes in mortality and socio-economic characteristics, may give some clues. Changes in hospital bed density (BED) and general practitioner density (GP) do not seem to be associated with rates of mortality decline. On the other hand, Perinatal mortality, Cerebrovascular disease, the "Amenable" selection and Total mortality declined faster where average income (INC) and/or education level (EDUC) increased more, mirrorring the well-known negative association between mortality levels and socio-economic conditions in cross-sectional analyses. Again, declines in Ischemic heart disease mortality show the reverse.

We included the association between changes in mortality and changes in unemployment levels (UNEMP) in table IX.5, because the rise in unemployment has been one of the most significant socio-economic developments in The Netherlands during this period. The correlations are however low, and not very consistent.

IX.4 Discussion

In the analysis reported above we explored an alternative approach to the study of geographical variation in mortality. Whereas most studies focus on differences in level of mortality, we tried to measure differences in trend. Cause-specific mortality trends are frequently quite dynamic, so that "snap-shots" of regional mortality levels at one moment in time can only give an incomplete picture of the regional mortality experience. We found regional differences in decline of mortality from selected conditions in The Netherlands to be of a relevant magnitude, although the range of variation did not include 0 % mortality decline.

Mere description of regional rates of mortality decline may already prove a useful addition to more conventional methods of surveillance. This applies both to the surveillance of mortality from conditions considered to be amenable to medical intervention [12] and to that of mortality from many other conditions, including those amenable to forms of primary prevention, such as Traffic accidents.

For the area of infant mortality Kleinman has recently suggested to look for the combination of a higher mortality level and a slower mortality decline, in order to focus further investigation on those regions where concern is certainly warranted [13]. Such regions can indeed be identified. For The Netherlands, examples of a combination of a higher level and a slower decline were pointed out above in the case of Perinatal mortality. The relevance of further study is enhanced here by the fact that national mortality declines for Perinatal mortality have recently been less favourable than in e.g. the Scandinavian countries, Switzerland and West-Germany [14]. For Ischemic heart disease, many areas in the north-east and south-east of The Netherlands are characterized by high mortality levels and unfavourable mortality trends.

Regional differences in decline of cause-specific mortality may be due to: - different trends in cause-of-death certification; - different trends in incidence; - and different trends in case fatality. Different trends in incidence and case fatality could be due to differences in effectiveness of certain interventions (primary and secondary prevention, treatment), but could also be "spontaneous".

In our very simple, exploratory analysis we found no evidence for an effect of differences in medical care on regional patterns of mortality decline. For Ischemic heart disease, the associations with other regional characteristics suggest that faster decline reflects a faster diffusion of new life-styles. If this were to be confirmed in further study, a clear case for primary prevention efforts in areas with slower decline would be present.

In addition some interesting associations with socio-economic characteristics were found. Mortality from Ischemic heart disease declined faster in high income areas, which already had favourable

mortality levels at the beginning of the study-period. This suggests a widening of mortality differentials, analogous to that reported on the basis of occupational mortality data from England and Wales [15]. Total mortality declined faster in areas where average income levels increased more. This may increase confidence in the existence of a causal relationship between socio-economic circumstances and mortality [16, 17]. The absence of an association at the regional level between trends in Total mortality and changes in unemployment levels is in line with the findings of a similar study from England and Wales [18].

The analysis of regional variation in mortality decline had a number of limitations. Although over-all geographical heterogeneity was statistically significant in all but two cases, the small number of regions for which the departure from the national mortality trend was significant at conventional levels, even for large causes of death, suggests that there are power problems which warrant further investigation.

One assumption on which the analysis is based was already mentioned in the Data and methods section (no interaction between age/sex and calendar-year or region). Another assumption is linearity, on a logarithmic scale, of the relationship between mortality density and calendar-year (for each region !). Visual inspection of regional mortality trends suggested that in the case of Ischemic heart disease this assumption was to some extent violated. Regions which apparently had faster mortality declines, actually were sometimes characterized by an early onset of mortality decline (i.e. before 1972, or even 1969). Regions for which the estimated value of β' was positive, sometimes had a relatively late onset of mortality decline. Geographic variation in the onset of mortality decline for Ischemic heart disease may more adequately be described with a quadratic regression model [19].

A general conclusion could be that the area of regional variation in mortality trends offers interesting prospects for further study.

IX.5 Summary

In The Netherlands, as in many other industrialized countries, recent mortality developments have been characterized by rapid declines for a number of important causes of death. The results of an analysis of regional variation in mortality decline within The Netherlands are reported, covering the period 1969-1984. The causes of death included in this analysis are Perinatal mortality, Cerebrovascular disease, a more global "Amenable" selection (formed by aggregating a number of causes of death considered to be amenable to medical intervention),

Cancer of the stomach, Ischemic heart disease and Traffic accidents.

For Perinatal mortality, Cerebrovascular disease, the "Amenable" selection, and Ischemic heart disease, as well as for Total mortality, declines have not been geographically homogeneous. Perinatal mortality had a tendency to decline faster in regions where starting levels were higher, suggesting a certain convergence. For Cerebrovascular disease and the "Amenable" selection, but especially for Ischemic heart disease, the reverse was true.

A simple correlation analysis shows that for Perinatal mortality, as well as for the "Amenable" selection, mortality declined faster in less urbanized, more peripherally located, lower income areas. There is no association with the presence of a university hospital. This pattern suggests that faster mortality decline for these conditions is due to other factors than faster diffusion of new medical technologies.

For Ischemic heart disease, mortality declined faster in more urbanized, more centrally located, higher income areas. Although this pattern is what one would expect as a result of regional differences in the diffusion of new medical technologies, it may also be due to differences in the diffusion of new life-styles. The absence of an association with the presence of university hospitals supports the latter view.

It is concluded that the monitoring of changes in mortality at the regional level is an important addition to the more usual analyses of mortality variation at one moment in time.

Acknowledgements

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X General discussion

X.1 Summary of the main findings and conclusions

Not so very long ago, the mortality rate in The Netherlands was much higher than it is to-day. In the mid-nineteenth century, the mortality rate fluctuated between 25 and 30 per 1000 person-years, and the average life expectancy at birth was less than 40 years. In the 1980's, the mortality rate is only 8 per 1000 person-years, and at current mortality rates life expectancy is well above 70 years. Although appr. 120.000 people die each year in The Netherlands death has become a rare event.

Nevertheless, even in recent time-periods important differences in mortality rates, by cause of death, can be observed between different "times, places and persons". The studies in the preceding chapters show that the words of one of the pioneers of mortality analysis in the nineteenth century, William Farr, still apply to-day: "Deaths and causes of death are scientific facts which admit of numerical analysis; and science has nothing to offer more inviting in speculation than the laws of vitality, the variations of those laws in the two sexes at different ages, and the influence of civilization, occupations, locality, seasons, and other physical agencies, either in generating disease and inducing death, or in improving the public health" (First Annual Report of the Registrar General, 1839, quoted in ref. 1).

X.1.1 Validity of cause-of-death statistics

This is of course dependent on the validity of cause-of-death information. Possible causes of bias in international comparisons of mortality were investigated in chapter II for two (groups of) causes of death, Chronic Obstructive Pulmonary Disease and a number of can-

cers. Differences in certification and coding of causes of death between countries of the European Community were studied by sending sets of case histories to samples of certifying physicians.

Detection fractions (the proportion of deaths with a true underlying cause X which actually receives the code number for X) ranged from 60 to 92% in the study of Chronic Obstructive Pulmonary Disease, and from 80 to 94% in the study of cancer. The contribution of errors in certification and errors in coding differed from country to country. The findings clearly suggest that differences in certification and coding of causes of death can bias international mortality comparisons. Case history studies as reported in chapter II are a convenient way of obtaining estimates of detection fractions (for a further discussion, see sections X.2.4 and X.4.4).

The study also showed that Dutch certification and coding practices compare favourably with those in other countries of the European Community. Detection fractions for Chronic Obstructive Pulmonary Disease and cancer were estimated to be 91% and 94% respectively in The Netherlands. Although these may be overestimates of real life detection fractions (a part of the diagnostic process was not included in the test situation, and the study may have stimulated participating doctors to behave less suboptimally than in every-day life), the results do justify some confidence in the validity of Dutch cause-of-death statistics.

A detailed analysis of the certificates completed by the Dutch participants in the study revealed a substantial frequency of errors in certification (which were in part corrected in the coding process). The nature of these errors points to possibilities for improvement of the validity of cause-of-death information, both by changes in the lay-out and phrasing of the death certificate and by education of doctors (see section X.4.1).

X.1.2 Use of mortality data to address health care policy questions

The use of mortality data by cause of death in health policy has a long history. The use of mortality data to address health care policy questions is of more recent origin, probably because health care policy has only grown in importance with the recent expansion of the health care system. Chapter III contains a discussion of one of the most widely cited examples of the use of mortality data in a health care policy context. In England and several other countries, mortality data are used in formulas for the allocation of financial resources to regions, on the assumption that mortality differences reflect differences in morbidity and thus "need" for health care services.

Although it is probably true that regional mortality differences generally reflect differences in incidence (and not case fatality) of potentially fatal conditions, there are at least two objections to this use of mortality data. The first of these is that

the translation into money equivalents requires an accurate picture of the excess incidence in regions with higher mortality. The crucial question is: how much, and of which conditions (conditions differ in resource requirements). The results of the study of provincial differences in mortality, hospital admissions and new cases of disability benefits, reported in chapter III, show that for a number of conditions a reasonable degree of correspondence between these three sources of information existed, but for other conditions none at all. Given doubts regarding the validity of cause-of-death information, and given the possibility of differences in case fatality, it is not likely that regional mortality data by cause of death give a sufficiently accurate picture of morbidity differences. This was interpreted as giving insufficient support for a general identification of regional mortality with morbidity for a wide range of health problems, as assumed in the allocation formulas mentioned above.

A second objection is that mortality data may also be "outcome" indicators. Mortality rates reflect, at least in part, the outcome of preventive and curative efforts, either within or outside the health care system. It would seem to be unwise to take away incentives for mortality reduction by "rewarding" high mortality regions with more health care resources (most of which will not be spent on mortality reduction), especially now that health care policy is imbedded in a broader framework of health policy.

Both objections combine into the same general conclusion. If regional mortality data by cause of death are used as a criterion for the allocation of health care resources, it should be in a less "mechanical" way. A more informal procedure would create room for a careful interpretation of mortality differences, as well as for a linkage with efforts at mortality reduction (see section X.4.2 for further elaboration).

X.1.3 Mortality time trends and medical care

The decline of mortality since the eighteenth and nineteenth centuries is largely due to other factors than the introduction of efficacious medical interventions. But that is not to say that there has been no effect of improvements in medical care on time trends of cause-specific mortality at all.

Our analysis of the "tail" of the declining mortality curves for 21 infectious diseases (chapter IV) has shown that the introduction of antibiotics was accompanied by important changes in mortality. Late effects of World War II made it difficult to assess whether sharp reductions in mortality at the moment when antibiotics were introduced, were present. However, a longer lasting (acceleration of) mortality decline after the introduction was present in many infectious diseases. No acceleration of mortality decline could be shown in mortality from "All other diseases".

Other factors than antibiotics, such as the acceleration of

economic development after World War II and preventive programs against Tuberculosis, may have contributed also to these changes. On the whole, however, the results of the analysis are consistent with the hypothesis of substantial effects of antibiotics on infectious disease mortality in The Netherlands.

Contrary to popular belief, changes in mortality since 1950 have not been much smaller than those in the period 1850-1950. Changes in average life expectancy at birth were generally more impressive before 1950, but this does not apply to changes in age-specific mortality rates. With the exception of a temporary increase in mortality in certain age-groups in males, between the early 1950's and the late 1960's, the proportional declines in age-specific mortality rates were as large after 1950 as they had been before (section I.4.2).

Many conditions have contributed to favourable mortality developments after 1950, or after 1970 for males. The most important exception is cancer: mortality rates for many forms of cancer have remained stable or have even increased (section I.4.2). One of the reasons (apart from unfavourable incidence developments) is that medical care has only made modest advances in the treatment of cancer. The analysis of cancer survival data from the United States, Norway and Finland in chapter V shows that survival has on the average increased only slightly since the 1950's.

It is only for a small number of cancers, and mostly not the quantitatively important ones, that increases in survival were more considerable. These changes in survival are partly due to earlier diagnosis ("lead time bias"), changes in registration, and perhaps also changes in the degree of malignancy of the disease. For Hodgkin's disease, Cancer of the testis, Wilm's tumour, and Acute lymphocytic leukemia, on the other hand, increases in survival are probably due to dramatic improvements in medical care. These changes have also become visible in mortality trends for these conditions in The Netherlands.

Conditions which have become amenable to medical intervention have contributed appreciably to favourable mortality changes since 1950 (chapter VI). Trends in mortality from a selection of conditions suggested by Rutstein et al.'s lists of "unnecessary untimely mortality" were analysed. This selection covered 11 types of medical care innovation and included 35 conditions which have to some extent become amenable to medical intervention. Apart from a number of infectious diseases and treatable cancers, the selection included some endocrine and hemopoietic disorders, a number of "surgical" conditions, Maternal and Perinatal mortality, some congenital anomalies, Rheumatic heart disease, Diphtheria/whooping cough/tetanus/poliomyelitis, Nephritis and nephrosis, Hypertensive and Cerebrovascular disease, and Cancer of the cervix uteri.

For most of these conditions, mortality declined during each of two subperiods (1950-1968; 1969-1984). Mortality decline accelerated in the second subperiod for many conditions. Reductions in mortality from these conditions between 1950-54 and 1980-84 added appr. 3 years and appr. 4 years to the average life expectancy at

birth of Dutch males and Dutch females respectively. Part, but not all, of the mortality decline may be due to "spontaneous" incidence declines, as indicated by declines in hospital admission rates in the second subperiod. The evidence that these mortality declines are (at least partly) due to improvements in medical care will be reviewed more extensively in section X.2.

These analyses of recent changes in mortality were intended to supplement McKeown's analysis of changes in mortality since the eighteenth century. The findings show that improvements in medical care have probably led to substantial mortality reductions during the second half of this century.

X.1.4 Regional mortality differences and medical care

There is important regional variation in cause-specific mortality within The Netherlands, but there is no evidence for a substantial relationship with the level of supply of medical care. An effect of regional differences in the level of medical care supply on mortality is most likely to be found for conditions which have become amenable to medical intervention. Mortality from these conditions varies considerably between regions, but generally is not associated with a number of simple measures of medical care supply, like hospital bed and general practitioner density.

This is a finding common to many countries, as is shown in our analysis of variations in mortality within countries of the European Community (chapter VII). The parallel analysis for 10 EC countries of mortality from conditions which have become amenable to medical intervention, shows that the percentage of variance explained by medical care variables, after controlling for socio-economic variables, is generally small, especially in countries with a large number of regions. Moreover, the nature of the (weak) associations with medical care supply is puzzling, as negative and positive associations are found in approximately equal frequencies.

One hypothesis which we have tested is that these findings are to be explained by time-dependence of the association between mortality from the selected conditions and the level of supply of medical care. Mortality from conditions which have become amenable to medical intervention has decreased in the past decades, and an effect of medical care supply would perhaps be expected in a certain phase of mortality decline only, for example during early diffusion of the relevant innovation. The results of our analysis of regional variation in mortality from the selected conditions in The Netherlands, in which 4 time-periods were compared (1950-54, 1960-64, 1970-74, 1980-84), do however not provide clear support for this hypothesis (chapter VIII).

Associations between mortality and a number of simple measures of the supply of medical care (hospital bed density, general practitioner density, percentage of hospital beds located in universi-

ty hospitals, idem in small hospitals) were generally weak and inconsistent in 1980-84. A comparison with earlier time-periods shows that although the percentage of variance explained by medical care variables did change over time, and although the pattern of change was more or less consistent with the hypothesis for some causes of death, the nature of the associations was puzzling.

The number of statistically significant associations between mortality and medical care supply variables, both before and after controlling for possible confounding variables, was very small, and apart from some expected negative associations with the percentage of hospital beds located in university hospitals, also some positive associations between mortality and general practitioner density were found. A more thorough discussion of these weak and inconsistent associations between mortality and medical care supply at the regional level will be presented in section X.3.2.

Whereas the studies reported in chapters VII and VIII focussed on regional variation in the level of mortality, chapter IX was concerned with an exploratory analysis of regional variation in the rate of decline of mortality from a number of conditions in the period 1969-84. Apart from the two largest among the conditions which have become amenable to medical intervention (Perinatal mortality and Cerebrovascular disease), also some other conditions with important mortality declines (Cancer of the stomach, Ischemic heart disease, Traffic accidents) were included in the analysis.

For Perinatal mortality, Cerebrovascular disease, and Ischemic heart disease, as well as for Total mortality, the rate of mortality decline differed between regions in The Netherlands. The analysis permits the identification of regions where progress has been less satisfactory. In combination with a higher average level of mortality, a slower rate of mortality decline should be an important warning signal to health policy makers, including health care policy makers in the case of conditions which have become amenable to medical intervention. Possible approaches to the investigation of the causes of a higher mortality level and/or a slower rate of mortality decline will be discussed in section X.4.4.

A simple analysis of correlations between regional rates of mortality decline and other regional characteristics shows that changes in hospital bed or general practitioner density between 1970 and 1980 were not associated with changes in mortality, confirming the findings on the relationship between medical care supply and mortality from the cross-sectional studies in chapter VII and VIII. Changes in some indicators of socio-economic status, on the other hand, were associated with changes in mortality: mortality declined faster where average income and/or education level rose faster. The relationship between mortality and indicators of socio-economic status will be taken up again in section X.3.3.

X.2 Additional comments I: recent mortality time trends and medical care

X.2.1 A note on the evidence

Chapter VI presented a comprehensive analysis of recent mortality changes for conditions which have to some extent become amenable to medical intervention. Reductions in mortality at population level are a measure of the "effectiveness" of medical care, defined here as "the ability to reduce incidence or case fatality of a condition in the population". A distinction has to be made between effectiveness and "efficacy". The latter is defined as "the ability to reduce incidence or case fatality in selected patient groups under optimal circumstances".

Effectiveness is of course dependent on efficacy, but requires something more. Effectiveness can be thought of as the end-product of: - the efficacy of the intervention; - the proportion of the patient population that comes into contact with medical care; - the sensitivity of the diagnostic procedures used to identify patients who are eligible for the intervention; - the degree of provider compliance with professional standards; - and the degree of patient compliance.

Selection of causes of death

Although we only included conditions for which the evidence on efficacy or effectiveness of medical interventions is relatively undisputed, the evidence is in fact not entirely uncontroversial. Table VI.1 linked 11 innovations to 35 conditions which, due to these innovations, became amenable to medical intervention. Table X.1 lists most of these conditions again, and includes the crude mortality rates in 1950-54 and 1980-84. The 11 groups have been chosen to reflect the chronology of different innovations and to produce nosologically more or less homogeneous groups of causes of death (see table VI.I for the titles of the groups). Although separate causes are sometimes quite small, all causes together were responsible for an important part of Total mortality in the early 1950's: 33% for males, and 37% for females. Mortality declines, and increases in mortality from other causes of death, reduced this contribution to Total mortality to 16% for males and 24 % for females in 1980-84.

Our selection of conditions is based upon that of Rutstein et al. [2] and akin to selections used in other studies of mortality trends and medical care [3, 4], but there are also differences, some of which have been mentioned in section VI.1. For each condition, Annex 2 renders a detailed account of the reasons for inclusion in our selection, and also gives a short discussion of the main weaknesses in the evidence. The fact that these selections of conditions, although basically similar, are not identical, illustrates the lack of consensus inside and ouside the medical profession on the

Table X.1 Mortality rates of the selected conditions (per 10^5 person-years).

		1950-54		1980-84	
		males	females	males	females
I	Diseases of the thyroid	0.35	1.85	0.18	0.84
	Pernicious anemia	0.75	0.99	0.09	0.18
	Other anemias	0.87	0.92	0.98	1.21
II	Peptic ulcer	8.38	2.20	3.61	3.11
	Appendicitis	2.36	1.47	0.37	0.30
	Cholelithiasis/-cystitis	3.23	8.85	2.76	4.03
	Abdominal hernia	2.42	1.75	1.34	1.29
	Ileus without hernia	2.10	1.86	1.98	3.51
	Benign prostatic hyperplasia	15.66	-	3.54	-
III	Maternal causes	-	3.67	-	0.19
	Perinatal causes	30.79	19.83	4.50	3.09
IV	Tuberculosis	14.14	11.35	1.49	0.88
	Pneumonia/influenza	34.22	35.29	19.96	23.48
	Septicemia	1.33	1.13	1.60	1.71
	Infections urinary system	1.42	2.37	1.37	2.77
	Other infectious diseases	13.20	9.85	2.47	2.48
V	Congenital digestive anomalies	2.17	1.30	0.24	0.23
	Congenital digestive anomalies	6.14	4.93	2.46	1.69
VI	Rheumatic heart disease	8.57	10.52	5.47	8.02
VII	Diphtheria/whooping cough/tetanus/polio	3.10	2.80	0.05	0.05
VIII	Nephritis and nephrosis	11.38	12.96	8.57	10.12
IX	Hypertensive disease	12.13	17.98	4.01	5.76
	Cerebrovascular disease	79.68	101.31	73.50	94.76
X	Cancer of lip and skin	1.50	1.03	0.82	0.46
	Morbus Hodgkin	2.32	1.55	1.26	0.78
	Cancer of testis	1.31	-	0.64	-
XI	Cancer of cervix uteri	-	6.37	-	4.38
	Subtotal	260	264	143	175
	Total mortality, all causes	781	717	903	734

This selection of diseases is identical to that of tables VI.1 and VI.2, except that Diabetes mellitus (< 25 y.), Cancer of the kidney (< 15 y.) and Leukemia (< 15 y.) have been omitted.

efficacy and effectiveness of medical care.

This is due in the first place to the lack of methodologically sound studies evaluating the efficacy of medical interventions, and to difficulties in the synthesis of findings from different studies (see section V.1). The Randomized Controlled Trial was introduced into this area of research in the late 1940's, with the Medical Research Council Study of the effects of streptomycin in the treatment of Tuberculosis [5]. Innovations introduced earlier have not had the chance to be tested in such a rigorous way. For example, the most important study accompanying the introduction of penicillin for the treatment of acute infections involved its application to a large number of patients, after which the results were compared informally with those of previous treatment methods [6]. But even after the introduction of the Randomized Controlled Trial many interventions have only been evaluated with methodologically inferior designs [7].

Mortality decline as a measure of effectiveness

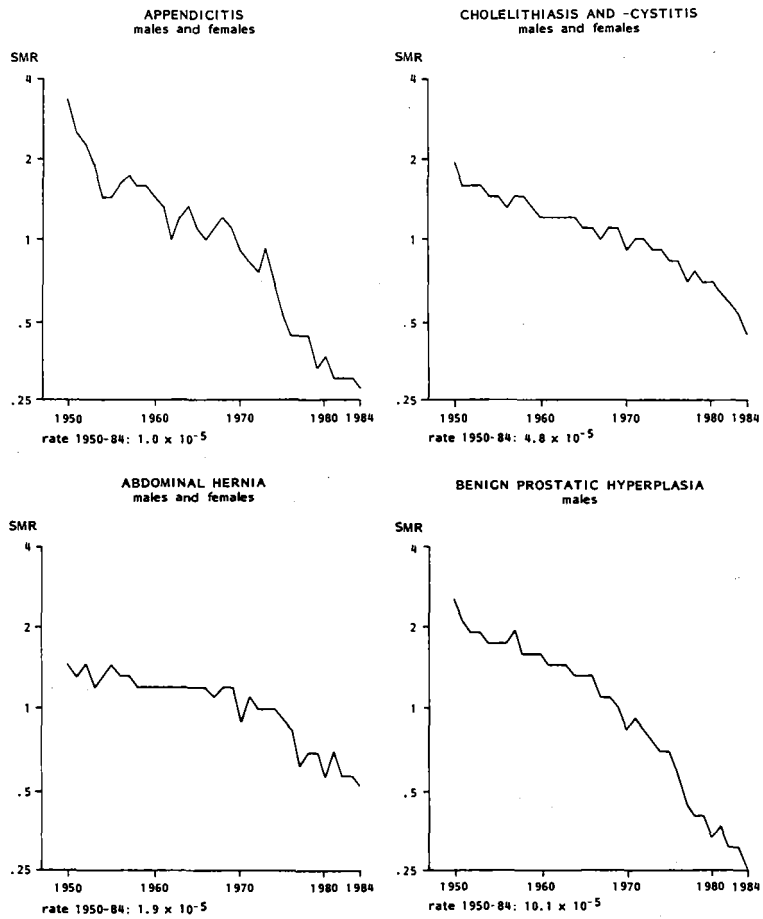
Given these uncertainties on the efficacy of medical interventions, and given the possibility of other causes of mortality change, the observed reductions in mortality cannot simply be interpreted as measures of the increased effectiveness of medical care. The separation of the effects of medical care from those of other influences is unfortunately a rather difficult enterprise. Over time, improvements in medical care are frequently closely correlated with changes in other significant factors.

It is not by chance, for example, that the introduction of penicillin and other antibiotics coincided with the beginning of an era of rapid economic development. Both the development of efficacious treatment methods for infectious diseases and the start of a new economic growth phase were related in one way or other to World War II.

A careful interpretation of changes in mortality over time, and a comparison with other causes of death, are about as far as one can go in these (necessarily "observational") mortality analyses. The "simple interrupted time series design" [8], chosen in chapter IV for the assessment of changes in mortality coincident with the introduction of antibiotics, is a good example of a formalized comparison of mortality before and after the introduction of an innovation. The comparison with non-infectious disease mortality was a further aid in interpretation, although it remained difficult to rule out the possibility that the change in mortality is (partly) due to other changes, occurring at approximately the same moment as the change in medical care.

In the following sections the discussion on the interpretation of post-1950 trends in mortality from conditions which have become amenable to medical intervention, will be extended along two lines: by a comparison with other causes of death (section X.2.2), and by a consideration of differences in mortality trends between age-groups (section X.2.3).

Figure X.1 Post-1950 time trends of mortality from Appendicitis, Cholelithiasis/-cystitis, Abdominal hernia, and Benign prostatic hyperplasia (Standardized Mortality Ratios).



Note: The rates shown at the bottom of each graph are the average crude death rates (per person-year) for the entire period 1950-84.

Figure X.2 Post-1950 time trends of mortality from four causes of Perinatal mortality (Standardized Mortality Ratios).

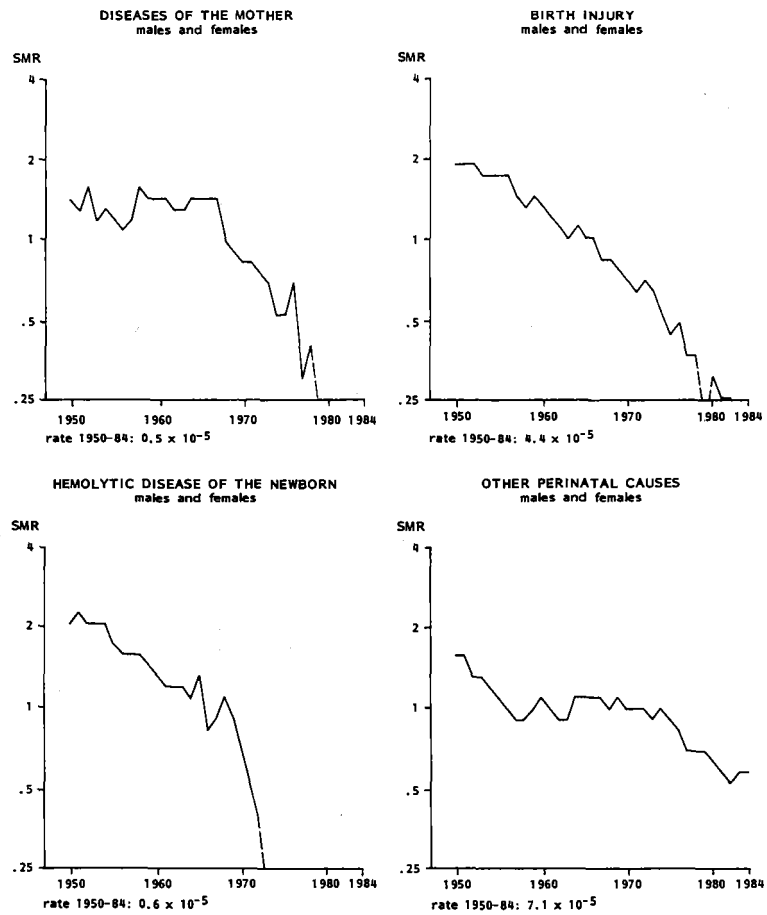


Figure X.3 Post-1950 time trends of mortality from Congenital digestive anomalies and Congenital cardiovascular anomalies (Standardized Mortality Ratios).

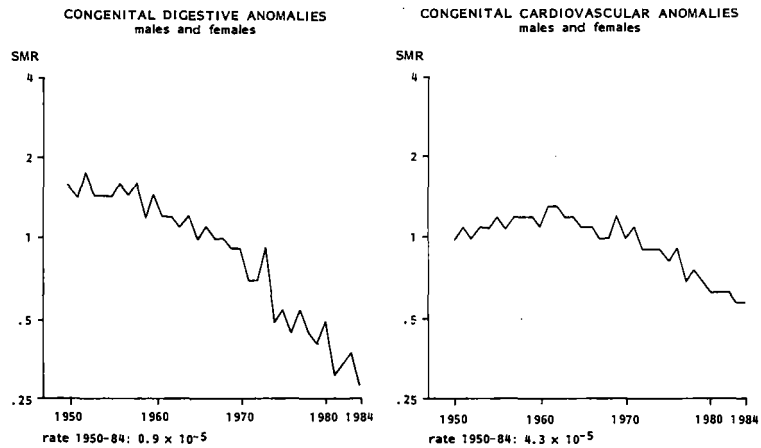
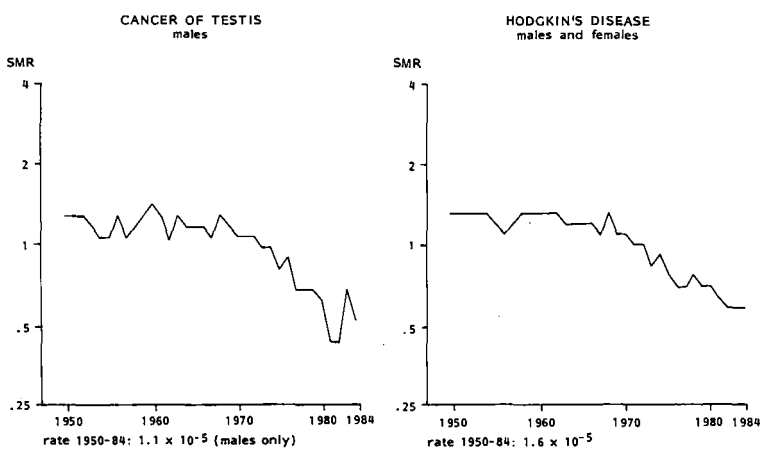


Figure X.4 Post-1950 time trends of mortality from Morbus Hodgkin and Cancer of the testis (Standardized Mortality Ratios).



X.2.2 A comparison with other causes of death

One of the remarkable findings of the analysis of post-1950 trends in mortality from conditions amenable to medical intervention was, that mortality decline accelerated for many of the selected conditions in the second part of this period (1969-1984) (cf. table VI.2). Although the uniform periodization hides some differences in timing between causes, figures X.1, X.2, X.3 and X.4 show that the late 1960's and early 1970's are indeed characterized by accelerating mortality declines. The same applies to many other of the selected causes, not shown in these figures.

Trends in mortality from other, i.c. the largest causes of death have been presented graphically in section I.4.2 (figure I.9). Some of these causes also show favourable changes in trend in the late 1960's or early 1970's, just as many of the causes which have become amenable to medical intervention: Ischemic heart disease, Diabetes mellitus, Chronic Obstructive Pulmonary Disease (in males), Traffic accidents, Non-traffic accidents.

The similarity could of course be coincidence, but might also point at a common cause of the changes in mortality from the selected and some other conditions. Two possibilities will have to be considered: either these other conditions have also been affected by increasing effectiveness of medical care, or a factor reducing incidence or case fatality for many conditions, but not related to medical care, has begun to operate around 1970.

Medical care and other causes of death

It is possible to argue that improvements in medical care have also had an effect on mortality from at least some causes which were not in our selection of conditions amenable to medical intervention.

There is no consensus on the role of medical care in the decline in Ischemic heart disease mortality [9]. Changes in risk factor prevalence, reducing incidence, have probably been important. Studies of trends in incidence have produced conflicting findings [10-14], but on the whole it seems probable that changes in lifestyle, specifically reductions in serum cholesterol level and cigarette smoking, have contributed to declining mortality through incidence reductions [15]. (The favourable change in mortality trend for Chronic Obstructive Pulmonary Disease is perhaps also related to changes in smoking habits.)

On the other hand, it is also increasingly becoming clear that there have been case fatality reductions in Ischemic heart disease, showing as declines in rates of sudden death among people with a prior history of myocardial infarction and as improved short term survival among hospitalized patients [10-14]. Coronary care units, and medical treatment of clinical Ischemic heart disease and hypertension have been identified as possibly important contributors [15].

Another condition which was not included in our selection but which may to some extent have become amenable to medical intervention, is Fracture of the neck of the femur. Trends in mortality from Non-traffic accidents (figure I.9) are mainly based on trends in mortality from this type of injury, common in elderly people. It has been argued that the decline is due to better treatment, specifically a higher frequency of surgery. Surgery rates have indeed gone up, and in-hospital case fatality rates have gone down [16]. Others have suggested a favourable effect of early mobilization after hip operation [17].

Favourable changes in other common determinants

Medical care is not the only possible candidate for a factor common to many causes of death which caused (an acceleration of) mortality decline after ca. 1970. A general improvement in health could also show as a simultaneous mortality decline for a number of conditions. The reversal of the mortality trend for Ischemic heart disease suggests an improvement in the condition of the cardiovascular system. Failure of the cardiovascular system is an important "immediate" or "contributory" cause of death, even if non-cardiovascular disease is the "underlying cause". It is thus possible that an improvement in the condition of the cardiovascular system has contributed to declines in mortality from other diseases. This remains however entirely speculative.

The reversal of the mortality trend is at least partly due to changes in life-styles (vide supra), and these changes could have reduced the risks of dying from other diseases too. An obvious example is Cerebrovascular disease, but for many of the other selected conditions this is not very likely.

(The rapid post-1970 decline in Perinatal mortality can only for a small part be explained by changes in the birth-weight distribution of babies ("general health") or changes in the birth rate and the age and parity of mothers ("life-style")[18-20].)

The reversal of the time trend for mortality from Traffic accidents has at least two major causes. The first is a deceleration of the increase in car driving, prompted by the economic recession which started in the early 1970's, and the second a number of preventive measures taken in the same time-period (safety belts, anti-alcohol law, speed-limits, compulsory helmet wearing for moped drivers) [21].

Specific preventive efforts, not involving medical care, were taken for none of the selected causes around 1970, but the possible effects of the economic recession deserve a little more consideration. It is conceivable that the economic recession has removed a number of health risks for other conditions too, for example through the modification of income-related hazardous life-styles. This is, again, entirely speculative, and not very likely in view of the fact that the recession did not have major effects on average income levels until the end of the 1970's [22]. Also, the analysis of regional

mortality declines in chapter IX showed that mortality from conditions amenable to medical intervention declined faster where income increased more.

A cautious conclusion is that the similarity between the trends in mortality from conditions amenable to medical intervention and those of some other conditions, is probably partly due to an effect of medical care on a few of these other conditions, partly due to an effect of life-style changes on some of the conditions amenable to medical intervention, and partly "due to" coincidence.

X.2.3 Differences in mortality decline between age-groups

Differences in mortality decline between age-groups may give additional information on the contribution of improvements in medical care. In general, mortality reductions due to improvements in medical care are expected to be smaller in older age-groups because of the effects of multi-morbidity.

Differences between age-groups have been ignored in chapter VI, and the mortality trends (β) have been calculated assuming that mortality trends are the same (on a logarithmic scale) for all age-groups (cf. section VI.2). Just as in the case of infectious disease mortality time trends (see section IV.5 for a discussion), this assumption does not hold for the post-1950 trends in mortality. The loglinear regression model used for the analysis of mortality trends can be expanded to include the interaction between calendar-year and age-group. The result is a series of different estimates of the trend parameter β for different age-groups i (β_i).

The results of such an analysis are presented in summary form in table X.2. Formal testing for statistical significance revealed that this interaction is highly statistically significant for almost all diseases studied. For a selection of causes of death, table X.2 shows the "sign" of the estimates for β_i in those cases where β_i is significantly different (two-sided test; $^1p < .05$) from 0. Negative values imply mortality decline.

The results do indicate that for many of the selected conditions the higher age-groups did not experience statistically significant mortality declines, or even experienced mortality increases. On the other hand, it is surprising that mortality declines are still quite general among those 65-74 years old. Most studies of regional differences in mortality from conditions amenable to medical interventions have applied strict age-limits to mortality, by excluding deaths over 65 years of age (e.g. refs. 23, 24). Mortality among elderly people was supposed to be less "avoidable" - an argument which seems to be contradicted, at least for those between 65 and 74, by these mortality declines. (For this reason we applied other age-limits in the studies reported in chapters VIII and IX.)

Table X.2 Age-specific mortality trends for selected "amenable" conditions, 1950-68 and 1969-1984.

			1950-1968											
			0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85-94	95+
I	Diabetes mellitus	M					+	+	+	+	+	+	+	
		F				-	-	+		+	+	+		
II	Peptic ulcer	M				-	-	-	-	-	-		+	
		F						-		-	-	+	+	
	Cholelithiasis/-cystitis	M	-		-		-	-	-	-		+	+	
		F				-	-	-	-	-	-	-		
	Ileus w.o. hernia	M	-	-		-		-	-	-				
		F	-		+									+
IV	Influenza and pneumonia	M	-	-	-	-	-	-	-	-	-	-	-	-
		F	-	-	-	-	-	-	-	-	-	-	-	-
	Septicemia	M	-	-		-	-	-		-				
		F		-	-			-	-	-	-			
VI	Rheumatic heart disease	M		-	-	-	-				-	-	-	
		F		-	-	-	-	-	-	-	-	-		
VIII	Nephritis and nephrosis	M		-		-	-	-	-	-	-	-		
		F			-	-	-	-	-	-	-	-		
IX	Cerebrovascular disease	M						+		-	-	-	-	
		F				+	+		-	-	-	-	-	+
X	Cancer of kidney	M						+		+	+	+	+	
		F								+	+	+	+	
	Leukemia	M			+					+	+	+	+	
		F		-							+	+	+	
-	Total mortality	M	-	-	-		-		+	+	+	-	-	-
		F	-	-	-	-	-	-	-	-	-	-	-	-

- Declining mortality ($p < .05$).
+ Increasing mortality ($p < .05$).

Table X.2 (continued) Age-specific mortality trends for selected "amenable" conditions, 1950-68 and 1969-1984.

			1969-1984												
			0	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85-94	95+
I	Diabetes mellitus	M			-				-	-	-	-		
		F			-			-	-	-	-	-		
II	Peptic ulcer	M	-			-	-	-	-	-	-	-		
		F							-	-	-	+		
	Cholelithiasis/-cystitis	M						-	-	-	-			
		F				-	-	-	-	-	-	-		
	Ileus w.o. hernia	M	-						-	-	-			
		F	-				-	-	-	-	-		+	+
IV	Influenza and pneumonia	M	-	-	-	-	-	-	-	-	-	-	-	
		F	-	-	-	-	-	-	-	-	-	-	-	
	Septicemia	M	+							+	+	+	+	
		F	+								+	+	+	
VI	Rheumatic heart disease	M				-	-	-	-	-	-	+	+	
		F			-	-	-	-	-	-	-			+
VIII	Nephritis and nephrosis	M			-	-	-	-	-	-	-	+	+	+
		F		-	-	-		-	-	-	-	+	+	+
IX	Cerebrovascular disease	M	-		-	-		-	-	-	-	-	-	-
		F	-					-	-	-	-	-	-	
X	Cancer of kidney	M		-							+	+	+	
		F		-						+		+	+	
	Leukemia	M		-	-					-		+		
		F		-	-		-		-		-		+	
-	Total mortality	M	-	-	-	-	-	-	-	-	-	-	-	
		F	-	-	-	-	-	-	-	-	-	-	-	

\- Declining mortality ($p < .05$)
\+ Increasing mortality ($p < .05$).

For some conditions the absence of mortality decline for all ages combined can be explained by extreme heterogeneity of mortality decline with respect to age. For the second subperiod this applies to Ileus without mention of hernia and Nephritis and nephrosis. For both conditions statistically significant mortality declines are seen for ages below 75, and mortality increases for higher ages (which have a larger share in mortality for all ages combined).

The increase in mortality from Ileus without mention of hernia at higher ages has been ascribed to increasing frequencies of intra-abdominal surgery, the adverse effects of which will only become manifest at higher ages [25].

For Nephritis and nephrosis, the conclusion reached in chapter VI on the apparent absence of an effect of hemodialysis on mortality has to be modified in the light of these findings.

The unfavourable trend for Septicemia in the second subperiod, however, is seen in all age-groups. A possible explanation is that it is an effect of increasing non-specificity in cause-of-death certification (cf. section I.2.2). Mortality trends for Septicemia could easily be affected by such a development, if it also causes increased reporting of only an "immediate" cause of death: Septicemia is a frequent immediate cause of death (cf. section I.2.1).

X.2.4 Differences in recent mortality levels between The Netherlands and other countries of the European Community

Declines in mortality from conditions which have to some extent become amenable to medical intervention, have been observed in many countries [3, 4]. It is interesting to see that mortality levels for these conditions are generally lower in The Netherlands than in most other countries of the European Community. Large differences between countries of the European Community are apparent from table X.3, which presents 1974-78 Standardized Mortality Ratios (using average mortality rates by age and sex for the whole EC as standardrates) for a number of conditions amenable to medical intervention.

The SMR's for Total mortality again show the low Total mortality levels in Greece and The Netherlands (cf. section I.5.1). In The Netherlands mortality rates are lower than the EC average for almost all amenable causes, lower also than Total mortality levels alone can explain.

The only exception is Cancer of the cervix uteri, but this is, ironically enough, probably due to differences in cause-of-death certification and coding between EC countries (see chapter II and ref. 26). In the study reported in chapter II one of the case histories described a patient with Cancer of the cervix uteri. The results for this case history are presented in table X.4. Greece was not yet an EC member when this study was carried out, and Scotland was not included as a separate country, so the comparison between tables X.3 and X.4 must be limited to 8 countries.

Table X.3 Mortality differences between countries of the European Community for a number of conditions amenable to medical intervention, Standardized Mortality Ratios for both sexes, 1974-78.

	B	D	DK	F	GR	I	IRL	NL	E/W	Sc
Tuberculosis	91	106	40	131	140	125	165	23	54	86
Appendicitis	53	159	59	98	37	98	111	66	69	70
Abdominal hernia	69	115	38	105	47	110	83	78	94	99
Cholelithiasis/-cystitis	60	136	45	84	44	173	36	65	37	37
Chronic Rheum. Heart Dis.	30	79	40	65	115	187	126	56	87	134
Maternal mortality [a]	12	34	6	20	n.a.	23	14	11	12	60
Perinatal mortality [b]	19	17	12	17	n.a.	23	20	14	18	19
Hypertensive and cerebrovascular disease	94	90	66	92	93	116	134	65	107	151
Hodgkin's disease	103	94	75	83	118	135	95	84	91	88
Cancer of the cervix uteri	75	142	246	67	29	28	81	115	151	153
Total mortality	108	104	95	96	88	96	117	91	104	115

B = Belgium; D = West-Germany; DK = Denmark; F = France; GR = Greece; I = Italy; IRL = Ireland; NL = Netherlands; E/W = England and Wales; Sc = Scotland;
n.a. = not available
[a] Maternal deaths per 100.000 births.
[b] Still-births and first-week deaths per 1000 births.
Data from ref. 24.

Table X.4 International differences in certification and coding of Cancer of the cervix: results of a case history study.

	Den-mark	W-Ger-many	Engl./ Wales	Ire-land	Neth.-lands	Bel-gium	France	Italy	All
Detection fraction (%)	90	82	100	94	98	86	72	82	88

There is a positive correlation between the observed SMR's of table X.3 and the detection fractions of table X.4 (.38, n.s.), suggesting that countries with higher mortality from Cervical cancer, including The Netherlands, simply have more complete reporting. In countries with lower detection fractions, a transfer has taken place from Cancer of the cervix uteri to "Cancer of the uterus, site unspecified".

Differences in certification and coding of causes of death, and in incidence of conditions may be behind some of the mortality differences (see ref. 27 for a detailed analysis of the differences between The Netherlands and Belgium). The over-all picture does however suggest a greater-than-average effectiveness of medical care in The Netherlands.

The case of Perinatal mortality

In 1974-78, The Netherlands had lower Perinatal mortality than all other countries of the EC, with the exception of Denmark (table X.3). Since then, the Dutch Perinatal mortality rate has decreased to 10 per 1000 births. This compares unfavourably with mortality declines in a number of other European countries, for example England and Wales and West-Germany, which had higher mortality levels in 1974-78, but mortality levels equal to or just below those of The Netherlands in the early 1980's. Perinatal mortality in Sweden, Norway, Finland, Denmark and Switzerland are presently all considerably below that of The Netherlands [28].

The explanation of this relatively unfavourable development is as yet unknown. At first sight, registration artefacts do not seem to be a plausible explanation: it is unlikely that the degree of underregistration in The Netherlands (cf. section I.6.1) has diminished in recent years, relative to that in all the countries mentioned above. Further study is clearly necessary.

These trends for Perinatal mortality again demonstrate the importance of a continuous surveillance of mortality time trends.

X.3 Additional comments II: regional mortality differences and medical care

X.3.1 A remark on the "avoidable mortality" approach

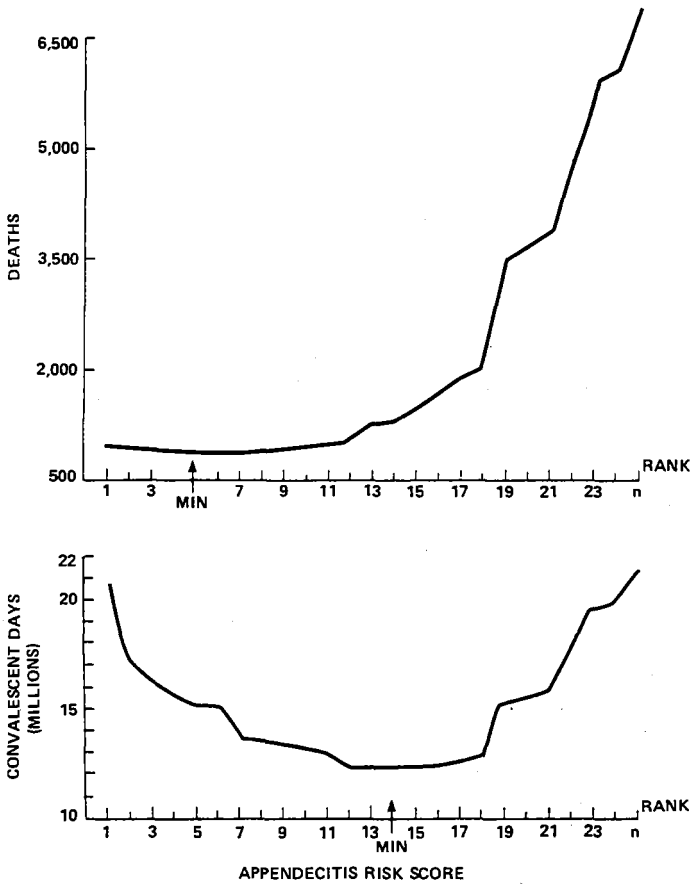
The studies reported in chapters VII, VIII and IX have focussed on regional differences in mortality from selected conditions. The term "avoidable mortality" has become the current abbreviation of "mortality from conditions (which have to some extent become) amenable to medical intervention", and is almost sure to attract the attention of health care policy makers. Contrary to what this term suggests, however, it is not true that every single death from the selected causes can be avoided by adequate medical care.

Important constraints are operating which may render the prevention of every single death from these causes practically impossible. There is a resource constraint: the prevention of the last deaths will probably require efforts for which the cost-effectiveness ratio is very high. The problem of cost-effectiveness can be taken even further, however, to include the adverse effects of medical intervention itself.

Case fatality in patients with Appendicitis is the sum of the mortality risks of the disease itself (mainly through perforation) and the mortality risks of operation. Frequently, there is uncertainty on the diagnosis of patients presenting with complaints resembling those of Appendicitis. In these situations a trade-off is necessary between the two mortality risks: operation reduces the risk of death due to perforation, but introduces a risk of death due to the procedure itself.

Figure X.5 illustrates another important trade-off. (The figure is based upon the assumption that the mortality risks of operation are minimal, but there is substantial controversy about this [30].) The objective of medical care is not only to prevent death, but also to prevent other adverse outcomes of disease. One measure of such adverse outcomes, convalescent days necessary to recover from disease (and operation!), will actually increase if the decision to operate is taken too frequently. The curves of mortality and convalescent days have their optimum at a different frequency of operation.

Figure X.5 Deaths and convalescent days associated with various degrees of surgical interventionism in Appendicitis.



Note: This figure shows the expected deaths and convalescent days for every one of the possible ranks which could be used as a cutoff point between operative and nonoperative treatment assuming that 100% of Appendicitis patients not operated upon would perforate.

The death curve is flat near its minimum which occurs when patients with mild symptoms are operated. There is a conflict between the optimum strategies for reducing deaths and for reducing convalescence.

Reprinted from ref. 29.

X.3.2 The interpretation of a "weak and inconsistent" relationship between mortality and the supply of medical care

The "weak and inconsistent" relationships between the level of supply of medical care and mortality from conditions which have become amenable to medical intervention, as found in the studies reported in chapters VII, VIII and IX, do not have an immediately clear interpretation. That this is an artefact of the analysis can practically be excluded, given the fact that essentially the same results were found in studies in which different statistical techniques were employed (not only the studies reported in chapters VII, VIII and IX, but also those in refs. 31 and 32). Are we to conclude that in general regional differences in medical care supply have no consequences for the effectiveness of medical care (as far as mortality reduction is concerned)? Or is it also possible that differences in effectiveness of medical care have gone undetected in regional mortality data?

Possibility no. 1:
Differences in medical care supply do not cause differences in effectiveness, as far as mortality reduction is concerned

What circumstances could account for the absence of a relationship between regional differences in the effectiveness of medical care and differences in supply, as measured in the studies reported in chapters VII, VIII and IX?

A possible explanation is that the decisive factor in achieving effectiveness of medical care is the correct application of specific medical procedures to as many eligible patients in the community as possible, and that this varies more or less independently from the level of supply (cf. figure I.18). At the levels observed in most industrialized countries, an increase in supply of hospital beds and physicians will mainly lead to an increase in "discretionary" admissions and procedures, and much less to an increase in admissions and procedures for more serious conditions, which are treated anyhow [33]. (This increasing efficiency at low levels of supply may be an example of a "structural" effect, which modifies the original relationship between supply and mortality (see section I.6.4).) Effects of cross-regional patient flows may further reduce any effects of different supply of medical care (an effect of mobility, section I.6.5).

Possibility no. 2:
Differences in supply cause differences in effectiveness, but these are not reflected in mortality statistics

At first sight, it is also possible to argue that differences in effectiveness of medical care (with regard to mortality reduction) caused by differences in supply, may have gone unnoticed because of e.g.: - misclassification of causes of death; - overwhelming influence of chance fluctuations on mortality rates; - lag-times and migration; - and/or overwhelming influence of "spontaneous" differences in inci-

dence.

A certain degree of **misclassification** of causes of death does exist (cf. chapter II), and even when it is the same in all regions will tend to bias all associations between cause-specific mortality and other characteristics, including the level of medical care supply, towards the null [34]. On the whole, however, it is unlikely that important differences in effectiveness, associated with the level of supply of medical care, would not have found expression in mortality from the selected conditions. Given the fact that cause-specific mortality patterns have been shown to reflect geographic patterns of smoking, diet, exposure to sun-light, religion, ethnicity, socio-economic status, etc. [35], it is unclear why they would be unable to reflect differences in effectiveness of medical care.

As table VIII.1 has shown, the national number of deaths, in the selected age-groups and pooled over a 5-year period, is typically in the range between 1000 and 2500 in 1980-84 in The Netherlands. Only Perinatal mortality and Cerebrovascular disease are larger (9000 and 18000, respectively). This introduces important problems of **statistical power** in an analysis of regional variation: only large differences in mortality have a reasonably large chance of being detected.

(The population size of the median COROP-region is approximately 2 % of the national population, so that the expected number of deaths under a null hypothesis (no difference with the national mortality level) is between 20 and 50 for many of the selected causes of death. At conventional significance levels (α = 0.05), a true difference of 25% above the national level has a chance of going undetected (type II-error) of between 77% (20 deaths) and 58% (50 deaths). For a difference of +50% these chances are between 42% and 10%, and for a difference of +75% between 15% and <1% [36].)

The "noise" of chance fluctuations may also to some extent have drowned the associations with other variables, although this does not really apply to the findings from some of the larger EC countries (chapter VII) and those for larger causes of death, like Perinatal mortality and Cerebrovascular disease.

For most of the conditions analysed in chapters VII, VIII and IX, the effects of medical intervention on mortality would not seem to have very long (say, more than 5 years) **lag-times**. Rheumatic heart disease may be an exception, as far as prevention by treatment of streptococcal infections is concerned.

Mortality patterns for the selected causes of death may also be dominated by **"spontaneous" differences in incidence.** An important part of chapter III was devoted to the question whether regional mortality differences by cause of death reflect differences in "morbidity". Generally speaking, they probably do. Some of the conditions considered to be amenable to medical intervention were included in this analysis. For Cancer of the cervix uteri, Cerebrovascular disease and Influenza and pneumonia correlations between mortality and hospital admissions were clearly positive, just as for many conditions not amenable to medical intervention. This suggests underlying differences

in incidence of these conditions (table III.4). However, for Cancer of the cervix and Cerebrovascular disease incidence differences are not necessarily spontaneous, because incidence can be modified by medical intervention. Furthermore, we tried to control for spontaneous differences in incidence by the inclusion of a number of potential confounding variables in the multiple regression analyses.

It is difficult to make a definite choice between these two possibilities. Both may be true to some extent, but the first appears to be the most plausible of the two. Although we cannot exclude the possibility that some subtle differences in mortality, associated with regional differences in medical care supply, were missed, the findings suggest that on the whole these differences have no important consequences for mortality. Which is not to say, of course, that there are no effects on other outcome measures, nor that there are no effects of other aspects of medical care on mortality.

X.3.3 Mortality and socio-economic status: a contribution of medical care?

Patterns of regional variation in mortality from amenable conditions have something important in common with the patterns of variation for other causes of death and Total mortality. Where socio-economic conditions are unfavourable, mortality is higher for many causes of death, whether amenable or not. This is one of the reasons why mortality from conditions amenable to medical intervention is generally higher in regions which also have higher Total mortality, as was demonstrated in chapter VII for most European countries.

That mortality from conditions amenable to medical intervention is higher in unfavourable socio-economic circumstances has also been found in data collected on individuals, instead of regions (table X.5). The "Occupational mortality" data from England and Wales show that for most of these causes of death, mortality is higher in the lower socio-economic strata [37]. Respiratory tuberculosis and Pneumonia have extremely steep gradients.

Socio-economic mortality differentials in The Netherlands

Although Dutch data on mortality by socio-economic status are very scarce, there is enough evidence that these differences are also present in The Netherlands. Most of this evidence derives from aggregate data studies, e.g. the analysis of differences between neighbourhoods of the city of Amsterdam [38]. It is interesting to see that mortality differences by socio-economic status also seem to shine through at the regional level (table X.6).

Table X.5 Mortality from conditions amenable to medical intervention, by socio-economic status, Standardized Mortality Ratios, England and Wales, 1970-72.

	Socio-economic status [a]						
	I	II	IIIN	IIIM	IV	V	All
Respiratory tuberculosis [b]	26	41	84	89	124	254	100
Pneumonia [b]	41	53	78	92	115	195	100
Perinatal mortality [c]	72	82	90	99	106	143	100
Maternal mortality [d]	79	63	86	99	147	144	100
Appendicitis [b]	60	95	125	99	89	117	100
Abdominal hernia [b]	60	56	65	88	130	143	100
Cholelithiasis and -cystitis [b]	114	102	99	88	127	80	100
Chronic rheum. heart dis. [b]	77	80	117	103	116	124	100
Hypertensive disease [b]	71	85	104	104	112	141	100
Cerebrovascular disease [b]	80	86	98	106	111	136	100
Total mortality [b]	77	81	99	106	114	137	100

Data from ref. 37.

[a] I: professionals; II: intermediate; IIIN: skilled non-manual; IIIM: skilled manual; IV: partly skilled; V: unskilled.

[b] Males 15-64 years.

[c] Still-births and first-week deaths, males and females.

[d] Females 15-64 years.

In 1980-84, Total mortality tended to be higher in regions with a lower average income per inhabitant. Such negative associations are also present for many separate causes of death, and more strongly so for Ischemic heart disease, Cancer of the stomach, and Traffic accidents. A small number of causes of death is more frequent in regions with a higher average income, notably Cancer of the lung and Cancer of the prostate.

Between 1950-54 and 1980-84 the relationship between mortality and average income seems to have changed for a number of conditions, e.g. for Ischemic heart disease, where the association has made a dramatic reversal, and Cancer of the colon.

Table X.6 Correlations [a] between age-standardized mortality for the largest causes of death and average income, The Netherlands, 1980-84 and 1950-54.

	1980-84	1950-54
Ischemic heart disease	-.66*	.51*
Other heart disease [b]	-.13	-.28
Cerebrovascular disease	-.24	.17
Hypertensive disease	-.14	.11
Diseases of arteries	.29	-.37*
Cancer of stomach	-.50*	-.41*
Cancer of colon	-.23	.51*
Cancer of lung	.48*	.65*
Cancer of breast	.20	.50*
Cancer of prostate	.32*	.46*
Diabetes mellitus	-.37*	.02
Influenza/pneumonia	.13	-.23
Chronic Obstructive Pulmonary Dis.	-.07	-.37*
Perinatal mortality [c]	-.27	-.56*
Traffic accidents	-.73*	-.51*
Non-traffic accidents	-.21	-.22
Total mortality	-.31*	-.23

Significance level (two-sided test): * $p < .05$.
[a] Product-moment correlations, unweighted (n=39).
[b] Non-ischemic, non-rheumatic heart disease.
[c] Still-births plus first-week deaths.

Reversals from positive to negative associations have been documented repeatedly in other studies. The "epidemic" of Ischemic heart disease probably started in the upper socio-economic strata but is now a disease with higher mortality in the lower strata [39, 40]. Another example is Diabetes mellitus. In England and Wales, mortality was highest in the higher social classes in the 1920's and 1930's, but after World War II the association has gradually changed to a negative one in 1970-72 (cf. table X.6) [37]. Just as Total mortality, mortality from specific conditions seems to go through an "epidemiologic transition". A certain analogy between socio-economic differences within countries and international differences (section I.4.1) is apparent: populations or population groups which lag behind in socio-

economic development, also lag behind a number of years in the development of their mortality pattern.

Specific factors which may account for the relationship between socio-economic status and mortality are material life circumstances, work environment, health related habits, psychosocial factors, and also use of health care services, including medical care [42]. The association between socio-economic status and mortality from conditions amenable to medical intervention may provide a good starting-point for further study of the contribution of medical care factors.

X.4 A few recommendations

X.4.1 Further improvement of cause-of-death statistics

The studies reported in chapters III-IX have demonstrated that mortality data by cause of death are a rich source of information, which permits detailed analyses of time trends and geographical variation in mortality from a wide range of conditions. The interpretation of these trends and differences is frequently dependent on the assumption of a reasonable validity of cause-of-death information.

Fortunately, the case history studies of chapter II have indicated that the Dutch certification and coding process has a satisfactory performance, and compares favourably to that of other European Community countries, at least as far as detection fractions for Chronic Obstructive Pulmonary Disease and a number of cancers are concerned. The results from these case history studies however also suggest that some further improvement is possible. This will largely depend on the dedication of certifying physicians, but some minor changes of the death certificate might also be helpful.

Careful completion of death certificates is an important contribution of medical care to the furtherance of public health. This is not always appreciated by the medical profession, which tends to regard cause-of-death certification as a mere bureacratic obligation. Physicians will perhaps be stimulated to improve their cause-of-death certification practices, if the usefulness of cause-of-death statistics is demonstrated regularly to them. Medical education, including post-graduate education, and general medical journals have an important role to play here.

As was already mentioned in section I.2.1, the Dutch death certificate has some subtle differences with the internationally agreed upon death certificate. The lay-out of the Dutch certificate slightly emphasizes the immediate cause of death (cf. Figure I.1), by printing the Dutch word for "immediate" in italics. This may be a partial explanation for our finding of a high frequency of "Correct diagnosis in part I, but in the wrong sequence" (chapter II). The phrasing of part II of the certificate is also not very clear (cf. section I.2.1), which may partly explain our finding of a "Correct diagnosis in part II". The fact that the instructions for filling in the certificate are placed on the back-side, will not be very helpful either. A recent proposal intended to take away some of these problems, while retaining correspondence with the international certificate of cause of death, therefore deserves serious consideration [43].

Whereas the proposals mentioned above would be investments in the quality of cause-of-death information at the national level, one might in addition consider the possibility of conducting some small-scale experiments to provide more extensive and/or more thoroughly validated information on causes of death [44]. A sample of

doctors sending in death certificates could be asked to provide more information on the deceased, in order to assess the validity of stated causes of death. The same approach could be used to elicit more information on "secondary" causes of death, which could then be coded systematically in order to give a more complete picture of conditions present at and contributing to death [45].

Such experiments could be linked to in-depth studies of "avoidable" factors in deaths from selected causes (see section X.4.4).

X.4.2 Using mortality data to address health care policy questions

The health care policy question addressed in chapter III was, whether regional mortality data by cause of death can be used as indicators of the need for health care in a formula for the allocation of financial resources. The conclusion was that, although in general regional mortality differences appeared to reflect morbidity differences, a more judicious approach is preferable. It is uncertain whether regional mortality profiles by cause of death give a sufficiently accurate picture of these morbidity differences, and mortality at least in part also reflects the "outcome" of preventive and curative efforts.

A more judicious approach to the use of mortality data could be based on a Swedish model, in which regional mortality data are being used in a more informal planning process. Data which contribute to "community diagnosis" are combined in a "planning base" with "state-of-the-art reports", in which knowledge on the possibilities for prevention and treatment is compiled from various sources. This planning base is analysed and discussed regionally with policy makers and health care professionals, in an attempt to create conditions for change, where necessary. Such a change could be the organization of a prevention programme. An example of this is the cardiovascular disease prevention programme undertaken in the county of Västerbotten, after an extensive phase of community diagnosis in which the possible causes of the high cardiovascular disease mortality rates were investigated. Decisions on budget allocations can be taken in the same process, in which negotiations to a large extent replace mathematical formulas [46].

The conclusion on the use of regional mortality data in the context of resource allocation decisions is generalizable to most or all uses of mortality data to address health care policy questions (or health policy questions, for that matter). Mortality analyses contribute fragments of a community diagnosis, but in most cases our knowledge of the ailment and its causes will not immediately be sufficient to decide upon a treatment plan, and additional information will have to be collected.

Recent developments in health care policy in The Netherlands

When the study reported in chapter III was carried out, the prevailing

trend was towards more state intervention in the health care sector. Adoption and implementation of the Health Care Services Act, which formed the direct background to the study, has been very slow. After many years of preparation it was adopted by Parliament in 1982, and it has not yet been implemented, except for a small number of regions where introduction experiments are carried out. In the mean time, the climate has changed considerably, and the utility of extensive state intervention is increasingly being questioned.

A recent product of this trend reversal is the report of the Dekker commission, called after its chairman, former president of the Philips company Dr. W. Dekker [47]. Among other measures, the commission has recommended the abolishment of the Health Care Services Act, in order to reintroduce an element of free enterprise and competition in the health care "market". One of the remaining roles of the state, however, will be to provide rules and mechanisms for quality assurance in the health care sector. It is interesting to note that one of the possible uses of mortality data is in monitoring the effectiveness of health care services. It is thus to be expected that, although the political climate and bureaucratic context may change a bit, the results of studies of the relationship between mortality and medical care will continue to be relevant to health care policy.

X.4.3 Monitoring the effectiveness of medical care

The decline of infectious disease mortality since the eighteenth and nineteenth centuries is largely due to other factors than improvements in medical care. Nevertheless, a closer look at mortality time trends for infectious diseases reveals that the introduction of antibiotics was accompanied by important changes (chapter IV).

Since 1950 improvements in life expectancy have been modest, but proportional declines in age-specific mortality rates have on the whole not been less impressive than in the period 1850-1950. An analysis of cause-specific changes in mortality since 1950 showed that large declines in mortality have occurred for conditions which have become amenable to medical intervention. These mortality declines have made an important contribution to improvements in life expectancy since 1950. More than in earlier time-periods, the effects of improvements in medical care may thus have been important, relative to changes induced by other factors (chapter VI).

These findings show that, contrary to what is frequently believed, recent mortality time trends do not provide reasons for skepticism on the effectiveness of medical care. It is, however, disappointing that important progress in the treatment of cancer has been limited to a small number of relatively infrequent cancers (chapter V).

It is important to continue monitoring mortality trends by cause of death in The Netherlands. Some of the conditions which have

become amenable to medical intervention continue to cause substantial numbers of deaths, and further analysis of mortality may help to reveal barriers to progress that can be removed.

Perinatal mortality trends are not as favourable in recent years as in a number of comparable countries (section X.2.4). A further analysis of mortality changes, including an analysis of the possible causes of regional differences in trends of Perinatal mortality (cf. chapter IX), might be helpful in finding barriers to progress.

The importance of other data than mortality

Monitoring the effectiveness of medical care cannot exclusively rely on analyses of mortality time trends. The availability of information on trends in incidence and survival of specific conditions would greatly help the interpretation of mortality time trends. A registry of (incidence and) survival of cancer, still not available in The Netherlands, except for Leukemia in children [48], is an obvious example (chapter V).

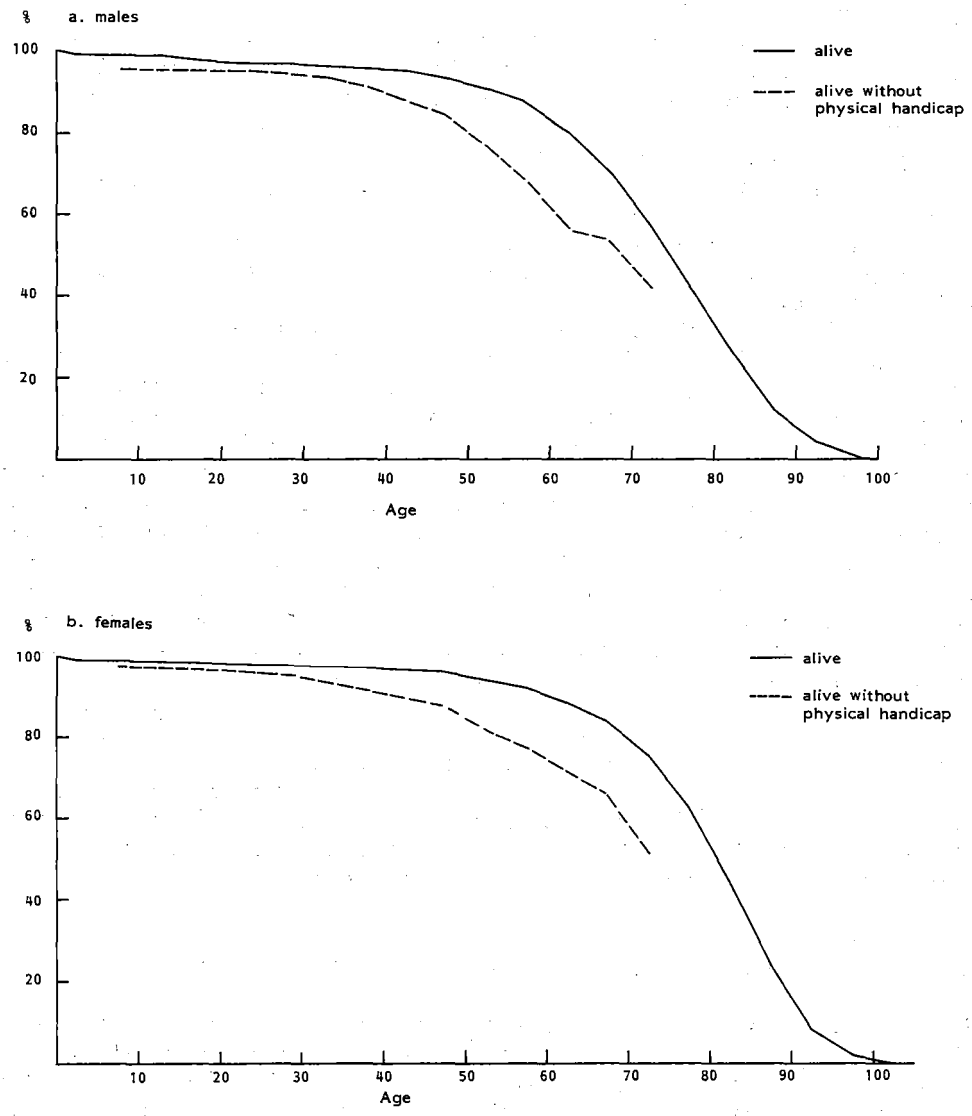
Information on trends in morbidity is also necessary to answer questions about the effects of medical care on other outcome measures than mortality. One unanswered question, for example, is whether mortality declines have led to changes in prevalence of disease in the population. Changes in the prevalence of disease, for example due to increasing survival, may have consequences for the need for health care services. Some have claimed that the "rectangularization" of the survival curve (section I.4.1), i.e. the "compression" of mortality in higher age-groups, has been accompanied by a compression of morbidity, leading to a lower prevalence of disease [49].

Increasing or decreasing prevalence of disease?

In a short intermezzo, intended to suggest an important area for additional data collection and further study, we will discuss this question on the basis of figure X.6. Data on the prevalence of disease, by age, are not routinely available in The Netherlands, but the results of a large survey held in 1971/1972 may provide some illustrative material [30]. (The survey did not intend to measure the prevalence of disease, but to measure the prevalence of physical handicap, and its causes. Most physical handicaps are caused by chronic disease. Diseases which do not lead to physical handicaps until perhaps late in their course, such as Diabetes mellitus, are underrepresented in these data.)

The information on prevalence of handicap permits the calculation of "survival without handicap" for males and females, in selected age-groups, under the rates prevailing at that particular moment in time. With advancing age, the vertical distance between the curves for survival and survival-without-handicap increases, indicating that physical handicap due to disease is more prevalent at higher ages. At the same time, the horizontal distance between the two curves decreases with age, reflecting the fact that the average length of

Figure X.6 Survival and survival without physical handicap in The Netherlands, by sex, ca. 1971/1972.



Data from ref. 50.

survival after a physical handicap has arisen, is less at higher ages. The surface between both curves, expressed as a fraction of the surface below the curve for survival, is an estimate for the (crude) prevalence of physical handicap in the Dutch population, under the rates prevailing in 1971/1972.

If a shift in survival curves to the right is not accompanied by a shift to the right of the curves for survival without physical handicap, the prevalence rate of physical handicap in the population increases. So the crucial question is: what happened to age-specific incidence and survival of (causes of) physical handicap?

The effect of mortality reductions on the prevalence of diseases which are themselves seldomly fatal, such as Rheumatoid arthritis and disorders of sight and hearing, is relatively simple. Assuming that age-specific incidence remains unchanged, prevalence will increase.

The effect of mortality reductions on the prevalence of frequently fatal conditions is more complicated. We have seen that mortality reductions for e.g. Ischemic heart disease have probably been caused by both a decrease in incidence and a decrease in case fatality (section X.2.2). In general it can be said that both incidence and case fatality reductions have contributed to mortality declines. Reductions in incidence shift the curve for survival without disease to the right, and will generally increase the average age at incidence. Due to the fact that length of survival with disease is frequently shorter at higher ages, the surface between the curve for survival and survival without disease will shrink. Reductions in case fatality, however, increase the horizontal distance between the two curves, and thus lead to an increase in prevalence.

The question is complicated even further by the fact that improvements in medical care may not only have affected incidence and case fatality, but also chances of complete recovery.

Without information on trends in the prevalence of specific conditions it is impossible to infer the net effect of these changes, which also implies that recent speculations on the "compression of morbidity" in higher age-groups [49] are premature.

X.4.4 Further study of regional mortality differences

Substantial regional differences in mortality by cause of death within The Netherlands have been documented in the preceding chapters (section I.5.2, chapter VIII). We also found regional differences in trend of mortality from a number of conditions (chapter IX). Regional mortality differences do not appear to be related to differences in the level of supply of medical care, and, except for a short discussion of the contribution of socio-economic factors (chapter IX and section X.3.3), have largely remained unexplained.

Finding out the reasons for regional differences in mortality may lead to opportunities for effective intervention, and is thus important from a health policy perspective. Reducing the long-standing higher mortality rate in parts of the south-east of The Netherlands (section I.5.2), for example, should be recognized as a challenge of the first importance. Because the causes of death for which the differences were found are to some extent amenable to medical intervention, further study may also be relevant for health care policy makers.

A number of approaches has been developed for such further study [51-53]. A compilation of these various approaches is presented in table X.7. Two purposes of further study are distinguished: verification, and assessment of possible causal factors. As a matter of fact, some of the studies reported in the previous chapters fit into this schematic representation. The case history approach used in chapter II could also be used for the analysis of possible differences in cause-of-death certification between regions. The studies discussed in chapters VII, VIII and IX may be viewed as examples of studies of "aggregate associations" with determinants of health status.

The possibilities for further aggregate data studies are certainly not yet exhausted; it would be interesting to see whether more specific medical care data, for example on the application of specific interventions, would be able to explain more of regional differences in mortality from conditions amenable to medical intervention, preferably controlling for "spontaneous" differences in incidence. Regional mortality trends can be related to trends in other aspects of health status and trends in determinants.

A promising new line of enquiry, currently in development, is that of studies of "avoidable factors" in individual deaths. This approach builds upon the experience in the surveillance of Maternal [54, 55] and Perinatal mortality [56-58], and can be regarded as the equivalent of the clinical audit at population level. The identification of shortcomings in the delivery or uptake of medical care in the history of patients who died from specific causes, may contribute appreciably to a further improvement of medical care. The finding of a higher proportion of such "avoidable" deaths in regions with higher mortality would strongly support the hypothesis that mortality differences are related to the delivery and uptake of medical care.

Table X.7 Approaches to the analysis of possible causes of a regional deviation from national mortality levels or trends by cause of death

Purpose	Approach	Additional sources of information required
Verification	Consistency	
	- in time, in space, across population groups	None
	- with other data	Other data on health status of population
	Validation of recorded causes of death	
	- by simulation of death certification	Case history study
	- by retrospective evaluation	Death certificates, patient records, autopsy records
Assessment of possible causal factors	Aggregate associations	
	- with other aspects of health status	Other data on health status of population
	- with determinants of health status	Data on health care, sociodemographic factors, and other determinants
	Individual associations	
	- with other aspects of health status	Death certificates, patient records, interviews with family and health care providers, etc.
	- with determinants of health status	Patient records, interviews with family and health care providers

X.5 Epilogue

The preceding pages were devoted to death ("mortality") as a reflection of changes and differences in the health status of populations. In this epilogue we will write a few, probably insufficient, words on the rather obvious fact that death is more than this. Needless to say, the "vital event" of demographers and epidemiologists is in the first place the event that terminates precious lives, and that inspires most of us, including those who study death professionally, with a certain awe.

One of the consequences of the recession of death into old age has been that death has at the same time lost and gained in terror. When life was expected to be short, death was accepted with a certain equanimity. The studies of Philippe Ariès have shown that Western attitudes towards death have gradually changed, and that in modern times death has become something unfamiliar, laden with feelings of repulsion [59].

On the other hand, changing attitudes towards matters of life and death may themselves have contributed to the successful elimination of premature death by environmental change and medical care. In the eighteenth century, the idea that modification of mortality risks was possible, and that death was not entirely unavoidable, gradually found acceptance. Health became a serious preoccupation, and physicians acquired more importance than ever before [60]. Confidence in the powers of medical care anteceded the era of effective intervention by two centuries, and, although unfounded at that moment in time, may have created a favourable climate for scientific development.

There is of course no guarantee that war, famine and epidemics, the main causes of the high mortality rates before the demographic transition, have left us forever. The final passage of Camus' novel "La peste" [61] expresses this eloquently, and also illustrates the powerful metaphors that lethal diseases, due to their awe-inspiring character, give rise to [62].

The Plague epidemic which occurred in Oran (Algeria) in the 1940's has left the city, and Rieux, the physician through whose eyes the events have been described, realizes that it may not be forever. "Car il savait ce que cette foule en joie ignorait, et qu'on peut lire dans les livres, que le bacille de la peste ne meurt ni ne disparaît jamais, qu'il peut rester pendant des dizaines d'années endormi dans les meubles et le linge, qu'il attend patiemment dans les chambres, les caves, les malles, les mouchoirs et les paperasses, et que, peut-être, le jour viendrait où, pour le malheur et l'enseignement des hommes, la peste réveillerait ses rats et les enverrait mourir dans une cité heureuse."

References of chapter X

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Samenvatting

Dit proefschrift gaat over sterfte en doodsoorzaken, over het gebruik dat van sterftegegevens in het gezondheidszorgbeleid gemaakt zou kunnen worden, en meer in het bijzonder over het gebruik van sterftecijfers als indicator van de effectiviteit van medische zorg. Het bevat, grotendeels in de vorm van al dan niet reeds gepubliceerde artikelen, de resultaten van een aantal analyses van de sterfte in Nederland in heden en verleden, op verschillende plaatsen aangevuld met gegevens uit andere landen.

In een uitvoerige inleiding (hoofdstuk I) wordt eerst geschetst hoe sterftecijfers naar doodsoorzaak totstandkomen, en wat er bekend is over de kwaliteit van deze gegevens. Daarna wordt, mede aan de hand van een aantal historische voorbeelden, besproken welke functie sterfte-analyses voor het beleid ten aanzien van de volksgezondheid kunnen hebben. Tenslotte volgt een overzicht van wat er in de literatuur bekend is over de effecten van verbeteringen van medische zorg op de sterfte-ontwikkeling in historisch perspectief, en over de effecten van verschillen in medische zorg op regionale sterfteverschillen.

De resultaten van de verschillende analyses zijn gegroepeerd in 4 thema's. Het eerste thema is dat van de validiteit (geldigheid) van de doodsoorzaakgegevens zoals deze in de sterftestatistiek beschikbaar zijn. Bij de aangifte van overlijden moet door de behandelend arts een doodsoorzaakverklaring worden ingevuld, waarvan de gegevens op het Centraal Bureau voor de Statistiek worden verwerkt. Aan de kwaliteit van deze gegevens wordt nogal eens getwijfeld. De studie waarvan in hoofdstuk II verslag wordt gedaan was een poging om van die kwaliteit een indruk te krijgen. Het betrof een onderzoek naar de onderlinge vergelijkbaarheid van de sterftecijfers voor CARA (chronische aspecifieke respiratoire aandoeningen) en kanker van een aantal Europese landen. Door aan steekproeven van artsen in die landen een aantal "papieren" ziektegeschiedenissen van patiënten die aan deze ziekten waren overleden, toe te zenden, en hun te vragen van die

patiënten een doodsoorzaakformulier in te vullen, kon het proces van aangifte en codering van doodsoorzaken worden nagebootst. Er bleken aanzienlijke verschillen tussen de deelnemende landen te bestaan in de kans dat een patiënt die aan CARA of kanker was overleden, ook werkelijk onder die ziekte in de statistiek terechtkomt. Opmerkelijk was dat die kans in Nederland hoog is: 91% voor CARA en 94% voor kanker. Dit geeft enig vertrouwen in de Nederlandse doodsoorzaakstatistiek.

Het tweede thema is dat van het gebruik van sterftecijfers voor het beantwoorden van vragen uit het gezondheidszorgbeleid. Sterftecijfers geven informatie over de gezondheidstoestand van de bevolking. In het gezondheidszorgbeleid is aan dat type informatie uiteraard nogal eens behoefte, bijvoorbeeld wanneer het gaat om de vraag hoe de (financiële) middelen verdeeld moeten worden. Het ligt voor de hand die verdeling op de gezondheidstoestand van de bevolking af te stemmen. In het onderzoek waarvan hoofdstuk III verslag doet, is nagegaan of regionale sterftecijfers een voldoende nauwkeurige indruk geven van verschillen in het vóórkomen van aandoeningen in de bevolking om ze als verdelingscriterium te kunnen gebruiken. Uit een vergelijking tussen sterftecijfers naar doodsoorzaak enerzijds en ziekenhuisopname- en arbeidsongeschiktheidscijfers anderzijds moest worden geconcludeerd dat dit vermoedelijk niet het geval is. Hoewel sterftecijfers waardevolle informatie geven over de gezondheidstoestand van de bevolking, is de interpretatie van regionale verschillen onvoldoende eenduidig om belangrijke beslissingen als die van de verdeling van middelen klakkeloos op sterfteverschillen te baseren.

Het derde en vierde thema borduren op deze conclusie voort. Eén van de redenen waarom regionale sterfteverschillen niet zonder meer een nauwkeurige afspiegeling van het vóórkomen van aandoeningen in de bevolking vormen, is dat de kans om aan die aandoeningen te overlijden ook op de hoogte van het sterftecijfer van invloed is. Anders gezegd: sterftecijfers weerspiegelen mede het effect van medische zorg.

De vraag of verbeteringen in medische zorg een belangrijk effect hebben gehad op de ontwikkeling van de sterfte in het recente verleden vormt het derde thema van dit proefschrift. Sinds het werk van de Engelse onderzoeker McKeown is, terecht, twijfel ontstaan aan de bijdrage van de medische zorg aan de grote sterftedaling zoals die sinds de achttiende en negentiende eeuw in vele Europese landen is opgetreden. Deze sterftedaling, die voornamelijk op een reductie van de infectieziekten-sterfte berustte, had zich eenvoudigweg al grotendeels voltrokken toen de eerste echt effectieve medische behandelingen beschikbaar kwamen. De verklaring van de sterftedaling moet hoofdzakelijk bij andere factoren gezocht worden, zoals een betere voeding en verschillende hygiënische maatregelen.

Dat neemt niet weg dat een zorgvuldige bestudering van de ontwikkeling van de sterfte aan infectieziekten laat zien, dat de introductie van antibiotica vermoedelijk wel degelijk nog een be-

langrijk effect gesorteerd heeft (hoofdstuk IV). In Nederland is voor een groot aantal infectieziekten een versnelling van de sterftedaling zichtbaar nadat de eerste antibiotica aan het eind van de jaren dertig en in de jaren veertig beschikbaar waren gekomen. Hoewel het niet uitgesloten is dat andere factoren aan die versnelling ook een bijdrage geleverd hebben, wijst alles er toch op dat deze geneesmiddelen een belangrijk effect op de sterfte-ontwikkeling hebben gehad.

Vormen infectieziekten een voorbeeld van een groep ziekten waartegen de geneeskunde niet langer machteloos staat, bij veel vormen van kanker is dat helaas anders. Toch zijn in de overlevingskansen bij kanker wel degelijk verbeteringen waarneembaar (hoofdstuk V). Gegevens uit een aantal buitenlandse kankerregistraties laten zien, dat voor veel vormen van kanker een lichte verbetering van de overlevingskansen is opgetreden sinds de jaren vijftig. Voor een aantal vormen van kanker is die verbetering meer uitgesproken, maar ten dele berust dit op veranderingen in het tijdstip van diagnose, registratieprocedures e.d. Niettemin kan de aanzienlijke verlenging van de overlevingsduur bij de ziekte van Hodgkin, Kanker van de testis, Acute lymfatische leukemie, en Wilm's tumor (een vorm van nierkanker die bij kinderen voorkomt) vermoedelijk wel aan verbetering van de behandeling worden toegeschreven.

Op grond van een systematisch overzicht van alle aandoeningen waartegen in de laatste decennia effectieve medische zorg beschikbaar is gekomen, is tenslotte een globale analyse gemaakt van mogelijke effecten van medische zorg op ontwikkelingen in de sterfte sinds 1950 (hoofdstuk VI). Het gaat hierbij in totaal om 35 aandoeningen, sommige kwantitatief belangrijk, andere niet, waarvoor in de meeste gevallen in Nederland aanzienlijke sterftedalingen zijn opgetreden. In tegenstelling tot wat wel wordt gedacht, zijn ook na 1950 nog belangrijke sterftereducties gerealiseerd, en aandoeningen die door medische zorg voorkóómbaar of behandelbaar zijn geworden, hebben hieraan een grote bijdrage geleverd. Sterftedalingen voor deze aandoeningen sinds 1950 hebben ca. 3 jaar aan de gemiddelde levensverwachting van Nederlandse mannen, en ca. 4 jaar aan die van Nederlandse vrouwen toegevoegd. (Door ongunstige ontwikkelingen bij andere doodsoorzaken is de levensverwachting bij de geboorte van mannen netto slechts ca. 2 jaar toegenomen. Voor vrouwen waren de ontwikkelingen bij andere doodsoorzaken gunstiger, en is de levensverwachting in totaal met ca. 6 jaar toegenomen.) Ook hier geldt weer dat verbeteringen in medische zorg waarschijnlijk niet de enige verklaring voor deze sterftedalingen zijn, maar dat een effect van enige betekenis toch wel aannemelijk is.

Het vierde thema is dat van de regionale sterfteverschillen, en van het mogelijke verband tussen deze sterfteverschillen en verschillen in het aanbod van medische zorg. Binnen Nederland, evenals binnen andere landen, bestaan behoorlijke geografische sterfteverschillen. Deze zijn een intrigerend verschijnsel, en suggereren dat met de juiste maatregel de sterfte aan bepaalde doodsoorzaken in een

aantal gebieden nog behoorlijk gereduceerd zou kunnen worden. Dit geldt eens te meer voor de sterfte aan aandoeningen waartegen effectief medisch ingrijpen mogelijk is. Ook voor de sterfte aan deze aandoeningen worden belangrijke regionale sterfteverschillen gezien.

In de hoofdstukken VII en VIII is nagegaan of deze sterfteverschillen wellicht samenhangen met verschillen in het aantal ziekenhuisbedden, het aantal arten e.d. In hoofdstuk VII gebeurt dit in een parallelle analyse voor een aantal Europese landen; dit heeft als voordeel dat het verband tussen zorgaanbod en sterfte in een groot aantal verschillende contexten betudeerd kan worden. In hoofdstuk VIII gebeurt dit voor Nederland, maar op 4 verschillende tijdstippen: 1950-54, 1960-64, 1970-74 en 1980-84; het voordeel hiervan is dat ook verbanden die slechts in een bepaalde fase van de ontwikkeling van medische zorg bestaan, zo naar voren moeten komen. Het resultaat van beide analyses is min of meer hetzelfde: er zijn geen duidelijke verbanden tussen de "omvang" van de medische zorg op regionaal niveau, en de hoogte van de sterfte aan aandoeningen die toch geselecteerd waren op een zekere afhankelijkheid van goede medische zorg.

Voor de verklaring van deze sterfteverschillen moet dus een beroep worden gedaan op andere factoren. Hiervoor is meer gedetailleerd onderzoek noodzakelijk. Eén van de elementen van zulk verder onderzoek kan ook een studie van regionale verschillen in ontwikkeling (i.t.t. niveau op één of meer momenten) van de sterfte zijn. Omdat de sterfte voor een aantal aandoeningen nogal sterk gedaald is, kan het van belang zijn na te gaan of bepaalde regio's zijn achtergebleven. Een verkennende analyse van regionale verschillen in sterftetrend in Nederland in de periode 1969-1984 liet zien dat de sterfte aan een aantal aandoeningen inderdaad niet in alle regio's even snel gedaald is (hoofdstuk IX). Evenals dit met verschillen in sterfteniveau het geval is, blijken ook verschillen in sterftetrend samen te hangen met sociaal-demografische kenmerken van de bevolking, o.a. met indicatoren voor de sociaal-economische status.

In hoofdstuk X wordt tenslotte, na enkele aanvullende commentaren op de resultaten van de analyses, een aantal conclusies en aanbevelingen geformuleerd. Deze hebben betrekking op verdere verbetering van de sterftestatistiek, op het belang van sterftecijfers voor gezondheidszorgbeleid, met name voor de evaluatie van verbeteringen in medische zorg, en op de verdere analyse van regionale sterfteverschillen.

Curriculum vitae

De schrijver van dit proefschrift, Johan P. Mackenbach, werd op 1 oktober 1953 te Rotterdam geboren. Van 1966 tot 1972 volgde hij een Gymnasium β opleiding aan achtereenvolgens de scholengemeenschappen Johannes Calvijn en Melanchthon, beide te Rotterdam. Van 1972 tot 1979 studeerde hij Geneeskunde aan de Erasmus Universiteit te Rotterdam. Van 1979 tot 1984 was hij wetenschappelijk medewerker bij het Nederlands Instituut voor Praeventieve Gezondheidszorg TNO te Leiden. Sinds 1984 is hij als universitair docent verbonden aan het Instituut Maatschappelijke Gezondheidszorg van de Erasmus Universiteit.

Dankwoord

Aan de totstandkoming van dit proefschrift is, behalve door degene wiens naam op de omslag staat, ook door vele anderen een belangrijke bijdrage geleverd. Dit geldt niet alleen voor de artikelen (alias de hoofdstukken II t/m IX), waarvan een aantal samen met co-auteurs is geschreven, maar ook voor het proefschrift als geheel.

Tijdens de ruim drie jaar die ik aan de voorbereiding van dit proefschrift heb gewerkt, maar vooral tijdens de laatste fase, waarin de afzonderlijke studies tot één geheel moesten worden gesmeed en van een in- en uitleiding moesten worden voorzien, heb ik me steeds gestimuleerd gevoeld door Paul van der Maas, mijn gewaardeerde promotor. Onze verwantschap vond een mooie bezegeling in de gedachtenwisseling over de laatste passage van hoofdstuk X, en de literatuurverwijzing die dit opleverde, voor me opgediept uit een grijs verleden.

De andere leden van de promotiecommissie, Prof. dr H.A. Valkenburg, Prof. dr R.M. Lapré en Prof. dr G. Hennemann, hebben met hun opbouwende kritiek nog aanleiding gegeven tot menige "finishing touch".

During the last seven years, Professor Walter Holland has played an important role in my professional development. His bold pragmatism in finding applications of epidemiology to health (care) policy issues has produced the points of reference for several of the studies reported in this thesis. Although I have not always reached the same conclusions, I am very grateful for having had the opportunity to collaborate with him in the framework of several European Community studies.

Ik heb verder veel profijt gehad van het commentaar van een aantal collega's, zowel binnen als buiten het instituut Maatschappelijke Gezondheidszorg. Anton Kunst wist me door nauwgezette lezing nog voor verschillende misstappen te behoeden. Verder denk ik aan Guido Moens,

Jeroen van Ginniken, Ed van Beeck, Caspar Looman, mevr. Friden-Kill, en Dik Hoogendoorn, die elk een aantal stukken van waardevol commentaar hebben voorzien. Dik Hoogendoorn is daarnaast vermoedelijk ook de meest geciteerde auteur; mijn grote waardering voor zijn werk is één van de drijfveren achter dit proefschrift.

De meeste studies die in dit proefschrift zijn gebundeld (hoofdstukken IV t/m IX), heb ik uitgevoerd op het instituut Maatschappelijke Gezondheidszorg. Met de co-auteurs van de betreffende artikelen, Anton Kunst, Caspar Looman, Dik Habbema en Paul van der Maas, heb ik plezierig en in een hoog tempo samengewerkt, en zij hebben vele inhoudelijke en praktische bijdragen geleverd.
Er wordt wel gezegd dat Simon Vestdijk sneller schreef dan God kan lezen; als die vergelijking niet aan mijn kant mank zou gaan, zou ik hier opschrijven dat Caspar Looman sneller analyses uitvoerde dan ik kon verwerken. Anton Kunst was niet alleen een nauwgezet lezer, maar ook een nauwgezet onderzoeker die aan het welslagen van het onderzoek daardoor veel heeft bijgedragen.
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Het Audiovisueel Centrum van de Erasmus Universiteit heeft een groot deel van de illustraties verzorgd.

Aan de onderzoeken die in de hoofdstukken II en III worden gerapporteerd, heb ik gewerkt toen ik nog aan het Nederlands Instituut voor Praeventieve Gezondheidszorg TNO verbonden was. Dit dienstverband heeft een onverwacht staartje gekregen in de genereuze steun die het NIPG bij het drukken van dit proefschrift heeft verleend. Hiervoor wil ik in de eerste plaats Wim van Duyne bedanken, en verder diegenen die de technische afwerking hebben verzorgd: Nico de Kleijn, de medewerkers van de drukkerij, en iemand die hier niet vermeld wil worden.

Tenslotte een woord van dank aan het adres van twee instanties, die veel van het onderzoek dat in dit proefschrift wordt gerapporteerd, hebben mogelijk gemaakt. Het Centraal Bureau voor de Statistiek, in het bijzonder de Hoofdafdeling Gezondheidsstatistiek (hoofd: Drs J.T.P. Bonte), heeft ten behoeve van de levering van een groot gegevensbestand een speciale samenwerkingsovereenkomst willen sluiten. Het Ministerie van Welzijn, Volksgezondheid en Cultuur, in het bijzonder de Stafafdeling Beleidsontwikkeling (hoofd: Dr G.M. van Etten), heeft verschillende van de onderzoeken financieel gesteund.

Mijn familie kon niet altijd volgen wat er toch valt te beleven aan al die sterftecijfers (volgens hen kon mijn onderzoek niet veel meer opleveren dan "dat het merendeel van de Nederlandse bevolking van 18 jaar en ouder minstens eenmaal overlijdt, en wel in het laatste levensjaar"). Desondanks heb ik ook de laatste tijd veel warmte ondervonden van mijn ouders, mijn broers en schoonzusters, en mijn grootvader, die ik daarvoor, en voor de wortels die ze me gegeven hebben, hartelijk wil bedanken. Mijn schoonouders hebben me bij herhaling hun huis in Haamstede ter beschikking gesteld, zodat ik geconcentreerd aan die lange in- en uitleiding kon werken.

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Rotterdam, december 1987.

Annex 1
ICD-codes for the causes of death analysed in Chapters I, IV, VI, VIII, IX and X

Introduction

The mortality data used in many of the analyses reported in this thesis have been extracted from a large computer-file, supplied by the Central Bureau of Statistics, which contained detailed information on all deaths registered in The Netherlands since 1950. Besides age, sex, year of death and region (i.e. the COROP-region where the deceased was last registered as having his/her domicily), this information included a numerical code for the underlying cause of death. This numerical code was the four-digit code according to the International Classification of Diseases (ICD) [1], of which four different Revisions were in force during the period 1950-1984. The 6th Revision was used for classification in The Netherlands from 1950-1957; the 7th Revision from 1958-1968; the 8th Revision from 1969-1978; and the 9th Revision from 1979 onwards.

Simply stated, each Revision of the International Classification of Diseases consists of a list of code-numbers, for each code-number a longer or shorter list of the nosological entities designated by it, and a set of coding rules which help coders to select the right nosological entity from the information present on the death certificate. Revisions differ in all three respects, although these differences are sometimes minor. The 6th and 7th Revisions are practically identical as far as the code-numbers and the corresponding nosological entities are concerned, but rules for coding did change a little. The other Revisions each brought about major changes in the structure of the list of code-numbers and in the assignment of nosological entities to code-numbers; also, some coding rules changed.

Every analysis of mortality by cause of death covering a time-period during which more than one ICD-revision was in force, requires a careful consideration of possible changes in classification. Before the analyses reported in Chapters I, VI, VIII, IX and X

were carried out, a list of causes of death was created, of which the nosological content had remained more or less the same during the period 1950-84. A number of studies in which a detailed comparison was made between two ICD-revisions, mainly carried out in the United States, was very helpful in constructing this list [2, 3, 4], although changes between Revisions were sometimes different in The Netherlands, probably due to other interpretations of coding rules. For each of these causes of death, numbers of death were tabled against calendar-year to check for sudden changes coinciding with the introduction of a new ICD-revision. Several modifications were necessary in this stage, but the resulting causes of death were reasonably robust against changes introduced by new ICD-revisions. Table 1 gives the exact specifications.

Not all the analyses reported in this thesis have been performed with the same mortality data-file. Mortality data presented in Chapters II, III, IV, V, and VII were drawn from different (intermediate) sources, and sometimes slightly different groupings of code-numbers have been used. The data of Chapter IV, on secular trends of infectious disease mortality, form a special case, because a longer time-period had to be covered (1911-1978). Table 2 gives the specifications for the selection of causes of death used in this analysis.

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Table 1 ICD-codes used for mortality analysis by cause of death, 1950-1984.

Cause of death	ICD-6/7	ICD-8	ICD-9
Tuberculosis	001-019	010-019	010-018,137
Specific bacterial infections	030-039,050-052, 057	098,099,034-036	092,099,034-036
Diphtheria/whooping cough/ tetanus/poliomyelitis	055,056,061,080, 081	032,033,037,040-044	032,033,037,045, 138
Septicemia	053,054,767,768	038	038,790.7,771.8
Viral infections of children	085-087,089	052,055,056,057, 072	052,055,056,057, 072
Syphilis	020-029	090-097	090-097
Cancer of lip and skin	140,191	140,173	140,173
Cancer of the stomach	151	151	151
Cancer of the colon	153	153	153
Cancer of the lung	162,163	162,163.0,163.9	162,163,165
Cancer of the breast	170	174	174,175
Cancer of the cervix uteri	171	180	180
Cancer of the prostate	177	185	185
Cancer of the testis	178	186	186
Cancer of the kidney	180	189	189
Morbus Hodgkin	201	201	201
Leukemia	204	204-207	204-208
Diseases of the thyroid	250-254	240-246	240-246
Diabetes mellitus	260	250	250
Pernicious anemia	290	281	281
Other anemias	291-293	280,282-285	280,282-285
Infections of central nervous system	082,083, 340-344	045,046,064-066, 320-324	046-049,139.0, 320-326
Rheumatic heart disease	400-416,421	390-398,424	390-398,424
Hypertensive disease	440-447	400-404	401-405
Ischemic heart disease	420,422.1	410-414	410-414,429.2
(Sub)acute endocarditis	430	421	421
Other heart disease	r422,431-434, 782.4	420,r(422-426), 427-429,782.4	416,420,422,423, 425-428,r429
Cerebrovascular disease	330-334	430-438	430-438
Arterial disease	450-456	440-448, excl. 444.2	440-448,785.4

Table 1 (continued)

Cause of death	ICD-6/7	ICD-8	ICD-9
Infections of respiratory system	390-394, 470-475,500	380-384, 460-466	380-385, 460-466
Influenza and pneumonia	480-483, 490-493,763	470-474, 480-486	487, 480-486
Chronic obstructive pulmonary disease	501,502,526, 527.1,241	490-493,518	490-496
Peptic ulcer	540-542	531-534	531-534
Appendicitis	550-553	540-543	540-543
Abdominal hernia	560,561	550-553	550-553
Ileus w.o. mention of hernia	570,excl.570.2	560	560
Cholelithiasis/-cystitis	584-586	574-576	574-576
Nephritis/nephrosis	590-594,603,792	580-584,593,792	580-589,593
Infections of the urinary system	600,605	590,595	590,595
Benign prostatic hyperplasia	610	600	600
Maternal causes:			
Complications of pregnancy	640-649,680	630-639	630-633,640-648
Complications of delivery	650-652,660-678	640-645,650-662	634-639,650-669
Complications of puerperium	681-689	670-678	670-676
Infections of the skin	690-698	680-686	680-686
Infections of the locomotor system	720,730	710,720	711,730
Congenital cardiovascular anomalies	754	746,747	745-747
Congenital digestive anomalies	756	750,751	750,751
Perinatal causes:			
Diseases of mother	769	760-763	760
Birth injury	760,761	764-768,770-772	762,763,767
Hemolytic disease of newborn	770	774,775	773,774
Other perinatal causes	r(760-776)	r(760-779)	r(760-779)

Table 1 (continued)

Cause of death	ICD-6/7	ICD-8	ICD-9
Senility without mention of psychosis	794	794	797
Sudden death	795.2	795	798.0,798.1
Other ill-defined causes	r(780-796) 286.5,286.6	r(780-799), 267-269, excl.269.0	r(780-799), 260-263,578.0, 578.1
Traffic accidents	E800-866,960	E800-845,940,941	E800-848,929.0, 929.1
Other accidents	E900-904,910-929 930-936,961,962, 870-895	E880-887,890-909, 910-929,943-946, 980-989, 850-877,942	E880-888,890-909, 910-928,929.2-.9, 980-989, 850-869

r = remainder of

Table 2 ICD-codes for causes of death analysed in Chapter IV.

	ICD-2 1911-1920	ICD-3* 1921-1930	ICD-4 1931-1940	ICD-5 1941-1949	ICD-6 1950-1957	ICD-7 1958-1968	ICD-8 1969-1978
Puerperal fever	137	146	140,145a	140a,b, 147a,b	651,681	651,681	670
Scarlet fever	7	8	8	8	050	050	034
Rheumatic fever	47,72	51,81	56,87a	58,87a	400-402	400-402	390-392
Erysipelas	18	21	15	11	052	052	035
Septicemia	20	41	36a,b,c	24a,b,c, 767,768	053,063, 767,768	053,063, 767,768	038
Meningococcal meningitis	61bis	24	18	6	057	057	036
Non-meningoc. meningitis	61	71	79	81a,b	340	340	320
Acute bronchitis	89	99a	106a	106a	500	500	466
Pneumonia	91,92	100,101a, 101b	107-109	107-109,	490-493, 763	480-493, 763	480-486
Otitis media, mastoiditis	76	86	89a,b	89a,b	391-393	391-393	381-383
Upper resp. infections	86,87, 99,100	97,98, 108b,109	104,105, 115	104a,b, 105,115	470-475, 510-516	470-475, 510-516	460-465 500-506
Influenza	10	11a,b	11a,b	33a,b	480-483	480-483	470-474
Measles	6	7	7	35	085	085	055
Pyelo-nephritis	122	131	133a	133a	600	600	590
Cystitis	124	133	135a	135a	605	605	595
Skin/subcut. infections	142-144	151-153	151,152	151,152	690-693	690-693	680-682
Osteomyelitis	146	156	154	154a,b,c	730	730	720
Syphilis	37,62,67	38,72,76	34,80, 83,96	30	020-029	020-029	090-097

Table 2 (continued)

	ICD-2 1911-1920	ICD-3* 1921-1930	ICD-4 1931-1940	ICD-5 1941-1949	ICD-6 1950-1957	ICD-7 1958-1968	ICD-8 1969-1978
Tuberculosis	28-35	31-37	23-32	13-22	001-019	001-019	010-019
Bacillary dysentery	14	16b,c	13b,c	27a,c	045,048	045,048	004
Typhoid fever, paratyph. fever	1	1a,b,c	1,2a,b	1,2a,b,c	040,041	040,041	001,002
All other diseases	all other	all other	all other	all other	all other	all other	all other

* In the period 1922-1924 a slightly different classification was used in The Netherlands.

Annex 2
Short bibliography on causes of death selected for analysis in Chapter VI

Introduction

This short annotated bibliography is presented as background material to table VI.1 in chapter VI. This table contains a selection of causes of death which have become amenable to medical intervention, and which have been used in the time trend analysis. For each of these conditions references will be given to literature which describes favourable incidence or case fatality effects of medical care innovations. The bibliography also includes references to literature providing evidence on "spontaneous" changes in incidence or case fatality.

As others have noted before, available evidence on the efficacy and effectiveness of specific medical intervention can be characterized as scarce and therefore incomplete, and more often than not as methodologically questionable. Methodological problems include the following:

- Most studies are observational, with at best a historical or contemporary reference group of dubious comparability with the study-group.
- Many studies use selected patient groups (e.g. hospital patients), rendering difficult the necessary extrapolation from "efficacy" to "effectiveness" at population level.
- Many studies employ a fragmentary outcome measure, such as post-operative or hospital mortality.

As no other comprehensive bibliography on this subject exists (cf. the absent or cursory justification of comparable selections of conditions in references 1-6), this compilation of evidence is not much more than a first attempt. Further study is certainly necessary, for example employing formal synthesis methods.

Specific medical therapies (group I)

In the period 1920-1945 a number of efficacious drugs was introduced, affecting case fatality of several endocrine and hemopoietic disorders [7]. In the first decennia after the introduction of insulin in 1922 case fatality of Diabetes mellitus appeared to decline considerably, especially among younger patients; this decline continued during the 1950's [8]. The introduction of liver therapy for Pernicious anemia in 1927 was followed immediately by moderate reductions in mortality in many countries [9]. Antithyroid drugs and radioiodine treatment were introduced in the years immediately following World War II. Treatment of deficiency anemias may have improved by the systematic application of substitution therapies.

Improvements in surgery and anesthesia (group II)

There has been a wide range of improvements in surgery and anesthesia, facilitating progress in the treatment of a number of specific diseases. The introduction of antibiotics (group IV) may have contributed also. The start of this series of major improvements has arbitrarily been fixed at 1930 in table VI.1, when intravenous fluid therapy was introduced.

Reviews of studies on bleeding Peptic ulcer show reductions in case fatality since the 1940's [10, 11]. Continuing reductions in case fatality of Appendicitis, starting in the 1930's, have been reported from many centres [14-17]. The same applies to acute Cholecystitis, and non-malignant biliary tract disease in general [21-23]. Although elective hernioplasties will have become safer as part of the general trend, developments of case fatality of strangulated hernia are less clear [24]. Case fatality in intestinal obstruction (ileus) appears to have decreased since the 1940's, according to a review of the literature [25]. This also applies to specific subgroups like Gallstone ileus [25] and Intussusception [26], a cause of ileus in infants. Case fatality in prostatectomy for Benign prostatic hyperplasia has fallen too [28]. Part of this could be due to a shift from suprapubic and other surgical approaches to transurethral resection, but case fatality has fallen for each of these procedures separately too [29, 30].

There have been reports from several countries on declining incidence of Peptic ulcer, especially Duodenal ulcer, mainly based on hospital admission data [12, 13]. The same applies to acute Appendicitis [18-20]. Probably the incidence of ileus due to peritoneal adhesions has risen [25, 27].

Improvements in antenatal and perinatal care (group III)

Gradual improvements of antenatal and obstetric care probably started in the first decennia of this century, but it was not until the 1930's that Maternal mortality started to decline substantially [31]. Part of this advance has been ascribed to improvements in antenatal and obstetric care, resulting from the movement for a safe maternity [32], like systematic antenatal checkups and screening, improved standard of obstetric care, an increasing proportion of hospital deliveries, and the introduction of a number of specific technologies. Important among these were blood transfusions, antibiotics, and cesarian section [31, 33, 34].

Substantial declines in Perinatal mortality started around 1940 [31, 35]. This decline may in part be due to the same factors as the decline in maternal mortality. Reports from several countries indicate that mortality decline accelerated in the late 1960's (figures corrected for changes in age and parity distributions of mothers, and for birth weight) [36, 37]. This development approximately coincided with the introduction of neonatal intensive care. Reviews of the experience of centres where neonatal intensive care was introduced suggest significant improvements of survival among low birth weight infants [38]. Control of Hemolytic disease of the newborn by improved treatment and prevention (anti-D immunoglobulin was introduced around 1970), probably had a moderate separate effect on Perinatal mortality [40].

Other influences have also had a lowering effect upon both Maternal and Perinatal mortality during the study period. The most notable among these have been changes in age and parity distributions of mothers [33, 39].

Chemotherapeutics and antibiotics (group IV)

In the Netherlands, sulphonamides were introduced in 1936, penicillin in 1944 (but availability was very limited before 1947), and streptomycin in 1947. Effects were probably substantial in a wide range of infectious diseases. Both sulphonamides and penicillin appeared to reduce case fatality in Pneumonia [44, 45]. A randomized controlled trial proved the efficacy of streptomycin in reducing case fatality in Tuberculosis [41]. Chemoprophylaxis in contacts is effective in preventing Tuberculosis [42]. Case fatality of Septicemia went down during the 1940's in a hospital population [46].

Other improvements in medical care may have contributed also to a decline in Tuberculosis mortality, e.g. the introduction of mass screening by radiography in 1949. During the study period, incidence of Tuberculosis declined due to a number of factors, including pasteurization of milk and other public health measures, and the ever smaller number of infectious hosts (itself resulting from reductions

in incidence, already apparent before World War II) [43].

There have been suggestions of increasing incidence of Pyelonephritis, possibly due to increased intake of analgesics [47].

Surgical repair of certain congenital anomalies (group V)

Case fatality of Oesophageal atresia, an important congenital anomaly of the digestive system, was reduced when direct anastomosis proved successful in the late 1940's [48].

Except for Patent ductus arteriosus, for which surgical therapy became available in the 1940's [49], relatively safe palliative and definitive surgical treatments for Congenital anomalies of heart and great vessels were gradually introduced in the 1950's and 1960's. Reports on survival are mainly limited to early postoperative survival which has clearly improved for many procedures [50, 51].

Prophylaxis and surgical treatment of heart valve disease (group VI)

Several trials have shown that treatment with antibiotics of streptococcal infections prevents Acute rheumatic fever [52], and that prophylactic administration of antibiotics after a first attack of rheumatic fever prevents recurrences [53]. Introduction of these procedures was around 1950.

The first surgical treatment of heart valve disease was valvotomy for mitral stenosis, which was introduced in the United Stated in 1948 [54]. The first mitral valve prosthesis was implanted in 1961, and the first aortic valve prosthesis in 1963 [55]. Early mortality appears to have decreased considerably [55].

Rheumatic heart disease mortality started to decline in the 1930's, which has been ascribed to a change in character of streptococci [56]. As there is an association between crowding and incidence of rheumatic fever, the decline in incidence has also been attributed to improved housing conditions.

Mass vaccination (group VII)

Mass vaccination against Diphtheria, Whooping cough, Tetanus and Smallpox was introduced in the Netherlands in 1953. Poliomyelitis was added to the regimen in 1957. Vaccination campaigns have reduced incidence and mortality from these diseases in many countries [56-58].

Mortality from Diphtheria and Whooping cough was already declining during the first half of this century, which has been ascribed to improvements in living conditions and, for Diphtheria, possibly the introduction of antitoxin [56].

Hemodialysis (group VIII)

After small-scale applications during the 1940's and 1950's hemodialysis became accepted therapy for end-stage renal disease in the 1960's. There has been an exponential rise in the dialysis population since then due to liberal financing and extension of treatment to patient groups like diabetics who formerly were excluded. Three-year survival is above 50% in many patient series [59-61]. These patients would otherwise have had a very poor prognosis [62].

Before hemodialysis the introduction of corticosteroids in the 1950's may have prolonged survival in childhood nephrosis. Kidney transplantation has had a more limited use than hemodialysis; survival rates are comparable and probably improving.

Mortality from Nephritis and nephrosis declines since the 1930's. As this condition is believed to frequently be a sequel to streptococcal and other infections, just as Rheumatic heart disease which shows the same decline, the decline in mortality has been attributed to a change in character of the infectious agent(s) [56].

Hypertension detection and treatment (group IX)

The first antihypertensive drugs were introduced in the 1950's, but by 1960 a number of effective drugs was in use [63]. Systematic blood pressure control by casefinding and subsequent treatment started in the 1970's. Several trials have shown the effectiveness of hypertension control in reducing case fatality, especially that due to Cerebrovascular accidents [64-67]. Incidence of stroke, especially due to hemorrhage, appears to have declined subsequently [68].

Mortality due to Hypertensive disease and Cerebrovascular disease has been declining since 1940 [63], so other factors than improved medical care must also have been involved.

Improvements in cancer treatment (a.o. combination chemotherapy)(group X)

Cancer of the skin, other than melanoma, is a mild form of cancer, which can be treated effectively, if diagnosed in time, by surgery and/or radiotherapy [69]. Adequate treatment methods have been available for a longer period, and survival has been improving since the 1950's [70].

Successful treatment of Wilm's tumour, a cancer of the kidney which occurs in children, was already possible before 1970 with surgery, radiotherapy and Actinomycin D [73].

Intensive radiotherapy and combination chemotherapy led to the sucessful treatment of Hodgkin's disease, starting around 1970

[75, 76]. Combination chemotherapy was also an important breakthrough for Cancer of the testis [77, 78] and for Acute lymphocytic leukemia, an important cancer in children [80, 81]. For all these forms of cancer, survival has improved dramatically [74].

Incidence of Cancer of the skin appears to be increasing [71, 72], just as the incidence of Cancer of the testis [71, 79].

Mass screening for cancer of cervix uteri (group XI)

Mass screening with cervical smears in the Netherlands started in 1976. It has been shown to have reduced the incidence of invasive cancer and mortality from Cervical cancer in many countries [82, 83, 84].

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Druk:
Huisdrukkerij NIPG-TNO