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Dutch DisMod
Constructing a set of consistent data for chronic disease modelling

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Abstract

Using the simulation model context we analysed data the consistency of data on incidence, prevalence and mortality for specific chronic diseases so as to construct an appropriate data set for chronic disease models. These simulation models integrate data from different sources and are used to estimate the public health effects of trends in and interventions on disease risk factors. Disease incidence and prevalence data are derived from disease registration in general practice, epidemiological surveys and health-care registration. Disease-specific mortality data are collected from national statistics, while remission and case fatality rates are taken from the scientific literature. The successive steps followed in the consistency analyses were: (visual) comparison of data from different sources, calculation of remission and mortality rates from given disease incidence and prevalence rates and comparison of results with remission and mortality data from other sources. Data was evaluated on lung cancer, asthma and COPD, coronary heart diseases and congestive heartfailure, diabetes mellitus, and dementia and stroke.

From the results it can be concluded that differences between data from several sources can often be explained by differences in registration coding rules. For most diseases, calculated excess mortality rates are much greater than the mortality where the disease is the primary cause of death, registered in national statistics. In general, the estimated mortality parameters are in agreement with data from the literature, with the estimation of age-specific rates being complicated by time-trends.

Preface

Simulation models based on the multistate lifetable method are increasingly used to estimate the effects over time and age of public health intervention programs, for example Weinstein et al., 1987, Gunning-Schepers, 1998, and Barendregt, Bonneux, 1998. These models describe several population risk factors and disease categories simultaneously taking into account some main integrative aspects. These models share the same mathematical methodology, but differ in the selection of risk factors, diseases, model specification and data used. The main model parameters are the initial population numbers, that are specified by gender, age, risk factor classes and disease states, and the transition rates between these states. When restricted to the part of the model describing the disease processes the main parameters are the initial disease prevalence rates, the disease incidence and remission rates, and the disease-specific mortality rates. As data are derived from various sources it is necessary to evaluate their consistency within the context of our model structure. Murray&Lopez (1996) have called this type of evaluation of data consistency 'Disease Modelling'(DisMod).

Disease Modelling is similar to the general process of developing simulation models in public health. The knowledge and expertise are integrated of the fields of epidemiology, public health, and mathematical biology. Many persons have directly and indirectly contributed to the foregoing report. Especially we would like to thank dr HC Boshuizen, drs ME Kruijshaar and drs TL Feenstra, who made several critical but inspiring comments on the analyses.

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Samenvatting

Om te komen tot consistente verzamelingen van invoergegevens voor dynamische modellen van chronische ziekten hebben we de consistentie binnen de modelcontext geanalyseerd van gegevens over incidentie, prevalentie en sterfte voor specifieke ziekten. Dergelijke modellen integreren gegevens uit verschillende bronnen en worden gebruikt om de volksgezondheids-effecten van trends in en interventies op risicofactoren door te rekenen. Bijvoorbeeld, de effecten van anti-rook campagnes in termen van toekomstige oorzaak-specifieke ziekte en sterfte, gespecificeerd naar geslacht en leeftijd. Incidentie- en prevalentiegegevens komen uit huisartsenregistraties, epidemiologische onderzoeken en registraties in de gezondheidszorg, gegevens over overleving uit de wetenschappelijke literatuur, terwijl ziekte-specifieke sterftecijfers uit de CBS-statistieken komen.

De opeenvolgende analysestappen zijn: een vergelijking van de gegevens uit verschillende bronnen, de berekening van remissie- en sterfterates uit gegeven incidentie- en prevalentie-rates, en vervolgens een vergelijking met data uit de literatuur. We hebben data geëvalueerd met betrekking tot longkanker, astma en COPD, coronaire hartziekten en hartfalen, diabetes mellitus, dementie, en beroerte. Omdat ziekte-specifieke cijfers omtrent de ‘excess’ sterfte zelden beschikbaar zijn, zijn de door ons berekende ‘excess’ sterfterates omgezet in ratio’s, die vergeleken zijn met relatieve risico’s en hazard ratio’s uit de literatuur.

De gevonden verschillen tussen incidentie- en prevalentiecijfers uit verschillende bronnen zijn meestal terug te vertalen naar verschillen in registratiekarakteristieken. Voor veel aandoeningen is de berekende ‘excess’ sterfte veel groter dan de sterfte met de ziekte als de primaire doodsoorzaak in de CBS-statistieken. Verschillende ‘mechanismen’ kunnen dit verschil verklaren. Personen met de ene ziekte kunnen een vergrote kans hebben op andere, meer fatale ziekten. Deze vergrote kansen kunnen het gevolg zijn van een onderliggend gemeenschappeljk pathophysiologisch proces. Zo vormt bijvoorbeeld diabetes een risicofactor voor coronaire hartziekten. Daarnaast kunnen gemeenschappelijke risicofactoren een rol spelen. Bijvoorbeeld, roken is een belangrijke risicofactor voor COPD en longkanker. Tenslotte kunnen ziekten de algemene gezondheidstoestand zodanig negatief beïnvloeden, dat patiënten vatbaarder worden voor andere ziekten. De geschatte sterfteparameters komen in de meeste gevallen goed overeen met die uit de literatuur. De resultaten voor longkanker, astma, COPD, hartfalen, diabetes en beroerte lijken valide ‘at face value’ en in vergelijking met gegevens uit de literatuur. Voor CHZ en dementie zijn nog verbeteringen mogelijk. De aanwezigheid van trends in de tijd maakt het schatten van leeftijd-specifieke cijfers lastig, omdat de achter de rekenmethode liggende veronderstelling van tijd-constante parameters dan niet meer opgaat.

Summary

Using the simulation model context we analysed the consistency of data on incidence, prevalence and mortality for specific chronic diseases so as to construct an appropriate dataset for the chronic disease models. These simulation models integrate data from different sources and are used to estimate the public health effects of trends in and interventions on disease risk factors. For example, to calculate the effects of smoking interventions on future cause-specific morbidity and mortality, specified by gender and age. The parameters of the model that describe the disease processes are initial disease prevalence rates, incidence and remission rates, and mortality rates. Mortality rates are specified by cause. Disease incidence and prevalence data are derived from disease registration in general practice, epidemiological surveys and health-care registration. Disease-specific mortality data are collected from national statistics, while remission and case fatality rates are taken from the scientific literature. The successive steps followed in the consistency analyses were: (visual) comparison of data from different sources, calculation of remission and mortality rates from given disease incidence and prevalence rates and comparison of results with remission and mortality data from other sources. Data was evaluated on lung cancer, asthma and COPD, coronary heart diseases and congestive heartfailure, diabetes mellitus and dementia and stroke. Since disease-specific excess mortality rates are rarely reported in literature, we have transformed the calculated excess mortality rates to hazard ratios and compared these ratios to reported cause-specific relative mortality risks and hazard ratios.

From the results it can be concluded that differences between disease incidence and prevalence figures from several sources can often be explained by differences in coding rules of registrations. So the types of patients we describe in our model are ‘mean’ patients of all sources that have been selected. For most diseases the calculated excess mortality rates are much larger than the mortality with the disease as the primary cause of death as registered in national statistics. Several ‘mechanisms’ can explain these differences. Patients having one disease may have increased risks for other, more fatal diseases. These increased risks may be the result of shared pathophysiological processes, for example diabetes mellitus being a risk factor for coronary heart diseases. The increased risks also may be the result of joint risk factors, for example smoking being an important risk factor for COPD and lung cancer. Moreover, non-fatal diseases may decrease the general health state of patients such that they are more susceptible to more fatal diseases. In general the estimated mortality parameters are in agreement with data from the literature. The results for lung cancer, asthma, COPD, heartfailure, diabetes and stroke seem to be valid at face value and compared to data from literature. For CHD and dementia the results can still be improved. The estimation of age-specific rates is complicated by time-trends, because the assumption of time-constant model parameters underlying the model equations is not valid.

1. Introduction

1.1 Consistent model input

At the RIVM we have developed a modelling approach to calculate chronic diseases morbidity and mortality as a function of risk factor prevalence in the Dutch population. A dynamic multistate model has been constructed to describe demographic and epidemiological processes, such as ageing, changes in risk factor prevalence, and their effect on morbidity and mortality. The model structure will be applied to assess the public health gain of preventive measures or changes in disease treatment. Such applications are performed in the framework of the National Public Health Status and Forecasts Report of the RIVM (Ruwaard&Kramers, 1998). Important model parameters are initial disease prevalence rates and annual disease incidence, remission and mortality rates.

The model parameters have to be estimated from data that are available from registrations, epidemiological surveys, and the medical literature. As data are derived from various sources it is necessary to evaluate their consistency within the context of our model structure. Lack of consistency may result from differences in sampling period or population, definition of disease incidence and/or prevalence (systematic differences) as well as from random error. Thus, apart from analysing data on incidence, prevalence, remission, and mortality separately, simultaneous analyses within the framework of the chronic disease model are required. Using the model equations and given disease incidence and prevalence data, disease remission and mortality rates can be calculated. Subsequently consistency can be checked by comparing the results to mortality and remission data from registrations and literature.

The approach we have applied here is similar to the approach Murray and Lopez used to ascertain consistency within their disease projections in the Global Burden of Disease project, called Dis(ease) Mod(elling) (Murray&Lopez, 1993).

1.2 Research goal and methods

Our goal was to obtain consistent input figures for our chronic disease modelling activities. Data on disease incidence and prevalence were available from registrations in general practice, epidemilogical surveys and registrations in health care. The data sources have been selected applying a set of explicit criteria (see §1.6). Disease remission and mortality rates have been estimated from these data employing the chronic disease model equations. Subsequently, consistency was evaluated by comparing the model results to data from other sources, e.g. cause-specific mortality data from Statistics Netherlands (CBS), and mortality hazard ratios, relative risks and remission rates from the scientific literature. We have evaluated a series of relevant disease categories in the Netherlands with respect to mortality,

health care costs, and healthy life years lost, including lung cancer, coronary heart disease, asthma and chronic obstructive pulmonary disease (COPD), dementia, stroke, and diabetes mellitus. All data refer to the starting year of the chronic disease model, i.e. 1994. All disease incidence, prevalence and mortality data have already been assessed in the framework of the RIVM Public Health Status and Forecasting Document (VTV-1997; Ruwaard&Kramers, 1998).

The evaluation of the disease data consisted of the following steps:

Step 1 Comparison of data from different sources, for instance through visualisation of gender- and age-specific data. To adjust for random fluctuation data on disease incidence and prevalence were smoothed, using the method described in appendix 4.

Step 2 Calculation of excess mortality rates, mortality hazard ratios and disease duration times given disease incidence, prevalence and remission data.

Step 3 Comparison of results to data on mortality.

We estimated all parameters by solving the chronic disease model equations with disease-specific data (see §1.4). So in step 2 the excess mortality rate is the parameter to be estimated given data on disease incidence, remission and prevalence. Since in the case of lung cancer reliable excess mortality data are also available, we estimated the prevalence rates as well given data on disease incidence and mortality. Subsequently we compared the estimated prevalence rates with available prevalence data from disease registration.

The estimation of excess mortality and prevalence rates respectively may apply to data from the same source as well as to aggregated data. Results are compared to data from literature, whenever possible and appropriate, to check the consistency. We have scanned the literature databases for relevant publications with respect to each disease category using the key-words ‘excess mortality’,’prognosis’, ‘hazard ratio’, ‘relative risk’ and ‘remission’. This search was restricted to articles published over the last 10 years dealing with populations in Western societies.

If large (at visual comparison) differences between model results and data from the literature were found, we have tried to explain these inconsistencies. The explanations that have generally been found are the following. (1) Differences between the patient population inclusion criteria, e.g. total patient population versus hospitalised patients. (2) Differences between definition of disease-specific mortality, i.e. excess mortality versus registered cause-specific mortality. (3) Past time trends in disease prevalence rates that result in non-equilibrium situations. That means, the model assumption of time-constant prevalence rate values is unvalid. Adjustment for time trends is possible, but leads to some difficulties. Time-trends may be different for different ageclasses, and the calculated excess mortality rates are

sensitive to prevalence time trends (see Appendix 3.5.). In case of differences we have generally concluded that the disease incidence and prevalence data are valid (sometimes after omitting data from one or two sources). Sometimes we concluded that calculated gender-specific excess mortality rates were unvalid. Most often we decided to choose mean values or values for males, when no significant differences between both genders were reported in the literature.

The chronic disease modelling approach has been documented in a recent RIVM-publication (Hoogenveen et al., 1998). We have not developed new, more detailed disease models for our analyses. However, in some cases suggestions for further model development are given that may be utilised to answer more detailed research questions.

1.3 Modelling mortality in the context of chronic diseases

In mortality statistics one can distinguish primary and secondary causes of death. The primary cause is the underlying condition leading to death and the second cause is the condition directly leading to death. In practice this distinction is not always easy to define. For instance many patients with diabetes will eventually die from complications such as coronary heart disease. Sometimes it is far from obvious which of both diseases will be registered as the primary cause of death. It depends on the physician who fills in the death certificate, the age of the patient and the coding rules of the central coding administration.

In chronic disease modelling one is confronted with similar problems. Patients with a specific disease have a higher mortality risk than persons without the disease, all other variables equal. The difference in mortality is expressed here as excess mortality. However in general only part of this excess mortality can be attributed to the specific disease. Thus the difference between the excess mortality and ‘primary cause’ mortality can be interpreted as being due to competing death risks. The higher the ‘fatality’ of a given disease, the smaller the mortality due to competing death risks. Competing death risks can be modelled using covariables (joint risk factors, see Appendix 3). The mortality due to competing death risks is especially important on high ages for chronic diseases, such as COPD for which smoking is an important risk factor. So part of the excess mortality must be attributed to coronary heart disease, lung cancer etc. (Zahl, 1997). We will elaborate on this aspect of dependent competing death risks in more detail in another report (Hoogenveen et al., 1999).

In our chronic diseases model disease morbidity is described in terms of disease incidence and prevalence. As a consequence mortality can be related to both disease variables. Mortality that is proportional to disease incidence is called ‘acute mortality’ here; mortality that is proportional to disease prevalence is called ‘chronic mortality’. The example of myocardial infarction may clarify this. In the literature several types of mortality after myocardial infarction are distinguished, like the mortality within one month after the

infarction and the mortality during the years after surviving the first month. These two types are defined here as ‘acute mortality’ and ‘chronic mortality’ respectively.

1.4 Basic model equations

The chronic disease model equations describe the changes in disease prevalence numbers over time, specified by gender and age. The prevalence numbers change due to disease incidence (inflow), remission and mortality (outflow) (see *Figure 1*).

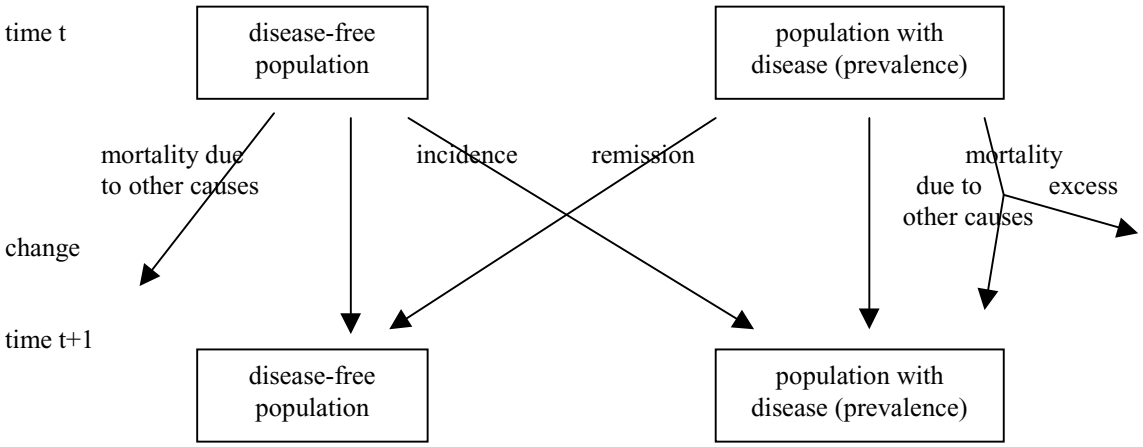


Figure 1 The chronic diseases model structure

We describe here the several steps that result in the model equation of the change of the disease prevalence rate over age. The formal derivation is presented in Appendix 3. The disease prevalence number changes due to so-called inflow and outflow transitions. Inflows result in increasing prevalence numbers, outflows in decreasing numbers. For reason of simplicity we omit the changes due to birth and migration here. Then the transitions to be distinguished are disease incidence (inflow out of the state ‘disease-free’), remission (outflow to the state ‘disease-free’) and mortality (outflow to the state ‘deceased’). The disease incidence number is assumed proportional to the total population number here (see also note below). The disease remission number is assumed proportional to the disease prevalence number. The mortality rate for a patient is assumed to be the sum of a baseline mortality rate and an excess mortality rate. The baseline mortality rate is assumed to be the same for persons with and without the disease. Because the excess mortality results in both decreasing disease prevalence numbers and total population numbers, the relative decrease of the disease prevalence rate due to the excess mortality is smaller than the relative decrease of the prevalence number. The difference equals the proportion of the population having the disease. Because the baseline mortality is the same for both persons having the disease and without the disease, it has no affect on the proportion of the population having the disease. So

the model equation that describes the change of the disease prevalence rate over age due to incidence, remission and excess mortality is:

$$d/dt\ prev_i = inc_i - rem_i\ prev_i - cf_i\ prev_i\ (1\text{-}prev_i) \quad (1)$$

with:
- $prev_i$ the disease i (point) prevalence rate over age interval
- d/dt the instantaneous (continuous-time) change
- inc_i the disease i incidence rate
- rem_i the disease i remission rate
- cf_i the excess mortality rate for patients with disease i

The disease-specific excess mortality on the population level is described by:

$$mort_i = cf_i\ prev_i \quad (2)$$

with: $mort_i$: the disease-specific excess mortality rate on the population level, i.e. with the total population number instead of the prevalence number in the denominator. The incidence rate in model equation (1) refers to the total population, not to the disease-free population. When using incidence rates that refer to the disease-free population a factor '1-$prev_i$' has to be added. In Appendix 3.1 it is shown that competing death risks, for example due to joint risk factors, result in more complex model equations. In Appendix 3.4 it is shown how the calculated excess mortality rates can be used to calculate disease duration times and mortality hazard ratios.

The main assumptions that underlie the model equations are the following. Equation (1) describes the change of the prevalence rate over age for any cohort. It is assumed that the prevalence rates are constant over time (see Figure 2). However, it is possible to adjust for time trends. All cause-specific mortality rates are assumed independent conditional on gender and age (see also Appendix 3). For example, COPD incidence rates are assumed equal for persons with and without coronary heart disease. Only 'chronic' cause-specific mortality has been described in formula (1), i.e. the mortality is defined proportional to the disease prevalence. 'Acute' mortality is defined proportional to the disease incidence, and has been included in the model equation for diseases with acute events, i.e. coronary heart disease and stroke.

Disease incidence and prevalence data are available specified by five-year age classes. We have found large fluctuations over age in these data, mainly due to small sample sizes. While the estimated mortality and remission rates are very sensitive to these fluctuations, we have smoothed the data and interpolated them over age, before estimating the model parameters. Smoothing is made by using a penalty matrix including weighting coefficients (see Appendix 4).

In *Figure 2* the aspects of time and age are presented. The chronic disease model equations describe the change of the prevalence rate for any cohort (the diagonal line), the data are from cross-sectional studies (the vertical line). When the situation is stable, i.e. no time trends, the prevalence rate at the start and end of the year are equal. In case of time trends, we have to adjust the prevalence at the end of the year for the trend over the year. Time trends in the Netherlands can be assessed from the study with the longest registration period, i.e. CMR Nijmegen. Trend values are based on the time period until 1994 that shows a stable trend.

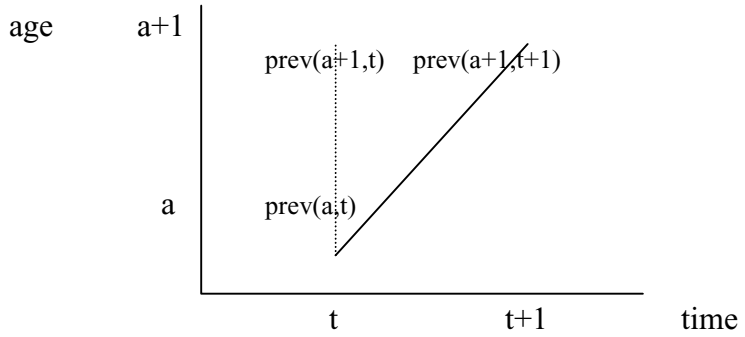


Figure 2 Time and age in the model equations (Lexis-diagram)
Note: a: age, t: time point, prev: disease prevalence.

Using the excess mortality rates it is possible to calculate mortality hazard rate ratios for patients, i.e. the ratio of the mortality rate for any patient to the mortality rate for a person without that disease. The formulas used are presented in Appendix 3.4.

1.5 Data sources

The data are derived from different sources.

- Disease incidence and prevalence rates come from several sources that have been established for general chronic conditions (such as registration projects in general practice) or for specific diseases (such as the Netherlands Cancer Registry). In the framework of VTV-1997 a panel of experts has evaluated all disease-specific data from these sources (Ruwaard&Kramers, 1998). The main data sources used are:
  - Dutch Survey of General Practice (National Study, NS), account: Netherlands Institute of Primary Health Care (NIVEL)
  - Continuous Morbidity Registration Nijmegen (CMR), account: Medical Department of the University of Nijmegen (KUN)
  - Amsterdam Transition Project (Trans), account: Medical Department of the University of Amsterdam
  - Registration Network Family Practices (RNH), account: Medical Department of University Maastricht
  - Dutch Sentinel Practice Network (CMR Peilstations, Peil), account: NIVEL

- Netherlands Cancer Registry (NKR), account: Association of Comprehensive Cancer Centers (VvIK)
- Eindhoven Cancer Registry (IKZ), account: Comprehensive Cancer Center South; note: NKR is nation-wide, but IKZ is over much longer time period
- Monitoring Risk Factors and Health Status in The Netherlands (MORGEN), account: National Institute on Public Health and the Environment (RIVM)
- Rotterdam Elderly Study (ERGO), account: Erasmus University Rotterdam

- Cause-specific mortality rates from Statistics Netherlands (CBS)
- Disease remission, cause-specific case-fatality rates, mortality rate ratios and relative risks from literature on the specific diseases

The characteristics of the main data sources are given in *Table 1*.

Table 1 Characteristics of the data sources used

Registration projects in general practice:	**Disease variables**	**Region**	**Period**	**Size**
National Study NIVEL (NS)	incidence[4]	national	1987/1988 3 months	330.000 persons 85.000 pers-years
CMR Nijmegen	incidence[2,3,4,5,6] prevalence[2,3,4,5,6]	region Nijmegen	since 1971 continuous	12.000 persons
Transition Project (Trans)	incidence[2,4,6] prevalence[2]	multi-regional	1985-1995	93.000 pers-years
RNH Limburg	incidence[2,3,4,6] prevelence[2,3,4,6]	region Limburg	since 1988 continuous	78.000 persons
CMR Peilstations (Peil)	incidence	national	since 1970 continuous	140.000 persons (1995)
Other data sources:				
Statistics Netherlands (CBS)	mortality[1,2,3,4,5,6]	national	continuous	national
ERGO Rotterdam	prevalence[6]	Rotterdam	since 1990 continuous	8000 persons
Cancer Registration South-Netherlands (IKZ)	incidence prevalence[1] mortality[1]	region Eindhoven	since 1955 continuous	1 million persons
National Cancer Registration (NKR)	incidence[1] mortality	national	since 1989 continuous	national
Health Care Information (SIG)	incidence	national	since 1963 continuous	national

Notes: data used for lung cancer (1), asthma and COPD (2), CHD and CHF (3), diabetes mellitus (4), dementia (5) and stroke (6).

More information on the diseases can be found in VTV-1997 (Ruwaard&Kramers, 1998), and in disease-specific literature (see References).

1.6 Data selection criteria

The main criteria for selecting the sources of disease incidence and prevalence data to be used in the analyses are:

1 The observation period is around year 1994. In absence of indications for time trends, also data from the National Study are used.
2 Ideally one would like to have data from a national and representative system which would continually monitor all disorders in the population on the basis of unambiguous diagnosis criteria. Since such a system is not available, data from various sources have been used, for example from epidemiological surveys and registrations in general practice. The former data involve the total population and are only available for a limited number of disorders. The latter data generally involve persons with serious complaints and therefore visiting the general practitioner. Because we do not want to use data from many different sources, and we also want to assess the effects of diseases in terms of health care use, we mainly employ registrations in general practices. In the framework of VTV-1997 (Ruwaard&Kramers, 1998; Gijsen et al., 1997) the validity of all data from the registrations has already been assessed by evaluating the degree of representativeness, continuity, completeness and freedom from ambiguity of each source. Where possible, we have used also data from epidemiological surveys.
3 In general only sources that provide both disease incidence and prevalence data are selected. As both figures are used within one model equation they have to be compatible. Exceptions to this rule are allowed when the data do not differ much after visual comparison.
4 For registrations in general practice it is necessary that even patients who only rarely visit the practice are registered as prevalent cases.

Note that these criteria may result in different data source selections for different diseases. As a consequence of criteria 1 and 3 the National Study (NS) has rarely been selected. CMR Nijmegen has mostly been selected, often the Transition Project and RNH Limburg as well. For chronic diseases with long disease duration and low frequency of GP-visits, the Transition Project often provides an underestimation of prevalence figures and for that reason has not been used (criterion 4). In the case of lung cancer we have used data from cancer registration projects.

Incidence and prevalence data are presented in graphical form and in tabular form. All rates are per 1000 persons (per year). They are specified by gender, age (in tabular form by 5-year age classes with rest class 85+), and source. All incidence and prevalence data used in the

model calculations are smoothed using the penalty smoothing method (see Appendix 4). The smoothing penalty coefficient used has been specified for each disease separately. The age-standardised incidence and prevalence rates have been calculated for each selected source using the non-smoothed five-year age class data, or the calculated mean values respectively, using 1994 Dutch population numbers.

Data from general practices include acute mortality and cases that are not hospitalised. Only for some diseases with high hospital admission rates, such as myocardial infarctions, health care data have been analysed.

1.7 Reader

In separate chapters the results of the analyses have been provided for the selected disease categories. Each chapter presents a short epidemiological introduction to the disease, and an overview of the data sources available and those that have been selected according to the selection criteria that have been presented in §1.6. Based on the incidence and prevalence figures used, mortality rates are calculated using the chronic diseases model equations. Because the calculated mortality rates are often unstable for lower ages, they are generally only presented for the higher ages. The calculated mortality rates are compared to those from national statistics. For lung cancer also prevalence rates are calculated based on given incidence and survival rates. For asthma remission rates are calculated as well, given incidence, prevalence and mortality rates. The calculated mortality rates and relative risks are compared to data from the literature. Concluding remarks are presented in a final paragraph. The gender- and age-specific incidence and prevalence figures are presented in appendices.

In the appendices data and methods are described in more detail. In Appendix 2 the gender- and age-specific incidence and prevalence figures are presented for the diseases selected. In Appendix 3 the chronic disease model equations are derived. The original equation is given in terms of changing disease prevalence numbers specified by gender, age and other covariables. It is shown how these equations can be simplified under specific assumptions and by describing rates instead of numbers, and how the equation can be interpreted in terms of time trends instead of changes over age. In Appendix 4 the data smoothing method used is described. In Appendix 5 a simple model is presented that explains the differences between the incidence and prevalence rate ratios found in population surveys compared to those found in registrations in general practice. In Appendix 6 the symbols and abbreviations used are summarised. At the end of the report a list of references is presented, general and specified by disease.

2. Lung cancer

2.1 Introduction

Lung cancer (ICD 162) is the type of cancer with the highest mortality in the Netherlands and other Western countries. Lung tumours are divided in small-cell type (SCLC, approx. 20%) and other (NSCLC, approx. 80%). Most lung cancer patients already have metastases in the local or regional glands the moment they are diagnosed. For most new cases diagnosed the disease progression is such that only palliative treatment has become possible. In case of limited or localised stage cure may be possible. Lung cancer incidence in the Netherlands has decreased for men and increased for women in the Netherlands over the last years, reflecting different past trends in smoking prevalence trends among men and women.

2.2 Data sources

The lung cancer data used in the analyses are from:

incidence	**prevalence**	**survival**
NKR	**IKZ**	**IKZ**

Only one (national) source is available for incidence data and one (regional) source for prevalence data.

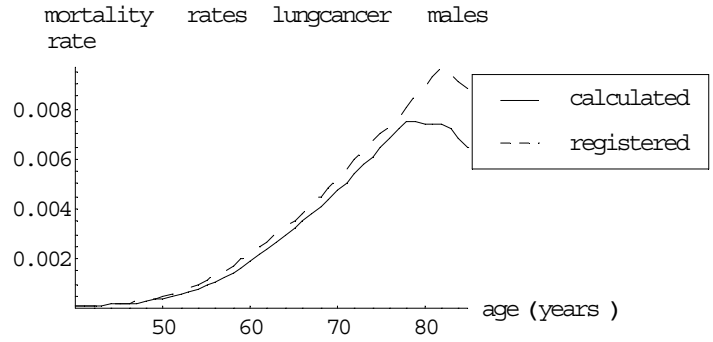
2.3 Data on incidence and prevalence

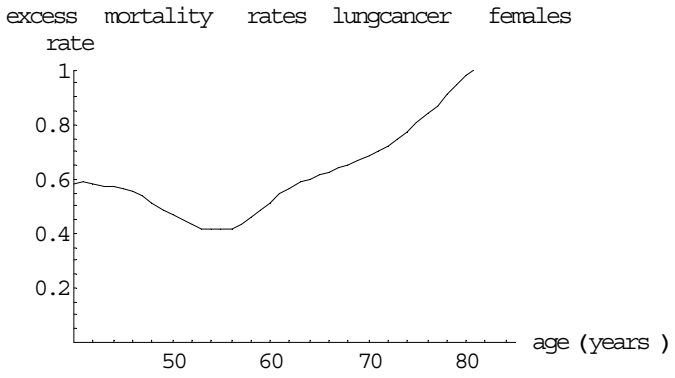
The 1994 lung cancer incidence and prevalence data are presented in *Table 40* and *Figure 23* (Appendix 2). Incidence and prevalence rates are higher for males than for females. The age at which rates are highest is lower for females than for males. A possible explanation for these differences is the increasing smoking prevalence for females during the last decades. Rates have decreased for males and increased for females, except for the highest ages.

The national NKR and regional IKZ data can be compared on disease incidence. The IKZ-incidence rates for males are larger than the NKR figures, for females they are smaller. The incidence rate ratios IKZ/NKR are 1.17 (males) and 0.89 (females) respectively for age 50+. We have not applied these ratios to adjust the IKZ regional prevalence data, because we have don't know whether the rate ratios found for the incidence are also valid for the prevalence. Besides the differences of the rate ratios between men and women are substantial, and we cannot explain them.

2.4 Estimated mortality rates

Lung cancer excess mortality rates can be calculated from incidence and prevalence data using the equations given in §1.4. They were calculated assuming no remission and prevalence trends of 0.7 % (men) and 2.3% (women) per year. These trends were based on prevalence trends found in IKZ/SOOZ (period 1989-1993). The excess mortality rates are presented in *Figure 3* and *Table 2* (only for males). Based on the calculated excess mortality rates also the disease duration times can be calculated, see *Figure 4*.





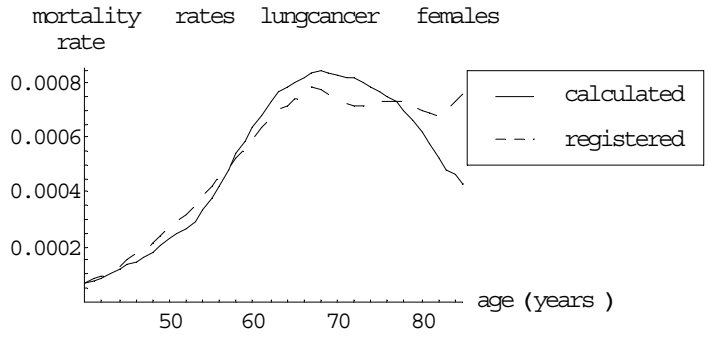


Figure 3 The calculated excess mortality and cause-specific population mortality rates, the mortality rates are also compared to empirical data

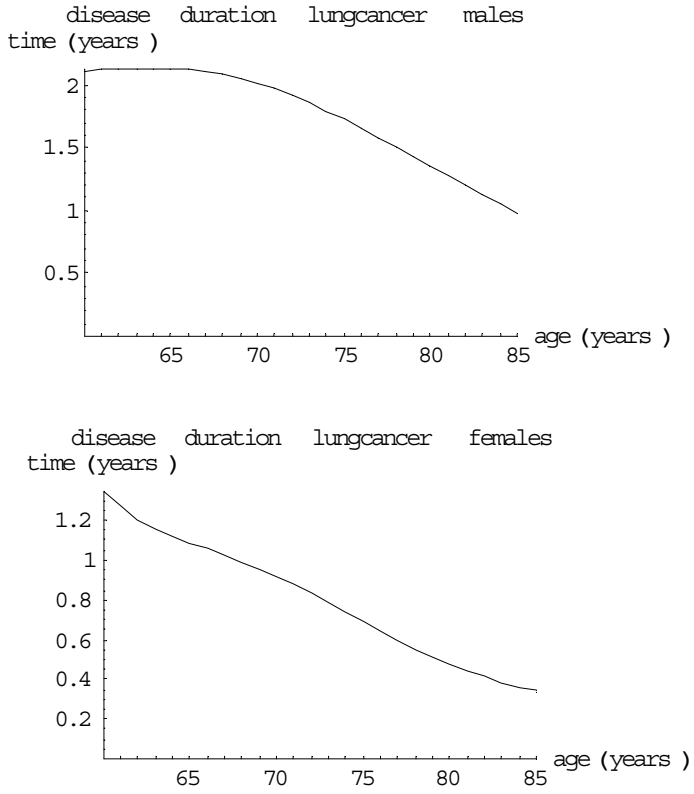


Figure 4 The calculated lung cancer disease duration times for males and females

The calculated excess mortality rates are much higher for females than for males. This results in shorter disease duration times and calculated population mortality rates that are higher than the empirical ones. The main explanation is that the time trend adjustment applied does not work well enough for females. Therefore we have not presented the results for females in *Table 2*. The estimated lung cancer mortality rates are smaller than the empirical rates for the highest ages, for males and females (*Figure 3*). This is very surprising. We did not find an explanation.

Table 2 The calculated lung cancer excess mortality rates for males

age	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
calculated males	.56	.45	.39	.37	.36	.36	.36	.40	.46	.53

Note: unit: /patient/year.

Table 3 Lung cancer mortality rates from the literature

Berrino et al, 1995 .53 (all ages,M+F)						
IKZ, 1997	observed survival fraction			calculated 1-year excess mortality		
age	15-59	60-74	75+	15-59	60-74	75+
from survival data over						
5 year	.18	.13	.032	.29	.34	.39
10 year	.14	.05	.042	.19	.25	.29

Note: The 1-year survival fractions were calculated from the n-year survival data using the formula: '1-year survival fraction' = 'n-year survival fraction^(1/n)'. The excess mortality rates are calculated as: calculated 1-year mortality rate – population mortality rate (Statistics Netherlands).

The 10-year survival is relatively better than the 5-year survival because conditional on survival after 5 years the 5-years rest prognosis is better than the 5-years prognosis on the time of onset. In the 1993 chronic diseases model version smaller lung cancer mortality rate values have been used. One reason is the different time discretisation method used: in the 1993 model version it was assumed that the all new cases 'occur' at the beginning of each year, whereas we have assumed occurrence halfway each year.

2.5 Estimated prevalence rates

For lung cancer reliable mortality data are available. Therefore we can also estimate lung cancer prevalence rates given incidence and mortality rates. The prevalence rates are calculated using equation (1) and the mortality rates using equation (2) (see §1.4). The estimated prevalence and mortality rates are compared to prevalence and mortality data respectively (see *Table 4*). The 1st column describes the age-specification, the 2nd column the data values, and the 3rd to 6th column the calculated values for four different excess mortality data figures. The 1st block compares results on prevalence for males, the 2nd block those for females, in the 3rd and 4th block results are given on mortality. The four mortality data figures used are: 3-year survival probability = 0.1, 5-year survival probability = 0.1, and relative 5-year survival fractions and 10-year fractions (Coebergh, 1995) respectively.

Table 4 Calculated lung cancer prevalence and population mortality rates, compared to data

age		mortality data for lung cancer patients used				
		3-year=0.1	5-year=0.1	5-year	relat.	10-year relat.
age	data	results				
calculated prevalence rates (*.001)						
males (block 1)						
40	.1	.2	.2	.2		.3
50	.8	.9	1.1	1.3		1.7
60	5.0	4.0	5.3	6.0		7.8
70	13.2	9.9	13.7	14.3		19.2
80	17.5	15.1	22.8	18.0		27.6
females (block 2)						
40	.1	.1	.2	.2		.2
50	.5	.5	.6	.7		1.0
60	1.2	1.1	1.5	1.8		2.5
70	1.2	1.6	2.3	2.5		3.6
80	.6	1.3	2.0	1.7		2.8
calculated population mortality rates						
males (*.001) (block 3)						
40	.1	.1	.1	.1		.0
50	.4	.5	.4	.4		.3
60	2.1	2.2	2.0	2.0		1.7
70	5.0	5.2	5.1	5.1		4.9
80	8.8	8.1	8.4	8.8		9.3
females (*.0001) (block 4)						
40	.6	.6	.6	.5		.4
50	2.5	2.5	2.3	2.2		1.8
60	5.8	6.0	5.7	5.7		5.3
70	7.5	8.4	8.5	8.5		8.6
80	7.1	6.9	7.3	7.7		8.5

Notes: prevalence rates calculated using life-table method; population mortality rates calculated by multiplying the calculated prevalence rates by the given patient mortality rate.

Table 4 shows that for males the 5-year relative survival data result in prevalence and mortality rates that fit best to the data. The calculated prevalence rates based on these survival fractions are also presented in graphics (see *Figure 5*). For females the 5-year relative survival data does not result in prevalence rates that fit well to data. The main explanation is that lung cancer incidence rates have increased for females over the last years, and so the trend of the prevalence rate follows the trend of the incidence rate with a delay time (see also §2.4).

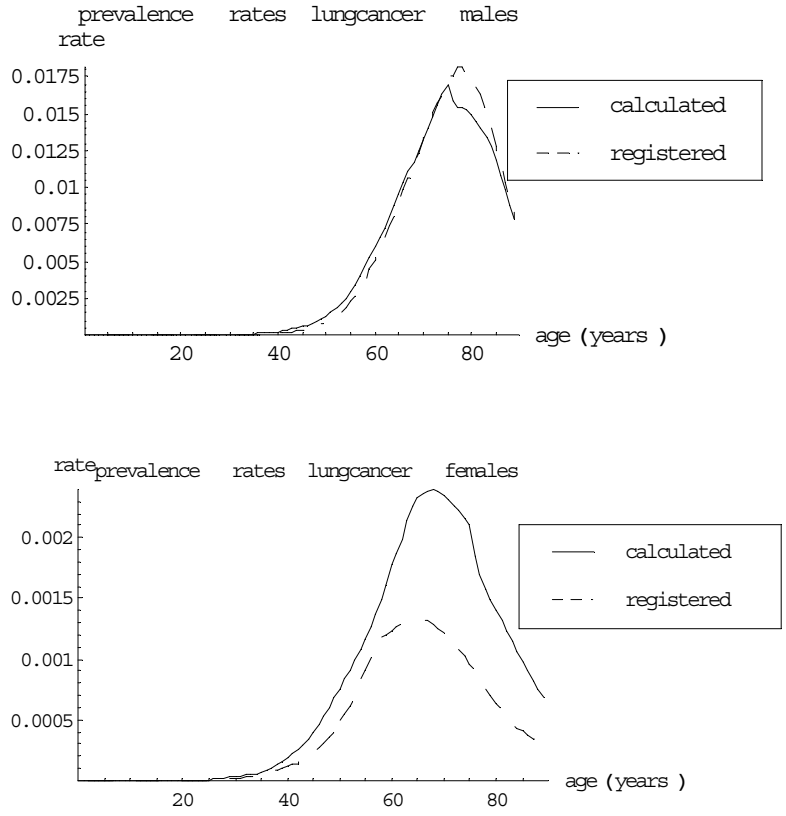


Figure 5 Calculated prevalence rates using 5-year relative survival data, for males and females

2.6 Concluding remarks

New lung cancer cases are registered by the National Cancer Registration (NKR). This national registration has become active only recently. For lung cancer prevalence, we have only figures from a regional registration (IKZ) that has been active since 1955. The regional incidence rates for males are smaller than the national figures, and for females are larger. We have not yet adjusted the prevalence rates, because the relevance of this result is still unclear. Moreover, future prevalence rates are not very sensitive to the initial prevalence figures because of the short disease duration time.

For excess mortality we also used data from the IKZ-registration. The rates have also been estimated assuming no remission and for given trends in lung cancer prevalence. For males the estimated excess mortality rates fit well to the data on relative 5-years survival. Moreover, using the latter data results in prevalence and mortality figures that fit well to the data, especially for males. For females the excess mortality rates could not be estimated well. One important reason is probably time trends. We have decided to use the 5-year relative survival data from IKZ (1997) to calculate the lung cancer excess mortality rates.

3. Chronic non-specific lung diseases: asthma and chronic obstructive pulmonary disease

3.1 Introduction

Chronic aspecific respiratory diseases (ICD 490-496) is a group of diseases of the bronchial tubes and alveoli. Based on insight in the pathophysiology two subgroups are distinguished: asthma (493) and chronic obstructive pulmonary disease (COPD). Asthma is mainly but not exclusively found in children, COPD mainly in the elderly. Asthma prevalence rates in the Netherlands have increased in the last decade. COPD prevalence has not changed for men, but has increased for women, probably as a result of changing smoking behaviour. Mortality due to both diseases is neglectable in lower ages. For the elderly mortality due to asthma is still very small, but for COPD mortality rates increase with age, especially for women.

Modelling asthma and COPD differs substantially from modelling lung cancer for several reasons. (1) We have to compare data and make a selection, as several data sources are available. (2) For asthma two types of 'outflow' are possible: remission and mortality. Both parameters cannot be identified uniquely using only incidence and prevalence figures. (3) There are significant trends in disease incidence and prevalence that have to be taken into account. (4) There is a relation between asthma and COPD. They can be interpreted as 'competing' diseases because the differences in symptoms are small.

3.2 Data sources

The asthma and COPD data used in the analyses are from:

incidence	**prevalence**
National Study	
CMR Nijmegen	**CMR Nijmegen**
Transition Project	**Transition Project** (asthma)
RNH Limburg	**RNH Limburg** (COPD)

No data are available from epidemiological sources. CMR Nijmegen provides reliable data on both incidence and prevalence. The Transition Project provides low COPD prevalence figures, maybe as a result of a short time window (1year) of registration. For RNH Limburg it is supposed that the coding rules for asthma are too strict ('once asthma, always asthma') and yields prevalence figures that are too large. Therefore they have not been used in our analyses. The data sources on incidence and prevalence selected have been presented in bold.

3.3 Data on incidence and prevalence

In *Table 41* and Figures 25 & 26 (Appendix 2) we present the 1994 incidence and prevalence data that have been used in our analyses. Asthma incidence and prevalence rates are highest for the lower ages. However, asthma incidence rates seem to increase again slightly for the higher ages, especially for males (for a possible explanation, see §3.5). According to CMR Nijmegen asthma prevalence rates seem to have increased in the period 1981-1994 for the lower ages. COPD incidence and prevalence rates increase over age. They are larger for males than for females. The prevalence rates seem to have increased in the period 1984-1994 for elderly women according to CMR Nijmegen. The results for COPD can be explained by smoking behaviour, since smoking is an important risk factor.

3.4 Estimated remission and mortality rates

Asthma remission and COPD excess mortality rates can be calculated from incidence and prevalence data using the equations given in §1.4. Based on CMR Nijmegen time series data (1984-1994) we assume the annual asthma prevalence trend to be 8% (males) and 11% (females) per year respectively, and for COPD 0% (males) and 7% (females) respectively. The calculated rates are presented in *Table 5* and *Figures 6&7* respectively. Based on data from literature (see *Table 6*) we have assumed that the mortality rate for asthma patients is 1.5 times the population mortality rate. For COPD it is assumed that there is no remission. Based on the calculated mortality rates also the disease duration times can be calculated, see *Figures 8&9*.

For females no reliable COPD excess mortality rates could be calculated assuming an annual prevalence trend of 7%. Assuming no trend an excess mortality rate of 0.07 was found, that was almost constant over age. One possible explanation for the bad results for women is the time trend of COPD prevalence rates that is hard to deal with. Because in the literature no clear differences between men and women have been found, we assume that the mortality rates found for males also are valid for females. The excess mortality rate values are presented in *Table 5*.

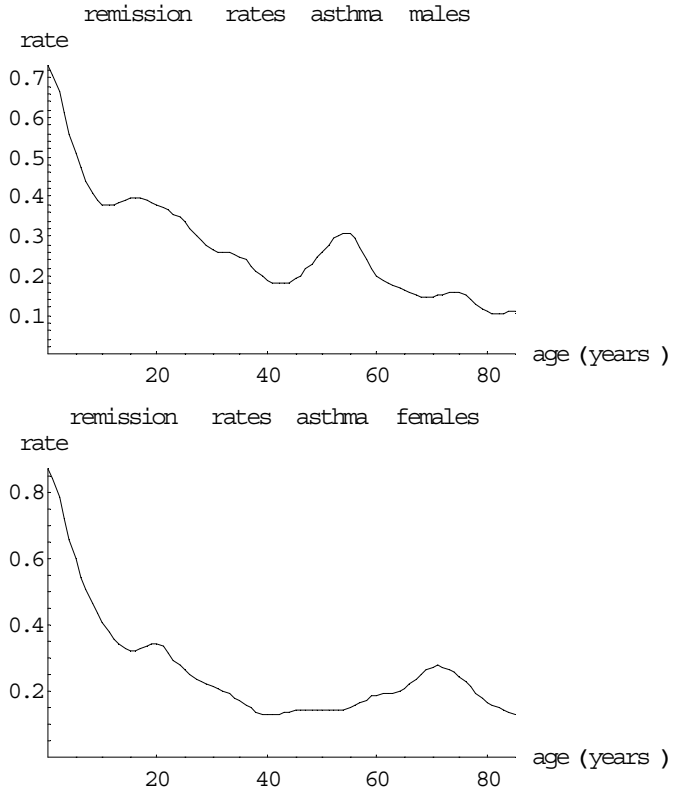


Figure 6 The calculated asthma remission rates for males and females

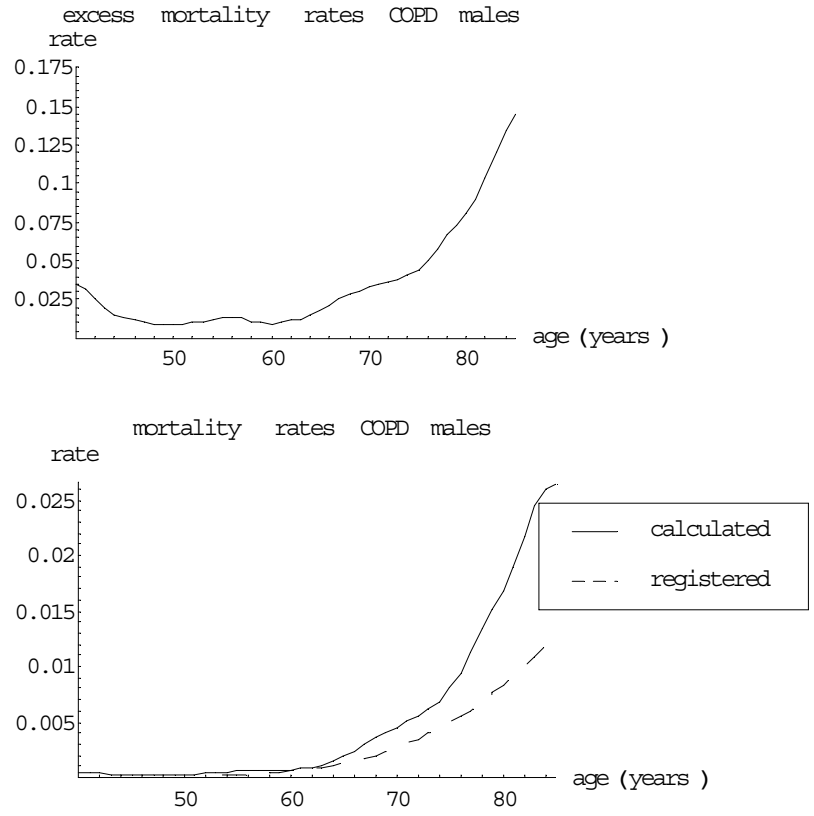


Figure 7 The calculated COPD excess mortality and cause-specific population mortality rates for males, the mortality rates are also compared to empirical data (CBS)

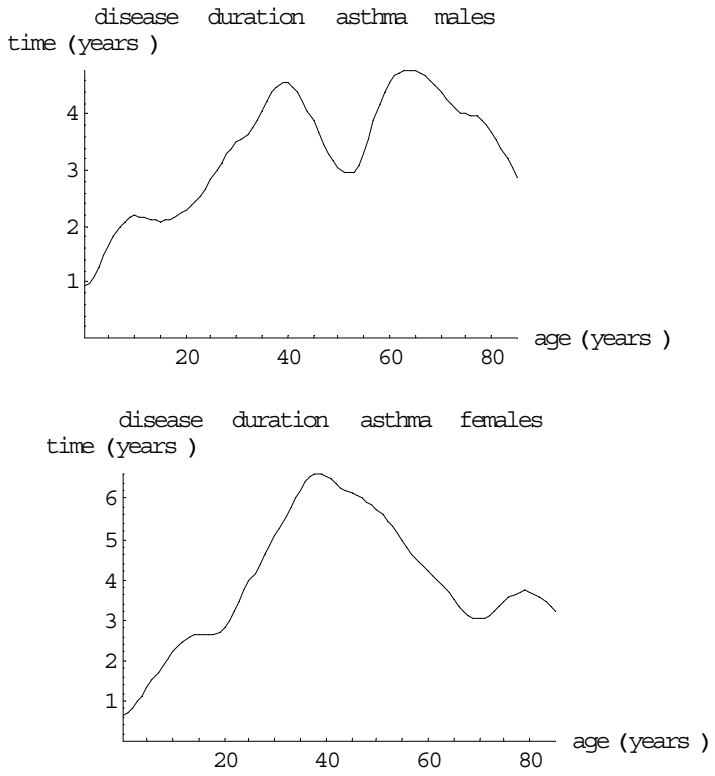


Figure 8 The calculated asthma duration times for males and females

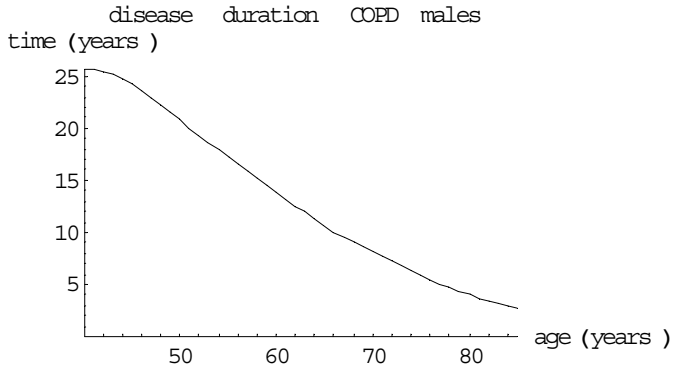


Figure 9 The calculated COPD duration times for males

Table 5 The calculated asthma and COPD remission and excess mortality rates respectively

asthma	remission			COPD excess mortality
	males	females	select (M+F)	males
age:				
0-4	.65	.77	.71	.10
5-9	.45	.51	.48	.06
10-14	.38	.36	.37	.06
15-19	.39	.33	.36	.05
20-24	.37	.31	.35	.04
25-29	.30	.24	.27	.03
30-34	.26	.20	.23	.03
35-39	.22	.15	.18	.03
40-44	.18	.13	.16	.024
45-49	.22	.14	.18	.014
50-54	.29	.14	.21	.013
55-59	.27	.17	.21	.014
60-64	.18	.19	.20	.017
65-69	.15	.24	.20	.03
70-74	.15	.27	.20	.04
75-79	.14	.21	.18	.07
80-84	.11	.15	.13	.11
85+	.11	.12	.11	.15

Notes: unit:/person/year; select: mean over males and females for COPD for females no excess mortality rates could be calculated.

Calculated asthma remission rates decrease over age, with some irregularities for the higher ages. They are unstable for the lowest ages, and we have found differences between male and females for the higher ages. Because all differences are small, we have concluded that asthma remission rates are equal for men and women, with constant values for ages above 35 years (see *Table 5*).

3.5 Other data from literature on remission and mortality

We have presented data from literature on mortality for asthma (*Table 6*), for COPD (*Table 8*) and on remission for asthma (*Table 7*). Mortality hazard ratios, relative risks and standardised mortality ratios are similar parameters to describe increasing risks, and so have been presented in one table. However, they differ when hazard ratios change over age.

Table 6 Mortality hazard ratios, relative risks and standardised mortality ratios for asthma patients, together with the applied model value

author	country	year	population	size	foll(yr)	males	females	total
Alderson	Great-Britain	1977	patients,adult	1892	20	1.65	1.52	
Markowe	Great-Britain	1987	sample GP,adult	2547	8			1.61
Burrows	USA	1991	gen.pop.,age≤ 65	46	7.4			1.9
Almind	Denmark	1992	outpatients,adult	214	7	1.55		
Ulrik	Denmark	1992	hospital,adult	213				2
Silverstein	USA	1994	gen.pop.,all ages	2499	14			1.00
Lange	Denmark	1996	self-reported,adult	13540	17	1.5	1.7	
Ulrik	Denmark	1996	pat treated,adult	1075	8.6			2.4
Huovinen	Finland	1997	self-reported,adult	471	16	1.49	1.53	
Connolly	UK	1998		597	10			1.47
applied			patients GP		1	1.5	1.5	

Notes: foll: follow-up

Table 7 Proportions of remission for asthma

author	country	year	population	size	follow-up(yr)	proportion (%)
Blair	Great-Britain	1977	patients,child	417	20	52
Schachter	Lebanon	1984	general,age≤ 7	73	6	68
Burrows	USA	1987	general,all		9	35/65/30/15/5/15/30/30[1]
Aberg	Sweden	1990	patients,age 14	1335	3-13	74/55/44/25[2]
Gerritsen	Netherlands	1990	patients,child			50
Burrows	USA	1991	general,age≤ 65	46	7.5	19
Panhuysen	USA	1997	patients,adult	181	25	11
Barbee	USA	1998	general,child	review	retrospective	50
Norrman	Sweden	1998	students	990	1	5.7
calculated			general		1	55/38/34/23/22/22/22/22[1]

Notes: (1): proportions for age classes 0-10 .. 70-79, (2): proportions for age classes at onset: 0-2,2-4,4-7,7-11.

Table 8 COPD mortality rates

author	country	year	population	size	follow-up(yr)	rate(/yr)
Tager	USA	1991	hospital,adult		<=17	.058

The asthma relative mortality risks found do not differ much, except for the one Danish study. A large part of the asthma excess mortality described has been found to be due to COPD. The asthma remission proportions (see *Table 7*) have been presented in their original form and have not been standardised to 1-year figures. The reason is that standardisation is only possible with extra data or extra assumptions on asthma incidence. That's also why direct comparison with the calculated remission rates is difficult.

3.6 Concluding remarks

For asthma and COPD several data sources are available. According to our selection criteria CMR Nijmegen, Transition Project (not for COPD prevalence) and RNH Limburg (only for COPD) have been selected.

For asthma the remission rates for males and females are almost equal after adjustment for the trend, except for higher ages. Because all differences are small, we have concluded that the asthma remission rates are equal for both sexes for all ages.

The remission rates found are relatively large and result in small disease duration times compared to the literature. We have found several possible explanations. (1) Remission is defined here in terms of 'inactivating' the registration, and so may be different from the definition of remission used in literature. (2) We have presented 1-year remission rates, whereas in literature remission fractions are presented mainly over larger follow-up periods. Remission rates over different time periods cannot be compared easily. One reason is that part of the remission may relapse to asthma again after a longer time period.

For COPD the excess mortality rates are different for males and females, especially for high ages. However, for females there have been large changes in COPD incidence and prevalence over the past years. So although we have adjusted for time trends, the results may still be biased. Therefore we have concluded that the calculated rates are unreliable for females and that the excess mortality rates for females are equal to those for males.

There is a strong statistical correlation between the calculated excess mortality and remission rates for asthma. Assuming no excess mortality the calculated remission rates increase again for the higher ages, applying the mortality hazard ratio of 1.5 based on literature the rates decrease over age. According to literature a large part of the excess mortality among asthma patients is due to COPD.

4. Coronary heart diseases and congestive heart failure

4.1 Introduction

Coronary heart diseases (CHD, ICD 410-414) are the most common type of cardiovascular diseases. They are characterised by the narrowing of the coronary arteries. The most important types of CHD are acute myocardial infarction (AMI, ICD 410) and angina pectoris (AP, ICD 413). One example of 'other acute and subacute CHD types' (ICD 411) is unstable AP. An old infarction (ICD 412) is an AMI without symptoms that is confirmed afterwards. It could be a 'silent infarction'. To the other forms of CHD (ICD 414) belong diseases such as chronic atherosclerosis. Time trends in the Netherlands suggest a change from the acute types of CHD to the chronic types. This change may result in a future increase of the incidence of AP and congestive heartfailure (heart decompensation, CHF, ICD 402,404,428,429.1 and 429.4) according to Barendregt&Bonneux (1998). Congestive heartfailure is characterised by a deficient blood circulation due to an insufficient pumping function of the heart, leading to shortness of breath, tiredness and oedema. The main risk factors for heartfailure are CHD and hypertension.

In our analyses we distinguish only two manifestations of CHD, AMI (ICD 410) and other forms of CHD, mainly stable and unstable AP (ICD 411-414). Both CHD manifestations and CHF are strongly interrelated. For example, persons with AP have relatively high risks of an AMI, persons surviving an AMI are registered in some registrations in general practice as belonging to the group of CHD-patients, persons having AP or AMI have high risks of developing CHF, and persons having CHF have high mortality risks for AP and AMI.

4.2 Data sources

The CHD and CHF data used in the analyses are:

incidence	**prevalence**
National Study NIVEL	
CMR Nijmegen	**CMR Nijmegen**
Transition Project	
RNH Limburg	**RNH Limburg**
CMR Peilstations	ERGO Rotterdam
Health Care Information (SIG)	

Prevalence figures from epidemiological studies are available (e.g. ERGO), but only for myocardial infarction (life-prevalence; assessment by anamnesis) and CHF (point-prevalence; assessment by anamnesis and examination). We do not use them, because no matching incidence figures are available.

Persons having an AMI are generally hospitalised, contrary to persons with AP. So only for the former patients admission data for inpatient care can be useful. Data from the National Medical Register can be used.

For AMI, AP as well as CHF data from registrations in general practice are available. In these registration projects the denomination of the terms is complicated. Registrations differ in their classification system and registration practice. That's why the morbidity figures are not at once comparable. However, in general the registrations distinguish AMI, a chronic form of CHD, and heart failure. But some registrations do not use a specific code for AMI, and register AMI as an incident CHD. In some registrations patients who survive an AMI are generally registered twice in one year, once as AMI incident, and once as incident for (a chronic form of) CHD. So the total CHD patient numbers are less than the sum of AMI and CHD cases. Other registrations distinguish suspected from confirmed myocardial infarction. Some projects register only first infarctions, other projects register all infarctions including recurrent ones. For selecting the appropriate registrations and codes in this report we use the decisions made for the Dutch PHSF-report (Gijsen et al., 1997; Maas et al., 1997). CHF is more or less registered on the same way in all registrations.

A summary of the characteristics of the data from the registration projects in general practice about CHD is presented below:

Incidence:

National Study	AMI	K75.1	confirmed infarctions including recurrent ones
	AP	K76.1	stable and unstable AP; a patient can have recurrent episodes
CMR Nijmegen	AMI	2110	only first occurring infarctions excluding recurrent AMIs
	AP	2120	stable and unstable AP episode; a patient can have recurrent episodes
Trans 10 Project	CHD	K76	clinical relevant CHD: AMI or AP or old AMI; corrected for double counts, so only first occurring events
Trans 5 Project	AMI	K75	in a period of 4/5 years only one infarction per patient is registered
	AP	K74	stable and unstable AP; in a period of 4/5 years only the new AP-episode Per patient is registered
RNH Limburg	AMI	K75	not consistently registered because AMI is not a chronic problem; if registered, it is only for a short time period; after becoming inactive, AMI can become active again; so recurrent AMIs are included in the figures
	AP	K74	stable and unstable AP; after some period this code often becomes inactive and code K76 becomes active
	CHD	K76	clinical problem often following AMI or AP
CMR Peilstations	AMI	--	confirmed infarctions, including recurrent ones

Prevalence:

National Study			no data
CMR Nijmegen	AMI	2110	life-prevalence: ever had one or more myocardial infarctions
	AP	2120	stable and unstable AP
Trans 10 Project	CHD	K76	AMI or AP or old AMI with clinical significance; corrected for double Counts
Trans 5 Project	AMI	K75	no meaning; duration of an AMI is short
	AP	K74	stable and unstable AP; it describes the number of patients with one or more episodes of AP in a period of 4/5 years
RNH Limburg	AMI	K75	no meaning; duration of an AMI is short
	AP	K74	stable and unstable AP; after some period this code becomes often inactive and K76 active
	CHD	K76	clinical problem; interpreted as a status after an AMI, with AP or after AP; no complaints, with medication or regularly monitored

We have decided not to use data from the following sources: the National Study, CMR Peilstations and the 5-year database of the Transition Project because they provide only reliable disease incidence data; the 10-year database of the Transition Project because they provide only reliable incidence data and because the subgroup of patients with other forms of CHD is hard to attribute to the CHD subgroups we have distinguished. Finally we selected data from CMR Nijmegen and RNH Limburg, presented in bold.

4.3 Data on incidence and prevalence for CHD

In *Table 42* and *Figures 27, 28 & 29* (Appendix 2) we present the 1994 data on incidence and prevalence and the selected values after smoothing.

Unlike CMR Nijmegen, RNH Limburg distinguishes CHD apart from AMI and AP. Both AMI and AP patients can ‘flow’ to the group of CHD patients. According to Gijsen et al. (1997) patients who survive an AMI the AMI-code is made ‘inactive’ and the CHD-code (K76) is made ‘active’ soon after the disease onset. So we have decided to take the AMI and AP figures for the incidence rates, and to add the CHD figures to the AMI and AP prevalence rates. Because we have no explicit information on the disease history of CHD patients, we have decided to add the CHD prevalence numbers to the AMI and AP prevalence numbers proportional to the AMI and AP incidence numbers, i.e. AP : AMI = 1:1 (males), 3:1 (females). The AMI-prevalence is defined as lifetime prevalence.

AMI incidence and prevalence rates increase over age, with decreasing prevalence rates for the highest ages. The rates are larger for males. CHD incidence and prevalence rates also increase over age, with decreasing incidence rates for the highest ages. The rates are slightly higher for males. After redistributing the CHD numbers for RNH over the AMI and AP numbers, the CMR and RNH data on incidence and prevalence do not differ much, except for incidence of AP. This may be due to different coding rules and/or inclusion criteria.

4.4 Data on incidence and prevalence for CHF

In *Figure 29* and *Table 43* we present the 1994 data on CHF incidence and prevalence and the selected rate values after smoothing. CHF incidence figures from CMR and RNH are similar. Prevalence figures are larger for CMR for higher ages.

4.5 Estimated mortality rates for CHD

Excess mortality rates are estimated for AMI and AP-patients using the chronic disease model equation given in §1.4. We have assumed no remission. For AMI we have assumed an annual change of the prevalence rate of –2% for men and –3% for women, for AP of +3% and –1% respectively. These trends are based on CMR Nijmegen time series over 1987-1993. For AMI we have included 'acute' mortality. The differences between calculating the AMI and AP excess mortality rates become more clear from *Figure 10*.

The AMI incidence numbers in CMR Nijmegen exclude recurrent infarctions, the RNH Limburg include these infarctions. We have found some information on the proportion of all infarctions that are recurrent. According to Vrieze (1994) 9% of all hospitalisations of AMI patients are recurrent ones within one year, and 13% of all incidence numbers (including fatal infarctions and infarctions not admitted to a hospital) are recurrent in the same year (1988 data). According to Weinstein (1987) 22% of all patients with a history of AMI are relapsed cases, and the probability of a recurrent infarction for all AMI patients including those with congestive heart failure is 0.078. Based on Weinstein (1987), Barendregt&Bonneux (1998) state that the probability of a recurrent infarction in the same year (excluding those with CHF) is 0.062. In our current CHD model version it is assumed that AMI patients have a 8-fold risk of an infarction compared to CHD-free persons. Short calculation (15.0 million persons, 0.2 million AMI patients, 8-fold risk) results in the proportion of infarctions being recurrent is 0.11. Taking into account the increased life expectancy of CHD patients, we assume that nowadays 15% of all infarctions is recurrent.

Persons having an AMI have a large case fatality during the first days. We call this the 'acute' mortality, that is proportional to the AMI incidence. Case fatality can be defined for two types of cases, the infarctions in the general population and the patients that are hospitalised. The case fatality rates for the former group are larger than the latter, because many new cases die before they reach the hospital. According to Jansen (1994) the clinical fatality after an AMI is 0.10/case. This result is confirmed by other literature. The fatality of cases in the general population is much higher. Based on the literature we have selected the value 0.40/case. The fatal infarctions are included in both the CMR Nijmegen and RNH Limburg data. To adjust for the recurrent infarctions we have multiplied the RNH Limburg AMI incidence rates with 0.85.

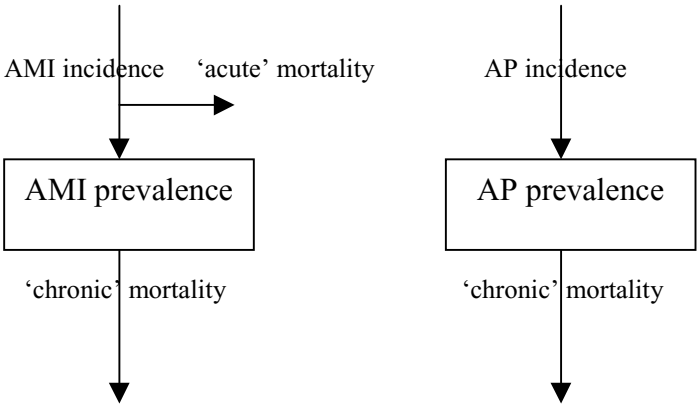


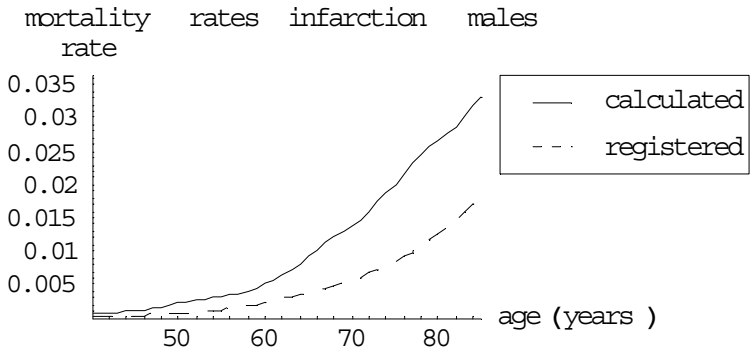
Figure 10 The CHD disease model used to calculate excess mortality rates
Notes: AMI incidence is from total population including those persons with AP; likewise AP incidence includes those with a history of AMI.

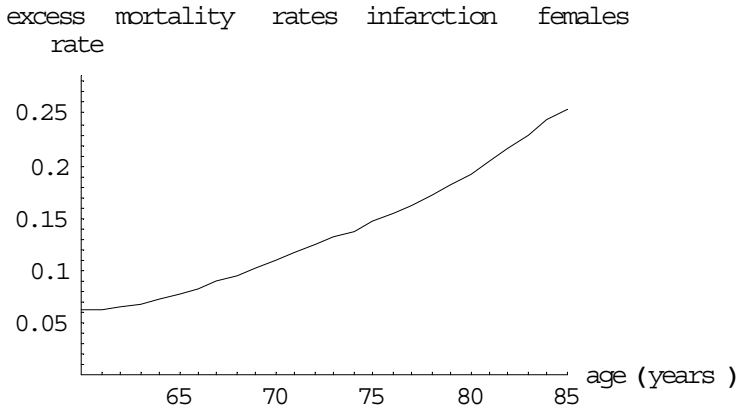
The resulting mortality rates are presented in *Table 9*, and *Figures 11&12*. For AMI the excess mortality rates relate to the 'chronic' mortality only, the cause-specific population mortality rates include the 'acute' mortality.

Table 9 The calculated AMI and AP excess mortality rates

age	AMI male	female	select	AP male	female	select
45-49	.02	.19	.06	.096	-	.050
50-54	.03	.10	.06	.072	-	.050
55-59	.03	.07	.06	.052	.087	.050
60-64	.04	.07	.06	.035	.074	.050
65-69	.06	.09	.08	.029	.069	.050
70-74	.09	.12	.10	.032	.065	.050
75-79	.14	.16	.15	.037	.063	.050
80-84	.20	.22	.21	.043	.062	.050
85+	.26	.27	.26	.043	.060	.050

Notes: select: mean over male and female





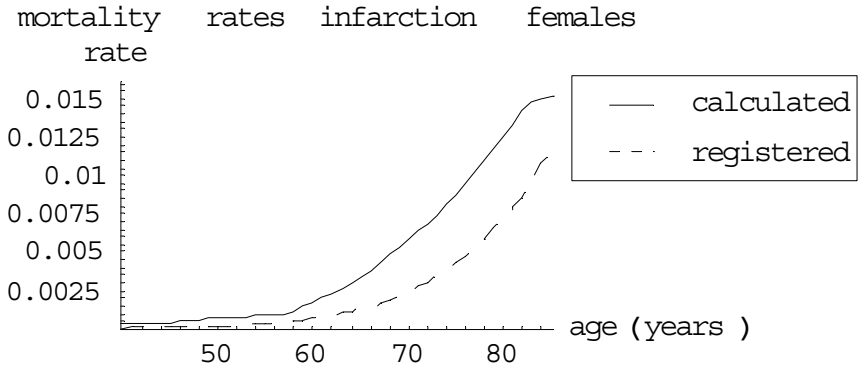
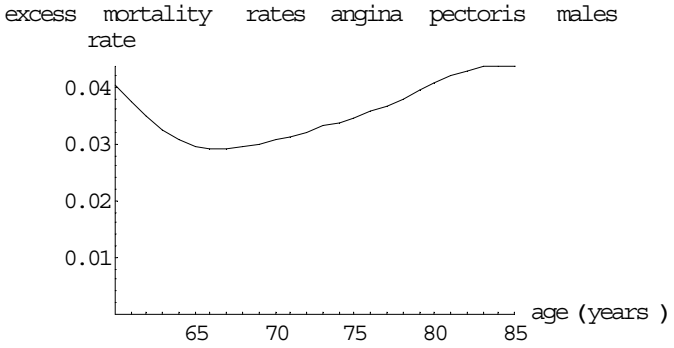
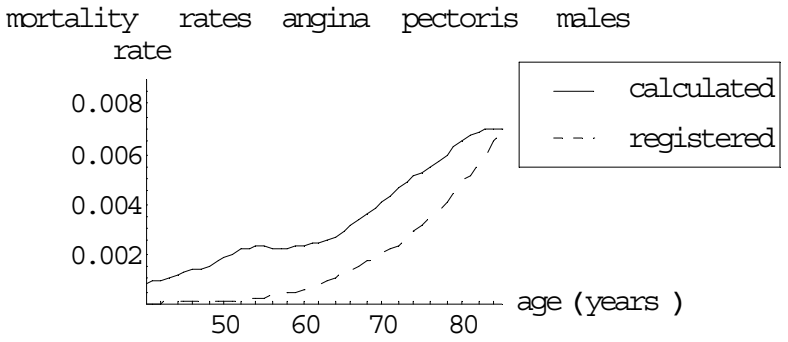
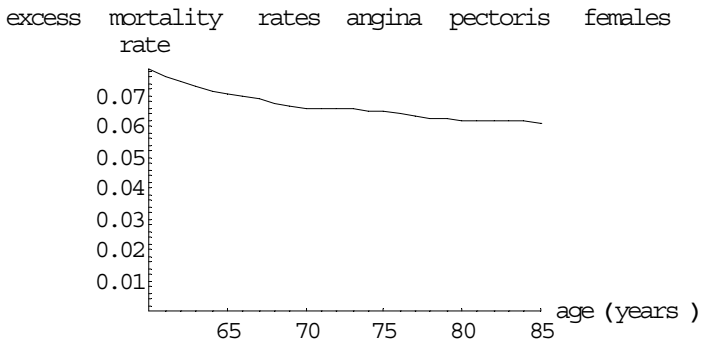


Figure 11 The calculated excess mortality ('chronic') and cause-specific population mortality (sum of 'acute' and 'chronic') rates for AMI, the mortality rates also compared to empirical data







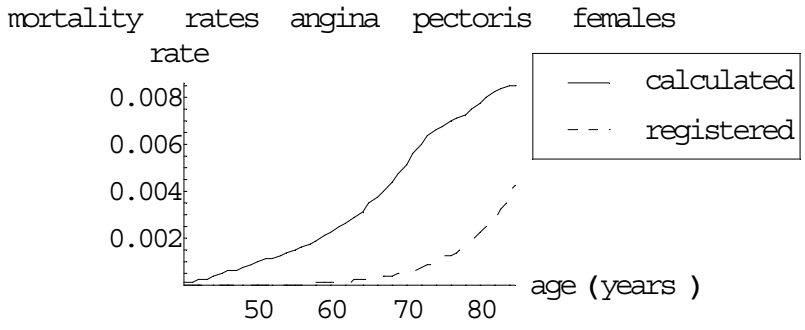


Figure 12 The calculated excess mortality and mortality rates for AP, the mortality rates also compared to empirical data

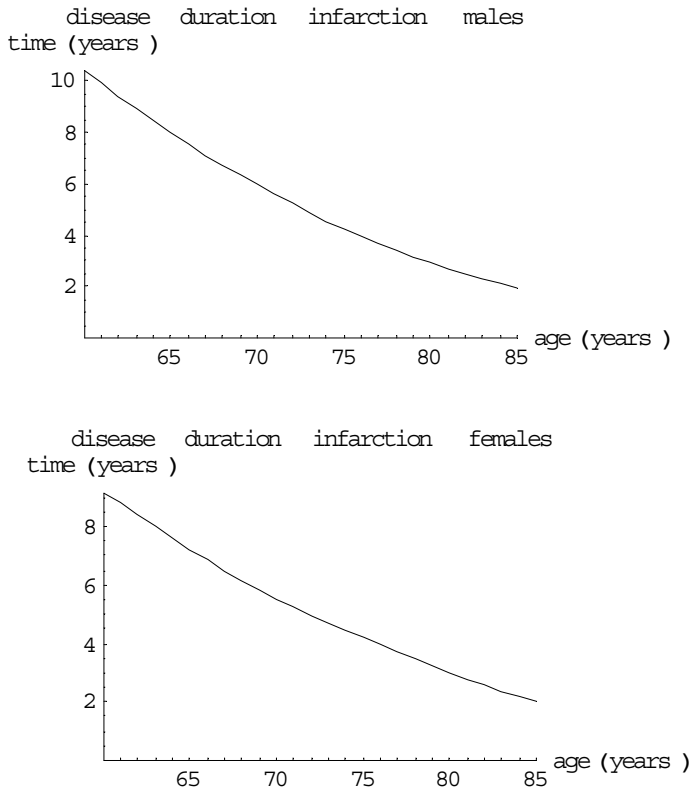


Figure 13 The AMI disease duration times for males and females

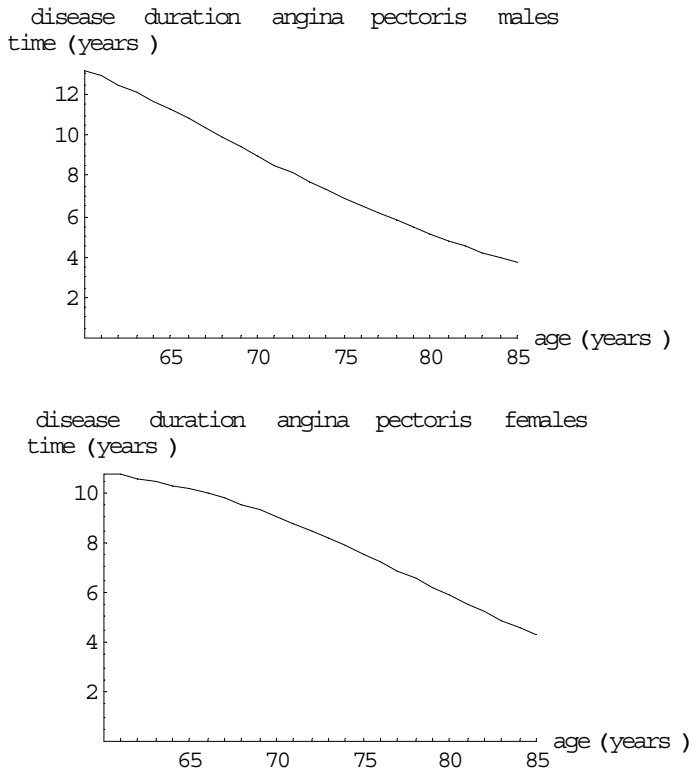
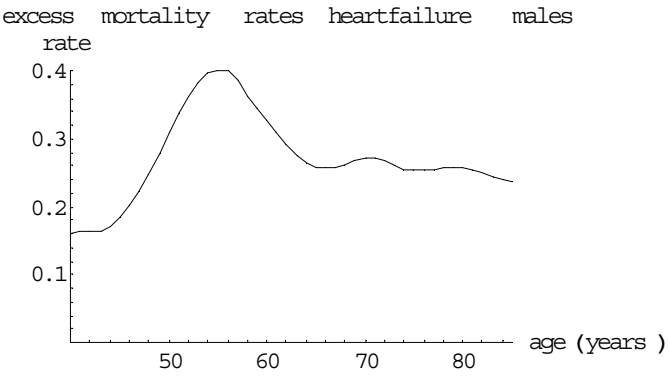


Figure 14 The AP disease duration times for males and females

For lower ages the calculated excess mortality rates are unstable due to the small incidence and prevalence rates for both AMI and AP types. The gender differences between the calculated excess mortality rates are small for AMI. Following the literature we have concluded that these differences are by chance and selected the mean value for both genders. For AP the calculated excess mortality rates are almost constant over age, but are clearly different for men and women. The calculated excess mortality rates are sensitive to the trend of the prevalence rates assumed. When we assume increasing prevalence rates in time for women, the calculated excess mortality rates decrease. So the higher excess mortality rates found for women could be explained by underestimating the prevalence time trend. There is not much literature on the prognosis of AP patients, and no indication of significant gender differences. Therefore we have selected the mean values over both genders resulting in constant values over age, and thus implicitly concluded that the time trends assumed are wrong.

4.6 Estimated mortality rates for CHF

The estimated mortality rates are presented in *Table 10* and *Figure 15*. We have assumed no remission and prevalence trends of 2% (males) and –3% (females) respectively.



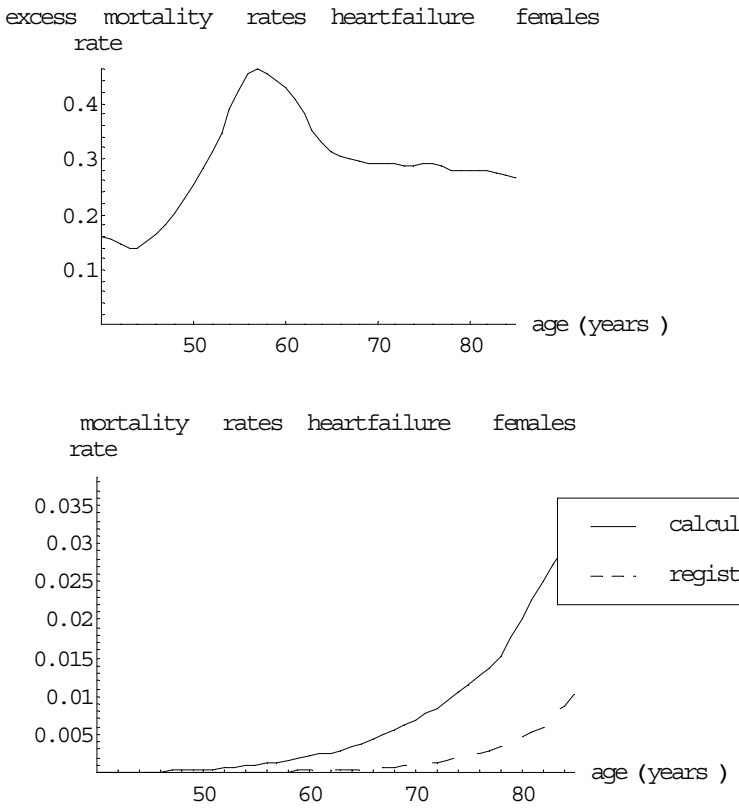


Figure 15 The calculated excess mortality and cause-specific population mortality rates for CHF, the population mortality rates also compared to empirical data

Table 10 The estimated excess mortality rates for CHF, together with the selected model parameter values

age:		40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
calc	males	.16	.23	.36	.38	.29	.26	.27	.26	.25	.23
	females	.15	.19	.32	.45	.38	.30	.29	.28	.28	.26
	select	.16	.21	.34	.41	.33	.29	.28	.27	.26	.26

Notes: calc: calculated gender-specific rate values, select: mean over men and women

For higher ages the excess mortality rate slowly decreases, and is for males slightly lower than for females. The estimated mortality is almost three times as high as the mortality registered by Statistics Netherlands. One important reason for this large difference is that many persons with CHF die with primary cause of death CHD. Because the differences between men and women are very small, we have concluded that both are equal. The final excess mortality rate values are the means of the calculated gender-specific ones. Because for lower ages the calculated rates are unstable, we have assumed that the rates are constant until age 45.

4.7 Combining CHD and CHF

The model that is used to describe coronary heart diseases (CHD) and congestive heartfailure (CHF) simultaneously is based on the model of CHD presented in §4.5 (see *Figure 10*). Because of the overlap in the data, we can only describe overlapping disease-specific prevalence numbers so far. Our resulting model combining CHD and CHF is presented in *Figure 16*.

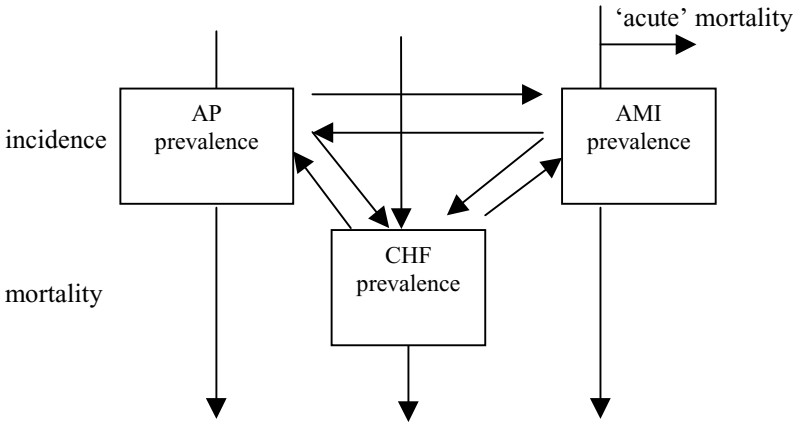


Figure 16 Model of CHD and CHF simultaneously
Notes: incidence of AP is from CHD-free population and from AMI prevalence after stabilisation; incidence of 1st AMI from CHD-free population, from AP prevalence and from CHF prevalence respectively; incidence of CHF from CHD- and CHF-free population, from AP and AMI prevalence respectively; mortality described includes excess mortality.

Because we describe overlapping disease prevalence numbers, we do not need to estimate rates for all transitions described in *Figure 16*. For example, the AMI incidence includes incidence from CHD-free population and persons with AP and CHF. For the same reason adding CHF to the CHD model does not affect the AMI and AP excess mortality rates estimated before. We need more information to disentangle the AMI, AP and CHF prevalence numbers. For example, Barendregt&Bonneux (1998) suggest that the ratios of the CHF incidence rates for CVD-free persons, persons with AP and those with history of AMI are 1:5:50. Given the total incidence rates, we can estimate the state-specific CHF incidence rates:

	age	50	60	70	80	85
free of CHD and CHF		.0004	.0007	.001	.0025	.0036
with AP		.002	.003	.006	.012	.018
with AMI		.02	.03	.06	.12	.18

4.8 Data from literature

Data from literature are presented on several aspects of coronary heart diseases. These aspects are: information on myocardial infarctions (*Table 11*&12), case fatality rates for AMI (*Table 13*), mortality rates and relative mortality risks of AP (*Table 14&15*) and of AMI after surviving the acute stage (*Table 16&17*), on CHD (recurrent) event risks of CHD patients (*Table 18*), of CHF incidence risks for CHD patients (*Table 19*), and finally on CHF mortality rates (*Table 20*).

Table 11 Proportion of suspected infarctions that are confirmed

author	country	year	populations	size	proportion confirmed (%)
Pal	Netherlands	1998	patients GP	742	57M;51F

Table 12 Proportion of infarctions that are first

author	country	year	population	size	proportion (%)
Vrieze	Netherlands	1994	patients hosp		91
Behar	Israel	1995	patients hosp		71

Table 13 Acute case fatality rates for AMI

author	country	year	population	size	foll(yr)	rate (/case)
Meeter	Netherlands	1993	pat hosp,age<=71	430	hosp stay	.10
Pashos	USA	1993	patients insurance	857000	30 days	.23
Naylor	Canada	1994	patients hosp	20000		.16
Tunstall	MONICA	1994	general,age 35-64		28 days	.43M;.46F
Behar	Israel	1995	patients hosp			.08
Lowel	Germany	1995	general		1 day	.53
Backer	Belgium	1996	general	2626		.42-.58
Feuvre	Canada	1996	patients hosp	831		.09
Norris	UK	1996	general	3523		.45 (.27-.53)
Rouleau	Canada	1996	patients hosp,age≥75	3178		.10
Tunstall-Pedoe	Scotland	1996	general		28 days	.49
Chambless	MONICA	1997	general;patients		28 days	M:.49;.22;F:.51;.27
Chun	South Korea	1997	general;1st event	5322		.21M;.17F
Perez	Spain	1998	general,age 35-64	1456	28 days	.27M;.20F

Note: foll: follow-up

Table 14 Mortality rates for patients with angina pectoris

author	country	year	population	size	follow-up (yr)	rate (/yr)
Ottervanger	Netherlands	1993	patients hosp,age<65	304	1;5;10	.065;.040;.043
Sigurdsson	Iceland	1995	general		4-20	.065
Kannel		USA	1997	patients hosp		10 .05

Table 15 Angina pectoris hazard ratios, relative risks and standardised mortality ratios

author	country	year	population	size	follow-up (yr)	ratio
Sigurdsson	Iceland	1995	general, age 34-79		16	1.7-2.2

Table 16 Mortality rates survival of acute phase of AMI (thus excluding 1 month mortality)

author	country	year	population	size	follow-up (yr)	rate (/yr)
Meeter	Netherlands	1993	patients hosp	430	1	.081
Pashos	USA	1993	patients insurance	857000	1	.16
Behar	Israel	1995	patients hosp			.06
Sigurdsson	Iceland	1995	patients hosp			.07
Torp-Pedersen	Denmark	1995	general	5175	5	.08
Backer	Belgium	1996	general	2626	5	.05
Feuvre	Canada	1996	patients hosp	831		.11
Rouleau	Canada	1996	pats hosp age≤75	3178		.07
Kannel	USA	1997	patients hosp	review	10	.08

Table 17 AMI mortality hazard ratios, relative risks and standardised mortality ratios

author	country	year	population	size	follow-up (yr)	ratio
Sigurdsson	Iceland	1995	general, age 34-79		16	3.7
Rosengren	Sweden	1998	general,age 51-59	826	16	5.22-2.93[1]

Notes: (1) first and last 4-year period of follow-up

Table 18 Relative (recurrent) CHD event risks of patients compared to CHD-free persons

author	country	year	population	size	follow-up (yr)	ratio
Hagman	Sweden	1988	general, men	350	11	3 (AP);7-8(AMI)

Table 19 Relative risks of CHF for CHD patients

author	country	year	population	size	follow-up (yr)	ratio
Kannel	USA	1997	review			4.8

Table 20 CHF mortality rates

author	country	year	population	size	follow-up (yr)	rate (/yr)
Kannel	USA	1989	general	485	30	.25M;.17F
Ertl	Germany	1993	patients	-	6	.13
Ho	USA	1993	general	-	30	.24M;.18F

4.9 Concluding remarks

Results have been presented for the three CHD manifestations being distinguished, i.e. for acute myocardial infarction (AMI), angina pectoris (or other CHD), and congestive heart failure (CHF). However, problems arise when combining these results. We can describe

incidence figures for the manifestations separately and together well, but prevalence figures only separately, because we have no information of the overlap in the registrations in general practice.

Data on CHD from morbidity registrations in general practice are difficult to compare due to differences in coding characteristics. We mention some of these differences here: (1) The inclusion criteria for new AMI patients are similar, for other forms of CHD incidence and for prevalence the criteria may differ substantially. Some registration projects distinguish three subgroups, AMI, AP and other forms of CHD that include patients with an AMI or AP history. (2) CMR Nijmegen defines AMI prevalence as lifetime prevalence: once an infarction, always prevalent. On the other hand, in the Transition Project the AMI prevalence is explicitly linked to the health care use of patients. CMR Nijmegen includes fatal infarctions, RNH Limburg does not.

Another aspect making the results hard to interpret is the nature of coronary diseases itself. (1) There is no clear hierarchy between the different types. For example, persons surviving an AMI have increased risk of CHF, may indeed develop CHF, but finally may die from a recurrent AMI. (2) The distinction between several forms of CHD by the general practitioner is partly based on interpreting the disease symptoms. Because symptoms may gradually change during disease history, there may be systematic differences between data for subgroups from different sources. From the disease registrations in general practice the CMR Nijmegen and RNH Limburg data seem to be most useful.

In general the excess mortality rates found for AMI seem realistic and are similar to data from the literature. For the highest ages much larger values have been found. The calculated excess mortality rates for other CHD types lead to some serious problems. For example, the relatively large differences found between men and women could be explained by the different prevalence rate time trends assumed for men and women. We have not found much information in the literature on the prognosis for AP, and finally have concluded that the ‘final’ excess mortality rates are the mean of the calculated gender-specific rate values.

The CHF disease module is only loosely linked to the CHD disease modules. This way of describing CHF meet our broad model requirements so far. However, for more detailed questions on the level of the patient and health care use, the overlap between CHD and CHF has to be made explicit. The same type of comments apply to other diseases such as diabetes mellitus and stroke that are related to CHD being a risk factor and another form of cardiovascular diseases respectively.

5. Diabetes mellitus

5.1 Introduction

Diabetes mellitus is a chronic metabolic disorder characterised by excessive levels of blood glucose. Two types of diabetes are distinguished: insulin-dependent (IDDM, type I) and non-insulin-dependent (NIDDM, type II). IDDM is irreversible and occurs mainly at younger ages. NIDDM may be reversible and the disease incidence is higher at older ages (over approximately 30 years). NIDDM can often be treated by changes of diet and level of physical activity, or oral medication. Most registrations in general practice do not distinguish both types of diabetes. Here we treat both types as one disease category. If necessary, the fractional distribution over both types can be approximated from past incidence numbers. Diabetes is an important risk factor for coronary heart diseases (see chapter 4).

5.2 Data sources

Diabetes mellitus data are available from:

incidence	**prevalence**
National Study NIVEL	
CMR Nijmegen	**CMR Nijmegen**
Transition Project	Transition Project
RNH Limburg	**RNH Limburg**
CMR Peilstations	CMR Peilstations

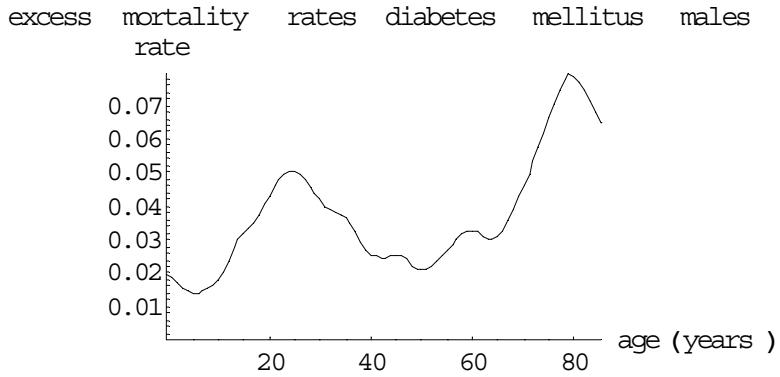
Although prevalence figures are available from epidemiological studies, we do not use them because no matching incidence figures are available. In most studies about diabetes prevalence it is found that 50% of the diabetes population is diagnosed (Maas et al., 1997). CMR Peilstations data are much lower than those from the other studies, probably due to different registration practice. The Transition Project seems to provide underestimated prevalence figures, such as is the case for a lot of chronic diseases with long disease duration times. The data sources used have been presented in bold.

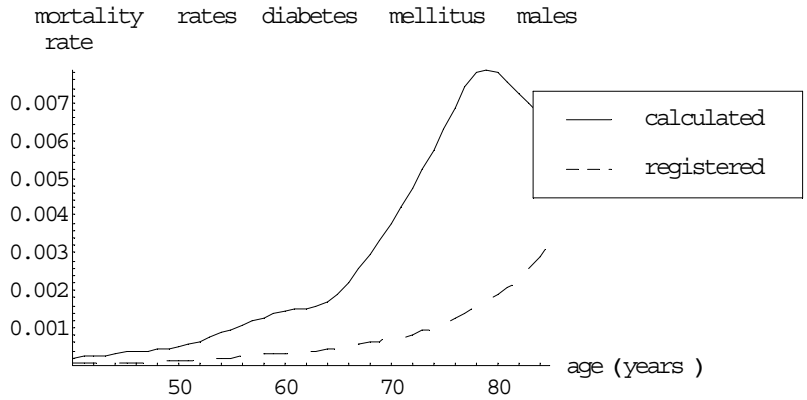
5.3 Data on incidence and prevalence

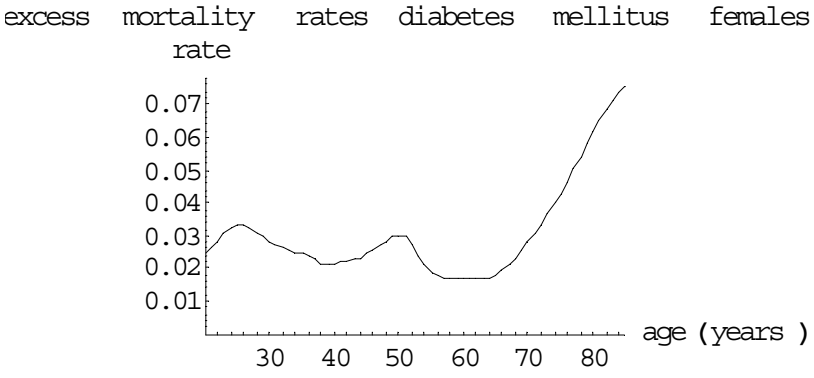
In *Figure 30* and *Table 44* (Appendix 2) we present the 1994 data that have been used in our analyses, and the model parameter values that have been selected.

5.4 Estimated mortality rates

Diabetes mellitus excess mortality rates can be calculated from incidence and prevalence data using the equations given in §1.4. We have assumed no remission and an annual change of the prevalence rate of 3% (men) and 2% (women) respectively, based on CMR data of 1972-1994. They are presented in *Figure 17* and *Table 21*. Based on the calculated excess mortality rates also disease duration times can be calculated, see *Figure 18*, and mortality hazard ratios, see *Figure 19*.







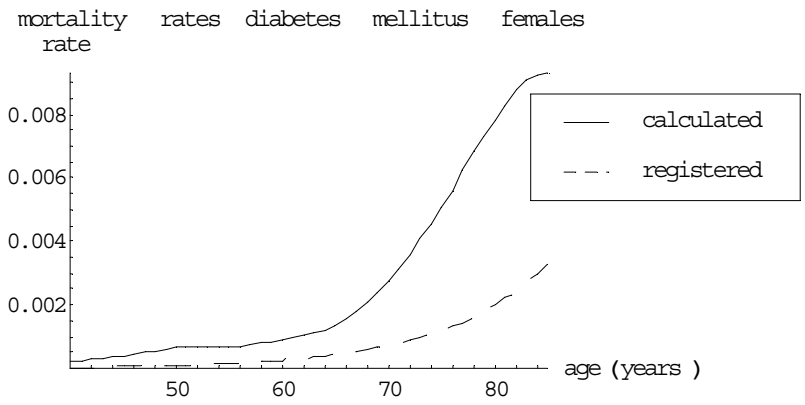


Figure 17 The estimated diabetes mellitus excess mortality and cause-specific population mortality rates, the mortality rates are compared to empirical data

Table 21 The calculated diabetes mellitus excess mortality rates

	males	females	select
age			
0-4	.017	-	.032
5-9	.015	.087	.032
10-14	.024	.047	.032
15-19	.036	.027	.032
20-24	.047	.028	.038
25-29	.047	.032	.038
30-34	.039	.026	.032
35-39	.032	.023	.027
40-44	.025	.022	.024
45-49	.024	.027	.024
50-54	.023	.026	.024
55-59	.030	.017	.024
60-64	.031	.017	.024
65-69	.036	.021	.028
70-74	.054	.034	.044
75-79	.073	.051	.062
80-84	.074	.068	.071
85+	.061	.077	.076

Notes: select: mean over gender-specific results with assumed constant values for lower ages

The calculated excess mortality rates are unstable for lower ages, due to the small mortality numbers for these ages. The differences between the calculated excess mortality rates for males and females are small. So we have concluded that the ‘final’ rate values are the means over the calculated gender-specific ones, and that for lower ages the rates are constant.

The differences between the calculated and empirical population mortality rates are small for lower ages, but increase substantially for higher ages. This is not surprising, because diabetes is not a fatal disease in itself, but rather a risk factor for more fatal diseases (complications) such as coronary heart diseases (see also *Table 24*). The registration of mortality due to

diabetes has been a popular research object during the last decade. One of the main problems is the interpretation of diabetes as being the primary or secondary cause of death or not. Mortality coding rules appear to have changed during the eighties in the Netherlands. The increase of the mortality rate with diabetes as the primary cause of death has almost been equal to the decrease of the mortality rate with diabetes as the secondary cause. Moreover, diabetes coding rules have been found to be different for higher than for lower ages (Mackenbach et al., 1991).

The calculated disease duration is small for very young female patients. This results from the calculated large excess mortality rates for this group, that are apparently overestimated. The calculated mortality hazard ratios are compared to data from literature (see *Table 22* for age-specific ratios and *Table 23* for aggregate data).

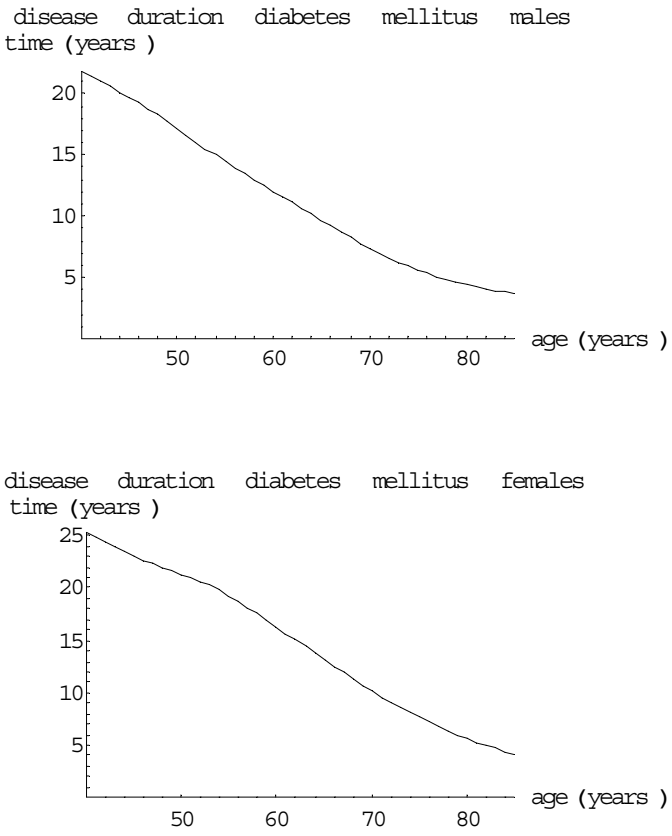


Figure 18 Diabetes mellitus disease duration

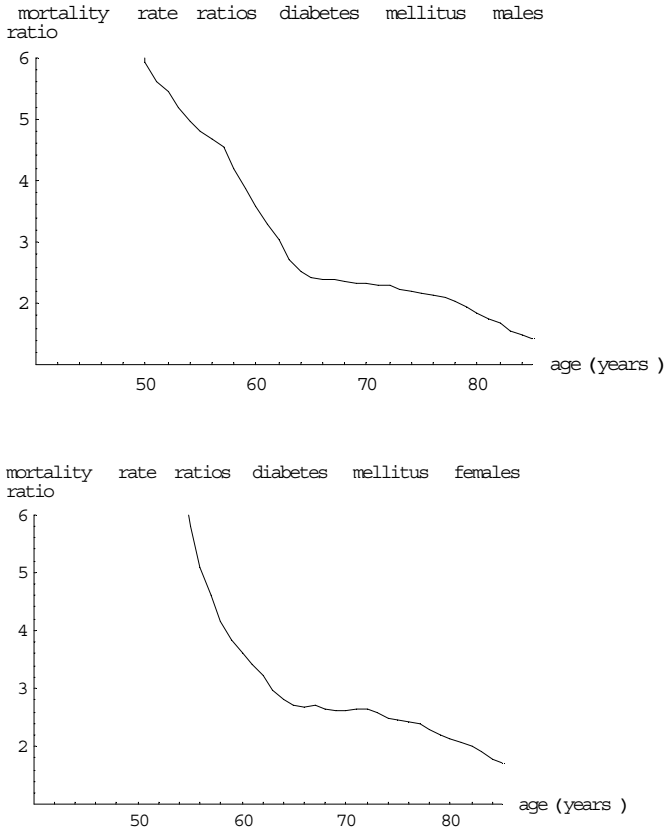


Figure 19 Diabetes mellitus mortality hazard ratios

Table 22 The calculated mortality hazard ratios, together with some data from literature

study	year	foll	50-54	55-59	60-64	65-69	70-74	75-79	80-84	ref. pop.	
males											
Joslin	1971	30	1.81	1.81	1.63	1.63	1.49	1.49	1.18	general	
Edinb	1979	8	2.39	2.39	1.65	1.65	1.35	1.35	1.01	general	
Panzram	1981	10	1.26	1.56	1.49	1.37	1.21	0.96		general	
Verona	1995	5	2.33	2.13	2.13	1.50	1.50	1.13	1.13	non-dm	
calc.			4.41	3.03	2.38	2.27	2.07	1.67	1.34	non-dm	
females											
Joslin			2.62	2.62	2.44	2.44	2.02	2.02	1.45		
Edinb			2.81	2.81	3.03	3.03	1.98	1.98	1.16		
Panzram		1.82	1.88	1.48	1.33	1.26	1.04				
Verona			3.43	2.33	2.33	2.27	2.27	1.32	1.32		
calc.					4.70	3.20	2.68	2.60	2.36	1.98	1.60

Notes: foll: follow-up (yr); ref. pop.: reference population that relative risk is defined to; source: Baan, 1999

We conclude that for males the calculated mortality hazard ratios fit to data from literature for the middle ages. For ages 50-59 the calculated ratios are larger. The absolutely larger values for females are confirmed by the data literature.

5.5 Other data from literature

We have presented data from literature on diabetes mortality (*Table 23*), and on the registration of diabetes as the cause of death (*Table 24*). Mortality hazard ratios, relative risks and standardised mortality ratios are similar parameters to describe increasing risks, and so have been presented in one table.

Table 23 Diabetes mortality hazard ratios, relative risks and standardised mortality ratios

author	country	year	population	size	foll (yr)	males	females	total
Kleinman	USA	1988		407	10	2.8-1.9	2.3-1.6	
Moss	USA	1991	IDDM;NIDDM	2972	8.5			7.5;2.0
Wong	Scotland	1991		4186	5			1.15
Knuiman	Australia	1992	NIDDM	888	5-9	1.43	1.83	
Nystrom	Sweden	1992	age 15-34	1983	ℵ5			2.1-4.8
Stengard	Finland	1992	age 65-84	<637	5	2.1		
Neil	UK	1993	median age 68	246	6.1			1.49
Croxson	England	1994	age∠ 65	71	4.5			4.5
Walters	England	1994	insulin users	717	11			1.75
Grauw	Netherlands	1995	NIDDM	265	6.8	1.61	1.47	1.54
Muggeo	Italy	1995	age 65-74	5996	5	1.50	2.27	1.46
Riley	Australia	1995	all	1232	8.5	4.6/1.8/2.2[1]		
Wei	USA	1995	patients	4875	7-8	2.1	3.2	
Hanefeld	Germany	1996	NIDDM,age 30-55	1139	11	5.1	7.0	
Simons	Australia	1996	elderly	2627	5			2
Swerdlow	England	1996	diabetic assoc.	5783	23-27	1.58	2.31	
Verlato	Italy	1996		7488	5			1.5
Damsgaard	Denmark	1997	NIDDM,age 60-74	236	5;13	1.9;1.5	-;2.2	
Fraser	USA	1997	age>83	-	12	1.51		
Gatling	UK	1997	all ages	917	8	1.89	2.16	1.99
Lowe	USA	1997	age 35-64	11554	22	1.88		
Adlerberth	Sweden	1998	men age 52-59	249	16	2.5		
Gu	USA	1998	age 25-74	700	22			3.6-1.5
Koskinen	Finland	1998	age 30-74,treated	11215	5	2.4	3.4	
Nilsson	Sweden	1998	self rep,age 25-74	780	<=16	2.24	3.67	
Rosenthal	USA	1998	age 61-88	135	3	1		
Warner	Gr-Britain	1998	IDDM,child	1800	9.3			2.47

Notes: foll: folow-up, (1) SMR's for onset of IDDM at childhood, of IDDM at adulthood, and of insulin-treated NIDDM at adulthood,

Table 24 Proportion of mortality with diabetes recorded as the cause of death

author	country	year	population	size	proportion (%)
Joner	Norway	1991	general,IDDM	1908	35
Gu	USA	1993	general	13830	7.7M;13.4F
Sprafka	USA	1993	general	540	54
Andersson	Sweden	1994	general		57 (48M;67F)
Warner	Gr-Britain	1998	child,IDDM	26	58

Note that the inclusion criteria are very important: young or old, IDDM or NIDDM, etc. It has been found that larger follow-up times result in lower hazard ratios.

5.6 Concluding remarks

The incidence and prevalence data from different sources are quite similar, except for the CMR Peilstations and the Transition Project. However, these differences partly seem to be explainable due to differences in registration practice.

The calculated excess mortality rates found for men and women are almost equal. We have concluded that the ‘final’ rate values are the means of the calculated gender-specific rates. As a consequence the relative mortality risks for women are larger than those for men, in agreement with literature. The absolute levels of the mortality risks for middle aged people are generally higher than the values presented in literature.

Diabetes mellitus is an important risk factor for coronary heart diseases (CHD). So part of the excess mortality of DM patients is mortality from CHD. We have not modelled this relationship so far.

6. Dementia

6.1 Introduction

Dementia occurs mainly in two types: Alzheimer type and vascular dementia. Approximately 70% of dementia prevalence is of Alzheimer type, 15% of vascular type (Ott et al., 1996). Prevalence and incidence can be based on the ERGO Study, a survey in the general population, or on registrations in general practice. In ERGO the DSM system of inclusion criteria has been used to define dementia. In general practice early symptoms of dementia are not always diagnosed. That's why prevalence rates in population studies are always higher than those in registrations in general practice. A relatively large part of the population with dementia is found in nursing homes, that are registered by the Nursing Home Information System (SIVIS) of the SIG Health Care Information and not by the registrations in general practice. Although the prevalence increase sharply for the highest ages, it is rarely registered as the primary cause of death.

6.2 Data sources

Data for dementia are available from several sources:

incidence	**prevalence**	**survival**
National Study NIVEL		
CMR Nijmegen	**CMR Nijmegen**	
Transition Project	Transition Project	
RNH Limburg	**RNH Limburg**	
ERGO Rotterdam	ERGO Rotterdam	ERGO Rotterdam
	SIVIS	

The Transition Project seems to provide underestimated prevalence figures, such as is the case for a lot of chronic diseases with long disease duration times; the National Study provides only incidence figures. Therefore both data sources have not been used. The prevalence numbers from registrations in general practice exclude those from nursing homes. The number of persons with dementia in nursing homes is 25.400, with males 27% and females 73%. We have assumed that all dementia patients that are housed in the nursing homes have once been registered as an incident case by the general practitioner, and that the age-distribution of the dementia prevalence numbers in the nursing homes equals that within the registration in general practice. The resulting age-specific prevalence rates from nursing homes have been added to the prevalence rates from the registrations in general practice.

Initially we used data from ERGO adjusted for the prevalence in nursing homes, because these data describe all dementia morbidity in the population. However, it turned out that the excess mortality rates calculated from these incidence and prevalence figures were much too small compared to mortality statistics. Therefore, we have chosen to use data from CMR Nijmegen and RNH Limburg adjusted for the prevalence in nursing homes. So our final model does not include the milder forms of dementia.

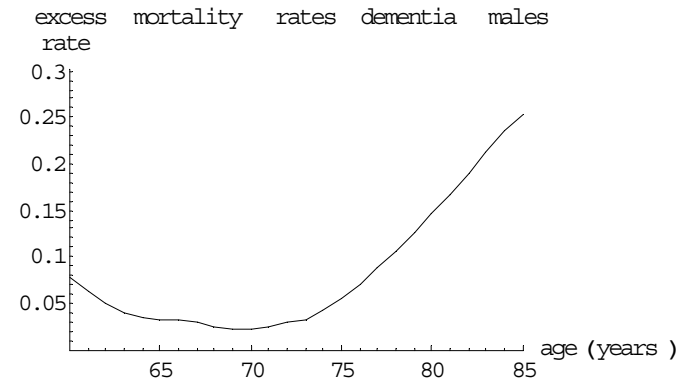
6.3 Data on incidence and prevalence

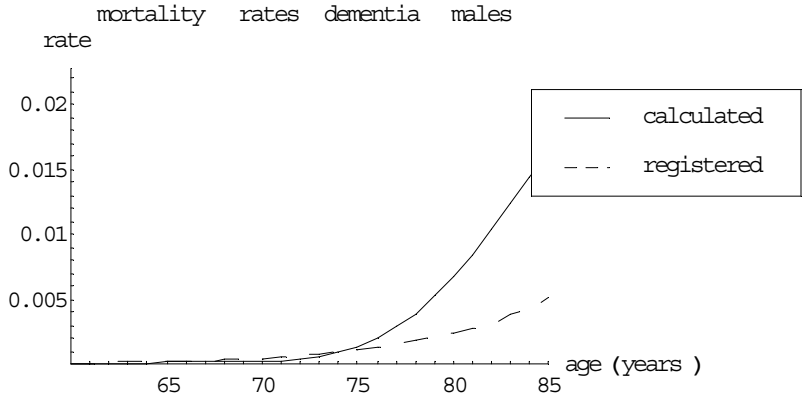
In *Figure 31* and *Table 45* (Appendix 2) we present the 1994 data on incidence and prevalence, and the calculated mean values after smoothing and adjustment for dementia prevalence in nursing homes. The prevalence figures from ERGO are much larger than those from the registrations in general practice. The main reason is the difference in sampling: from total population versus only from those who visit the general practitioner. The prevalence numbers according to ERGO include the less severe forms of dementia. The ratio of the prevalence rates in ERGO to those in the other registrations is larger than the ratio of the incidence rates. This can be explained using a simple mathematical model (see Appendix 5).

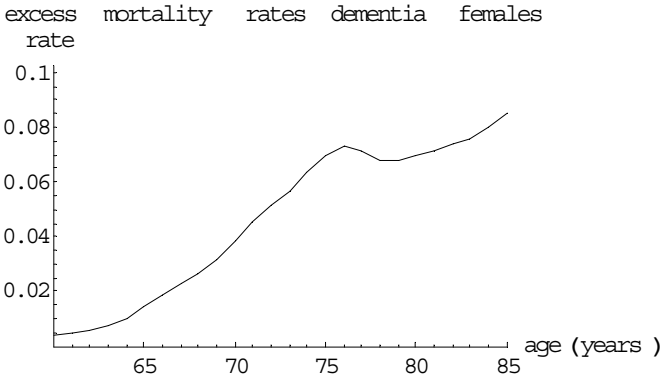
CMR Nijmegen data can be used to estimate time trends in the incidence and prevalence of dementia. Incidence and prevalence rates have increased between 1976 and 1994. The absolute numbers have increased even more due to the greying of the population. Mortality coding rules for dementia have changed. After 1990 dementia is more often mentioned as the primary cause of death than before. Empirical mortality rates have increased with approximately 250% for males and females compared to 1990.

6.4 Estimated mortality rates

The dementia excess mortality rates have been calculated using the chronic disease model equation presented in §1.4. We have assumed no remission. We assumed the annual change of the dementia prevalence rate to be 8% for males and females, based on CMR time series over 1984-1994.







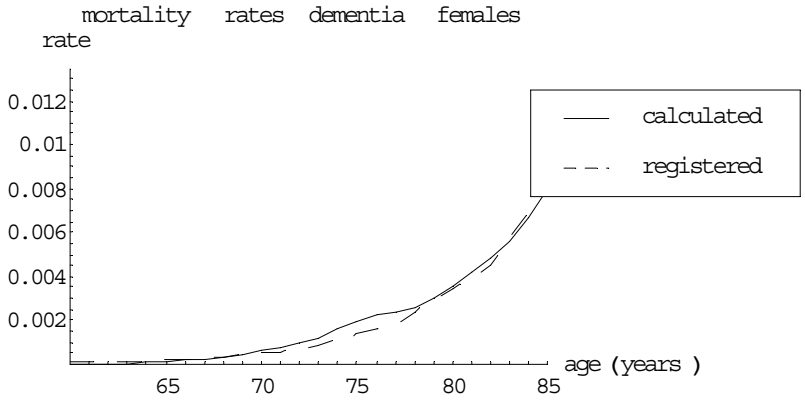


Figure 20 The estimated dementia excess mortality rates and cause-specific population mortality rates, the mortality rates are compared to empirical data

Table 25 The calculated dementia excess mortality rates, together with the selected values

age		65-69	70-74	75-79	80-84	85+	
calculated	males	.03	.03	.09	.19	.28	(=selected)
	females	.02	.05	.07	.07	.09	

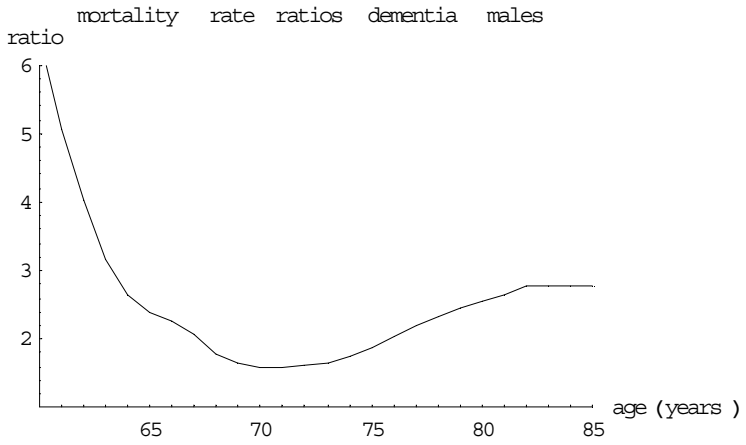


Figure 21 The calculated dementia mortality hazard ratios for males and females

In *Figure 20* and *Table 25* the calculated mortality reates have been presented, together with the empirical ones. The calculated excess mortality rates are clearly different for men and women. For lower ages the rates are clearly too small for women. Also for higher ages the rates seem to be too small, when compared to empirical mortality data. So we have serious doubts on the results found for females. We have found no indication in the literature that for females the prognosis of dementia patients is much better than for males. Therefore we have decided to choose the values found for males as the rate values for both men and women. As a consequence the calculated mortality hazard ratios are larger for females.

6.5 Data from literature

In *Table 26* dementia mortality hazard ratios from literature are presented, together with the calculated values.

Table 26 Dementia mortality hazard rate ratios

author	country	year	population	size	foll(yr)	AD	VD	unspec
Aronson	USA	1991	general, inc. cases	488	8			3
Evans	USA	1991	general, age≥65	467	4.9			1.44
Heeren	Netherlands	1992	instit.+general, age≥85	1259	<=4			1.9
Skoog	Sweden	1993	general, age≥85	-	3	1.8	2.9	
Mölsä	Finland	1995	general, mean age 78	333	14	6.9	7.8	
Rossler	Germany	1995	instutional	1821	2.5	8.0	5.9	
Bowen	USA	1996	general	327	3.3			2.1
Cale	GB	1996	GP, age≥65	-	20			2.2
Barendregt	Netherlands	1998	general, age≥55	494	2.3			2.1M;2.3F
calculated			instit.+general,age≥75					2.7M

Notes: foll: follow-up; AD: Alzheimer-type dementia; VD: vascular-type dementia.

The results found by Mölsä and Rossler seem to be outliers compared to all other figures.

6.6 Concluding remarks

Dementia differs from most diseases described so far in several ways. (1) Mortality is small except for the highest ages. (2) A relatively large part of the prevalence is found in nursing homes and so generally is not described by registrations or surveys. We have added these prevalence numbers to the registered numbers assuming equal age distributions.

Several combinations of assumptions are possible to calculate excess mortality rates from given incidence and prevalence figures: with/without adjusting for prevalence time trend, including/excluding prevalence numbers in nursing homes, data from registrations in general practice or from population surveys. Some combinations clearly resulted in underestimation of mortality rates. The sources giving ‘best’ results, compared to those from literature, were choosing data from CMR Nijmegen plus RNH Limburg including adjustment for the prevalence in nursing homes.

The assumptions given above are in some way artificial. For example, we do not know whether the assumption that all dementia incidence numbers in nursing homes have once been registered by the general practitioner, and we have found increasing dementia prevalence numbers in general practice. So we definitely need more data to improve the model assumptions.

The calculated excess mortality rates for males and females are different. For females the mortality rates are apparently underestimated, when compared to empirical mortality data. In the literature we have not found indications of gender differences. So we have assumed that the calculated values also can be applied to females.

7. Stroke

7.1 Introduction

Cerebrovascular diseases belong to the group of vascular diseases, just like coronary heart diseases (CHD, see chapter 4). Within the group of cerebrovascular diseases we distinguish TIA (accident with recovery within 24 hours), and stroke. Strokes can be divided in haemorrhiagic strokes (with sudden vascular bleedings) and cerebral infarctions. Registrations in general practice do not make this distinction; so we describe all strokes together. Persons having had a TIA are generally checked by the general practitioner for a given time period following standard protocols. The TIA prevalence data provide information on the length of this check-up period. Persons with a history of TIA have an increased risk of stroke. Both TIAs and strokes can be recurrent.

We have decided not to include 'TIA' in our CVA disease model for several reasons. (1) Both TIA and stroke share the same main epidemiological risk factors. As a consequence prevention programmes meant to decrease TIA incidence risks also result in decreasing stroke incidence risks, and vice versa. (2) TIA results in much smaller health care use than stroke. (3) Data on the risks of stroke for TIA patients show large variations (see *Table 32*) and so are unreliable.

7.2 Data sources

Data on stroke data are available from:

incidence	**prevalence**
National Study NIVEL	
CMR Nijmegen	**CMR Nijmegen**
Transition Project	Transition Project
RNH Limburg	**RNH Limburg**
CMR Peilstations	ERGO Rotterdam

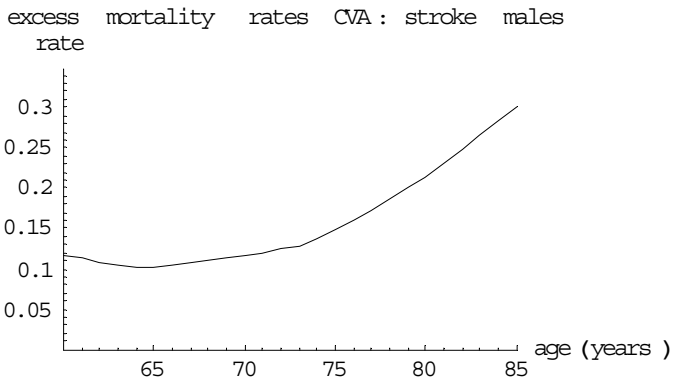
Data from the National Study and CMR Peilstations have not been used because they are only on incidence and show systematic differences from other data. Transition Project prevalence data have not been used because of a different follow-up registration method, resulting in clearly different prevalence figures. That means, in the other sources stroke prevalence data refer to lifetime prevalence. ERGO data have not been used, because they only provide prevalence data. The data sources selected have been presented in bold.

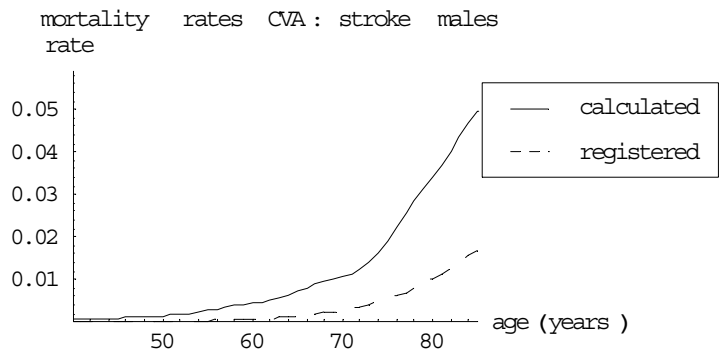
7.3 Data on incidence and prevalence

1994 stroke incidence and prevalence rates have been presented in *Figure 32* and *Table 46* (Appendix 2). TIA incidence rates have been presented in *Figure 33* (Appendix 2).

7.4 Estimated mortality rates

Survival after stroke can be divided in subsequent periods. The first 30 days show high mortality risks, followed by a fluctuating mortality for the next 150 days, and finally a constant mortality for the following years (e.g. see Scholte op Reimer et al., 1999). So we have decided to distinguish 'acute' stroke mortality, being proportional to the stroke incidence, and 'chronic' mortality, being proportional to the stroke prevalence. The 'acute' stroke mortality is known in the literature as the case fatality. The case fatality can be defined for two 'populations': for all cases in the general population after the event, and for those who have been hospitalised after admission. Because the mortality after the event includes the mortality in the hospital the former case fatality is higher than the latter. Based on data from literature on both case fatality and 'chronic' mortality we have assumed the case fatality to be 0.20/new case (see *Table 37*). The 'chronic' excess mortality rate is calculated from the stroke incidence and prevalence rates and has unit '/patient/year'. Moreover, we have assumed no remission and prevalence trends of –2% and 4% for men and women respectively, based on trends observed in CMR Nijmegen.





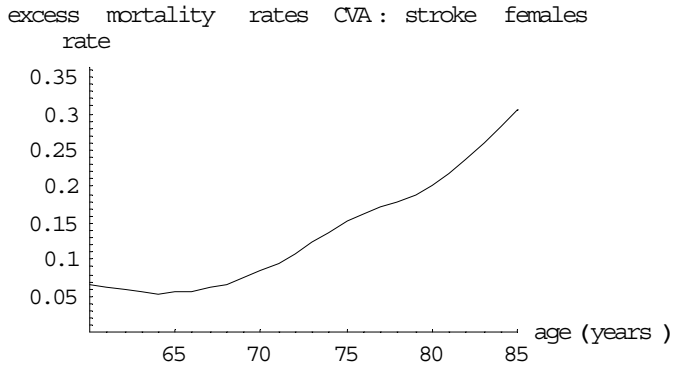


Figure 22 The calculated stroke excess mortality ('chronic') and cause-specific population mortality (sum of 'acute' and 'chronic') rates, the mortality rates are compared to empirical data

Table 27 The calculated stroke excess mortality rates

age		45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
calculated	M	.14	.11	.11	.11	.11	.13	.17	.25	.33
	F	.06	.07	.07	.06	.06	.11	.17	.24	.34
select	M+F	.09	.09	.09	.09	.09	.12	.17	.24	.33

Note: select: mean over both genders

Table 28 The calculated mortality hazard ratios

age		65-69	70-74	75-79	80-84	85+
calculated	M	5.4	4.1	3.7	3.6	3.1
	F	6.4	7.0	6.4	5.0	3.6

The calculated excess mortality and cause-specific population mortality rates are presented in *Table 27* and *Figure 22*. The calculated excess mortality rates are almost equal for both males and females for higher ages, but differ for lower ages. The mortality rates presented in literature are equal for men and women. Therefore we have decided to choose the mean values as the rate values for both genders.

7.5 Data from literature

In several tables data on CVA from literature, together with calculated values, have been presented. These data refer to the stroke incidence risks of TIA patients (*Table 29-32*), stroke recurrence rates (*Table 33*), TIA excess mortality rates (*Table 35&36*) and stroke excess mortality rates (*Table 37&38*).

Table 29 Proportion of stroke patients that have history of TIA

author	country	year	population	size	proportion (%)
Ree	Netherlands	1989	patients GP	214	8
Amrani	France	1995	patients hosp		9-25
Hankey	Australia	1998	patients 1st stroke	343	13
Petty	USA	1998	patients 1st stroke	1111	18
Scholte op Reiner	Netherlands	1999	patients hosp	760	33

Table 30 Proportion of TIA patients that develop stroke

author	country	year	population	size	foll (yr)	proportion(%)
Toole	USA	1978	patients	225	5.5	15
Ueda	Japan	1987			5	28-50
Ree	Netherlands	1989	patients GP	134	12.5	13 (6% within 2 yrs)
Dennis	England	1990	general	184	3.7	24-33
Giroud	France	1992	patients	175	2	21

Table 31 Stroke incidence rates for TIA patients

author	country	year	population	size	foll(yr)	rate (/yr)
Dennis	England	1990	general	184	3.7	.12 (1st year); then .06

Table 32 Relative risks of developing stroke for TIA patients

author	country	year	population	size	foll(yr)	ratio
Simonsen	Scandinavia	1981	patients	243		4
Dennis	England	1990	general	184	3.7	7
Mortel	USA	1996	1st event	366	4.4	2.3

Table 33 Stroke recurrence rates

author	country	year	population	size	foll(yr)	rate (/yr)
Meer van der	Netherlands	1990	1-year survivors	182	1.0	.20
Hier	USA	1991	patients	1273	1.1	.07
Burn	UK	1994	patients	675	1;5	.13;.07
Ryglewicz	Poland	1997	30 day survivors	209	1	.11
Hankey	Australia	1998	1st stroke, mean age 73	343	1;5	.04;.05
Petty	USA	1998	1st cer.infarction	1111	1;5	.12;.07
Prencipe	Italy	1998	1st attack, mean age 55	322	10	.015

Table 34 Proportion of stroke cases that are recurrent

author	country	year	population	size	proportion (%)
Schuling	Netherlands	1992	patients GP	185	14 (incl. acute mort)
Bonita	N Zealand	1993	general	2438	73
Du	England	1997	general	932	69
Ellekjaer	Norway	1997	general	593	73
Hankey	Australia	1998	general	492	25
Koliminsky	Germany	1998	general	465	24
Scholte op R.	Netherlands	1999	patients hospital	760	33 (excl. acute mort)

Table 35 TIA case fatality rates

author	country	year	population	size	foll(yr)	rate (/year)
Evans		USA	1994	patients	230	1 .06
Toole	USA	1978	patients	225	5.5	.079
Dennis	England	1993	general	675		.063

Table 36 Relative mortality risks for TIA patients

author	country	year	population	size	follow-up (yr)	ratio
Dennis	England	1990	general	184	3.7	1.4

Table 37 Stroke case fatality rates

author	country	year	population	size	follow-up (yr)	rate (/case)
Ree	Netherlands	1987	patients GP	214	1 month	.25
Scmidt	Russia	1988	patients	1538	3 weeks	.37
Giroud	France	1989	patients		1 month	.22
Meer van der	Netherlands	1990	patients GP	273	8 weeks	.26
Schuling	Netherlands	1992	patients GP	185	3 weeks	.23
Arbin	Sweden	1992	pat hosp,mean age 73	388	21 days	.13
Tapia	Chile	1992	patients	300	2 months	.19
Bonita	New Zealand	1993	general	2438	28 days	.22M;.26F
Dennis	England	1993	general	675	30 days	.19
Sarti	Finland	1993	general			.23M;.26F
Sacco	USA	1994	age>39	323	30 days	.08

Stegmayr	Sweden	1994	general		28 days	.15
Stegmayr	Sweden	1996	general ,age25-74	5700		.135
Du	England	1997	general	932	28 days	.34
Ellekjaer	Norway	1997	general	593	30 days	.21
Hop	Netherlands	1997	pat.subar.hemorr.	review	28 days	.32-.67
Immonen	Finland	1997	general, age 35-74	11171	28 days	.20M;.21F
Thorvaldsen	Den/Sweden	1997	general, age 35-64	1836	28 days	.20M;.24F
Hankey	Australia	1998	general, 1st attack	370	2 days	.05
Heinemann	Germany	1998	general	7435	28 days	.40
Jeng	Taiwan	1998	patients hosp	995	30 days	.11
Kolominsky	Germany	1998	general,1st attack	354	28 days	.194
Petty	USA	1998	1st cer.infarction	1111	30 days	.14
Scholte op R.	Netherlands	1999-08-24	patients hosp	760	1 month	.28

Table 38 Stroke mortality rates after surviving the acute stage

author	country	year	population	size	foll(yr)	rate (/yr)
Scmidt	Russia	1988	patients	1538	3;5;7	.16;.15;.13
Giroud	France	1989	patients		1	.30
Dennis	England	1993	general	675	<=6.5	.09
Sacco	USA	1994	age>39	323	1;5	.14;.10
Lai	USA	1995	patients	662	1;4	.13 ;.08
Leonhardt	Europe	1996	review		1	.42
Ryglewicz	Poland	1997	patients	209	1	.29
Elneihoum	Sweden	1998	patients	2290	3	.43 (/3years)
Hankey	Australia	1998	1st attack, mean age 73	343	5	.16
Kolominsky	Germany	1998	general	354	1	.20
Petty	USA	1998	1st attack	1111	1; 5	.14; .11
Prencipe	Italy	1998	1st attack, mean age 55	322	10	.04
Scholte op R.	Netherlands	1999	patients hosp	760	4.5	.12

Note: foll: follow-up

Table 39 Mortality hazard ratios and relative risks for stroke patients

author	country	year	population	size	follow-up(yr)	ratio
Arbin	Sweden	1992	pat.hosp,mean age 73	388	5-8	1.38
Dennis	England	1993	patients	675	<6.5	2.3
Lai	USA	1995	patients	662	4	1.7
Prencipe	Italy	1998	1st attack, mean age 55	322	10	1.7

We have only used data on stroke mortality (*Tables 37-39*) for our analyses. The other data can be used when we want to further develop the model such that (1) we can distinguish 1st strokes and recurrent strokes, or (2) we can describe the relation between TIA and stroke explicitly.

When interpreting the data we have to take account of the following aspects. Medical treatment of stroke has improved over the last decades in Western countries. This has resulted in decreasing mortality risks. Mortality risks vary over time after stroke incidence. We have found the following specification: 1st month, 1st year given survival over 1st month, and next

years given survival over 1st year. The differences between the stroke case fatality figures are relatively small compared to the differences between the hazard rate ratios.

7.6 Concluding remarks

Cerebrovascular accidents (CVA) can be distinguished in transient ischemic attacks (TIA) and strokes. We have decided to describe only stroke prevalence for several reasons. (1) Lack of reliable data on the relation between both types. (2) Both types share the same risk factors. (3) TIA does result in small health care use compared to stroke.

We have chosen to use data from CMR Nijmegen, Transition Project (with respect to incidence) and RNH Limburg.

In accordance with the literature we have decided to distinguish ‘acute’ and ‘chronic’ mortality. ‘Acute’ mortality is mortality during the 1st month and is in our model defined proportional to stroke incidence. The ‘acute’ case fatality rate used is 0.14, based on literature. However, some studies indicate much larger case fatality rates.

The ‘chronic’ mortality is defined as the mortality during the following years and is assumed to be proportional to stroke prevalence. The ‘chronic’ excess mortality rates are calculated from given incidence and prevalence figures adjusted for ‘acute’ mortality. The gender differences of the calculated rates are small. Because the literature gives no indication of significant gender differences, we have concluded that the rates are equal for men and women.

8. Concluding remarks

Analyses of the consistency of disease data are necessary before applying them in chronic disease computer simulation models. Inconsistent data may result in substantially increasing or decreasing disease prevalence and/or mortality rates over time that are wrongly interpreted as future time trends.

There is a lot of terminological confusion regarding analyses such as this present 'DisMod'. This is caused by the use of terms that have different interpretations in different contexts. For instance, in the epidemiological context remission is defined as a diseased person declared disease-free, in the context of registrations in general practice it is defined as the end of an episode of health care use. Because we mainly use data from registrations in general practice, we follow the latter definition. In our chronic disease models mortality is defined in terms of excess mortality: the mortality risk for any patient minus the mortality risk for a disease-free matched person. It has to be noted that depending on the disease fatality the total excess mortality may be much larger than merely the mortality with the disease as the primary or secondary cause of death (as defined in mortality statistics).

It is clear that longitudinal data are the best for estimating the parameters of the chronic disease model. These data are available from follow-up studies on patients that are presented in the scientific literature. However, these patients are often hospitalised and so may be quite different from patients in the general population that are described in the chronic disease model. Differences may also result from different age-categories, different time periods, different regions/countries, different patient inclusion criteria etc. As an alternative we have used data from registrations in general practice, cancer registrations and epidemiological surveys to calculate the model parameters. However, these data are not longitudinal, but cross-sectional with most often registration time periods that are short compared to disease duration times.

The model equation describes the annual change of the prevalence rate for persons within a cohort. This change is over both age and time. In mathematical terms: it is a total instead of partial differential with respect to time. So we have to include prevalence rate time trends when estimating the remission and mortality rates. Time trends of prevalence are hard to find. Moreover, it turns out that time trends, that may be different over age, complicate the estimation of age-specific rate values.

Annual changes of disease prevalence rates, incidence, remission and mortality are mathematically strongly correlated: both describe the change of the prevalence rate over one timestep. For instance, assuming no excess mortality for persons with asthma results in increasing remission rates for the higher ages.

For some diseases and/or ageclasses we find differences between the calculated excess mortality rates for men and women, for others they are almost equal. These differences can be real, or can be the result of poor data and/or wrong model assumptions. One of the critical assumptions is the time trend assumed. For most diseases we have found no gender differences reported in literature. So for most diseases we assumed that the mean rate values are valid for both genders. Note that assuming equal excess mortality rates for men and women always result in different mortality hazard ratios.

The analyses are not equally successful for all diseases being distinguished. The results for lung cancer, asthma, COPD, CHF, diabetes and stroke seem to be valid at face value and compared to data from literature. For CHD and dementia the results can still be improved. The main explanations for the differences found are the following: we had to make many extra assumptions to combine data from different sources (in case of dementia), the definitions of the distinguished disease states differ between the sources (in case of CHD), and the changes over time of the prevalence rates found are probably also age-dependent (in case of COPD for males and CHD).

The calculated excess mortality includes the mortality with the disease as the primary or secondary cause, but also the mortality due to competing death risks. Dependency may be caused by joint risk factors (such as smoking for COPD and CHD) or by joint pathofysiological processes (such as for CHD and CHF). In our analyses we have omitted this dependency structure so far, assuming that patients and disease-free persons have the same risk factor values, conditional on gender and age.

Due to competing death risks the mortality among persons with a specific disease is smaller than the mortality due to the disease, i.e. the mortality with the disease as the primary cause of death. The problem of attributing excess mortality to specific causes recurs when combining disease models. For example, excess mortality numbers for CHD and CHF include double counts.

Appendix 1 Mailing list

1 Directeur-Generaal RIVM
2 Dr HJ Schneider, Directeur-Generaal van de Volksgezondheid
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4 Drs PH Vree, waarnemend Hoofdinspecteur voor de Gezondheidszorg
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6 Dr JJM Barendregt (EUR)
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8 Drs SMAA Evers (UM)
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10 Prof dr H Lamberts (UvA)
11 Dr EH van de Lisdonk (KUN)
12 Dr JFM Metsemakers (UM)
13 Dr CJL Murray (WHO)
14 Drs LW Niessen (EUR)
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16 Dr MG Roberts (Wallaceville Animal Research Centre)
17 Dr MPMH Rutten-van Mölken (EUR)
18 Dr FG Schellevis (NIVEL)
19 Drs WJM Scholte op Reimer (EUR)
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23 Prof dr GAM van den Bos
24 Dr HC Boshuizen
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26 Dr TL Feenstra
27 Drs A van der Giessen
28 Dr ir N Hoeijmans
29 Ir J Jansen
30 Prof dr ir D Kromhout
31 Drs M Kruijshaar
32 Dr ing JAM van Oers
33 Dr D Ruwaard
34 Dr ir JC Seidell
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42 Bureau Rapportenregistratie
43 Bibliotheek RIVM

44-60 Bureau Rapportenbeheer
60-70 Reserve exemplaren

Appendix 2 Tables and figures of disease incidence and prevalence data

For all diseases being described the incidence and prevalence rates are presented in tabular and graphical form. In the tables only data from the sources being selected are presented, in the figures the raw data from all sources available. In each table in the last row the calculated total disease prevalence numbers are presented, i.e. the prevalence rates applied on the 1994 Dutch population. The overall calculated prevalence rates are the means over the sources that have been selected and that have been smoothed using a penalty method (see Appendix 4). In the last paragraph in tabular form all disease-specific prevalence trends assumed have been presented.

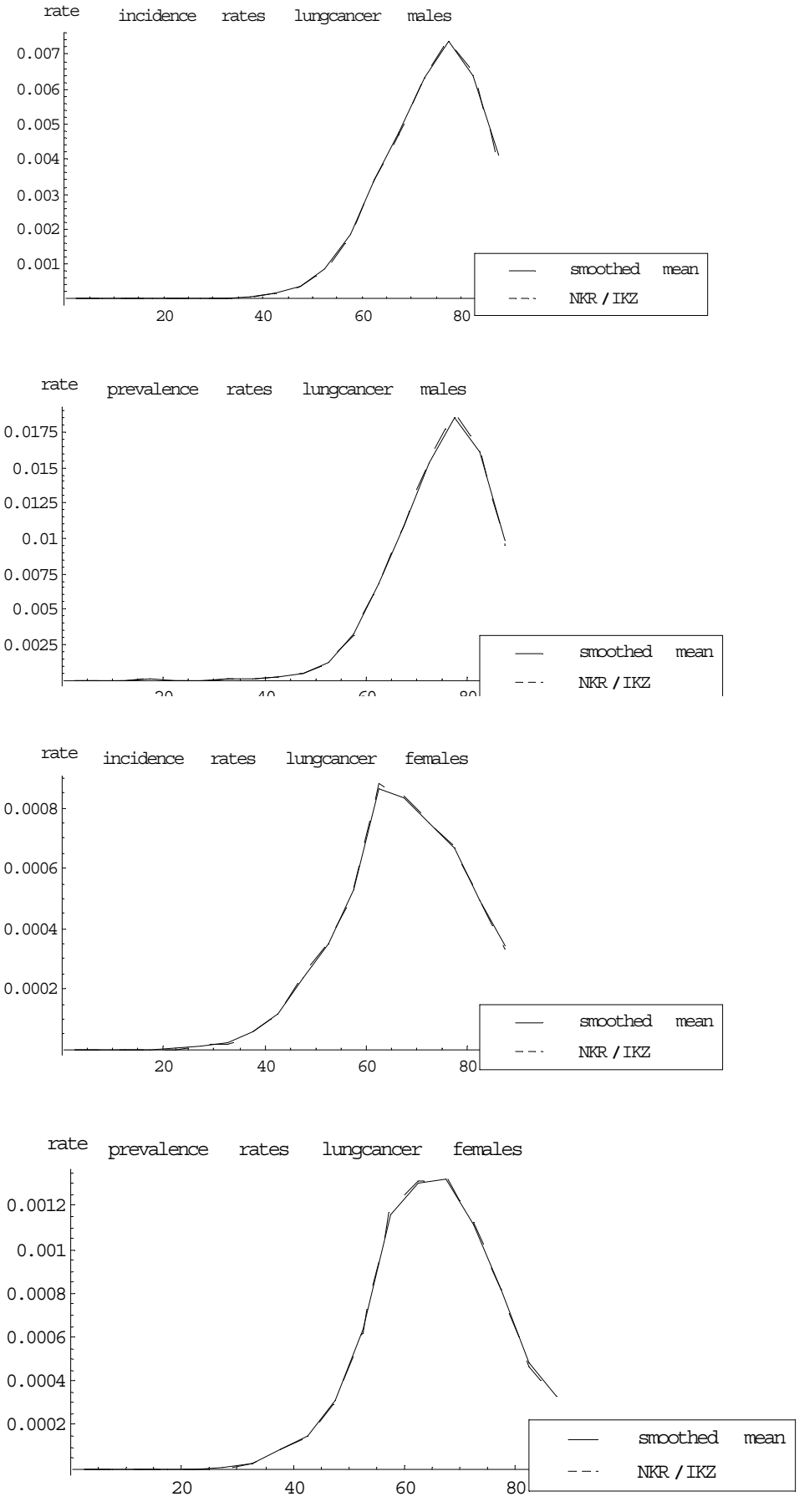
2.1 Lung cancer

Table 40 The 1994 lung cancer incidence and prevalence rates, together with the calculated age-specific values

1994	males				females			
	incidence		prevalence		incidence		prevalence	
	NKR	select	IKZ	select	NKR	select	IKZ	select
age:								
0-24	.00	.00	.00	.00	.00	.00	.00	.00
25-29	.00	.00	.00	.00	.01	.01	.00	.00
30-34	.01	.02	.02	.02	.02	.02	.03	.03
35-39	.06	.06	.05	.06	.05	.06	.08	.08
40-44	.16	.17	.15	.17	.11	.12	.14	.15
45-49	.36	.38	.45	.49	.24	.24	.30	.31
50-54	.80	.85	1.17	1.28	.35	.35	.62	.64
55-59	1.79	1.84	3.15	3.28	.52	.53	1.18	1.16
60-64	3.42	3.40	6.79	6.83	.88	.86	1.31	1.30
65-69	4.72	4.74	10.91	10.93	.84	.84	1.33	1.32
70-74	6.34	6.31	15.47	15.39	.75	.75	1.12	1.12
75-79	7.45	7.35	18.75	18.48	.67	.67	.82	.82
80-84	6.45	6.38	16.32	16.11	.49	.49	.47	.48
85+	3.95	4.10	9.50	9.91	.33	.34	.32	.33
population means:								
	.95	.96	2.10	2.11	.22	.22	.34	.34

Notes: incidence rates: /1000 pers.yrs, prevalence rates: /1000 pers., all data are zero for ages 0-24 except for 1994 prevalence males age 15-19 (.03), select: smoothed age-specific values

Figure 23 The 1994 lung cancer incidence and prevalence rates for males and females



2.2 Asthma and chronic obstructive pulmonary disease (COPD)

Table 41 The 1994 asthma and COPD incidence and prevalence rates, together with the calculated age-specific mean values

asthma	males						
	incidence (/1000 pers.yrs.)				prevalence (/1000 pers.)		
	CMR	Trans	RNH	select	CMR	Trans	select
age:							
0-4	11.33	22.89	22.13	16.66	8.09	14.21	13.66
5-9	6.64	8.38	7.33	9.76	26.56	16.37	20.30
10-14	4.84	5.55	3.90	5.61	44.26	14.79	25.30
15-19	5.37	4.08	2.38	4.04	26.32	6.94	18.68
20-24	1.97	3.85	2.30	2.90	19.71	5.03	13.11
25-29	.68	3.33	1.15	2.07	11.58	4.52	9.62
30-34	1.80	1.95	1.96	1.85	13.64	6.33	9.06
35-39	.87	2.39	1.84	1.62	5.22	6.90	7.31
40-44	.42	1.03	1.34	1.23	11.29	3.78	7.43
45-49	.49	2.28	1.14	1.33	12.19	4.55	7.76
50-54	1.16	1.55	2.19	1.61	8.13	5.69	6.63
55-59	1.29	3.33	1.44	1.90	2.58	3.33	4.75
60-64	.00	4.12	1.55	2.02	3.75	9.16	5.85
65-69	.82	5.01	1.65	2.35	5.73	7.32	6.75
70-74	.00	5.01	2.35	2.50	6.55	10.92	7.78
75-79	.00	7.34	1.59	2.62	1.95	10.67	7.19
80-84	.00	3.35	.98	2.21	.00	16.76	7.74
85+	.00	8.98	1.90	3.19	.00	14.36	7.38
population means:							
	2.48	4.88	3.53	3.76	13.80	7.88	11.00

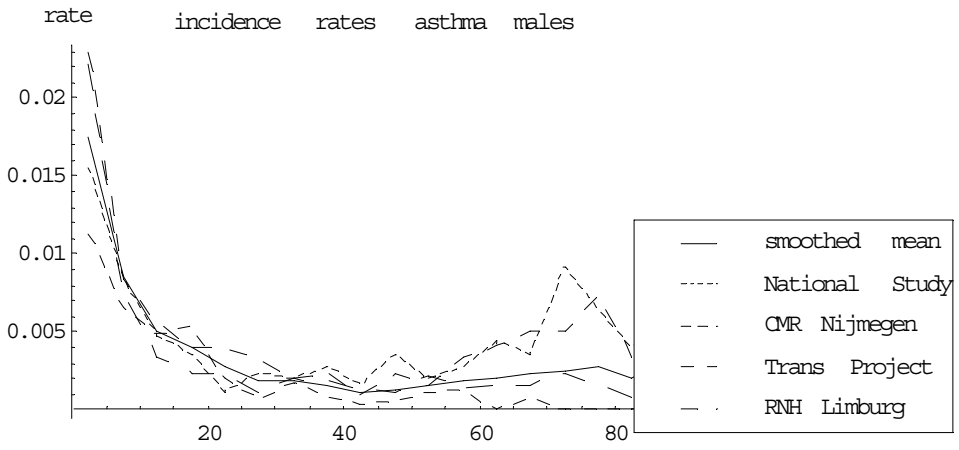
asthma	females						
	incidence (/1000 pers.yrs)				prevalence (/1000 pers.)		
	CMR	Trans	RNH	select	CMR	Trans	select
0-4	11.33	22.89	15.97	12.84	5.98	6.81	8.69
5-9	6.64	8.38	3.22	8.59	20.92	10.53	14.56
10-14	4.84	5.55	3.00	6.95	25.65	6.29	16.49
15-19	5.37	4.08	3.73	5.21	35.27	10.45	20.18
20-24	1.97	3.85	3.78	4.01	13.48	8.35	13.14
25-29	.68	3.33	2.51	3.34	17.59	7.96	12.68
30-34	1.80	1.95	2.26	3.08	17.08	6.91	11.95
35-39	.87	2.39	1.79	2.80	14.67	5.50	11.06
40-44	.42	1.03	1.77	2.78	20.04	7.90	13.00
45-49	.49	2.28	1.75	2.46	14.94	8.26	11.82
50-54	1.16	1.55	1.24	2.32	13.84	8.57	11.33
55-59	1.29	3.33	1.46	1.78	10.92	12.99	11.20
60-64	.00	4.12	1.38	1.71	5.65	9.90	8.77
65-69	.82	5.01	.79	1.97	8.59	11.48	9.01
70-74	.00	5.01	.53	2.00	4.39	6.92	6.32
75-79	.00	7.34	.76	1.90	1.18	8.16	5.27
80-84	.00	3.35	.75	2.00	6.81	4.99	5.70
85+	.00	8.98	1.14	1.95	6.54	4.61	5.61
poulation means:							
	3.50	5.37	2.95	4.01	15.04	8.22	11.76

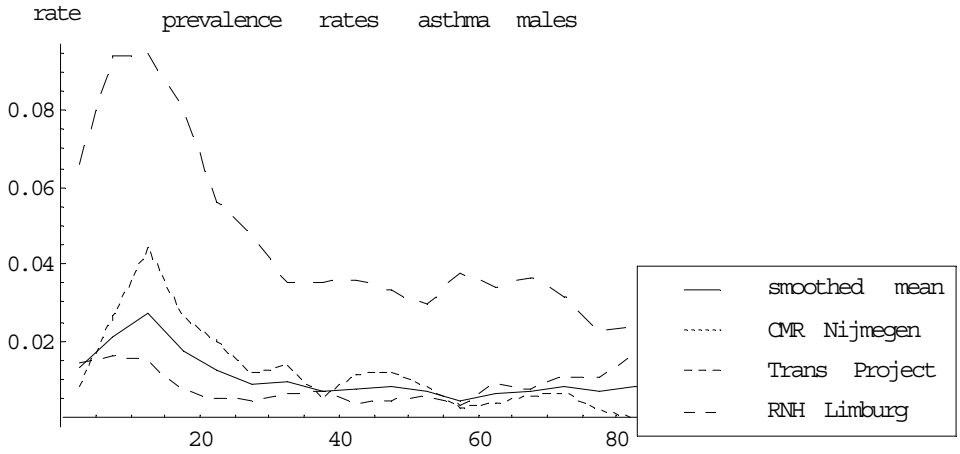
COPD	males						
	incidence (/1000 pers.yrs.)				prevalence (/1000 pers.)		
	CMR	Trans	RNH	select	CMR	RNH	select
age:							
0-4	.54	1.18	1.24	.86	1.62	5.14	4.80
5-9	.66	1.20	.00	.59	3.98	13.52	7.67
10-14	.00	.00	.15	.26	2.08	16.37	8.31
15-19	.00	.82	.32	.35	.00	12.85	7.04
20-24	.00	.89	.26	.37	1.97	10.65	7.05
25-29	.34	.48	.12	.36	8.52	9.41	8.57
30-34	.36	.24	.21	.46	7.54	9.89	9.29
35-39	2.17	.53	.51	.96	8.70	13.08	11.21
40-44	2.09	.34	.82	1.22	8.36	14.77	13.80
45-49	1.46	1.37	.80	1.76	16.09	20.68	21.09
50-54	4.64	3.62	1.75	3.47	29.03	34.57	34.23
55-59	9.03	3.81	4.31	5.51	52.88	43.22	52.92
60-64	7.50	5.95	5.17	7.01	77.99	83.50	83.40
65-69	17.19	8.48	8.62	10.74	121.15	122.21	121.09
70-74	10.91	11.37	12.93	12.13	138.53	170.35	156.96
75-79	23.36	14.01	11.94	14.87	190.79	229.60	201.27
80-84	9.05	14.53	6.38	11.34	235.18	219.68	211.22
85+	16.89	8.98	11.41	12.19	118.20	160.46	156.34
population means:							
	3.28	2.33	1.96	2.60	28.33	34.99	32.46

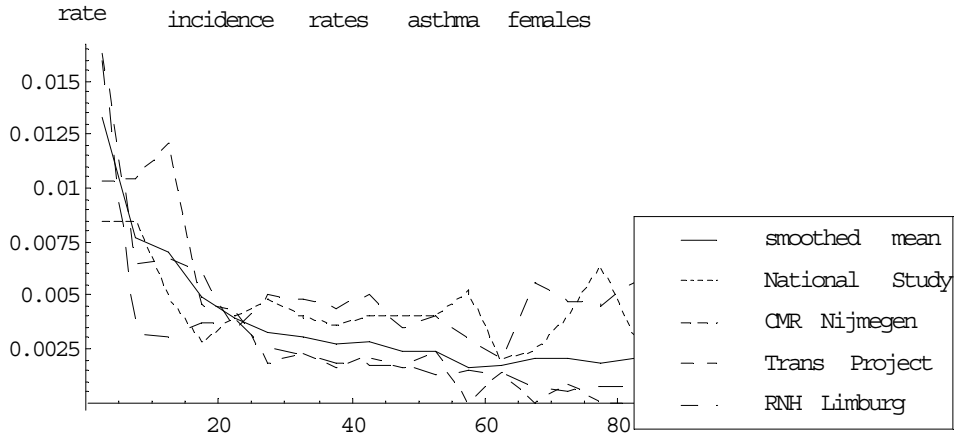
COPD	females						
	CMR	Trans	RNH	select	CMR	RNH	select
0-4	.00	.00	.33	.22	.00	3.46	3.09
5-9	.00	1.22	.44	.45	.00	13.91	5.87
10-14	.71	.45	.00	.47	.00	12.48	6.25
15-19	.57	1.49	.31	.67	3.41	8.19	6.65
20-24	.71	.28	.59	.58	12.06	8.79	8.91
25-29	.62	1.14	.11	.62	4.63	8.73	7.64
30-34	.66	.69	.10	.64	8.21	9.33	8.48
35-39	1.22	.55	.99	1.00	3.67	10.30	8.68
40-44	2.56	1.80	.67	1.55	12.37	12.71	12.64
45-49	1.07	2.17	1.38	1.79	19.20	14.41	16.85
50-54	3.61	2.71	1.70	2.67	19.26	23.22	21.18
55-59	5.78	3.77	1.46	3.55	14.78	31.69	25.36
60-64	7.06	3.17	1.99	4.01	31.77	36.84	35.33
65-69	7.03	2.95	2.69	4.24	47.65	53.96	48.46
70-74	5.27	4.73	3.36	4.51	50.89	58.75	53.21
75-79	4.72	7.25	3.78	4.97	43.63	57.54	51.99
80-84	3.40	4.98	3.73	4.35	62.97	47.10	55.82
85+	6.54	5.37	2.86	4.81	58.89	69.62	62.57
population means:							
	2.24	1.91	1.11	1.78	15.92	20.39	18.32

Notes: select: smoothed age-specific mean values

Figure 24 Asthma incidence and prevalence rates for males and females







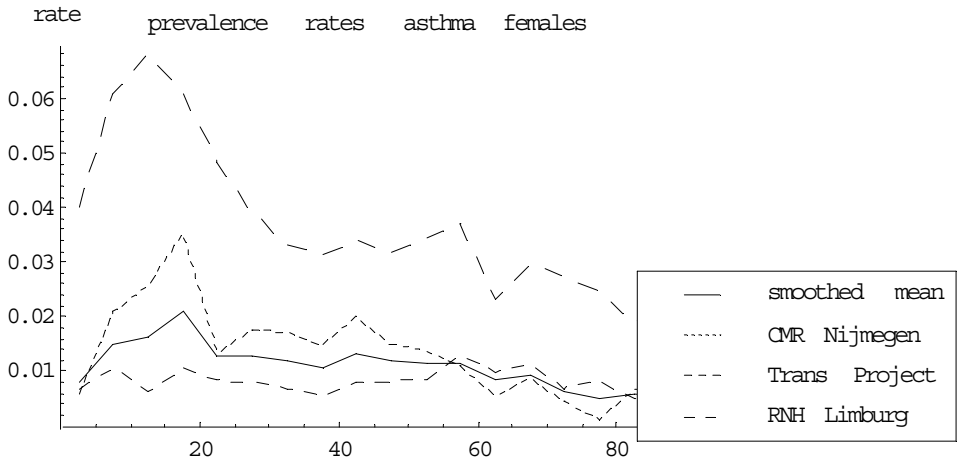
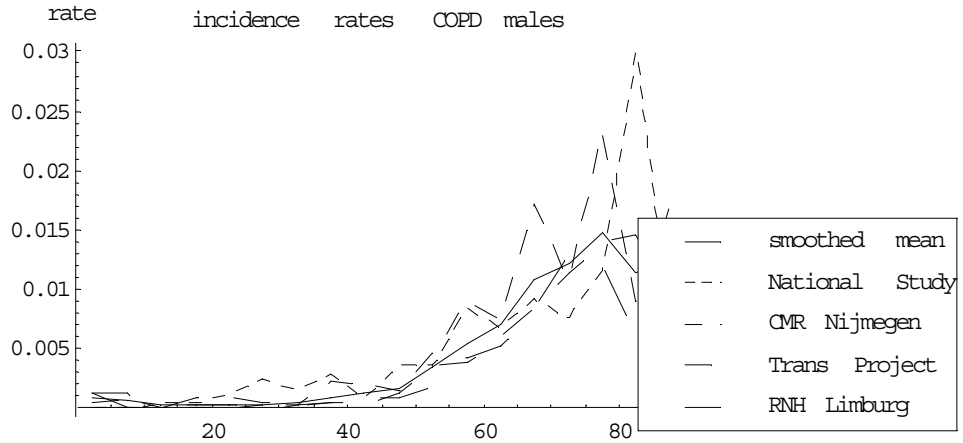
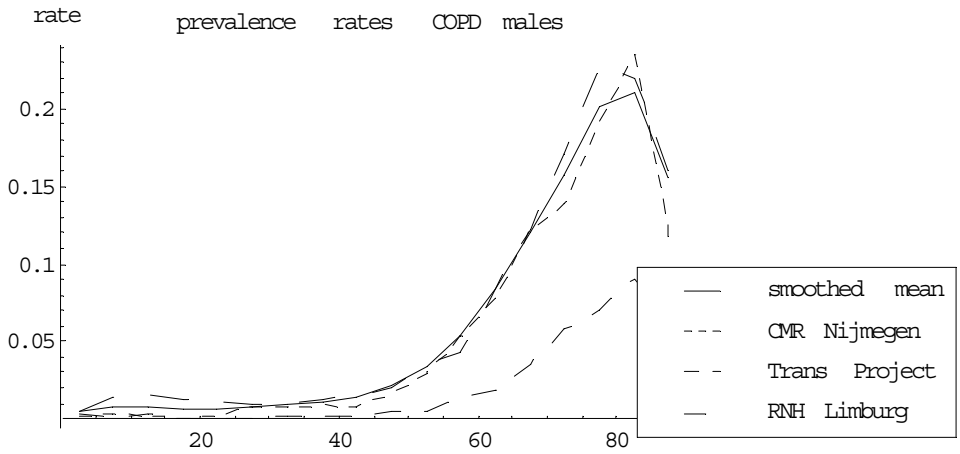
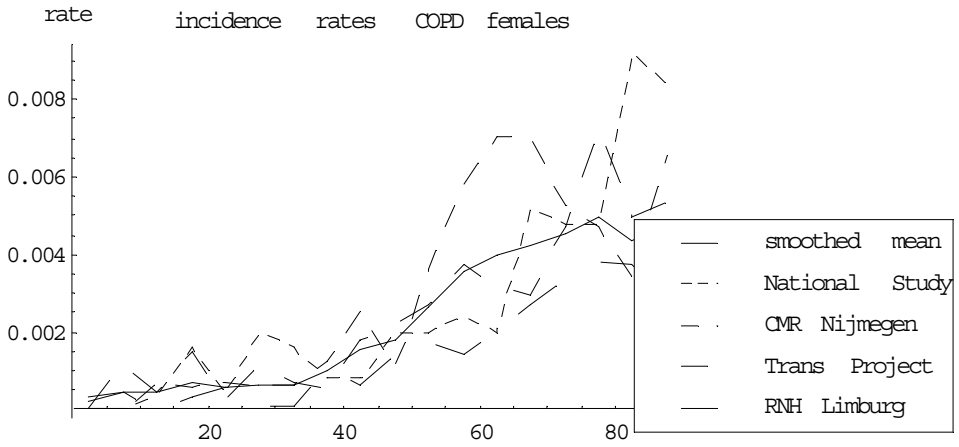
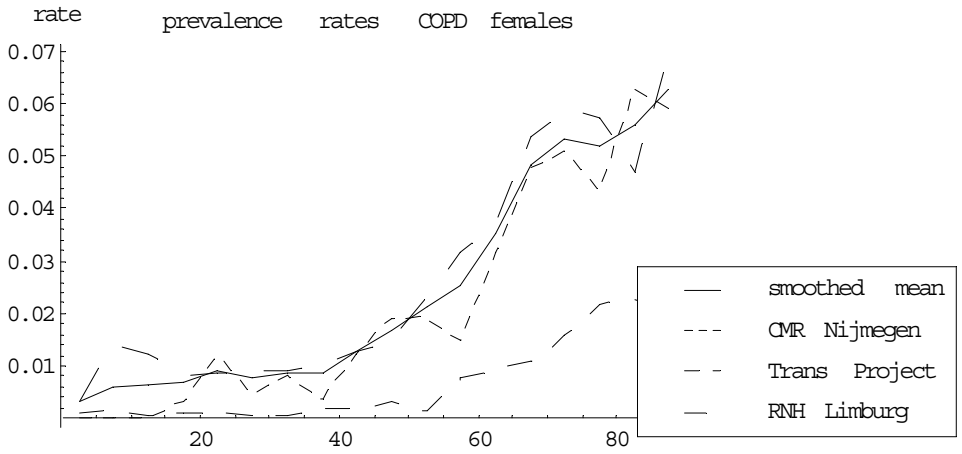


Figure 25 COPD incidence and prevalence rates for males and females



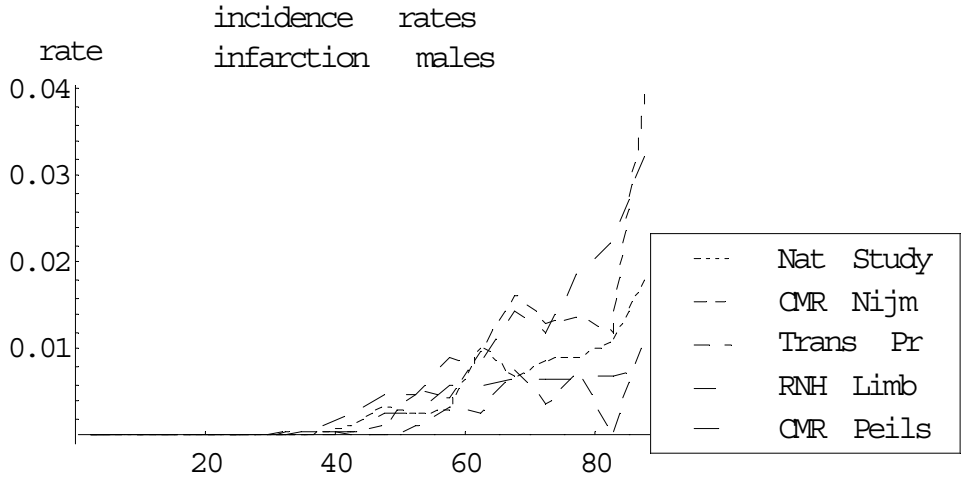


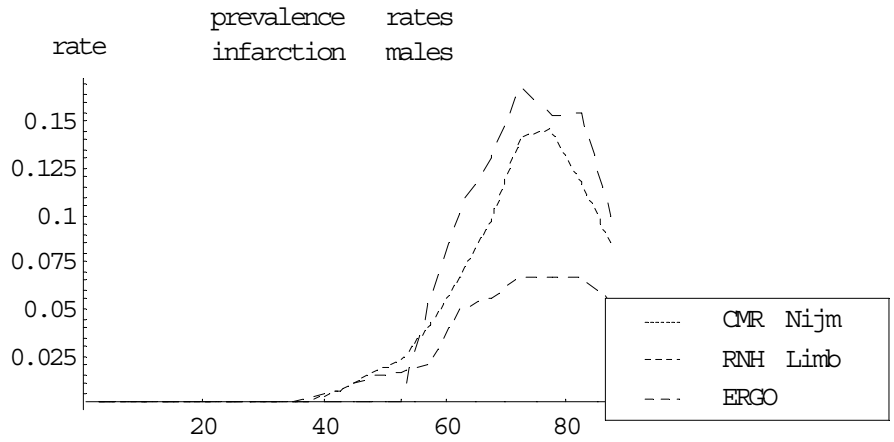


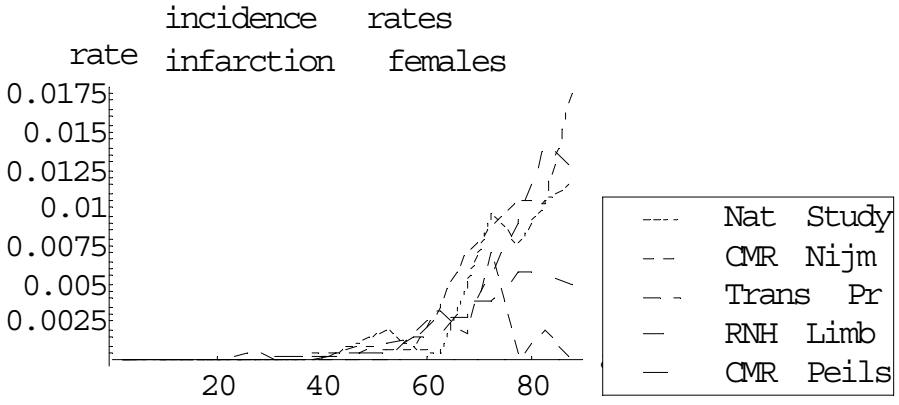


2.3 Coronary hearty diseases and congestive heart failure

Figure 26 The AMI incidence and prevalence rates for males and females




prevalence rates
rate
infarction males
0.15
0.125
0.1
0.075
0.05
0.025
20
40
60
80
CMR Nijm
RNH Limb
ERGO


incidence rates
rate
infarction females
0.0175
0.015
0.0125
0.01
0.0075
0.005
0.0025
20
40
60
80
Nat Study
CMR Nijm
Trans Pr
RNH Limb
CMR Peils

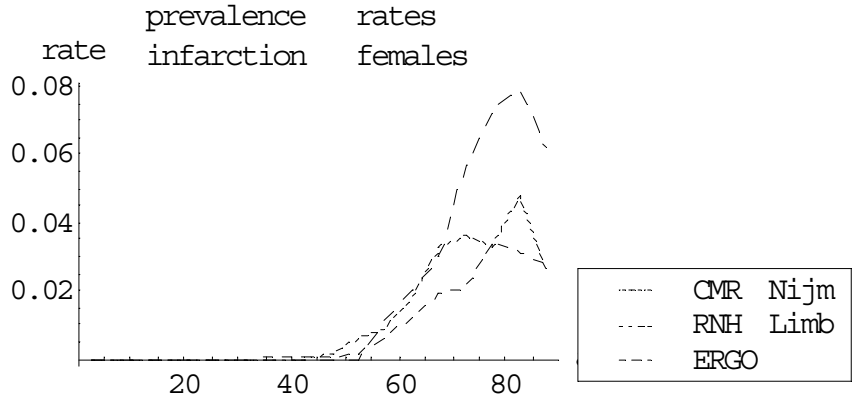

prevalence rates
rate
infarction females
0.08
0.06
0.04
0.02
20
40
60
80
CMR Nijm
RNH Limb
ERGO

Figure 27 The AP incidence and prevalence rates for males and females

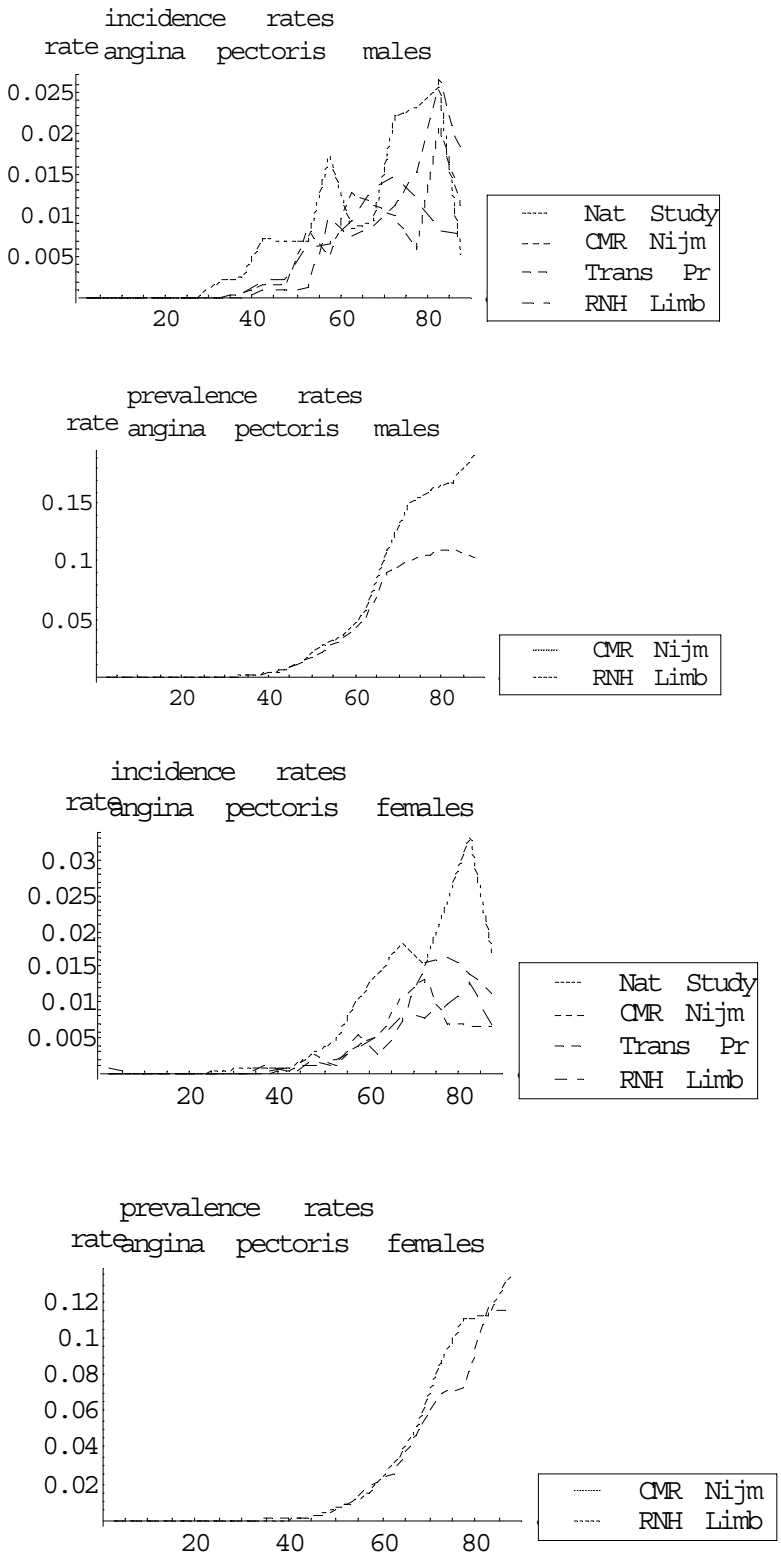
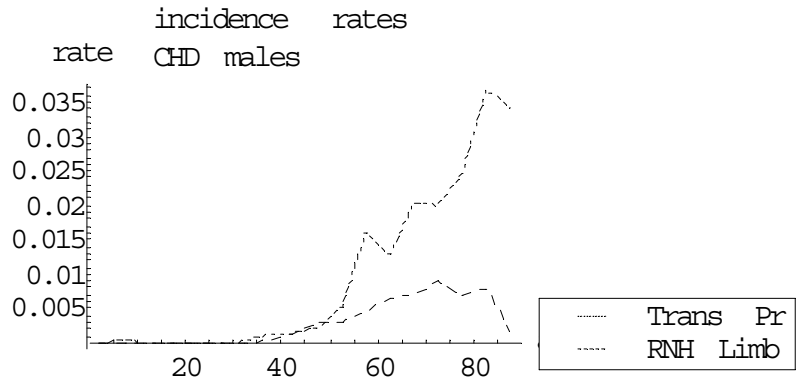
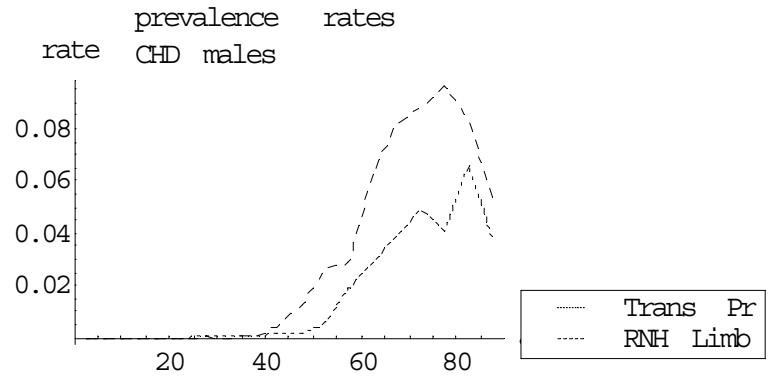
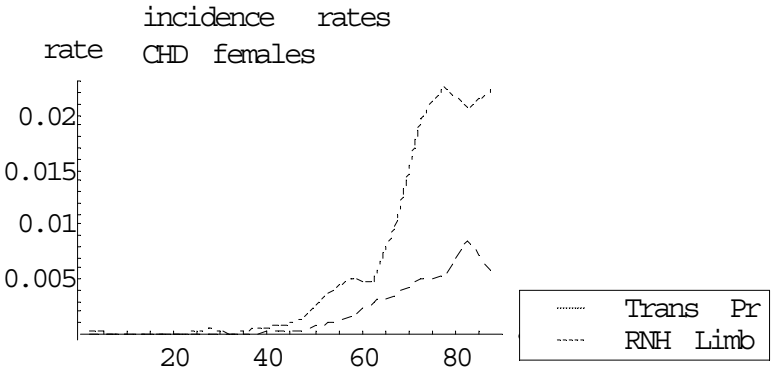


Figure 28 The incidence and prevalence rates for males and females, for other forms than AMI and AP







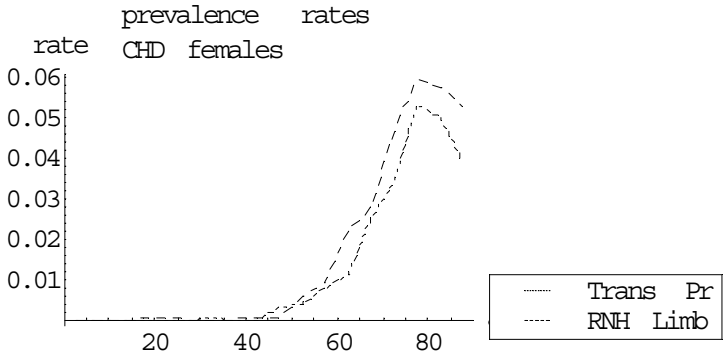


Table 42 The 1994 CHD incidence and prevalence rates, together with the calculated mean values

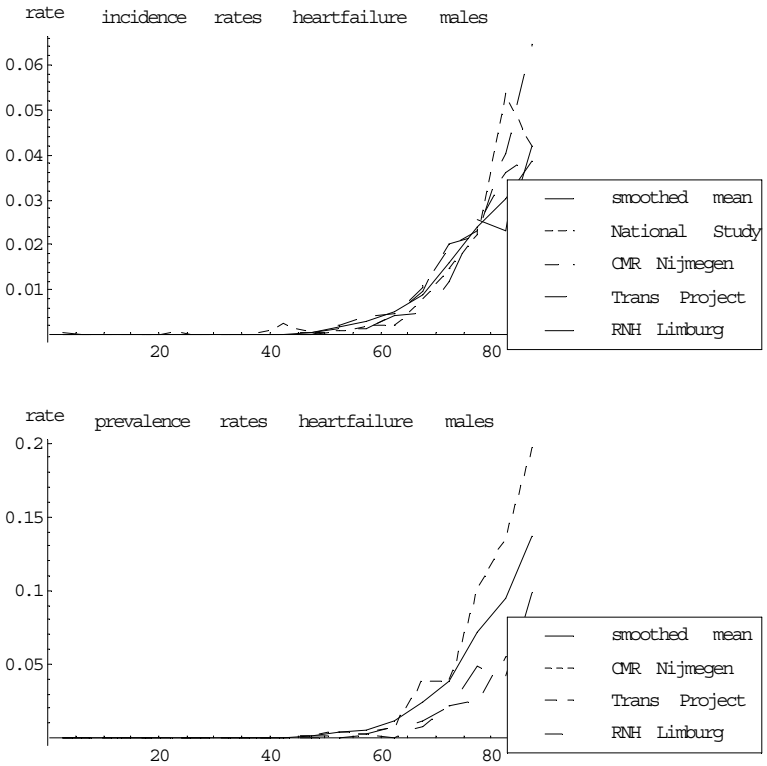
1994	incidence (/1000 pers.yrs.)			prevalence (/1000 pers.)		
AMI	males					
	CMR	RNH	select	CMR	RNH	select
age:						
0-19	0	0	0	0	0	0
20-24	0	0	0	0	.3	.1
25-29	0	0	.1	0	.3	.2
30-34	.4	0	.2	.4	.3	.5
35-39	0	1.0	.5	1.3	2.6	2.4
40-44	.4	2.1	1.3	6.7	9.1	8.2
45-49	1.5	4.2	2.8	16.1	20.1	18.0
50-54	5.2	4.0	4.6	22.1	29.4	26.2
55-59	4.5	7.6	6.1	41.9	35.6	40.2
60-64	9.7	7.5	8.8	66.7	82.0	73.7
65-69	16.4	12.3	13.9	96.6	96.7	96.9
70-74	13.1	10.2	12.0	142	112	126
75-79	13.6	16.2	14.8	146	115	129
80-84	12.1	19.0	16.5	118	108	112
85+	39.4	27.5	32.6	84.4	80.4	84.1
population means:						
	2.83	2.98	2.92	21.01	20.77	20.86
AMI	females					
	CMR	RNH	select	CMR	RNH	select
0-19	0	0	0	0	.0	0
20-24	0	0	0	0	.1	0
25-29	0	.1	0	0	.1	0
30-34	0	.2	.1	0	.1	.1
35-39	.4	.1	.2	0	.7	.3
40-44	.4	.3	.4	0	.5	.3
45-49	1.1	.4	.7	1.6	.6	1.3
50-54	.6	.9	.8	6.0	3.0	4.6
55-59	.6	1.1	1.0	9.0	8.5	9.1
60-64	3.5	2.5	3.0	17.6	18.2	18.1
65-69	7.0	2.4	4.8	32.8	26.1	29.1
70-74	8.8	5.0	6.9	36.0	32.5	34.3
75-79	10.6	7.7	9.1	33.0	49.1	41.0
80-84	10.2	12.0	11.2	47.7	45.7	45.8
85+	17.4	10.7	13.9	26.2	40.6	34.1
population means:						
	1.92	1.32	1.61	6.85	6.84	7.25
AP	males					
	CMR	RNH	select	CMR	RNH	select
0-14	0	0	0	0	0	0
15-19	0	0	0	0	0	0
20-24	0	0	0	0	0	.1
25-29	0	.1	.1	0	.0	.3
30-34	0	.1	.2	.4	.1	.9
35-39	.4	.5	.8	2.2	1.2	3.0
40-44	1.7	2.1	1.8	3.8	7.4	7.9
45-49	1.5	2.4	2.9	12.2	18.3	17.3
50-54	8.1	6.1	6.2	26.7	34.5	31.3
55-59	5.1	6.5	6.9	36.1	47.8	47.0
60-64	12.7	9.5	10.5	58.5	82.6	75.3
65-69	11.5	13.2	11.9	110	131	116

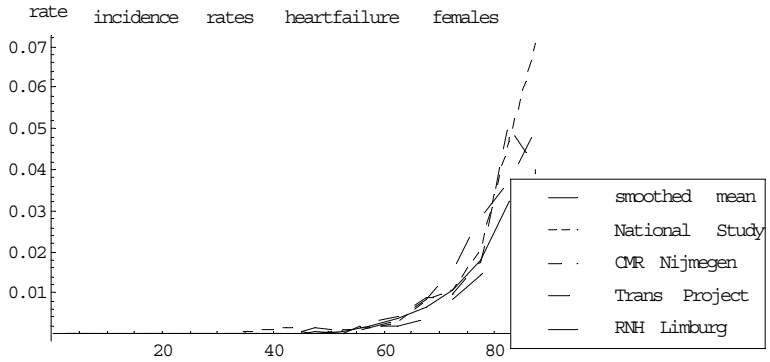
70-74	9.8	14.8	12.0	149	145	143
75-79	5.8	11.9	10.5	162	154	156
80-84	21.1	8.0	13.2	169	153	160
85+	11.3	7.6	10.4	191	129	160
population means:						
	2.75	2.83	2.86	22.59	25.22	24.41

AP	females					
	CMR	RNH	select	CMR	RNH	select
0-14	0	0	0	0	0	0
15-19	0	0	0	0	.1	.1
20-24	0	0	0	0	.3	.1
25-29	0	0	0	0	0	.1
30-34	0	0	.1	0	.1	.2
35-39	0	0	.3	0	.7	.7
40-44	.4	.2	.8	.4	1.2	1.9
45-49	2.7	.9	1.7	3.7	3.4	5.3
50-54	1.2	1.0	2.2	8.4	12.7	12.3
55-59	3.9	2.0	3.8	15.4	25.6	23.0
60-64	5.6	3.6	5.8	30.4	42.4	39.3
65-69	10.9	5.2	8.9	51.6	68.5	62.6
70-74	13.2	8.1	10.0	86.9	105	93.0
75-79	7.1	9.6	8.8	111	117	114
80-84	6.8	12.7	9.2	112	160	134
85+	6.5	6.9	7.3	135	154	143
population means:						
	2.24	2.06	2.18	17.19	21.71	19.81

Notes: select: incidence: smoothed age-specific mean values over two sources, with numbers from RNH Limburg times 0.85 (excluding second infarctions), prevalence: smoothed age-specific mean values over two sources, with for RNH Limburg including prevalence numbers for other CHD types distributed over AMI and AP with proportions 1:1 (males) and 1:3 (females).

Figure 29 CHF incidence and prevalence rates for males and females





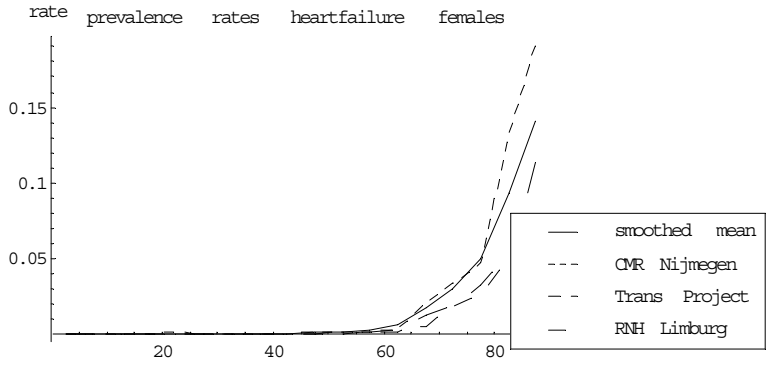


Table 43 The 1994 CHF incidence and prevalence rates, together with the calculated age-specific mean values

males	incidence (/1000 pers.yrs.)			prevalence (/1000 pers.)		
1994	CMR	RNH	select	CMR	RNH	select
age:						
0-4	.5	.2	.3	0	0	0
5-29	0	0	0	0	0	0
30-34	0	0	0	0.4	0	.2
35-39	0	.1	.1	0	.2	.3
40-44	0	.3	.3	0	.7	.7
45-49	0	.3	.6	2.0	1.2	1.8
50-54	2.3	1.5	1.9	4.6	2.2	3.5
55-59	3.9	1.8	3.2	2.6	3.2	5.1
60-64	4.5	4.1	5.2	8.2	7.7	11.4
65-69	10.6	4.8	9.1	38.5	11.7	25.0
70-74	19.6	11.8	16.1	39.3	21.0	38.3
75-79	23.4	25.9	24.1	101	48.5	71.4
80-84	36.2	23.1	30.3	136	40.4	94.3
85+	39.4	41.9	38.6	197	98.5	137
population means:						
	2.70	2.02	2.50	8.46	3.94	6.71

females	incidence			prevalence		
	CMR	RNH	select	CMR	RNH	select
0-14	0	0	0	0	0	0
15-19	0	0	0	0	0	.1
20-24	0	0	0	1.8	0	.5
25-29	.3	0	.1	0	0	.1
30-34	0	0	0	0	0	.1
35-39	0	0	0	0	.1	.1

40-44	0	.1	.1	0	.2	.3
45-49	0	.4	.3	1.6	.4	1.0
50-54	0	.2	.6	1.2	2.0	1.8
55-59	2.6	1.6	2.1	1.9	1.9	3.1
60-64	4.2	2.0	3.7	3.5	3.5	6.8
65-69	8.6	3.5	6.5	20.3	12.4	17.2
70-74	9.7	8.3	10.5	34.2	18.9	29.7
75-79	17.7	14.4	18.2	47.2	32.5	49.4
80-84	51.1	18.6	32.0	131	53.1	93.2
85+	39.3	31.4	34.7	192	113	141
population means:						
	3.55	2.15	2.99	10.86	6.04	8.95

Notes: select: smoothed mean values

2.4 Diabetes mellitus

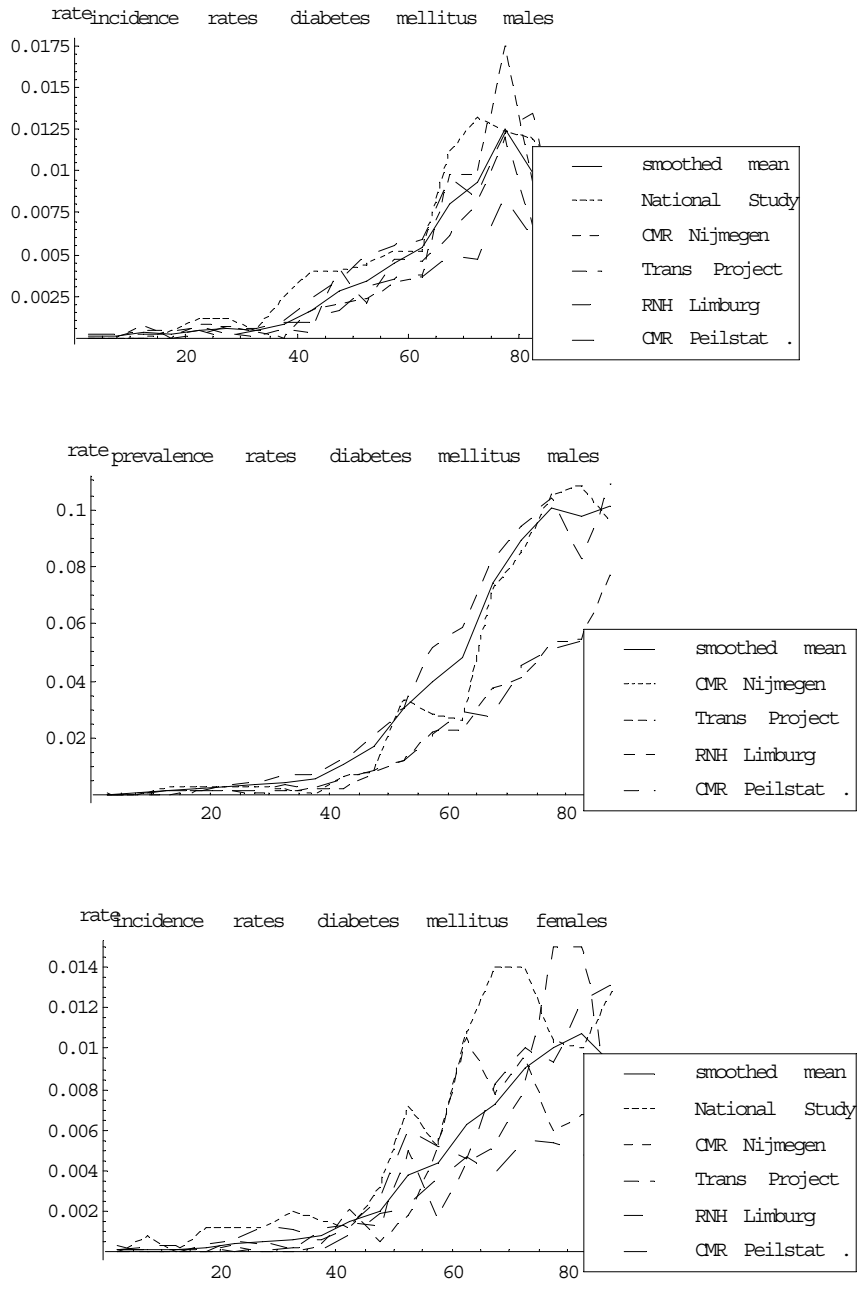
Table 44 The 1994 diabetes mellitus incidence and prevalence rates, together with the calculated age-specific mean values

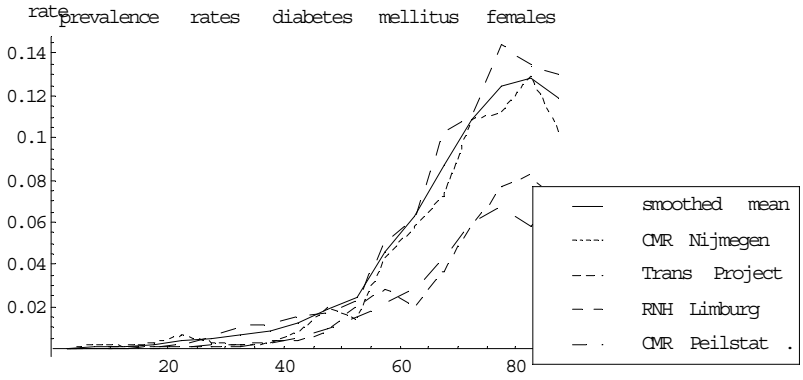
1994	incidence (/1000 pers.yrs.)					prevalence (/1000 pers.)		
	NS	CMR	Trans	RNH	select	CMR	RNH	select
age:								
males:								
0-4	.0	.0	.0	.0	.02	.5	.0	.4
5-9	.0	.0	.0	.0	.06	.0	.4	.6
10-14	.0	.7	.5	.0	.24	2.8	1.2	1.8
15-19	.4	.0	.4	.0	.30	3.2	1.4	2.4
20-24	1.2	.8	.6	.1	.58	2.8	3.2	3.0
25-29	1.2	.7	.2	.7	.65	3.1	4.3	3.8
30-34	.4	.4	.0	.5	.61	2.2	7.2	4.7
35-39	2.4	.0	.5	.9	1.16	.4	7.3	5.7
40-44	4.0	1.7	.3	2.4	2.12	6.7	12.5	10.5
45-49	4.0	2.0	4.1	3.4	3.15	8.3	20.0	17.1
50-54	4.4	2.3	2.1	5.0	3.65	33.7	30.7	30.6
55-59	5.2	3.2	4.8	5.6	4.67	28.4	51.9	39.9
60-64	5.2	3.8	4.6	5.9	5.63	26.2	58.4	48.4
65-69	11.2	9.8	6.2	9.5	8.70	72.0	82.3	74.0
70-74	13.2	9.8	8.2	8.5	10.16	85.1	94.3	88.9
75-79	12.4	17.5	12.1	12.3	12.47	105.1	103.9	100.8
80-84	12.0	9.0	6.7	13.6	10.41	108.5	83.1	97.6
85+	10.0	11.3	5.4	5.7	8.64	95.7	109.0	101.4
population means:								
	3.08	2.12	1.88	2.50	2.44	16.01	21.13	19.00
females:								
0-4	.0	.0	.5	.2	.17	.0	.2	.4
5-9	.8	.0	.0	.3	.23	2.2	.4	1.1
10-14	.0	.0	.0	.3	.20	1.4	.5	1.3
15-19	1.2	.0	.4	.0	.41	2.8	1.0	2.3
20-24	1.2	.4	.6	.7	.64	6.4	2.6	4.0
25-29	1.2	.0	.5	1.2	.74	3.4	5.6	4.8
30-34	2.0	.0	.2	1.2	.88	1.6	10.8	6.4
35-39	1.6	.4	1.2	.6	1.09	2.9	11.4	8.3
40-44	1.2	2.1	1.4	1.3	1.64	8.1	15.7	12.7
45-49	3.2	.5	1.3	2.6	2.44	19.7	17.4	18.7
50-54	7.2	1.8	5.0	6.0	4.47	14.4	22.7	24.9
55-59	5.2	5.1	1.7	5.2	4.97	43.0	51.0	45.6
60-64	10.8	10.6	4.4	4.6	7.32	57.9	61.9	62.5

65-69	14.0	7.8	5.2	8.2	8.79	72.6	103.0	87.0
70-74	14.0	9.7	8.0	10.1	10.12	108.8	111.3	108.6
75-79	10.4	5.9	15.0	9.3	10.24	112.0	144.3	124.9
80-84	10.0	6.8	15.0	12.3	10.72	129.3	134.5	128.6
85+	12.8	6.5	6.9	13.1	10.03	102.5	129.8	118.8
population means:								
	4.00	2.27	2.45	2.98	2.97	24.80	30.26	27.91

Notes: select: smoothed age-specific mean values

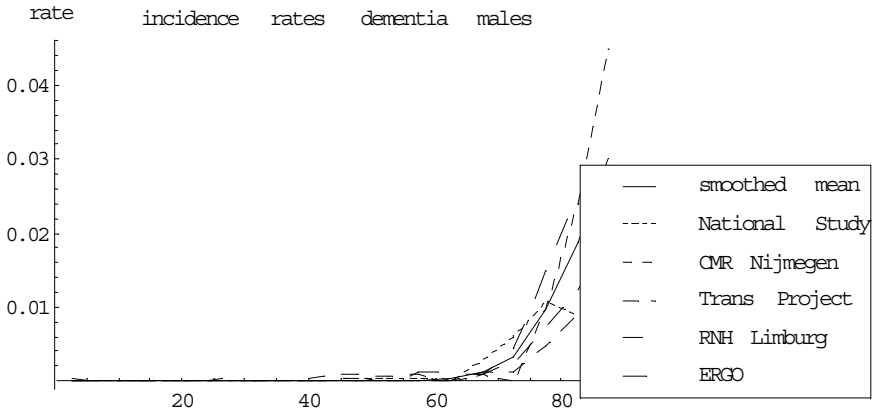
Figure 30 Diabetes mellitus incidence and prevalence figures for males and females, together with the calculated mean values

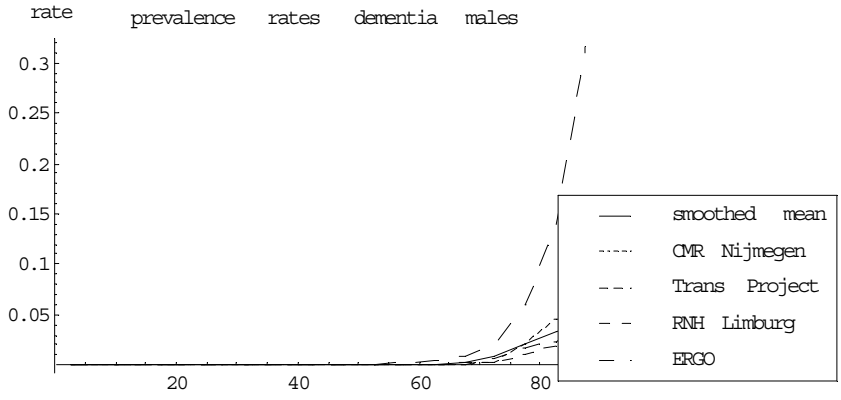




2.5 Dementia

Figure 31 Dementia incidence and prevalence figures for males and females





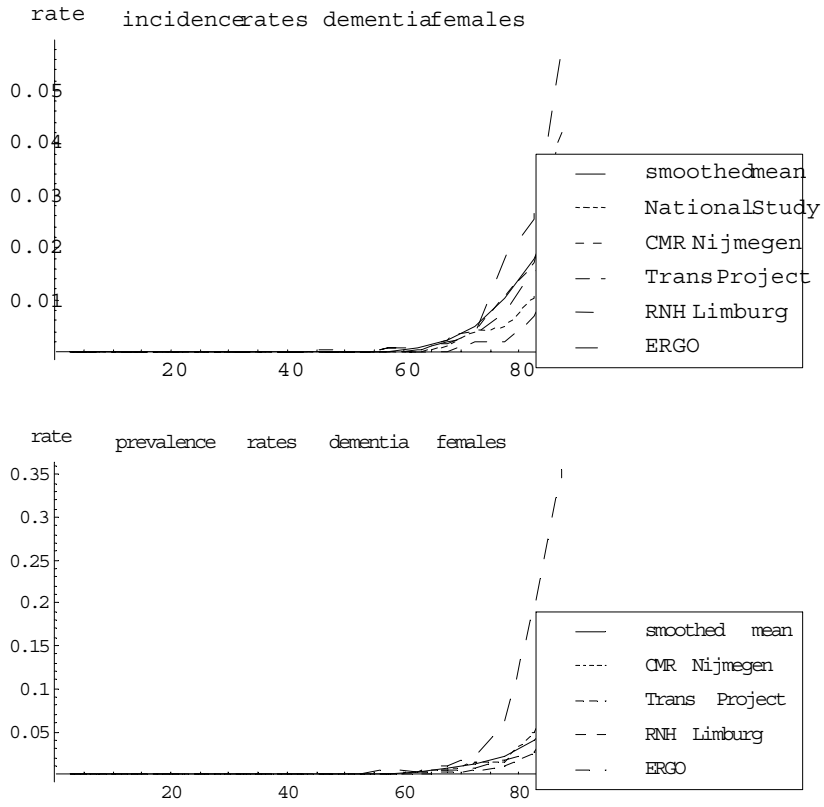


Table 45 The 1994 dementia incidence and prevalence rates, together with the calculated age-specific mean values

1994	incidence (/1000 pers.yrs)				prevalence (/1000 pers.)			
	CMR	RNH	ERGO	select	CMR	RNH	ERGO	select
age								
males								
55-59	0	0	1.1	.1	0	.2	2.0	.5
60-64	0	.2	1.1	.4	0	.6	4.8	1.5
65-69	.8	.9	.8	1.4	.8	1.1	8.0	4.5
70-74	0	2.4	4.5	3.3	3.3	6.4	20.3	13.5
75-79	9.7	7.6	14.8	9.7	21.4	17.6	60.3	34.0
80-84	24.1	12.0	25.1	18.8	45.2	23.5	137	56.4
85+	45.0	20.9	28.7	30.1	45.0	42.1	316	70.8
population means:								
	.84	.54	1.04	.80	1.38	1.17	6.15	2.47
females								
50-54	0	0	-	.1	0	.1	-	.8
55-59	0	0	.8	.2	0	1.0	6.0	1.9
60-64	0	.3	.8	.7	2.8	2.6	3.7	5.3
65-69	2.3	1.7	1.9	2.4	5.5	4.6	9.5	10.4
70-74	4.4	3.4	3.6	5.0	13.2	8.2	21.1	29.0
75-79	10.6	7.6	17.8	10.1	15.3	16.9	62.0	34.5
80-84	17.0	15.3	25.2	17.8	49.4	25.8	193	67.6
85+	43.6	23.4	58.3	30.4	82.9	70.8	356	115.8
population means:								
	1.81	1.26	2.52	1.65	4.05	3.16	14.70	6.42

Notes: all values 0 for ages<55 (males) and <50 (females) respectively; select: smoothed age-specific mean values, including patients in nursing homes

2.6 Stroke

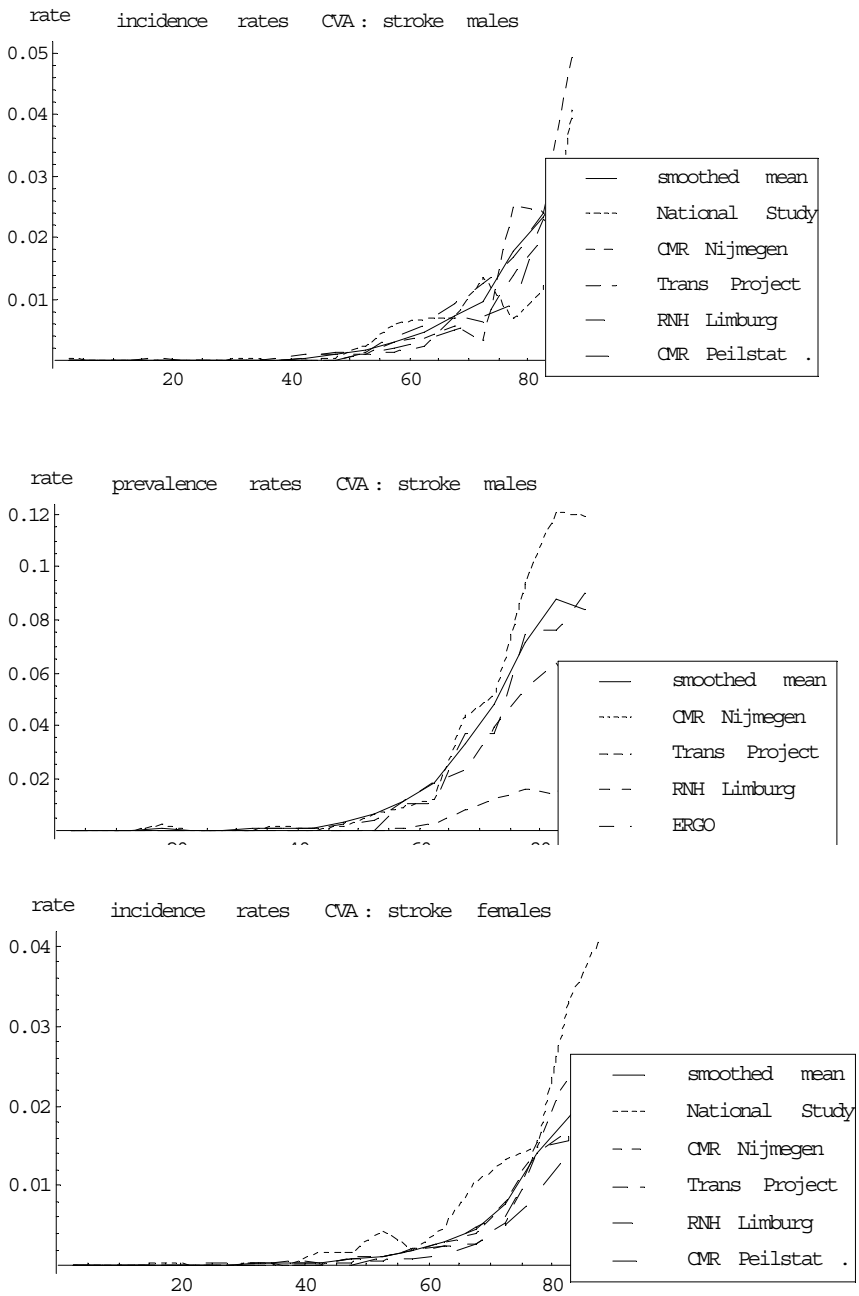
Table 46 The 1994 CVA incidence and prevalence rates, together with the calculated age-specific mean values

CVA	incidence (/1000 pers.yrs.)				prevalence (/1000 pers.)			
1994	CMR	Trans	RNH	select	CMR	RNH	select	
age:								
males:								
0-29	0	0	0	0	0	0	0	
30-34	.4	.3	0	.1	.4	.4	.5	
35-39	0	.3	0	.3	2.2	.7	1.1	
40-44	0	1.0	.5	.4	0	.9	1.1	
45-49	0	.9	1.5	.7	2.0	2.8	2.6	
50-54	1.2	1.0	1.3	1.4	6.4	4.0	5.5	
55-59	3.2	1.4	4.0	2.7	9.0	11.2	10.2	
60-64	3.7	2.3	5.9	4.3	12.0	18.2	17.2	
65-69	5.7	7.3	9.2	6.8	43.4	22.9	31.5	
70-74	3.3	6.4	12.5	9.3	51.3	39.6	47.0	
75-79	25.3	14.0	16.7	17.0	93.4	54.1	70.1	
80-84	24.1	20.1	23.9	23.2	57.3	63.9	86.6	
85+	50.7	19.7	30.4	32.0	202.6	47.1	84.3	
population means:								
	1.82	1.54	2.21	1.89	9.05	6.18	7.64	
females:								
0-29	0	0	0	0	0	0	0	0
30-34	.4	.3	0	.2	1.4	.7	.4	.4
35-39	0	0	0	.3	0	0	.2	.6
40-44	.5	0	.6	.4	4.0	1.7	2.2	1.8
45-49	0	1.1	.4	.7	2.4	3.7	3.6	3.4
50-54	0	1.2	.5	1.1	4.2	3.6	5.3	4.7
55-59	.7	1.9	2.1	1.9	6.1	10.3	4.0	7.2
60-64	.7	2.8	2.4	2.7	14.1	10.6	9.4	11.1
65-69	5.4	3.9	2.6	4.1	34.2	23.4	15.4	19.3
70-74	3.8	7.9	5.5	7.3	23.5	36.9	25.3	29.4
75-79	14.3	15.3	14.0	13.5	63.4	36.6	34.6	38.4
80-84	15.8	23.8	16.8	18.5	82.3	81.7	44.3	55.2
85+	38.6	24.0	22.3	23.2	108.7	58.9	38.7	50.6
population means:								
	1.97	2.33	1.90	2.13	9.69	8.23	5.92	7.02

TIA 1994 age:	incidence (/1000 pers.yrs.) CMR	Trans	ERGO	select	CMR	Trans	ERGO	select
males:					females:			
0-39	0	0	-	0	0	0	-	0
40-44	0	1.0	-	0	0	-	0	.1
45-49	0	0	-	.2	.5	.4	-	.3
50-54	0	.5	-	.4	0	0	-	.3
55-59	.6	1.0	8.1	3.1	0	.4	5.4	69
60-64	2.3	4.1	8.1	4.9	1.4	.8	5.4	1.5
65-69	.8	4.6	16.4	7.4	3.1	3.0	8.8	2.9
70-74	13.1	6.8	16.4	12.0	8.8	5.1	8.8	5.7
75-79	15.6	16.7	12.6	15.0	10.6	6.8	16.1	8.0
80-84	15.1	30.2	12.6	19.0	18.7	11.2	16.1	11.9
85+	10.7	11.3	19.7	17.9	17.4	17.7	16.4	14.5
population means:	1.15	1.46	2.41	1.70	1.66	1.25	2.40	1.32

Notes: select: smoothed age-specific mean values.

Figure 32 Stroke incidence and prevalence figures for males and females



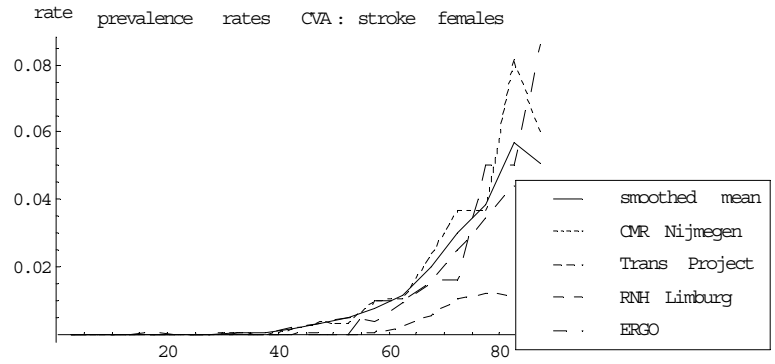
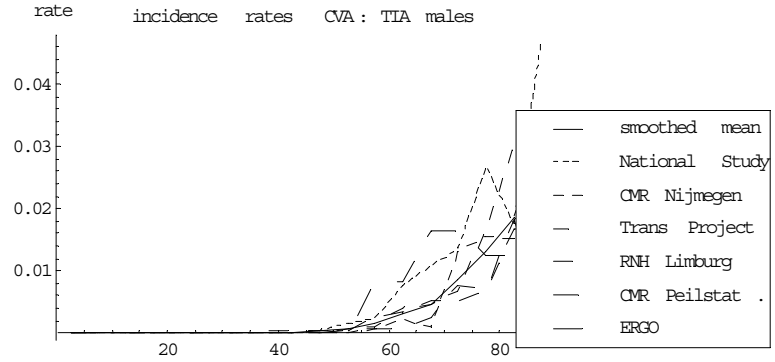
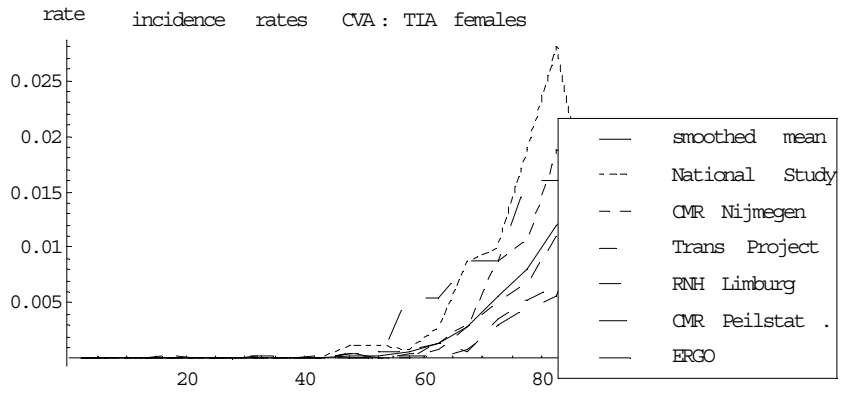


Figure 33 TIA incidence figures for males and females





2.7 All prevalence trends assumed

In *Table 47* the trends in the disease prevalence rates are presented that have been used for calculating the excess mortality and remission rates. They are calculated from time series of standardised disease prevalence rates. The sources used are the cancer registration (for lung cancer) and the only registration in the Netherlands with a sufficiently long registration time period (CMR Nijmegen, for all other diseases). The period chosen is the time period until 1994 that shows a stable trend.

Table 47 The trends in disease prevalence rates assumed (unit: %/year)

	males	females	period	source
lung cancer	0.7	2.3	1990-1994	IKZ
asthma	8	11	1984-1993	CMR
COPD	0	7	1984-1993	CMR
AMI	- 2	- 3	1987-1993	CMR
angina pectoris	3	- 1	1987-1993	CMR
coronary heartfailure	2	- 3	1989-1993	CMR
diabetes mellitus	3	2	1972-1993	CMR
dementia	8	8	1984-1994	CMR
stroke	- 2	4	1990-1993	CMR

Appendix 3 The chronic disease model equations

In this appendix the model equations used are formally derived.

3.1 The changes of the disease prevalence and total population numbers

Because the disease prevalence rates are the ratio of disease prevalence and total population numbers, the change of rates can be described from the change of numbers. We have omitted the dependency of all numbers on gender, age and time. The terms describing birth and migration have been omitted from the equation. Similar equations apply to new-borns, with starting age 0. In the current chronic diseases simulation model version it is assumed that immigrants have the same risk factor and disease characteristics as all inhabitants. So migration has effect on the total disease prevalence numbers, not on the rate values.

At first we have derived the chronic disease model equations for two cases, one case describing the changes of the prevalence numbers for two diseases simultaneously, the other case for only disease. To guarantee internal consistency of the model structure, we have required that the differential equations that describe the changes for one disease give the same results for both cases (see also the assumptions stated below). We present here the differential equations that describe the instantaneous change of the total population number and the prevalence number for one specific disease.

change of disease prevalence numbers

$$d/dt\ PREV_i = \Sigma_z\ inc_i(z)\ POP(z) - rem_i\ PREV_i - cf_i\ PREV_i -$$

$$\Sigma_{j,z}\ cf_j\ prev_j(z)\ PREV_i(z) - \Sigma_z\ mort_{oth}(z)\ PREV_i(z)$$

with terms:

instantaneous change of disease prevalence number $d/dt\ PREV_i$

inflow due to	
incidence	$\Sigma_z\ inc_i(z)\ POP(z)$
outflow due to	
remission	$rem_i\ PREV_i$
disease-specific excess mortality	$cf_i\ PREV_i$
mortality due to other ‘modelled’ diseases	$\Sigma_{j,z}\ cf_j\ prev_j(z)\ PREV_i(z)$
mortality due to remaining causes	$\Sigma_z\ mort_{oth}(z)\ PREV_i(z)$

with:	$PREV_i$	disease i prevalence number
	$prev_j$	disease j prevalence rate; so: $prev_j = PREV_j / POP$
	POP	total population number
	z	risk factors being distinguished
	inc_i	disease i incidence rate
	rem_i	disease i remission rate
	cf_i	excess mortality rate for person having disaease i
	$mort_{oth}$	risk factor-specific mortality rate for all remaining causes

change of total population numbers

$$d/dt\ POP = -\Sigma_{i,z}\ cf_i\ PREV_i(z) - \Sigma_z\ mort_{oth}(z)\ POP(z)$$

with terms:

instantaneous change of population number	d/dt POP
outflow due to mortality due to all 'modelled' diseases	$\Sigma_{i,z}\ cf_i\ PREV_i(z)$
mortality due to remaining causes	$\Sigma_z\ mort_{oth}(z)\ POP(z)$

Following the standard format the incidence rates refer to the total population, and not to the disease-free population. When using incidence rates that refer to the disease-free population a factor '1-$prev_i$' has to be added.

The main model assumptions are the following. (1) All diseases and mortality to the remaining causes are assumed independent conditional on gender, age and the covariable z. (2) Cause-specific mortality is assumed to be 'chronic' and so is assumed to be proportional to disease prevalence. 'Acute' mortality can be described analogously proportional to disease incidence. (3) The remission and excess mortality rates are assumed independent on risk factor status. (4) The excess mortality rate of patients with two diseases simultaneously is assumed to be the sum of the rates for patients with only the first and second disease respectively.

The latter assumption relates to the constraint on the chronic diseases model structure, that the change of the prevalence numbers for one disease has to be independent on which other diseases are described simultaneously. The specific assumption guarantees that the disease-specific excess mortality rates are independent on the other diseases described. If this assumption is not satisfied, the disease-specific excess mortality rates are dependent on the other diseases included in the model structure. The assumption affects the prevalence rates of the comorbidity disease states, not the marginal disease prevalence rates.

The mortality due to all other causes of death is calculated in the first year of the simulation period as: $mort_{oth}(z) = mort_{tot}(z) - \Sigma_i\, cf_i\, prev_i(z)$, with: $mort_{tot}$: empirical total mortality rate. The trend of the mortality rate for all other causes is given for the following years. The disease-specific excess mortality rates are generally larger than the registered cause-specific mortality rates. As a consequence the calculated rate of mortality due to all other causes is smaller than the empirical one. Using these equations the change of the disease prevalence rates can be calculated, taking into account the population heterogeneity described by the population risk factors:

change of disease prevalence rates

$$d/dt\ prev_i = d/dt\ (PREV_i/POP) = \{\ d/dt\ PREV_i - prev_i\ d/dt\ POP\ \} / POP\ =$$

$$E_z\ inc_i(Z) - cf_i\ prev_i\ (1\text{-}prev_i) - rem_i\ prev_i -$$

$$\Sigma_{j\neq i}\ cf_j\ \{\ E_z\ prev_i(z)\ prev_j(z) - prev_i\ prev_j\ \} -$$

$$\{\ E_z\ mort_{oth}(z)\ prev_i(z) - mort_{oth}\ prev_i\ \}$$

with terms:

change of disease prevalence rate	$d/dt\ prev_i$
change due to	
disease incidence	$E_z\ inc_i(Z)$
cause-specific mortality	$cf_i\ prev_i\ (1\text{-}prev_i)$
remission	$rem_i\ prev_i$
mortality due to	
other ‘modelled’ diseases	$\Sigma_{j\neq i}\ cf_j\{\ E_z\ prev_i(z)\ prev_j(z) - prev_i\ prev_j\ \}$
all remaining causes	$\{\ E_z\ mort_{oth}(z)\ prev_i(z) - mort_{oth}\ prev_i\ \}$

with: E_z: mean value over risk factor classes; e.g. $E_z\ inc_i(Z) = \int_z inc_i(z)\ dPOP(z) / \int_z dPOP(z)$.

The model equations of the change of the prevalence rates differ to those describing the change of prevalence numbers. (1) Introduction of the term ‘$1\text{-}prev_i$’ in the term describing the cause specific mortality. The reason is that cause-specific mortality results in both smaller disease prevalence and total population numbers. Therefore the relative decrease of the prevalence rate is smaller than that of the prevalence number. (2) In the terms describing the mortality to all other causes the effect of competing death risks due to joint risk factors becomes clear. The effect of dependent competing risks can also be interpreted in terms of comorbidity. Individuals belonging to high risk groups have higher disease risks, hence individuals with a disease have high probabilities of belonging to these high risk groups, and

thus persons having one disease have higher morbidity and mortality risks for all other diseases with joint risk factors (assuming all correlations are positive; see also Appendix 3.2).

3.2. Model simplifications

Under the extra assumption that the risk factor distribution in the disease prevalence equals that in the disease incidence, we can approximate:

$PREV_i(Z) / PREV_i = INC_i(Z) / INC_i \approx inc_{i0}\ RR(Z)\ POP(Z) / \Sigma_z\ inc_{i0}\ RR(z)\ POP(z) =$

$RM_i(Z)\ f(Z)$

$prev_i(Z) = PREV_i(Z)/POP(Z) \approx RM_i(Z)\ PREV_i\ f(Z) / \{\ f(Z)\ POP\ \} = prev_i\ RM_i(Z)$

with:

	$POP(Z)$	population number in risk factor class Z
	$PREV_i$	disease i prevalence number
	$f(Z)$	fraction of population in risk factor class Z
	inc_{i0}	baseline disease i incidence rate
	$RR_i(Z)$	relative risk for disease i, i.e. defined with respect to baseline risk
	$RM_i(Z)$	risk multiplier for disease i, i.e. defined with respect to mean risk

Substituting these relations in the terms of the model equation for the change of the disease prevalence rate results in:

With respect to incidence:

$$E_z\ inc_i(z) = \Sigma_z\ inc_{i0}\ RR_i(z)\ f(z) = \Sigma_z\ inc_i\ RM_i(z)\ f(z)$$

With respect to mortality for all other specific causes:

$$\Sigma_{j\neq i}\ cf_j\ \{\ E_z prev_i(z)\ prev_j(z) - prev_i\ prevj\ \} \approx\ prev_i\ \Sigma_{j\neq i}\ cf_j\ prev_j\ \{\ E_z RM_i(z) RM_j(z) -1\ \}$$

With respect to mortality for al remaining causes:

$$\{\ E_z\ mort_{oth}(z)\ prev_i(z) - mort_{oth}\ prev_i\ \} \approx mort_{oth}\ prev_i\ \{\ E_z\ RM_{oth}(z)\ RM_i(z) - 1\ \}$$

All disease risks are positively correlated, when the joint risk factors cluster (are positively correlated) and increased risk factor levels result in increased disease risks. These correlations are described by the terms $\{\ E_z\ RM_j(z)\ RM_i(z) - 1\ \}$. The correlations can also be interpreted in terms of comorbidity: they describe the excess comorbidity of disease j conditional on having disease i (or vice versa). Ignoring the positive correlation results in

overestimating the excess mortality rates, ceteris paribus. This systematic error is of course only numerically important in case of high mortality risks.

The term describing the mortality for all 'modelled' causes of death has the same format as the one describing the mortality for all remaining causes. The difference is that in the former case the mortality rate is written as the product of the disease prevalence rate and the excess mortality rate. The equation shows that, given disease incidence, remission and prevalence data, all excess mortality rates theoretically only can be estimated simultaneously because of the dependency structure due to joint risk factors. Again, this theoretical result has only numerically significant effects in case of high mortality risks.

Finally, assuming independent risks, and thus omitting the dependency relations through joint risk factors, the model equations simplify enormously:

$d/dt\ prev_i = inc_i - rem_i\ prev_i - cf_i\ prev_i\ (1-prev_i)$

This equation has been used for our consistency analyses. Note that the excess mortality rate after the model simplification describes the difference between the mortality of any patient with any person without the disease, for given gender and age. In the original model equations (see §B.1) the conditioning was also on all covariables. In another report (Hoogenveen et al., 1999) we describe the consequences of this difference in more detail.

3.3. Time trends in disease incidence, prevalence and mortality

We show how the DisMod model equation can be used to deal with two aspects of time trends: (1) adjustment of the calculated excess mortality rates for given time trends, and (2) comparing time trends in disease morbidity and mortality.

The DisMod model equation (formula (1), §1.4) describes the change of the disease prevalence rate of a cohort. That means, the change over time includes the change over age. So the mathematical model equation admitting time trends becomes:

$$d/dt\ prev = \delta/\delta t\ prev + \delta/\delta a\ prev\ da/dt$$

with:
- d/dt the so-called total differential over time
- $\delta/\delta t$ the so-called partial differential with respect to time, keeping the age constant
- $\delta/\delta a$ the partial differential with respect to age
- da/dt the change of age over time; $da/dt=1$

The term $\delta/\delta t$ prev can be interpreted as the autonomous change of the prevalence rate over time, the term $\delta/\delta a$ prev as the autonomous change over age. As a consequence, to calculate the excess mortality rates, we have to adjust the prevalence rates (available from cross-sectional studies) for the time trend. In our analyses the time trend has been estimated from time series of standardised disease prevalence rates. We have assumed that the empirical time trend is the same for all ages. This assumption can be questioned for several diseases, for example for coronary heart diseases where age-specific trends differ due to different past smoking histories of middle-aged and elderly women.

The relation that describes the change of the disease prevalence rate for a cohort can also be used to describe how different model input parameters (incidence and excess mortality rates) affect the disease prevalence rate. We present the model equations (1) and (2) (§1.4) including two extra model parameters, and assuming no remission:

$$d/dt\ prev_i(t;\alpha,\beta) = inc_i\ (1+\alpha) - cf_i\ (1+\beta)\ prev_i\ (1-prev_i)$$

$$mort_i(t;\alpha,\beta) = cf_i\ (1+\beta)\ prev_i(t;\alpha,\beta)$$

with: α, β: proportional change in incidence and excess mortality rate respectively; $prev_i(0;\alpha,\beta)=prev_{i0}$ given initial prevalence rate. Then the first order sensitivity of the prevalence rate to the incidence and excess mortality rate can be calculated:

$$Dprev_i(t;\alpha,\beta) \equiv prev_i(t;0,0)/prev_i(t;\alpha,\beta)-1 \approx \alpha\ inc/prev_{i0}\ t - \beta cf_i\ (1-prev_{i0})\ t$$

$$Dmort_i(t;\alpha,\beta) \equiv mort_i(t;0,0)/mort_i(t;\alpha,\beta)-1 \approx Dprev_i(t;\alpha,\beta) + \beta$$

with: $Dprev_i(t;\alpha,\beta)$, $Dmort_i(t;\alpha,\beta)$: relative sensitivity of calculated prevalence and mortality rate to the incidence and excess mortality rate respectively, t: small time. The results can be interpreted easily. The relative change of the prevalence rate of the cohort is proportional to the relative change of the incidence rate (with proportionality factor equal to the relative contribution of the incidence to the prevalence) and minus the relative change of the excess mortality rate (with proportionality factor almost equal to the excess mortality rate). The relative change of the mortality rate is equal to the relative change of the excess mortality rate plus the relative change of the prevalence rate. So a decrease of the excess mortality rate has two opposite effects on the mortality number: one direct positive effect (decreasing mortality rates), and one indirect negative effect (increasing prevalence rates). Note that the trends over time are assumed equal for all ages here.

3.4. Disease duration time and mortality hazard ratios

3.4.1 Disease duration

The model equations can be used to calculate mean disease duration time periods. The calculation method is the well-known life table method, that is used to calculate life expectancy figures from total mortality rates. The disease duration is defined for any patient, with the hazard rate being the sum of the excess mortality rate, the mortality rate for all other causes and the remission rate.

3.4.2 Mortality hazard ratio

Mortality hazard ratios can be calculated from the excess mortality rates. We assume that all cause specific mortality is 'chronic' and so is proportional to the disease prevalence. Then the total mortality can be described as:

$$mort_{oth} = mort_{tot} - cf_i\ prev_i$$

with: $mort_{tot}$ total mortality rate
$mort_{oth}$ mortality rate for all other causes than disease i

Then the mortality hazard ratio for disease i can be written as:

HR_i = { mortality rate for patient } / { mortality rate for person free of disease i } =

$$\{ mort_{oth} + cf_i \} / mort_{oth} \approx 1 + cf_i / \{ mort_{tot} - cf_i\ prev_i \}$$

with: cf_i: disease i excess mortality rate. The hazard ratio is conceptually comparable to relative risks. When the disease does not result in increased mortality risk, the HR equals 1. One has to take good notice in case of age-specification. In most studies follow-up studies age is measured at the start of the study. In the model equation above the age parameter refers to the time at death.

3.5. Model sensitivity analysis

We show the sensitivity of the model outcome variables to the model input parameters. We use the first order derivatives, based on model equation (1) (see par 1.4) to calculate the sensitivity relations. Then we find in first order approximation:

$$\delta cf / \delta trd = \delta cf / \delta rem = - (1\text{-}prev)^{-1}$$

$$\delta rem / \delta cf = \delta rem / \delta trd = \quad - (1\text{-}prev)$$

with: prev, cf, rem: prevalence, excess mortality and remission rate respectively, trd: annual relative change of prevalence rate. These formulas show that the variation of the calculated excess mortality rates is almost equal to the variation of the (given) remission rates and annual prevalence time trends. In other words, errors in given remission rates and prevalence time trends result in the same absolutely-valued errors in the calculated excess mortality rates.

Appendix 4 Smoothing the data

All disease incidence, prevalence and mortality data are specified by gender and five-year age classes. All data have been smoothed over age before making the calculations. There are two reasons for smoothing the data. (1) The mathematical equations of the chronic diseases simulation model describe changing population and disease prevalence numbers for cohorts. So the one-year calendar time step has to fit to a one-year age-interval. (2) The excess mortality rates that have been calculated are proportional to the difference of the disease prevalence rates over an age-interval. So they are very sensitive to errors in the prevalence data. Data smoothing reduces the fluctuations due to random errors.

Many methods to smooth time (age)-series of data are known (Hastie, Tibshirany, 1996). We have chosen the penalty-method for several reasons. (1) It can easily be implemented and applied. (2) It can easily be extended to more dimensions in case time-series of age-dependent data are available, for example from CMR Nijmegen. (3) The method is flexible meaning that the curve may have any form over age. (4) We can choose gradually between a rough curve that fits the data well and a smooth curve that fits the data badly, using the so-called penalty coefficient. We give a short mathematical presentation of the penalty smoothing method.

A target function has to be minimised that consists of two terms. Term 1 describes the model fit and is the weighted sum of squares of the differences between smoothed and data points. Term 2 describes the ‘roughness’ of the curve and is the sum of n-th order differentials between successive smoothed points. In mathematical form:

$\min_z (z-x)' W (z-x) + \beta z'Dz$

with:
- x raw data points given
- z smoothed points to be calculated
- W weighting matrix
- β penalty coefficient
- D smoothing matrix

For most chronic diseases, minimum rate values are found over a large interval of the lower ages, and maximum rate values are found for only small age intervals or for the highest ages. We have introduced the weighting matrix W to prevent the maximum rate values from flattening off. The matrix W is diagonal with diagonal elements chosen equal to the ratio of the x-value to the maximum x-value. The smoothing matrix D is symmetric and describes the n-th order differences between successive points of the curve. The matrix element values depend on the order of differentiating chosen. For example, in case of order 0 large values are

penalised, if n=1 differences from a constant value are penalised, and if n=2 differences from a straight line (linear curve) are penalised. In mathematical form:

0^{th} order difference $\Delta^0 z_i = z_i$
1^{st} order difference $\Delta^1 z_i = z_{i+1} - z_i$
2^{nd} order difference $\Delta^2 z_i = \Delta(\Delta z_i) = \Delta(z_{i+1}-z_i) = \Delta z_{i+1} - \Delta z_i = z_{i+2} - z_{i+1} - z_{i+1} + z_i = z_{i+1} - 2z_{i+1} + z_i$

with: i: index of successive data points. For our calculations we have chosen order n=1. The penalty coefficient β governs the exchange between a good model fit and a smooth curve. When $\beta=0$ the model equals the data, when $\beta=\infty$ the model equals the linear regression curve through the data points (for n=2). Matrix theory shows that the model solution z can be calculated directly:

$$z = (W+\beta D)^{-1} W x$$

One problem regarding smoothing methods is that random fluctuations around a clear trend have to be eliminated, but that systematic global minimum and maximum values have to be kept. The larger the smoothing penalty coefficient is chosen, the more both the random and systematic fluctuations will be flattened. The smoothing penalty coefficient is chosen such that systematic fluctuations are preserved, but random fluctuations are eliminated as far as possible. In the literature methods have been described that 'automatically' find penalty coefficients that meet both criteria best. They are based on the interpretation of smoothing in terms of linear regression (Hastie&Tibshirani, 1990). One method of choosing the smoothing parameter β is to minimise the cross-validation sum of squares:

$$\Sigma_i (x_i - z^{-i}{}_i(\beta))^2$$

with: $z^{-i}{}_i(\beta)$ the point i estimate using all data but the i-th data point. We have applied this method to the disease incidence and prevalence data. However, the resulting smoothed lines were not very satisfactory. One possible explanation might be that the random errors are not normally distributed. Therefore we chose to use fixed penalty parameters, with value 0.1 in case of lung cancer, and value 0.5 for all other diseases.

Appendix 5 Comparing incidence and prevalence ratios for dementia

We have found that the prevalence rate ratios of ERGO data (population study) to the other studies (registrations in general practice) are larger than the incidene rate ratios. This can be explained by a simple mathematical model. We consider two groups of patients, those registered in ERGO, and those registered in general practice. The following assumptions are made. (1) For both groups incidence rates increase exponentially over age, with the same coefficient but with different multiplicative constants (proportional hazards). (2) Mortality rates are independent on age, but with different values.

Mathematically, for group i on age t:

Incidence rate $C_i \exp(\alpha t)$

Prevalence rate = accumulation of past incidence rates adjusted for survival =

$$\int_0^t C_i \exp(\alpha u) \exp(-\mu_i(t-u)) \, du = C_i \{ \exp(\alpha t) - \exp(\mu_i t) \} / (\alpha+\mu_i)$$

with: $C_1>C_2$: incidence proportional coefficients, α: coefficient of age-dependency, $\mu_2>\mu_1$: mortality hazard rates. Then the two ratios are, dependent on age t:

ratio of incidence rates C_1 / C_2

ratio of prevalence rates $\{C_1/ C_2\} \{(\alpha+\mu_2)/(\alpha+\mu_1)\}$
$\{(\exp(\alpha t)-\exp(\mu_1 t)) / (\exp(\alpha t)-\exp(\mu_2 t))\}$

For t sufficiently large the 3rd term of the prevalence rates ratio approaches 1. The 2nd term is larger than 1, so the prevalence rates ratio is larger than the incidence rates ratio.

Appendix 6 Symbols and abbreviations

AD	Alzheimer-type dementia
AMI	acute myocardial infarction
AP	angina pectoris
CBS	Statistics Netherlands
CHD	coronary heart diseases
CHF	congestive heart failure
CMR	Continuous Morbidity Registration (in general practice)
COPD	chronic obstructive pulmonary diseases
CVA	cerebrovascular accidents
CVD	cardiovascular diseases
DM	diabetes mellitus
ERGO	Rotterdam Study (Erasmus Rotterdam Health in the Elderly)
GB	Great-Britain
GP	general practice
ICD	International Classification on Diseases
IDDM	insulin-dependent diabetes mellitus
IKZ	Integral Cancer Institute South
LOK	National Committee on Cancer Registrations
MORGEN	Monitoring Risk Factors and Health Status in the Netherlands
NIDDM	non insulin-dependent diabetes mellitus
NKR	National Cancer Registration
NS	National Survey of General Practice (National Study)
Peil	Dutch Sentinel Practice Network (CMR Peilstations)
RIVM	National Institute on Public Health and the Environment
RNH	Registration Network Family Practices
SIG	Health Care Information
TIA	transient ischemic attack
Trans	Amsterdam Transition Project
UK	United Kingdom
USA	United States of America
VD	vascular-type dementia
VTV	RIVM public health forecast (document)
M	males
F	females
a	age-parameter
β	smoothing coefficient
cf	excess mortality rate for given disease

HR	hazard ratio
inc	disease incidence rate
mort	mortality rate for given disease
POP	total population number
prev	disease prevalence rate
PREV	disease prevalence number
rem	disease remission rate
RM	risk multiplier; = risk relative to population mean value
RR	relative risk; = risk relative to baseline value
t	time parameter

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