THE HEALTH BENEFITS OF
PREVENTION
a simulation approach

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DE GEZONDHEIDSEFFECTEN VAN PREVENTIE
EEN SIMULATIE BENADERING

Proefschrift

ter verkrijging van de graad van Doctor

aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.Dr. A.H.G. Rinnooy Kan
en volgens besluit van het College van Dekanen
De openbare verdediging zal plaatsvinden op
woensdag 23 november 1988 om 15.45 uur

door

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geboren te Amsterdam

vi

Promotiecommisie

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Part I

INTRODUCTION

Chapter 1

Introduction

1.1 From health services planning to health planning

In health policy making there has been a shift in recent years away from the pure planning of health services towards a comprehensive health planning, in which an attempt is made to apply the increasingly scarce resources in such a way as to achieve the "maximum" health for the population. This shift is exemplified by the WHO campaign for Health for All in the year 2000 and by the use of targets in the European region (1). It has been noticeable in the Netherlands as well in the health policy statement of the Health 2000 Report (2) which was presented to parliament in 1986.

There are two interesting features in this shift. One is the tendency to measure the effectiveness of a policy, an intervention or a technology in terms of health, the outcome rather than the input, output or process. The other is the acceptance that choices need to be made since, however large the budget for health is, it will always be limited. Of course this last concern has received most of the attention in recent years politically, but both features have generated a demand for a different kind of information on which to base policy decisions. The orientation towards health has spurred the interest in the health benefits to be expected from interventions both at an individual level and at the level of a population, and the concern with the optimization of scarce resources has led to a vivid interest in cost effectiveness, again for the individual patient as well as for policy making at a population level. New disciplines have emerged to supply this information: a renewed interest in clinical epidemiology to document the health effects of curative care and in population epidemiology to monitor the changes in

health status of a population and to identify risk factors for which preventive interventions could be devised, and on the other hand the emergence of among others medical decision making, health technology assessment and health economics to help the priority setting. The Dutch government has started several projects in this field, for instance the scenario studies in which the possible and probable future developments in certain disease categories or technologies are identified and analyzed for the specific purpose of supplying information on which to base policy decisions.

In all these disciplines, estimates of the health effects of an intervention play a crucial role. These estimates are not easily provided for individual patients but the estimates of the effect of interventions at the population level, which is essential for health policy making, have proved to be particularly difficult. Epidemiology, the discipline best suited to supply this information, has only recently started to develop methodologies which allow for estimates into the future based on analysis of the past. The necessity for more detailed effect estimates is demonstrated by the cost effectiveness studies, which in recent years have made their cost estimates increasingly precise. In the absence of equally precise effect estimates, crude measures of attributable risk have been used to estimate health benefits of prevention. A discrepancy then evolves between the cost estimates and the measures of effect, which makes the value of the results debatable.

In the competition for the limited resources, advocates of preventive interventions have had to support their claims with facts about the expected returns of such an investment. Not only do they have to explain that prevention now will not lead to visible health benefits tomorrow, on the contrary it will at best result in the non-occurrence of a specific disease in the (far) future, but furthermore they have to do so at a time when the major multi factorial intervention trials yield disappointing results, while new curative technologies are widely acclaimed.

Some of that disappointment may be due to unrealistic expectations of the interventions and to limitations of the methodology used to estimate the effects of prevention. If prevention is to compete for the allocation of scarce resources, it will have to be able to apply existing knowledge about risk factors to realistically estimate the health benefits to be expected from an intervention on these risk factors. Although epidemiology has been good at identifying the risk factors on which to intervene, the application of this epidemiologic knowledge in health policy making is still very primitive.

Furthermore changing prevalences of risk factors in a population, will affect the health needs of that population. Careful estimates of the effect of prevalence changes are therefore not only important to assess the impact of preventive interventions, but also to estimate the health needs upon which to base decisions about levels of health services. These changing health

needs can be the result of preventive interventions but also of past changes in risk factor prevalence or autonomous changes in the future. If one is serious about a public health policy based on health needs, the interest in effect estimates of changing risk factor prevalences will go beyond their use in priority setting for preventive interventions, and will extend to health policy making in general for instance through realistic target setting.

1.2 From epidemiology to health policy

In traditional epidemiology certain characteristics of population groups can be identified which correlate with elevated or lowered disease incidence rates in these groups when compared to a reference population. These characteristics may be the causative agent of the disease as is the case, for instance, in the chromosomal abnormality in the Down's Syndrome, whereby the characteristic is directly related to the etiology of the disease.

It may also be a risk factor for the disease as for example, exposure to cigarette smoke is for lung cancer, in which case it is obvious that the characteristic in some way causes or helps to cause the disease, but the exact etiology is still unknown. Often several hypotheses exist about the biological reason for the effect of the risk factor and one can demonstrate that the occurrence of the disease varies with the prevalence and severity of exposure to the risk factor, and can be influenced by changing the distribution of the risk factor.

But a characteristic may also be a risk indicator. An example would be the relationship between the presence of an abnormal ECG and the risk of ischemic heart disease. Such a risk indicator will identify the population with a higher risk of developing the disease without knowing whether the characteristic has anything to do with the causation of the disease, whether it is the result of the disease or even simply an identification means for a population in which a hitherto unsuspected risk factor is responsible for the elevated disease incidence. Risk indicators are also those characteristics of a population, which may very well be real risk factors but which cannot or will not be subject to preventive intervention. Sex and age but also for instance marital status are examples of such risk indicators. It does not mean that these characteristics should not be studied in epidemiology but merely that their main use is in assessing the overall risk of the population (for instance as a result of demographic changes) and in identifying high risk groups within the population rather than in providing clues for preventive action. Finally, of course, every correlation, for which no etiologic hypothesis has been proven, may turn out to be a spurious relationship.

Awaiting definite proof of the etiology, it is the category of the risk

factors that is of particular interest for prevention since one can argue that
a reduction in risk factor prevalence will result in a reduction of disease
incidence, even if the exact pathway of causation has not yet been identified.
For the important causes of death there has been an extensive search for risk
factors in the hope of finding preventive measures for non communicable
diseases that would be as effective and as acceptable, as vaccinations were
for infectious diseases.

The Framingham Study for Cardiovascular Disease (3) and the British
Physicians Study for Lung cancer (4) are beyond any doubt the classics
of early epidemiology of non communicable diseases. These large longi-
tudinal studies not only supplied data from which risk factors for major
disease categories were identified, but they still supply the most thorough
quantitative material about that relationship. While the model for lung
cancer was relatively simple (smoking was found to be such an overwhelm-
ing risk factor that it eclipsed any other potential determinant), the model
that emerged for ischemic heart disease was more complex. Three major
risk factors (smoking, hypertension and hypercholesterolemia) proved to
be heavily correlated with the incidence of different forms of ischemic heart
disease. In the 1960's and 1970's, as the epidemic of ischemic heart disease
reached its peak, first in the United States and later in the West European
countries, the information about the relationship between these three risk
factors and the incidence of the disease resulted in a number of intervention
trials.

Some of the smaller trials focussed on one or two risk factor interventions
(Veterans study on hypertension, HDFP, LRC-CPPT etc.) but the inter
relationship between the three major risk factors, observed in the Framing-
ham data occasioned a number of large multi factorial intervention trials.
The best known of these are MRFIT (5), the WHO collaborative trial (6)
and the North Karelia Project in Finland (7). While all of these, and several
smaller trials as well (8-11) showed conclusively that risk factors could be
intervened upon in the study population, all of them showed disappointing
end results in terms of health benefits. Although in some subgroups there
was a reduced mortality for some categories of ischemic heart disease, the
overall mortality did not seem to be reduced by the interventions.

Several hypotheses have been formulated by the study groups, for the
apparent failure of prevention. One was that the overall down ward trend in
the prevalence of risk factors in the open population may have masked the
benefits in the intervention population. These might have been more ap-
parent, had one intervened in a different phase of the epidemic. One should
keep in mind that the follow up period has been relatively short so far, espe-
cially considering the often very lengthy disease process of atherosclerosis.
Also relatively little attention has been paid to trends in other causes of

death over that same period, that may well have influenced the total mortality rates. However the final aftertaste of these experiments has been a severe disappointment and prevention in general has suffered a setback (12).

While the Framingham Study and comparable studies, concentrated on the identification of risk factors for specific diseases, a concurrent interest developed in the influence of life styles and social determinants on more general indicators of health. These studies were the direct result of a redirection of attention away from disease and towards health. Health was no longer measured purely in terms of life expectancy, mortality or absence of disease, but following the WHO definition of health, it measured subjective well being as well. The best known of these lifestyle studies is perhaps the Alameda county project (13-15).

It showed a distinct relationship between health status and individual life styles, but also between health and more social determinants such as marital status and the presence of a "social network", the relationship between individuals in their direct community. These determinants of health were summarized as the health practices which proved to be positively associated with health outcomes after 9 years, after controlling for the initial levels of health. The message to the population was clear: don't drink, don't smoke, eat breakfast, sleep eight hours a night and get enough exercise. The result of this interest in health was a boom in joggers, health foods and mineral waters.

However since both the risk factors and the health outcomes measured were broadly defined, it has been difficult to formulate specific hypotheses concerning the underlying causal pathway and the more specific quantification of the health benefits to expect from interventions in risk factors, has necessarily remained vague. Although the results have had a major impact on the populations concern about health and the possible means of personally influencing ones own health, the impact of these studies on the rationalization of preventive health policy measures has remained disappointing. The fear is that the excessive interest in health, one could even say the fashion of healthism, may prove to be as short lived as all fashions and that the aftermath will be a disillusion with prevention in general (16).

If decisions on prevention or interventions on the determinants of health are to be rational, it will be of major importance to have realistic expectations of such policy measures. It is necessary that the extensive data that have emerged from epidemiologic research on non communicable diseases are reassembled in such a way that they can provide insight into the quantitative benefits to be expected of preventive interventions. For effect estimates of preventive interventions to be realistic the three following points will be essential:

- The emphasis on single disease categories has brought to light the
  fact that many risk factors can be identified for one disease, but it
  has given less attention to the fact that several major diseases have
  risk factors in common. For health policy this is important infor-
  mation since it means that an intervention on one risk factor will
  affect the incidence of several disease categories simultaneously. This
  may result in very different effect estimates when considering preven-
  tive interventions from the risk factor rather than from the disease
  perspective. Recently, at a workshop organized by the Brookings
  Institute, the absence of an accepted multi factorial model for effect
  estimates has been identified as a major handicap in cost effectiveness
  studies of prevention (17).

- The interest in the causation of disease has focussed research on the
  exposure to a risk factor and on the occurrence of disease. Often con-
  siderable time elapses before exposure leads to incidence of disease.
  This means that once risk factors are identified, preventive interven-
  tions will not only be directed towards preventing first exposure but
  also towards terminating existing exposure in the population. The
  traditional epidemiologic research has produced far less information
  about the effect of termination of exposure and the associated time
  lags before risk reduction is complete. The absence of sound time di-
  mensions when calculating the expected effects may have been partly
  responsible for the disappointment of the multi factorial intervention
  trials, it may just not be realistic to expect visible results after such
  a short follow up period.

- To be able to make changing patterns of disease in a population vis-
  ible, epidemiologists have greatly relied on age specific incidence or
  mortality rates, or standardized statistics to compare the health of
  populations over time or over geographic locations. This was done
  because incidence rates differ for age groups and therefore a different
  demographic structure may obscure the relative importance of dis-
  eases in different populations. For the same reasons effect measures
  are also often presented as proportional changes in age specific rates.
  However for policy purposes this can be very confusing, since in re-
  ality demographic changes do occur and a reduction in age specific
  incidence rates may not be accompanied by a reduction in absolute
  incidence in the population. For policy purposes it is important to
  work with absolute numbers, since these represent the real number of
  patients for whom services need to be planned. In an aging popula-
  tion with many chronic diseases in old age, this may mean that a very
  successful preventive intervention, causing a marked decline in the age

specific incidence rate, may still result in a higher number of cases in the population as the age group to which the reduced incidence rates apply increases in absolute numbers. This is often difficult to explain and makes it difficult to "sell" the intervention politically, since an appreciation of the health benefits requires an understanding of the dynamics underlying the effect estimates and a visualization of what would occur in the absence of the intervention.

Estimates of effect will have to be based on the existing epidemiologic knowledge but will have to be presented in a way that can be of direct use to health policy makers. For this purpose the Prevent model was developed. The Prevent model presented in the following chapters does not pretend to predict reality, it calculates to the best of the current epidemiologic knowledge what will happen to mortality in the population after an intervention on known risk factors. The final validation of such a model can only be made prospectively, its value now must lie primarily in its ability to perform complex calculations, and to present understandable conclusions.

1.3 Objectives of the project

The goal of the Prevent project was to devise a tool for policy makers to use epidemiologic data on the relationship between risk factors and diseases, to estimate the effect on the health of a population of changes in risk factor prevalence, either autonomous or through interventions. These effect estimates can either be used directly in policy making for instance to set realistic targets, or serve as input for formal priority setting exercises such as cost effectiveness analyses.

From this goal three main objectives of the project can be derived:

1. To adapt existent epidemiologic measures and techniques to devise a methodology that will allow an estimate of the effects of changes in risk factor prevalence in a population on a chosen measure of health. This methodology will have to be able to take into account the effect of one risk factor on several diseases and the effect of simultaneous interventions on several risk factors (the multi factorial nature of the model) and will have to incorporate a time dimension to allow for a slow risk reduction. The results must be presented both as proportional changes in age specific disease incidence rates and as changes in absolute measures of health.

2. To distill from existing epidemiologic studies the data necessary to apply the above tool to policy making in the Netherlands. There is a

vast body of literature on risk factors and intervention trials, and the purpose of the project was not to add to this pool but to see if the existing data could be used in a more effective way. Since most of the studies were done abroad the exercise would at the same time serve to see if data can be transferred from one population to another.

3. To use the methodology and the data to construct a tool which could be used by policy makers. One of the major problems in using scientific results in policy making is that very often the case presented in these results does not exactly correspond with the situation for which a policy decision needs to be made. The ability of the policy maker to experiment with the different circumstances or alternative interventions, may not lead to different conclusions but will greatly enhance the understanding of the dynamics underlying the effect estimates. This understanding in turn will lead to a more rational use of the effect estimates.

The organization of this book reflects these three objectives. Part II deals with the methodology. It reviews the existing epidemiologic measures and techniques on which the methodology is based, it analyses the necessary changes to fit these for our purpose and finally shows how the methodology is applied in a computer simulation program Prevent. The third part is concerned with the data input necessary for Prevent. It briefly reviews the epidemiologic knowledge about risk factors and diseases relevant for the Dutch population and then assigns relative risks to the risk factor-disease combinations for which there is sufficient evidence to accept the causal nature of the relationship, and for which prevalence data for the Dutch population exist. Finally, in part IV the results generated by the current version of the Prevent model are interpreted. The three sections are followed by two final chapters which contain a discussion of the possible uses of Prevent in Dutch health policy making and the conclusions of the project.

Not every reader may be equally interested in all parts. Each is therefore preceded by a short summary in which the most important questions and conclusions of those chapters are reviewed. A reader may read only those introductions, skip a part and still be able to follow the discussion in the final chapters. The input data used in the basic runs are summarized in appendix C to allow for easy reference.

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Part II

THE DEVELOPMENT
OF THE MODEL

Introduction and summary

In this first section we will discuss the methodology of Prevent, developed to achieve the first objective stated in chapter 1: "To adapt existent epidemiological measures and techniques in order to devise a methodology that will allow an estimate of the effects of changes in risk factor prevalence in a population on a chosen measure of health. This methodology will have to be able to take into account the effect of one risk factor on several diseases and the effect of simultaneous interventions on several risk factors and will have to incorporate a time dimension to allow for a slow risk reduction. The results must be presented both as proportional changes in age specific disease incidence rates and as changes in absolute measures of health."

In chapter 2 some existing epidemiological techniques that are relevant to the Prevent project will be reviewed. In the following chapter we will discuss the methodological adjustments necessary to meet the conditions stated in the objective. In the final chapter the computer model will be presented, for although the concept of Prevent is simple, the calculations are cumbersome and they are performed in a computer simulation model.

Existing epidemiologic measures in Prevent

In epidemiology an analysis of the distribution of disease incidence and risk factor prevalence in different populations is used to confirm the hypothesis of a causal relationship between risk factor and disease. The strength of the relationship is often expressed as the ratio of incidence between exposed and non exposed, the Incidence Density Ratio (IDR) or relative risk (2.2.1). The importance of a risk factor for the incidence of a certain disease in a population is usually expressed as the Etiologic Fraction (EF), the proportion of the total incidence of the disease that can be attributed

to the prevalence of that risk factor in the population (2.2.2). It also gives an indication of the proportion of incidence that could be prevented by the total elimination of that risk factor in the population.

However, since most often prevention will not eliminate but merely reduce the prevalence of a risk factor, a measure was developed to estimate the impact of a change in prevalence of a risk factor on the incidence of a disease, the Potential Impact Fraction (PIF). It stands for the incidence that is avoided by a preventive intervention as a proportion of the incidence that would have occurred in that population without the intervention. Both the EF and the PIF can be calculated when P's, the prevalences of exposure to a risk factor, in the population, and the corresponding IDR's are known. The potential impact fraction in the traditional epidemiological literature assumes an immediate elimination of excess risk after the termination of exposure. The ex-exposed are returned to the category of non exposed with, by definition, an IDR of 1.

The Prevent methodology

Prevent is a model which estimates the effect of changes in risk factor prevalence in a population in terms of health benefit. It is based on the epidemiologic effect measure the Potential Impact Fraction. To achieve the objectives stated it has incorporated the following three requirements in the methodology:

- the possibility that one risk factor affects several diseases, and that one disease is affected by several risk factors,

- a time dimension to simulate the reduction in excess risk after cessation of exposure to the risk factor,

- the interaction between the effect of the intervention and the demographic evolution in the population.

In the current version of Prevent all measures of health benefit are based on mortality. There are two steps in the methodology, in the first PIF's are calculated, in the second step these proportional measures are expressed in absolute health benefits. The first two requirements of the methodology are incorporated in the first step of the model (3.2), the third one dictated the format of the second step (3.3).

Step 1, the calculation of PIF's

In the first step of the Prevent model several risk factors and several diseases are analyzed simultaneously. The prevalence of each risk factor is denoted

by P, the proportion of the (sub)population exposed in a certain exposure category. In order to use the information on the causal relationship between risk factor exposure and disease incidence as effectively as possible, the prevalence is stratified by age and sex category. Since one risk factor can affect several diseases, each exposure category is assigned several IDR's, each representing the strength of the relationship between the risk factor and one of the diseases.

Knowing the existing distribution of a population over exposure categories (P) and the corresponding IDR's, we can estimate the proportional changes in incidence (PIF) for each disease affected by that risk factor, due to changes in P, for instance as a result of a preventive intervention. In a second step of the model these disease specific PIF's are applied to the disease specific mortality quotients and then to a population, so that the proportional PIF's are translated into absolute measures of health benefit.

Interventions on a risk factor will result in a shift of a proportion of the population from exposed to ex-exposed. These shifts cause proportional changes in incidence rates for all the diseases affected by that risk factor. In other words, it will result in several PIF's, age, sex and disease specific. The second condition of the methodology was the introduction of a time dimension. For each risk factor and disease combination a time period in years is assumed between the moment of cessation of exposure and the moment the lowest relative risk for ex-exposed, the remnant IDR is reached. This time period is called LAG. The introduction of this time dimension necessitates an adjustment of the equation used for the calculation of PIF as well as an additional dimension of the input data on prevalence and IDR. It means that the ultimate PIF is not reached immediately after the intervention but only after LAG years. It may take years before the intervention has its maximum effect.

The time dimension also means however, that past changes in risk factor prevalence, whatever their cause, may continue to affect disease incidence in the future. This change in disease specific incidence should not be ascribed to the intervention. To incorporate the proportional effect of such past (and possibly also of future) "autonomous trends" in risk factor prevalences, Prevent calculates Trend Impact Fractions TIF's, in a manner similar to the PIF's.

Step 2, the calculations of health benefits

By the end of LAG years the maximum PIF is reached, the effect of the intervention in proportional terms. The effect in absolute numbers, the health benefit, will of course also depend three other factors: on the proportional changes in disease specific incidence over that same period caused

by autonomous trend (the TIF's), the relative contribution of the diseases, influenced by that specific risk factor, on total mortality and the demographic changes in the population over those LAG years.

It is the time dimension in the first step of the model and the fact that it may vary for different diseases, which makes the interaction between the PIF's and the demographic changes interesting. In Prevent the second step of the model consists of a population model in one year age groups to which disease specific mortality quotients (M) are applied, to simulate the evolution of the population over time. The assumption is that the proportional changes in incidence from the first part of the model, the PIF's and TIF's, are translated into the same proportional changes in disease specific mortality after a certain latency period, LAT.

If the TIF's only are applied, the resulting new disease specific mortality quotients and the evolution of the population represent the so called *reference* or *trend* scenario, the developments expected when no intervention takes place. If however both TIF's and PIF's are applied to the mortality quotients, the population evolves as is expected as a result of the intervention. Note that prevalence changes in one risk factor may generate changes in disease specific mortality quotients for several diseases, and that risk factors for which no intervention is simulated nevertheless may cause changes in mortality quotients through TIF's as a result of autonomous trends in risk factor prevalences. The differences between the reference and the intervention population represent the effect of the intervention and can be expressed in several measures of health benefit: differences in mortality, potential years of life gained (PYLG) etc. To see the full effect of an intervention on such a measure of health benefit the model should simulate for at least LAG+LAT years.

In summary this means that an intervention on risk factor prevalence P at time t=0 will result in a proportional reduction in incidence, PIF spread over LAG years, from t=0 to LAG. These PIF's are applied to mortality quotients, M, after LAT years, from t=LAT to LAG+LAT. The resulting new disease specific mortality quotients are applied to the population together with the other mortality quotients over at least LAG+LAT years.

The Prevent model

The stratification and the time dimensions necessary for the methodology, make it imperative that the calculations of health benefits are done in a computer simulation model (4). One of the objectives of the project was that the tool developed should be useful for policy makers. We decided at the start of the model development that it should be an interactive model

which could run on an IBM compatible micro computer and which could be operated without prior knowledge of the epidemiologic techniques used in the model.

The files containing the array of data on P and IDR's, the time dimensions, the existing mortality quotients and the population data, can be adjusted for any population, but can not be changed directly by the user. The user can specify changes in risk factor prevalence as a result of autonomous trends or interventions, the time period over which the intervention occurs, the length of the simulation period and whether the first, proportional part of the model will take a cohort factor into account. Prevent will present the results in graphical or tabular output, for the intermediate output variables of EF, TIF and PIF and for the outcome variables: disease specific mortality, total mortality, (disease specific) mortality difference, PYLG, actual life years gained, survival curves and life expectancy at birth.

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Chapter 2

Theoretical background

2.1 Summary and definitions

In this chapter some existing epidemiological measures will be reviewed that were developed to estimate effects of risk factor interventions, and their applications in preventive policy making. In this summary we will first present the definitions and, if relevant, the detailed equations of the epidemiologic variables referred to in this chapter. In the text they are then only presented in a simplified version.

P is the proportion of the population exposed to a certain risk factor, possibly including a proportion that was never exposed. P is always age, sex and risk factor specific. It can be stratified further by exposure category and ex-exposure level. Within one age, sex specific subpopulation $\sum P = 1$.

Exposure category is a stratification by severity of exposure.

Ex-exposure level is a stratification by the remaining effect of exposure after cessation of exposure.

IDR is the incidence density ratio, the ratio of the incidence rate among exposed over the incidence rate among never exposed. In the text it is used interchangeably with RR or relative risk. The IDR is age, sex, risk factor, exposure category and disease specific. The IDR of the never exposed is always 1 by definition, the IDR of the exposed is always ≥ 1.

EF is the etiologic fraction, the proportion of incident cases attributable to the prevalence of a risk factor in a population at a certain moment

in time. It is the equivalent of what has been called attributable risk (percentage) by other authors.

$$EF = \frac{P_{ex}(IDR-1)}{P_{ex}(IDR-1)+1}$$

where:

- P_{ex}:proportion of the population exposed to a risk factor.

PIF is the potential impact fraction, the incident cases prevented at a certain moment in time, by an intervention to reduce risk factor prevalence, as a proportion of the incident cases that are expected to occur at that time in the absence of the intervention.

$$PIF = \frac{(P_{ex} - P'_{ex})(IDR-1)}{P_{ex}(IDR-1)+1}$$

where:

- P_{ex}: proportion of the population exposed.
- P'_{ex}: the remaining proportion of the population exposed after intervention.

M is a mortality quotient, the number of deaths per 100.000 of the population. It is age and sex specific, time dependent and can also be disease specific.

PYLG are the potential years of life gained by a death avoided. The total number of deaths at a point in time are each multiplied by the current life expectancy at the age of death. It is the mirror image of PYLL the potential years of life lost.

QALY is quality adjusted life years, a measure of health benefit based on the PYLG times the quality measure assigned to the health status during the PYLG.

2.2 Calculating the Potential Impact Fraction

2.2.1 The use of relative risks

The effect of exposure to a risk factor on disease incidence is often quantified as the relative risk or incidence density ratio IDR, the ratio of the incidence

among exposed over the incidence among the non exposed. Relative risks can be derived from cohort studies and are identical to incidence density ratio's when very short time spans are concerned (1). For some risk factors only data from case control studies are available, the resulting odds ratio's can be equated to relative risks under certain conditions (2).

Estimates of incidence density ratio's and estimates of the prevalence of risk factors in the Dutch population, will be necessary for the effect estimates of risk factor interventions. The prevalence of risk factors in a population is often known, but incidence density ratio's will have to be estimated from relative risk ratio's or odds ratio's, from previous epidemiologic studies (3-9). Ideally, they can be transferred to another population if the following conditions are met:

- *Relative risks need to be controlled* for the influence of other known or suspected etiological agents which overlap in distribution with the exposure of the risk factor of interest (confounders).

- *Relative risks have to apply to the general population.* If the controls are stratified to match cases they may not be representative of the general population.

The utilization of relative risk estimates from other populations involves the risk that populations differ on an important characteristic which makes it impossible to compare them. The most obvious variables for which one would wish to control are age, sex and race. The influence of different age structures in populations on total mortality has been extensively discussed and several methods for the standardization suggested (10-12).

Walter in 1978 (13) puts forward the hypothesis that a relative risk if properly standardized should perhaps be viewed as a biological constant and thus can easily be transferred from one population to another. This hypothesis seems to be corroborated by empirical data such as those presented by McIntosh on the relative risk of smoking and pregnancy (14).

2.2.2 Attributable risk and impact measures

In epidemiology the fraction of the incidence that can be attributed to the prevalence of a certain risk factor in a population has been referred to as the attributable risk in that population. Over the years this measure was refined by several authors (15-17) and some dispute over the terminology evolved. To avoid further misunderstanding we shall refer to the "Etiological Fraction" (EF) as suggested by Miettinen, and defined as "the proportion of incident cases attributable to the prevalence of a risk factor"

or the difference in the number of cases in a population *with* exposure and *without* exposure as a fraction of the number of cases in the population *with* exposure, or

$$EF = \frac{P(IDR-1)}{P(IDR-1)+1}$$

The etiological fraction in fact represents the incidence that could be avoided in a population if there was no exposure to that risk factor. As such it has been used to set priorities for preventive action.

B. Ouellet et al in 1979 (18) made an attempt to determine the percentage of premature mortality and of potential years of life lost (PYLL) in Canada attributable to smoking and alcohol. Mortality causes were screened for those believed to be related to smoking and drinking. Using relative risks from epidemiologic studies elsewhere, a calculation of the attributable fraction (as they call the EF) was made, based on the known distribution of risk factors in the Canadian population. The approach demonstrates how, using the EF, the ranking of causes of premature mortality can be transformed into a ranking of risk factors and used to establish preventive policy priorities. A couple of problems were identified but not solved in this exercise:

- the problem of the lead time between exposure and the increased risk of disease (no mention was made of its complement the lag time between preventive action and maximal reduction of relative risk).

- the problem of the interaction between risk factors and the importance of possible dependency in the distribution of risk factors.

On both issues the authors concluded that insufficient data exist to be able to take them into account.

Miettinen had already alluded to the possible use of the etiologic fraction as a measure of the fraction of disease prevented. He pointed out that this prevented fraction is not merely a negative etiologic fraction: it is the proportion of cases prevented by the factor, among the total number of cases that would have developed in the absence of the protective factor (hypothetical totality of cases both prevented and unprevented).

Walter (13) proposed that this prevented fraction may serve as a rational foundation for the choice between alternative preventive strategies for health planners. And Morgenstern and Bursic (19) argued that epidemiological research on risk factors should be implemented and used by health planners to estimate the potential impact of a preventive intervention. The proposed Potential Impact Fraction (PIF) is defined as "the proportional

reduction in the total number of new (incident) cases of a certain disease, resulting from a specific change in the distribution of a risk factor in the population at risk", or the difference between the number of cases that would have occurred *without* risk factor intervention and the number of cases that occurred *with* risk factor intervention as a fraction of the number of cases that would have occurred *without* risk factor intervention, or

$$PIF = \frac{(P_{ex} - P'_{ex})(IDR - 1)}{P_{ex}(IDR - 1) + 1}$$

where P_{ex} is the estimated proportion of the candidate population exposed before the planned intervention, P'_{ex} is the estimated proportion of the candidate population exposed after the intervention and IDR is the relative risk.

However, Morgenstern introduces certain assumptions which he considers necessary but which seriously hamper the use of his methodology by health planners. The first two have to do with the lack of a time dimension, the others with the limitation to a single disease/risk factor combination.

- *Post intervention risk must be identical to non exposed risk.*

- *No significant secular trends in age specific risks of disease may exist.*

  These assumptions by Morgenstern severely limit the possible use of the measure and illustrate the necessity of a time dimension and of a category of ex-exposed in effect estimates.

  We know from several studies that, for instance, the relative risk of lung cancer for ex-smokers falls rapidly after smoking cessation but that it never really seems to attain the non smoker level. If a reduction in relative risk over time, is to be taken into account the PIF can not remain a static measure.

  Furthermore risk factor prevalences change in a population over time, for instance as a result of previous interventions. This is illustrated by R.P. Ouellet in 1979 (20), who uses a community impact measurement of preventive interventions, adjusted for program acceptance and drug efficiency, to assess the impact of a new detection and treatment program, over and above the regular medical care sector. The example is worked out for hypertension and stroke in a black urban community in Baltimore. The importance of Ouellets paper lies primarily in the fact that the trends in incidence as a result of earlier preventive actions, are taken into account when estimating the impact attributable to the proposed intervention.

- *No significant secular trends may exist in the distribution of other risk factors.*

- *No allowance can be made for the fact that one risk factor may affect several diseases.*

  It has been argued before that from a policy perspective the multifactorial approach in the estimation of the effect of risk factor interventions is essential and the PIF will need to be adjusted to take this into account.

The necessity of looking at several relevant risk factors for one disease was already illustrated in the multi factorial intervention trials. Sturmans et al in 1977 (21), tried to calculate the impact of preventive interventions on hypertension, hypercholesterolemia and smoking on CHD mortality. They compared the maximum number of prevented deaths calculated with the traditional expressions for EF (without correction for possible interaction between risk factors) with the same estimates derived from the multi factorial approach.

Another example of a multi factorial approach in the sense that not only several risk factors for one disease but also several diseases are considered simultaneously, is the work on Health Risk Appraisal, HRA (22). The health risk appraisal method is basically a computer program in which risk characterizations of an individual are translated into a measure of life expectancy. Its main purpose is to aid health education as it provides a quantification of health benefits to be derived from specific behavior modification. The theory is that the reduction of life expectancy as shown by the computer will shock and thus the health education message will be more readily accepted. Although the quantification uses the same basis of relative risks for its calculation of the health benefits of risk reduction, it concentrates on individuals rather than populations. The micro approach resembles the macro approach but by its nature does not address the problems of a dynamic population with secular trends in risk factor prevalence, demographic trends etc.

2.2.3   Conclusions

The literature shows that epidemiology has produced some useful expressions: the Etiologic Fraction and the Potential Impact Fraction, with which the effects of changes in risk factor prevalence on changes in disease specific incidence can be estimated.

If relative risk ratio's were corrected for confounding influences they could be used. Age, sex and race are important determinants of incidence rates, and since we are not only interested in proportional but also in absolute measures of effect for the Dutch population, it is preferable not to

work with a "standard" population, but to use age, sex and race specific relative risks.

However the following adjustments will have to be made:

- Since age, sex and exposure levels all apparently greatly influence the relative risk found in epidemiology, the EF and PIF calculations will have to be *stratified* to take those into account. This is also necessary to be able to transfer relative risks from one population to another.

- Although mention is made of the "lead time", no time dimension is used in these traditional epidemiologic calculations. The introduction of a *time dimension* will not only allow for a lead time, and its complement the lag time, but will also make it possible to take secular trends in risk factor prevalence (possibly the result of earlier interventions) into account.

- The effect measures used until now have been restricted to one disease with one risk factor. The EF and PIF, as presented here, may not necessarily be correct even for a single risk factor intervention if we know that other risk factors simultaneously influence the incidence of the same disease.

2.3 Calculating health benefits

The proportional reductions in incidence are of limited interest as estimates of effect, when comparing interventions. In order to rank priorities for a specific population these PIF's will have to be expressed in absolute measures of health benefit and aggregated over several diseases. There are two main categories of health measures that could be used for this purpose: mortality measures and measures based on morbidity. These will be briefly reviewed and the special problems of the aggregation over several disease categories discussed.

2.3.1 Mortality measures

The most fundamental of all measures of health benefit is a reduction in the number of deaths. The evaluation of a health intervention is often expressed in terms of the number of deaths avoided. In order to make comparisons between populations of a different size, either between different populations or the same population at different points in time, the mortality benefit is sometimes expressed as a change in age and sex specific mortality rates. In developing countries, infant mortality rates are still a very useful measure of both health and available health care.

As populations age and causes of death are more concentrated in older age groups, a certain cause of death avoided sometimes results in a substitution by another cause of death. This created a need to express the benefit not in the number of deaths avoided but in the amount of life gained. Measures like life expectancy for populations and potential years of life gained (PYLG or potential years of life lost, PYLL, as its counterpart) for individuals evolved. An increase of life expectancy for a population indicates that an intervention does not merely substitute one cause of death for another, and PYLG allows to weigh causes of death according to the age at which death was avoided.

This concept of potential years of life lost has gained attention as a way of evaluating the impact of a cause of death (23). Each death is multiplied by the number of years the individual, considering his age, could have expected to live. The choice of the age specific life expectancy as the upper limit has been extensively discussed since especially in the older age groups, mortality rates are rapidly changing and the life expectancy measures may underestimate the true survival period. Some authors (24, 25) have settled this problem by choosing a rather arbitrary cutoff point and comparing the years of life gained from the avoided moment of death until that end point age, for instance 70 years. An additional argument for eliminating the very old from this analysis comes from the fact that the causes of death are much more difficult to ascertain with any degree of certainty in the oldest age group, and some suggest that the possibility of influencing mortality among the elderly by changing personal health habits may be limited (26).[1]

The implicit assumption in such an arbitrary end point is that death before that age is premature and deserves to be avoided, while prolongation of life beyond that age is not a political objective (27). Some authors even define health benefits as years of "productive" life gained (28).

All of these measures have in common, however, that they are static. They look at a population at a certain point in time and do not allow for the dynamics of an aging population. If a time dimension is introduced in the first part of the model we will have to develop a dynamic population model in which the above measures of mortality benefit are expressed over time.

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[1] For similar practical reasons the very young (i.e. under 1 year of age) are often eliminated from the analysis. The argument is that the infant death rate is determined by very special risk factors, and compared to mortality in later years infancy is a relatively "dangerous" period of life. Therefore causes of death in that age group tend to be of a different nature than those in later life. But they are accorded a very heavy weight since they add so many years of life gained.

2.3.2 Morbidity measures

In a population with a large share of chronic-degenerative diseases mortality measures may not be a very satisfactory measure of benefit. Some indication of the load of morbidity or invalidity avoided through an intervention may be required. The most fundamental measures of morbidity are incidence and prevalence. Although PIF's will give a proportional change in incidence, the translation into absolute measures of incidence and from there of prevalence are difficult because reliable data on disease incidence in a population are often not available. As a proxy for the number of cases, morbidity is sometimes measured through the utilization of health services, the "burden of disease". Each case of a certain disease is weighed with the average costs, not only financial but also in terms of health care utilization, or maybe even "suffering", associated with that disease. Although this type of measure was primarily developed to weigh the different disease categories as to the claim they placed on health services, it could also be adjusted to express more specifically the burden of disease for the individual. In most countries health services utilization statistics are available and some composite though often crude measure of the burden of disease by disease category could be developed. This should be specified by age and sex category, since the course of a disease may vary according to these characteristics.

Similarly in countries where life expectancy is high and most individuals lead long healthy lives before being struck by illness, the importance of an intervention should perhaps not be expressed in terms of increased life expectancy or PYLG, but more in terms of potential years of active life gained (29-33). Manton (34) showed that an addition of years of active life can either be achieved through a parallel shift in incidence and mortality (PYLG is identical to the potential years of active life gained) or through a compression in morbidity without a concurrent shift in mortality. With a benefit measure based solely on mortality the second type of benefit will not even become visible.

Several authors have come up with solutions for this dilemma. Katz (35) constructed an "invalidity" table comparable to a life table in which the (partial) elimination of a cause of death was shown in terms of increase in years of active life. Such a table can only be constructed for a population for which detailed information on invalidity rates is available, not only for each disease category but also age and sex specific. That type of information exists for few populations.

In line with the above measures, all of which basically weigh disease cases according to the resulting consequences for the individual, would be some subjective valuation of the different burdens of disease, some mea-

sure of quality of life. Although different diseases may entail the same
objective burden of disease in terms of, for instance, hospitalization, the
ultimate health status of those hospitalized and of survivors may differ by
disease. Furthermore they may be experienced differently by the individual.
This is exemplified by the emotional reactions to cancer and AIDS. Health
economists have also felt this need to weigh states of health not only by
their quantitative characteristics but also by their appreciation, and have
developed the concept of the QALY, the quality adjusted life years. There
is now a vast literature on this subject (for instance 36-39) and although
authors may disagree on the best methodology to estimate the weighing
factor to be assigned to different states of health, the QALY is defined as
a measure of potential years of life gained corrected for their quality.

However QALY research as it has been developed in health economics,
primarily to compare technologies and health services, has concentrated
on the valuation of health states, not diseases. There is little information
available on health status by diagnosis and of the different valuations of
health states by age group or sex, or by diagnosis. A further problem with
both the objective and the subjective measures of morbidity is that they
can vary considerably over time. Over long simulation periods they will be
less reliable than mortality measures.

2.3.3   Aggregation of mortality benefits

If one risk factor affects several diseases, the ultimate benefit of an in-
tervention will be the health benefits aggregated over the relevant disease
categories. In the case of mortality benefits this may be expressed as to-
tal mortality reduction or parallel to the potential years of life gained, an
actual growth in the population.

When analyzing the effect of a disease specific mortality reduction on
total mortality "competing death risks" or the "independency of causes of
death" have to be addressed (40-44). The conceptual problem of competing
death risks was first brought to light by the demographers. In the lifetable
techniques one can calculate the effect of a reduction of age specific mor-
tality due to the elimination of a specific cause of death. The problem is
whether one can assume that the population "saved" by the elimination
of a cause of death can simply be returned to the pool of survivors and
therefore runs the same risks of dying from the other causes of death. The
same problem obviously occurs with partial elimination of a cause of death.

In most life tables including the recent ones for the Netherlands by
van Ginneken (45) the choice was made to assume independence of causes
of death and therefore indeed subject survivors to the same age specific
mortality risks from other causes. However many authors have argued

that an interdependency between causes of death and a transition between them must exist (46, 47). The demographers have responded by developing different models to allow for such "competing death risks".

Manton et al developed the model of an underlying "lethal defect" (48, 49) resulting in Patterns of Failure rather than causes of death. Wong proposed a competing risk model in which a susceptibility ratio is taken into account (50) which links causes of death by assuming "saved individuals" to have a higher or lower susceptibility to the remaining causes of death than the general population.

All of the above models have in common that they approach the problem primarily from a demographical/mathematical point of view without a clear medical-biological hypothesis to explain this "susceptibility" or underlying "lethal defect". This can result in a *hypothesis* about the association between tuberculosis and cancer in general, based solely on a stable percentage of total mortality attributable to these joint causes of death (47).

For prevention it is of vital importance to know whether elimination of one cause of death will merely result in a replacement by another cause of death, as is suggested by Keyfitz and Fries (29, 51) or that one may truly expect an increase in life expectancy as defended by Schatzkin and Manton (42, 52).

A possible common disease process for the major diseases may bear with a closer look. If there is a relationship between the susceptibility for different causes of death this may either be genetically determined or influenced by an external risk factor. The first hypothesis would basically only allow for substitution of causes of death assuming a predetermined limit to life expectancy, and is supported by the multiple cause morbidity and mortality in the oldest age groups. The latter possibility assumes that because of the joint risk factors between different causes of death, an elimination of such a risk factor will result in a mortality reduction for several major diseases and therefore result in a sizeable increase in life expectancy (44).

In the Prevent model the causes of death will be clustered by their joint risk factors. The assumption will therefore be that those causes of death that are interrelated, will be influenced simultaneously by their joint risk factor, and other causes of death will be assumed to be independent.

2.3.4   Conclusions

Estimates of the simultaneous proportional reduction in the incidence of several diseases, as a result of a reduction in risk factor prevalence, will have to be translated into "health benefits".

What the ultimate effect of a proportional reduction in incidence will be, depends on the measure chosen as indicator of health. Theoretically there are three possible effects on the health indicator.

The changes in incidence of that particular disease have no effect on the chosen health indicator. This may sound paradoxical but this is for instance the case when one chooses mortality as the health indicator and one considers the effect of changes in the incidence of a non lethal disease. Changes in incidence will not affect the health indicator in question. Similarly acute diseases that are either cured or cause death, will not greatly influence measures of invalidity.

A change in incidence is identical to a change in health indicator, for instance in a disease for which the case fatality rate is 100%: the incidence is identical to the disease specific mortality and changes in disease incidence will be directly translated into changes in mortality.

Some cases result in changes in the relevant health indicator, in the case of mortality, when for instance the case fatality rate is less than 100%. The absolute number of incident cases prevented will not be equal to the number of deaths avoided. But not only will a mortality shift be but a partial reflection of the total health benefit gained by the incidence reduction, the case fatality rate may also be influenced by curative care, necessitating a clear distinction between benefits resulting from preventive action and those resulting from therapeutic progress.

Most diseases will affect most health indicators as described in the third situation, a reduction in incidence will be partially reflected in a reduction of the indicator.

The choice of health indicator will clearly determine the effect on health of the disease specific incidence reduction resulting from the risk factor intervention. The choice will thus also influence the priority setting.

In summary, the second step in the model will have to take the following points into account:

- Since the outcome of the first step is theoretically a proportional reduction in incidence, a *measure of health benefit will have to be chosen that evolves parallel to incidence changes.* For example proportional changes in incidence are identical to proportional changes in mortality as long as there is no difference in case fatality rates between avoided cases and the observed cases. The latency period between incidence and health outcome, and possible changes in case fatality rate over time will have to be addressed.

- Since the proportional incidence changes are at least *disease, age and sex specific*, the health benefit measure chosen will also have to be stratified by disease, age and sex.

- With the introduction of a time dimension in the first part of the model, it is impossible to have a static measure of health benefit if we want to go beyond proportional changes, and express the health benefit in absolute terms for a real population. A *dynamic population model*, that takes the aging of the population and the competing death risks into account will have to be constructed.

- Finally with a dynamic population model, a health benefit compared to the current level of the chosen health indicator will not be sufficient. The very fact that the population ages and that secular trends in risk factor prevalence are taken into account in step one, means that we will have to develop *a reference scenario* in which the evolution of the health indicator is simulated as it would have occurred had there been no intervention.

These points, together with the requirements for step 1 as formulated in the conclusions of the first section (2.2.3), will determine the methodology for the Prevent model. They will be discussed in the next chapter.

Chapter 3

Methodology of Prevent

3.1   Summary and definitions

In the previous chapter the epidemiological measure of Potential Impact Fraction, as developed by Morgenstern, was explored as a basis on which to estimate the proportional effect of a reduction in prevalence of a certain risk factor, on the disease specific incidence. It was subsequently argued that this proportional reduction in incidence calculated in the first step would have to be applied to a dynamic population model in the second step to allow for a translation into health benefits in absolute terms and an aggregation over several disease categories. For both steps a number of conditions were identified that are important for the Prevent model.

In this chapter we will explain how the methodology for the Prevent model evolved. The time dimension necessitated some adjustment of the equation used for the calculation of PIF, as well as additional stratification of the input data, on prevalence and IDR. It also dictated the dynamic population of step 2 and the two parallel scenario's, trend and intervention. All outcome measures will be based on differences in mortality between both scenario's.

Figure 3.1 shows a simplified version of the model, for only one time interval. This process is reiterative for all the years of the simulation period.

Figure 3.1: The basic version of the Prevent model
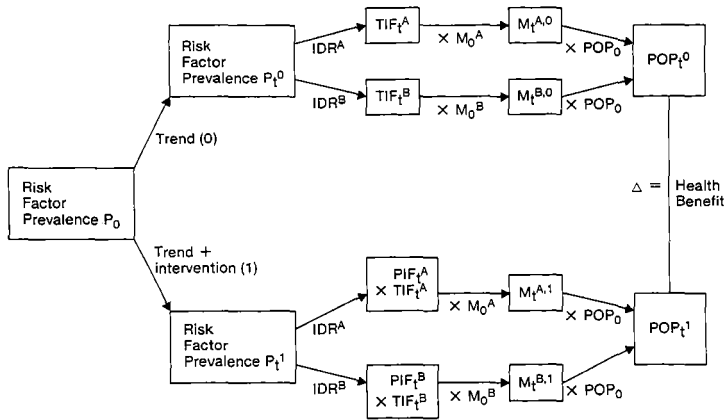
In the text the following abbreviations and equations will be used. The definitions and the equations will be presented here with all the necessary subscripts. Simplified versions will be used in the text. The equations used in the previous chapter will not be defined again unless they have been changed.

Remnant IDR is the lowest Incidence Density Ratio that can be achieved after cessation of exposure. It is risk factor and disease specific but is equal for all exposure categories.

LAG is the time it takes (in years) after cessation of exposure, for the Incidence Density Ratio associated with a certain exposure category, to reach the remnant IDR level, through linear reduction. Each year of LAG represents an ex-exposure level as defined earlier. LAG is risk factor and disease specific but is assumed to be equal for all age, sex and exposure categories.

Lead time is the time it takes (in years) after first exposure to a risk factor to reach the full relative risk associated with that exposure category. It is not used in the Prevent model.

LAT is the latency period, the time (in years) between incidence and mortality. It is disease and risk factor specific but assumed to be equal for all age, and sex categories, and to remain equal over time for each disease/risk factor combination.

PIDR is a intermediate variable, used to calculate EF's, TIF's and PIF's. It is risk factor, disease, sex, and age specific, it is time dependent, and there is a set of PIDR's for both the reference and the intervention population.

$$PIDR_t^{r,j,z,s,A} = \sum_{n=1}^{cn} \sum_{i=0}^{ID} P_{t-LAT^{r,s}}^{r,j,s,A,n,i} IDR^{r,z,s,A,n,i} \qquad (3.1)$$

Where:

- P: proportion of the population
- IDR: Incidence Density Ratio
- cn: total number of exposure categories;
- n: index for exposure category;
- r: index for risk factor;
- ID: total number of ex-exposure levels;
- i: index for ex-exposure level;
- j=0,1: index for reference (0) or intervention population (1).
- A: index for age;
- s: index for sex;
- z: index for disease;
- t: index for time.

EF the etiologic fraction is the proportion of incident cases attributable to the prevalence of a risk factor in a population at a certain moment in time. It is always age, sex, risk factor and disease specific, and time dependent.

$$EF_t^{r,j,z,s,A} = \frac{PIDR_t^{r,j,z,s,A} - 1}{PIDR_t^{r,j,z,s,A}} \qquad (3.2)$$

Where:

- r: index for risk factor;
- j=0,1: index for reference (0) or intervention population (1).
- A: index for age;
- s: index for sex;

- z: index for disease.

- t: index for time.

TIF is the trend impact fraction, the incident cases prevented at a certain moment in time, by an autonomous change in risk factor prevalence, as a proportion of the incident cases that would have occurred at that time in the absence of change. TIF is initially always age, sex, risk factor and disease specific and time dependent. In a second stage TIF's are aggregated over risk factors.

$$TIF_t^{r,z,s,A} = \frac{PIDR_0^{r,0,z,s,A} - PIDR_t^{r,0,z,s,A}}{PIDR_0^{r,0,z,s,A}} \tag{3.3}$$

Where:

- r: index for risk factor;

- j=0: index for reference population;

- A: index for age;

- s: index for sex;

- z: index for disease.

- t: index for time.

PIF is the potential impact fraction, the incident cases prevented at a certain moment in time, by an intervention to reduce risk factor prevalence, as a proportion of the incident cases that would have occurred at that time in the absence of the intervention. PIF is initially always age, sex, risk factor and disease specific and time dependent. In a second stage PIF's are aggregated over risk factors.

$$PIF_t^{r,z,s,A} = \frac{PIDR_t^{r,0,z,s,A} - PIDR_t^{r,1,z,s,A}}{PIDR_t^{r,0,z,s,A}} \tag{3.4}$$

Where:

- r: index for risk factor;

- j=0,1: index for reference (0) or intervention population (1).

- A: index for age;

- s: index for sex;

- z: index for disease.

- t: index for time.

Disease specific mortality is the absolute number of deaths due to a specific disease at each point in time. This can be differentiated by sex.

Total mortality is the absolute number of deaths at each point in time. This can be differentiated by sex.

(Disease specific) Mortality difference is the difference in the total number of deaths between the intervention and the reference population, at each point in time. This can be differentiated by sex.

PYLG are the potential years of life gained, the absolute number of deaths avoided by an intervention, at a point in time, multiplied by the current life expectancy associated with the age at death.

AYLG are the actual years of life gained, the difference between the total population in the intervention and in the reference scenario, at a point in time.

The methodology remains simple. What makes the model complicated are the multiple dimensions of exposure, the many consecutive steps due to the time variables that vary for each risk factor-disease combination and the multi factorial nature of the model. The time dimension and the interaction with demography are the reason why the outcomes can be unexpected and therefore interesting. The only way to process such a large number of basically simple calculations is in a computer model. The formal structure of the model will be the subject of the next chapter.

3.2 Calculating the potential impact fraction

In the first step of the model PIF stands for the incidence prevented by the intervention, as a proportion of the incidence that would have occurred had there been no intervention.

In the previous chapter we identified three adjustments to be made to use the PIF in the Prevent model: a stratification, a time dimension and an adjustment for the multi factorial nature of the model.

3.2.1 Stratification

The expression of PIF relies on data on prevalence P of a risk factor in a population and on data on relative risk ratio's as an approximation of

incidence density ratio's, IDR. To transfer relative risks from one population to another, either geographically or over time, the estimates need to be as "clean" as possible. This means that IDR's have to be corrected for possible other factors in the population which may influence the relative risk value found. Such factors are only important if they interact with both the risk factor and the disease studied and thereby affect the relative risk found.

Some factors are known and generally accounted for in epidemiologic literature. The most obvious examples are sex and age. When possible IDR's will be stratified into age and sex specific values. With the corresponding prevalence data, PIF's can then be calculated, which will be age and sex specific.

There are other population characteristics that influence certain disease incidences but for which at present there is no adequate quantification. Examples are race and social stratification of the population. It is well documented that socioeconomic status (SES) is correlated with disease specific mortality (for a recent overview see Marmot and Mackenbach 53, 54). It may be important to stratify PIF's for social class since there is evidence to suspect a considerable cumulation of risk factors in the lower socioeconomic groups and also evidence that the effectiveness of preventive interventions varies according to socioeconomic group.

Unfortunately when stratification of the exposure to a risk factor is available by socioeconomic status, it is seldom an extra dimension. Thus when using the SES data, the age and sex stratification has to be given up. We have chosen for the age and sex stratification, because there are also corresponding IDR values. An additional analysis by SES at a later stage may prove interesting, since the cumulation of risk factors may partly explain for the SES gradient in mortality and the Prevent model would allow for a hypothetical quantification of this effect.

Joint exposure to several risk factors will also affect the relative risks. If there is no interaction, we will assume that relative risks are multiplicative. In that case risk factors need not be considered jointly as long as they are distributed independently (see appendix A).

Other confounders, factors that interact with the risk factor under consideration and will therefore confound the relative risk values found, are not so easily dealt with. If it concerns known confounders, they are often corrected for in the relative risk estimates. However the possibility of unknown confounders remains, that may both influence the relative risk estimates and the effect of the risk factor in our population.

Finally the stratification within the risk factor under consideration needs to be addressed. For most risk factors there is a dose-effect relationship, in fact this is one of the conditions for a causal relationship. In the original PIF expression there is a dichotomy in the population between the exposed

proportion P of the population and the non exposed (1-P). In reality however we will want to specify the amount of exposure, when it influences the IDR value.

In summary, the availability of data on IDR and P will determine the detail of stratification of the PIF. For each risk factor considered, a separate PIF will be calculated for each disease. This PIF will be age and sex specific. The stratification by exposure categories, is aggregated in the PIF equation.

3.2.2 A time dimension

The original PIF expression by Morgenstern is static, the reference incidence is calculated from the original prevalence and the intervention is assumed to have an instantaneous effect on prevalence, so that PIF is a direct result of the difference between these two. Adding a time dimension simply means that P is indexed for time. However as soon as a time dimension is introduced, the reference incidence which by definition is the incidence as it would have been without the intervention may change autonomously over time.

The time index is important because it allows for the expression of the following time variables: LAG, LAT and time spread of an intervention.

Lag time

The lag time (LAG) is the time it takes for the excess risk associated with the risk factor to disappear when exposure ceases. In the case of alcohol and driving it usually is a matter of hours, but in the case of smoking and lung cancer it takes approximately ten years for an ex-smoker to reach the lowest possible risk level, and that level is not even the same as that of a lifelong non smoker. There is always a remnant relative risk for ex-smokers.

We assume that the IDR diminishes over time after a cessation of exposure. The "ex" population, after the successful intervention, can therefore not be added to the non exposed population in the PIF expression since they will not have the same IDR. Their IDR will depend on how long ago the intervention took place and on the ultimate IDR level an "ex" can achieve. In Prevent we will assume that the reduction in risk is linear over LAG years, between the IDR of the exposed and the remnant IDR of the "ex" exposed after LAG years. The prevalence P and IDR will thus be further stratified by the time dimension, ex-exposure level.

The introduction of this variable has certain consequences for the model. If there is a slow reduction of risk over time interventions now will only attain their full effect in the future but also prevalences in the past will determine incidence in the present. Prevent will thus have to take past

changes in exposure prevalence into account to estimate their influence on current incidence.

Changes in risk factor prevalence in the past are considered to be autonomous trends, even if they are due to past interventions. Because of the length of the LAG time for some risk factor-disease combinations, these past trends may even influence the incidence of the disease in the future, a change of disease incidence which should not be assigned to the intervention currently evaluated. Similarly there may be an autonomous trend in risk factor prevalence that will continue in the future, independent of an intervention. The effects of these trends in risk factor prevalence on incidence are calculated with the trend impact fraction TIF, which is derived with the following expression, almost identical to the PIF expression:

$$TIF_t = \frac{PIDR_0 - PIDR_t}{PIDR_0} \tag{3.5}$$

where $PIDR_0$ is the PIDR at time 0, $PIDR_t$ the PIDR at time t taking the trends into account.

A PIF by definition, calculates the incidence reduction as a fraction of the incidence that would have occurred had there been no intervention. This "reference" incidence can no longer be the PIDR at time 0, but will evolve over time as a result of (past or future) risk factor prevalence trends. The mathematical expression for PIF will therefore be adjusted as follows:

$$PIF_t = \frac{PIDR_t - PIDR'_t}{PIDR_t} \tag{3.6}$$

where $PIDR_t$ takes only the trends into account, and $PIDR'_t$ takes both the trends and the intervention into account.

TIF_t and PIF_t represent the proportional changes in incidence at time t. When this proportional change is applied to the mortality quotient at the start of the simulation, time 0, it will yield the mortality quotient at time t.

Lead time

As a complement to the lag time, which stands for the slow reduction in risk after cessation of exposure, there should be a time variable to indicate the slow increase in risk when first exposed, until the full relative risk ratio's apply. This lead time should apply if there is a positive trend in risk factor prevalence. From epidemiology we know relatively little about this variable, more commonly the length of exposure is given and an increase in relative risk assumed related to that length of exposure. Few empirical studies have considered the lead time specifically. A complicating factor is that first

exposure often occurs at an early age and subsequent incidence or mortality only occurs at a much older age. This is a reason why the lead time is not very important for the risk factors considered in Prevent. Theoretically it could be incorporated but in the current version it is omitted.

Latency period

A reduction in incidence is seldom reflected in an immediate change in the health indicator chosen to measure effect. If we consider mortality as the effect measure this means that there is a time between the incidence of the disease and subsequent death. In the Prevent model this time variable is called LAT for latency period. LAT simply stands for the number of years before a change in incidence will be reflected in a change in disease specific mortality.

Theoretically this time variable does not apply until the second step of the model since it denotes time between the PIF and its expression in mortality reduction. However, in the implementation of the model, LAT occurs in step 1. When reconstructing the past Prevent will go back LAG+LAT years and although the effect of an intervention will start to become apparent after LAT years, it will not reach its full potential until after LAG+LAT years.

In Prevent incidence as such is not calculated, only proportional changes in incidence. A proportional reduction in incidence is assumed to be identical to a proportional reduction in mortality as long as the case fatality rates between the population before and after intervention do not differ. In this condition lies the essence of the LAT period. First of all it is obvious that case fatality rates implicitly assume a time interval: incidence seldom causes instantaneous death as in the case of fatal motor vehicle accidents or sudden cardiac death. The introduction of the latency period LAT allows for a more realistic estimate of the effect of incidence reduction.

Secondly LAT stands for all that occurs between incidence and death: the moment of diagnosis, the level of curative care and the therapeutic success rate. In the condition as formulated above, Prevent assumes that these remain unchanged over time. In reality this will seldom occur. By introducing the LAT variable the model shows at which point assumptions about changing therapeutic care would have to be introduced.

In the present version of Prevent these changes are not taken into account and LAT is considered to be a constant that can take different values for each risk factor-disease combination. Obviously this is a simplification since it is but an average of the real survival period and will not show the distribution of the mortality reduction over time.

Time spread of an intervention

A reduction in risk factor prevalence will seldom be achieved immediately. With a time dimension, it is possible to spread prevalence changes over a number of years. This does not affect the methodology, it will just determine the rate of change of prevalence as a result of the intervention. It does mean that the full effect of an intervention will not be seen until LAG+LAT years after the completion of the intervention.

In summary, by adding a time dimension to the calculation of PIF, some changes in the methodology occur that go beyond the simple indexing of variables for time. Of the time variables introduced, LAG and LAT are the most important ones. LAG and LAT together determine which time span, both retrospectively and prospectively, has to be taken into account to see the full effect of an intervention. LAG determines the rate at which the IDR is reduced to the remnant IDR of the ultimate ex-exposed. It also means that historical developments in prevalence of exposure are taken into account. The incorporation of LAG thus adds an extra dimension to both prevalence and IDR. The time variable LAG necessitated adjustment of the PIF in order to take autonomous trends in risk factor prevalence from the past into account. As a consequence the variable TIF was introduced and the mathematical expression used to calculate PIF had to be adjusted.

3.2.3   A multi factorial model

In the objective of the project it was stated that the methodology should allow for the fact that one risk factor may affect several disease categories and one disease may be influenced by several risk factors. This is the multi factorial aspect of the model.

The fact that one risk factor affects several disease categories is not important in the first step of the model. The outcome PIF is still disease specific and only in the second step of the model will these disease specific incidence changes be aggregated into one health benefit measure.

The multi factorial character of certain diseases however, needs to be considered in the methodology for step 1. If several risk factors influence the incidence of a certain disease, all of these risk factors need to be considered to determine the ultimate changes in disease incidence. The resulting PIF needs to be disease specific but not risk factor specific.

Before applying the methodology to several overlapping risk factor-disease combinations two questions need to be addressed:

- Can the PIF equation designed for a single risk factor, be applied when several risk factors are known to be present?

- How can the interaction between risk factors be incorporated?

These questions need to be addressed because, except for rare exceptions, the lack of data on the joint exposure to several risk factors and on the relative risk of joint exposure, necessitate that each risk factor for a disease is considered separately.

In appendix A the mathematical derivation of the expressions for the etiological fraction and the potential impact fraction are given for a situation where more than one risk factor is present. It is shown there that the expressions remain the same if relative risk ratio's are assumed to be multiplicative and the distribution of risk factors in the population independent. This assumption of an independent distribution is not necessary when relative risk ratio's are assumed to be additive but then the expressions for EF and PIF need to be adjusted. This alternative is of interest if Prevent were to be used to estimate the cumulative effect of an unequal distribution of risk factors over socioeconomic strata.

Interaction between two risk factors is said to occur when joint exposure results in a relative risk that is either higher or lower than what would be expected from the relative risks of each risk factor separately. In some cases such interaction is well documented as in esophageal cancer where alcohol and cigarette smoking jointly result in a relative risk that is far more elevated than would be expected (55). For other disease categories such as IHD that are also affected by several risk factors, interaction would have a much greater effect if it was shown to exist. There is a considerable body of literature on the assessment of the influence of one risk factor in the presence of other (confounding) variables. The methodology to prove the existence of interaction hinges on the definition of the effect of two risk factors without interaction. In other words, interaction is present when the observed relative risk of joint exposure differs from the expected. The expected relative risk of joint exposure depends on what theoretical model is applied to the relative risks when two risk factors are present simultaneously.

In such an analysis a choice has to be made whether two relative risks are considered to be additive or multiplicative. Kleinbaum, Kupper and Morgenstern (1) argue that although the additive hypothesis is very useful to show the public health effects of the joint presence of two risk factors, the multiplicative theory better suits the pathobiological process of disease. This is corroborated by the multistage models developed for cancers (56).

From the empirical data on the effect of joint risk factors, it is obvious that for instance the IHD disease incidence greatly increases when more than one known risk factor is present, but there is still no consensus whether the ultimate effect is additive, multiplicative or whether interaction

is present (57-63).

Because of the absence of clear evidence on interaction we shall assume that no interaction exists for the risk factors considered. We will assume that relative risk ratio's are multiplicative, and that risk factors are distributed independently in the population. Risk factor- and disease specific PIF's and TIF's can then be calculated as if no other risk factors were present.

Because of the possibility of autonomous trends and of simultaneous interventions, all risk factors influencing one disease need to be considered. The effect of the different PIF's and TIF's are assumed to be multiplicative, and are calculated with the following equations:

$$PIF_t^z = 1 - \prod_{r=1}^{rf} [1 - PIF_t^{z,r}] \qquad (3.7)$$

The same procedure is also applied to the TIF's:

$$TIF_t^z = 1 - \prod_{r=1}^{rf} [1 - TIF_t^{z,r}] \qquad (3.8)$$

Where:

- rf: total number of risk factors influencing disease z;

- r: index for risk factor;

- $P(T)IF_t^{z,r}$, P(T)IF for a single risk factor disease combination.

3.3   Calculating health benefits

Given the methodology of step 1 the requirements for the methodology in step 2 were set. In the current version of Prevent the effect measures are all expressed as changes in mortality. As was discussed previously, other measures could easily be substituted if they are related to age and sex specific disease incidences. The incorporation of such a measure will not necessitate major changes in methodology.

In the following chapters all measures of health benefit are based on mortality changes. The advantage of mortality data is that they are reliable, even if the causes of death are not always correctly coded (64). There is little risk of double counting as often happens in morbidity data. Finally the assumption that all other circumstances will remain unchanged (the assumption of *ceteris paribus*) is slightly less unrealistic for mortality than for a measure of morbidity.

The PIF's, proportional changes in disease specific incidence, are considered to be identical to proportional changes in disease specific mortality after LAT years. To translate these proportional changes in disease specific mortality into deaths avoided, the PIF's are applied to disease specific mortality quotients and these to a population.

The consequence of the choice of a time dimension in step 1 is that step 2 needs to be a dynamic population model, in which the population changes over time as a result of changing age group sizes (demography) and changing age and sex specific mortality quotients (M). In Prevent disease specific mortality quotients M change only as a result of changing risk factor prevalences, either through trends or interventions (TIF's or PIF's).

As a logical result of the decision to have two parallel scenario's in step 1, the reference scenario based on TIF's and the intervention scenario based on TIF's and PIF's, step 2 works with two parallel populations, one of which evolves due to age and sex specific mortality changes caused by TIF and the other as a result of mortality changes caused by TIF and PIF together.

- Reference population is TIF × M × population

- Intervention population is PIF × TIF × M × population

The following available measures of health benefit are alternative ways of presenting the differences between these two populations:

Mortality Prevent will show the evolution over time of disease specific and total mortality in both the reference and the intervention population. This evolution is not only the result of changes of risk factor prevalence but also of demography. After LAG+LAT years the effect of the intervention wears off and that of trend and demography take over again.

Mortality reduction As deaths from a certain disease are prevented, the absolute number of deaths from a competing cause of death may actually increase. The mere substitution of one cause of death for another is a debatable health benefit. One is therefore not only interested in disease specific mortality reduction but also in the total mortality reduction over time. Prevent will show the difference in total mortality over time by subtracting total mortality in the intervention population from total mortality in the reference population for each year of the simulation period. Since everyone must ultimately die, there may eventually develop a slight surplus mortality, as all those "saved" die of another cause of death.

PYLG As was discussed in the previous chapter it is sometimes of interest
to weigh deaths according to the age at which they occur. The tradi-
tional Potential Years of Life Gained PYLG will simply multiply each
death prevented by the current life expectancy at the age of death.
Since of course the added benefit of the expected years of survival
gained, should in reality not all be assigned at the time of the death
avoided, PYLG should really be interpreted as a measure of mortality
reduction weighed by age at death.

AYLG Since we are nevertheless interested in some measure of the sur-
vival gained over time, due to an intervention, the health benefit
measure Actual Years of Life Gained was introduced. AYLG shows
the cumulative difference between the two populations. In AYLG the
individuals saved are returned to the total population and will remain
part of that population until they die. By subtracting the total in-
tervention population from the total trend population, AYLG shows
how the deaths prevented lead to a real increase in the surviving pop-
ulation. This is probably the best cumulative measure of the benefit
derived from an intervention since it takes the competing death risks
and the remaining survival period into account.

Survival curves In this outcome measure the *new* mortality quotients as
a result of the intervention, are applied to an imaginary cohort of
100,000 newborns. The resulting survival curve is shown alongside
the one produced without the intervention. It is specific to a certain
year.

Life expectancy at birth The increased survival will also affect the life
expectancy at birth. For a certain year, Prevent will show the life
expectancy in the starting year of the simulation, the life expectancy
as a result of trends and the life expectancy in the population with
an intervention.

EF, PIF, TIF There are also intermediate outcome variables. Prevent
will offer the option of EF's, PIF's and TIF's as effect measurements.

Chapter 4

Computer model Prevent[1]

In this chapter we will describe the actual Prevent computer model. The general class of models Prevent fits into is that of simulation models. Mathematically the model is a set of difference equations, that cannot be solved analytically. Thus numerical methods are used. The simulation step is one year.

The model consists of two main parts: a proportions model (step 1), in which P's and IDR's are transformed into PIF's, TIF's and EF's, and a population model (step 2), in which the TIF's and PIF's are used to calculate new disease specific mortality rates, and the trend and intervention populations.

Two new elements were added to the computer model which were not discussed previously in the methodological chapter: the "cohort" or "age group" calculations in step 1 and the IDRfac.

With the introduction of the time dimension and the stratification of exposure P by age, the problem arose what to do with the prevalence of risk factors in different age groups as the population ages. Prevalences of exposure or changes in prevalence can either be considered specific to an age group or to a birth cohort. If one assumes that the prevalence of a risk factor is specific to an age group, an aging birth cohort will take on the exposure values of the next age group. If however, risk factor prevalence is assumed to be cohort specific, prevalences in age groups will change over time as different birth cohorts move into that age group. Since both models can be used for different risk factors in Prevent, both computation methods will be discussed.

IDRfac is a variable with which an IDR of a certain exposure group can

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[1] By Jan Barendregt and Louise Gunning-Schepers.

be multiplied and which may change over time. It was used in the historical
testing (see chapter 8) to simulate the effect of changing exposure intensities
over time. In the basic Prevent runs it is set to 1 but we will briefly show
how it is incorporated in the calculations.

4.1   The proportions model

P, the proportions of the population exposed to a risk factor in different
exposure categories, are considered by age group, and by sex. The propor-
tions non exposed (defined as never exposed), exposed and ex-exposed, are
three stock variables connected by two flows: one from the non-exposed to
the exposed,the inflow[2], and one from the exposed to the ex-exposed, the
outflow (see figure 4.1 and 4.2). Both can be the result of an autonomous
trend or an intervention. There are always (LAG + 1) levels of risk: one
for the exposed and LAG for the ex-exposed.

Figure 4.1: Simple flows between stocks
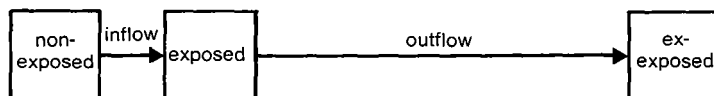
Figure 4.2: Flow from exposed to ex-exposed in discrete steps
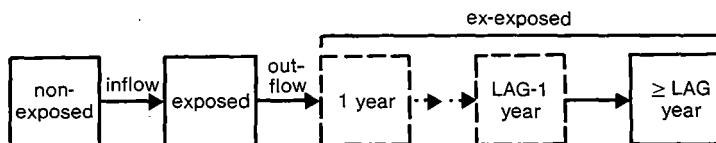
Two additional remarks need to be made:

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[2]This flow from non-exposed to exposed is calculated as a percentage of the exposed.

- There is no lead time in the model. Any proportion shifting from non exposed to exposed gets the exposed IDR in the following year.

- There is no flow back from the ex-exposed to exposed. Once a proportion has shifted to 1 year old ex-exposed, that proportion will inevitably end up as (LAG and over) year old ex-exposed.

As explained earlier, exposure is stratified into categories. Each exposure category has it's own IDR, possibly it's own remnant IDR and it's own set of associated proportions over ex-exposure levels. However all categories share the same pool of non-exposed (figure 4.3).

Figure 4.3: Flows with more than one exposure category

ex-exposed

category 1 | exposed | out-flow | 1 year | ... ... | LAG-1 year | ≥ LAG year

non-exposed | inflow

category 2 | exposed | out-flow | 1 year | ... ... | LAG-1 year | ≥ LAG year
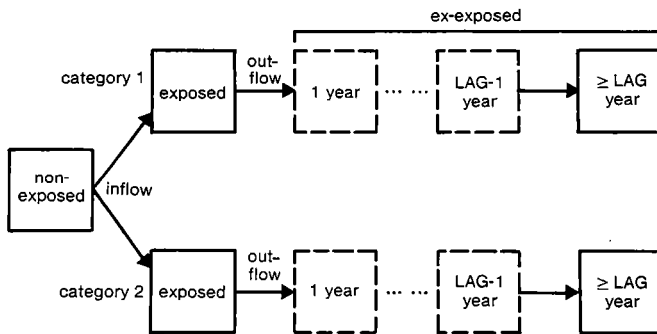
Within the model:

- Each category has it's own inflow and outflow trends.

- The simplifying assumption is made that in each category the ex-exposed need the same LAG number of years to arrive at the remnant IDR.

- The sum over all levels and categories of the proportions exposed plus the proportion non exposed always equals 1.

4.1.1 Shift in proportions due to trends

In the cohort version we assume that risk factor prevalence or changes in risk factor prevalence are not age dependent, but are characteristic of a cohort. The prevalences in age groups change as cohorts move in and out, with the aging of the population. With each year's simulation step not only

Figure 4.4: Shift of proportions at each time step
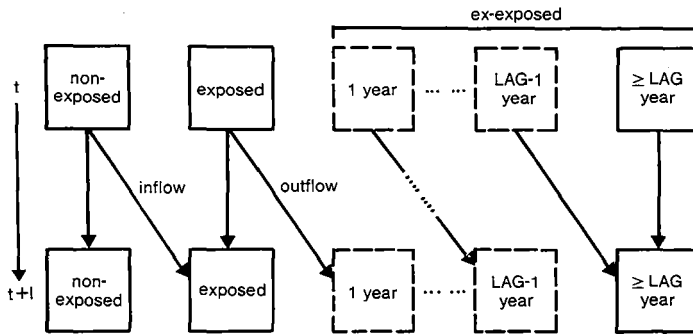
trends are applied and proportions shifted, but the age index is increased by 1 (figure 4.4).

Two points need to be decided on: what to do with the youngest and the oldest (95 and over) age groups. The youngest age group will take on the prevalences of exposure of the previous cohort in that age group, after that years trends have been applied. Moreover, it is assumed that there are no ex-exposed in the youngest age group, so the proportion non exposed equals (1-proportion exposed). The oldest age group, of 95 and over, each year is assigned the exposition of the 94 years old of the previous year, again after applying trends.

The available input data are not as detailed as is required here. At time 0 the proportions non-, ex- and currently exposed have an age group stratification. In the cohort version of the model those proportions will be applied to as many 1 year groups as will fit into that particular age group. Trends in prevalence continue to be specified by age group.

Let:

- A: 1 year age index, $A = Amin, \ldots, 95$.

- $Amin$: lowest age at risk.

- t: index for time.

- i: index for time since cessation of exposure.

- $P_t^{A,ID}$: proportion exposed.

- $P_t^{A,0}$: proportion non exposed.

- $P_t^{A,1}$: proportion ex-exposed after LAG years or more.

- $P_t^{A,i}$, $i = 2, \ldots, ID - 1$: proportion ex-exposed less than LAG years.

- $ID = LAG + 1$, i.e. the number of levels of ex-exposure.

- $rplus_t^A$: inflow trend in exposure.

- $rmin_t^A$: outflow trend in exposure.

$$P_{t+1}^{A+1,ID} = P_t^{A,ID}(1 - rmin_t^A + rplus_t^A) \tag{4.1}$$

$$P_{t+1}^{A+1,ID-1} = P_t^{A,ID} rmin_t^A \tag{4.2}$$

$$P_{t+1}^{A+1,0} = P_t^{A,0} - P_t^{A,ID} rplus_t^A \tag{4.3}$$

$$P_{t+1}^{A+1,i} = P_t^{A,i+1}, \; i = 2 \ldots ID - 2 \tag{4.4}$$

$$P_{t+1}^{A+1,1} = P_t^{A,1} + P_t^{A,2} \tag{4.5}$$

$$P_{t+1}^{Amin,ID} = P_{t+1}^{Amin+1,ID} \tag{4.6}$$

$$P_{t+1}^{Amin,i} = 0, \; i = 1 \ldots ID - 1 \tag{4.7}$$

$$P_{t+1}^{Amin,0} = 1 - P_{t+1}^{Amin,ID} \tag{4.8}$$

Remarks:

- indices for category and sex are suppressed.

- $P_t^{A,0}$ and $P_t^{A,ID}$ are constrained to be ≥ 0.

- the trends are not specified in 1 year age groups, but in the same age groups as in the age group version.

In the age group version of the model the proportions are shifted over time as follows: Let,

- A: index for age group.

$$P_{t+1}^{A,ID} = P_t^{A,ID}(1 - rmin_t^A + rplus_t^A) \tag{4.9}$$

$$P_{t+1}^{A,ID-1} = P_t^{A,ID} rmin_t^A \tag{4.10}$$

$$P_{t+1}^{A,0} = P_t^{A,0} - P_t^{A,ID} rplus_t^A \tag{4.11}$$

$$P_{t+1}^{A,i} = P_t^{A,i+1}, i = 2 \ldots ID - 2 \tag{4.12}$$

$$P_{t+1}^{A,1} = P_t^{A,1} + P_t^{A,2} \tag{4.13}$$

Remarks:

- indices for category and sex are suppressed.

- $P_t^{A,0}$ and $P_t^{A,ID}$ are constrained to be ≥ 0.

4.1.2   Proportions and IDR's, or PIDR's

For further calculations the PIDR's are needed, the sum product of P and IDR, for all exposure categories and ex-exposure levels within one age, sex group.

The model's database contains IDR's by disease and risk factor for the currently exposed. It also specifies the remnant IDR and the LAG. By way of a linear interpolation the intermediate ex-exposure levels are assigned an IDR.

$$IDR^{z,i} = \frac{(IDR^{z,ID} - IDR^{z,1})}{LAG}(i-1) + IDR^{z,1} \tag{4.14}$$

Where:

- z: index for disease;

- ID=LAG+1;

- i: index for time since cessation, from 0 (i=ID) to $\geq$LAG years (i=1);

- indices for risk factor, exposure category, age and sex are suppressed.

Because the model includes a LAT time dimension, proportions exposed ('P') and IDR's cannot simply be multiplied to arrive at the right PIDR. When proportions at time t are multiplied with the IDR's, we will get PIDR's at time $t + LAT$. To get PIDR's at $t = 0$, we need proportions at $t = -LAT$.

Prevent calculates past proportions, using past trends and current proportions non-, ex-and currently exposed. The proportions at $t = -LAT$ are used to calculate PIDR's at t=0, proportions at $t = -LAT + 1$ give PIDR's at $t = 1$, etc.[3]

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[3]The ex-exposed are as a rule not differentiated by the number of years since exposure ceased, so we need past trends. We reconstruct past prevalences by putting equations (4.1) and (4.3) in reverse, each year subtracting $rmin_t \times P_t^{ID}$ from the pool of ex-

All proportions P are now multiplied with the associated IDR's, summing over exposure categories and levels and thus producing PIDR's. Then the proportions are shifted, trends applied, time updated one year and once more proportions and IDR's are multiplied etc.

If the IDRfac is used, the PIDR becomes:

$$PIDR_t^{r,j,z,s,A} = \sum_{n=1}^{cn} \sum_{i=0}^{ID} P_{t-LAT^{r,z}}^{r,j,s,A,n,i} IDR^{r,z,s,A,n,i} IDRfac_t^z \qquad (4.15)$$

Where:

- cn: number of exposure categories;

- n: index for exposure category;

- r: index for risk factor;

- ID: number of years since cessation ;

- i: index for ex-exposure level;

- j=0,1: index for reference (0) or intervention population (1).

- A: index for age;

- s: index for sex;

- z: index for disease;

- t: index for time.

Three remarks must be made here:

- In the basic runs presented in the following chapters the time dependent variable IDRfac is always 1. It has been used only when testing the model (see chapter 8).

- One risk factor may influence several diseases each of which may have a different LAT. Prevent always starts at $t = -LAT$ with the disease with the longest LAT.

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exposed. If there are at t=-LAT still ex-exposed left, these are assigned to there proper place by calculating the proportions exposed from t=-LAT to t=-(LAT+LAG), again subtracting $rmin_t \times P_t^{ID}$ from the ex-exposed and putting it in $P_{-LAT}^{ID+LAT-t}$. If at $t = -(LAT + LAG - 1)$ the pool of ex-exposed is not exhausted, then the remaining proportion is assigned to P_{-LAT}^1, or the $\geq LAG$ year old ex-exposed.

- PIDR's (and TIF's, PIF's and EF's as well) are aggregated to 20
  5-year age groups (0-4,5-9,...90-94, 95 and over), since the disease
  specific mortality rates, that are used in the population model, are
  for 5 year age groups. In the cohort model, PIDR's are calculated
  as the mean of 5 one-year cohorts, in the age group model the PIDR
  calculated for one age group will be assigned to each 5-year age group
  within that age group. PIDR's for those age groups that are consid-
  ered not to be at risk, are set to 1.

PIDR's thus calculated concern the reference populations and can be used
to calculate TIF's. For the intervention population the cycle is reiterated
to take the intervention's shift in P into account.

4.1.3 Shift in proportions due to interventions

Interventions in the Prevent model are defined as changes in the prevalence
of one or more risk factors. Usually these will be reductions in risk factor
prevalence, although it is of course also possible to simulate an increase in
risk factor prevalence. Only the cohort model allows for a direct definition
of prevalence in the birth cohort entering the model at a certain time.

General intervention With a general intervention, the user can specify
new proportions of currently exposed by category, sex and age group.
If the intervention is a reduction in prevalence, i.e. if the new pro-
portion is lower, then some the currently exposed become next years
one year old ex-exposed. If positive, some non exposed will shift to
next years proportion exposed.[4] There are three characteristics of a
general intervention which can be defined:

1. All exposure groups (age, sex and exposure categories) can be
   given the same percentage change, or new prevalence proportions
   can be specified by group.
2. The year of intervention can be specified, default is 1985.
3. The intervention can be spread over more than one year (one year
   is default). If this option is chosen, then the proportion currently
   exposed will decrease (or increase) with the same percentage
   each year, so every year a diminishing (or increasing) proportion
   will shift into the 1 year old ex-exposed (or currently exposed).

Prevalence for the youngest one-year age group The second inter-
vention possibility, in the cohort version of the model only, is to

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[4]Interventions are supposed to happen end of period, i.e. an intervention in 1985 is
supposed to happen at the very end of that year and will take effect in 1986.

specify the prevalence of the risk factor for the youngest cohort at risk, by exposure category, sex and year. The default is that the youngest cohort at risk gets the same proportion currently exposed as the one year older cohort. This option allows the user to specify a proportion currently exposed between (and including) 0 and 1.

Unless the user decides to do no intervention at all, in which case the PIDR's of the 'intervention' population are identical to those of the reference population, Prevent starts the proportions model again, applying the same trends on the new proportions (resulting from the specified intervention) and calculating a second set of PIDR's.

With the two sets of PIDR's the next step is taken.

4.1.4   From PIDR's to TIF's, PIF's and EF's

As mentioned before, Prevent allows interventions on more than one risk factor simultaneously. PIF's and TIF's need to be disease specific but not risk factor specific. When calculating them from the two sets of PIDR's, Prevent will sequentially consider all the risk factors that affect a certain disease even if no intervention took place. Prevent aggregates all the risk factor disease specific PIF's into one disease specific PIF using equation 3.7. The same procedure is also applied to the TIF's using equation 3.8.

The EF's, on the other hand, are not aggregated, they are stored to disk, disease and risk factor specific, and are only used as output measures. They are calculated by equation 3.2. The PIF's and TIF's thus calculated, for the complete simulation period will be applied to the age, sex specific disease mortality quotients in the population model.

4.2   The population model

The population model is always a cohort model, the option 'cohort or age group' only exists in the proportions model. The population model consists of two parallel populations: one the reference, the other the intervention population. Each is divided into two sexes and 96 age groups (0-95).

In the basic runs, that are discussed in chapters 8-11, the populations at $t = 0$ (=1985) are both set equal to the population of the Netherlands on January 1, 1986, assuming that population to be equal to that of December 31, 1985 (65). For the general mortality, the mortality quotients as calculated over the period 1980-1984 (66), and the associated life expectancies from the same source are used. All these are in 1 year age groups.

The CBS prognosis for future mortality rates are not used, since the expected decrease in mortality depends, among other things, on expecta-

tions of decreasing risk factor exposition. In Prevent the user can specify his own expectations on future risk factor prevalence, and mortality will be adjusted accordingly.

For the number of births the CBS prognosis (medium variant) is used until 2000, thereafter the number of births is kept constant at the 2000 level.

The disease specific mortality quotients are calculated from the numbers of deaths from these diseases[5]. These figures are in 5 year groups, by primary cause of death in 1985 (67).

For the reference population the TIF's are applied to adjust disease specific mortality quotients, while for the intervention population both the TIF's and the PIF's are applied (see equations 4.16 and 4.17).

$$M_t^{0,s,A} = M^{s,A} - \sum_{z=1}^{zt} TIF_t^{z,s,A} M^{z,s,A} \tag{4.16}$$

$$M_t^{1,s,A} = M^{s,A} - \sum_{z=1}^{zt} \left[1 - \left(1 - TIF_t^{z,s,A} \right) \times \right.$$

$$\left. \left(1 - PIF_t^{z,s,A} \right) \right] M^{z,s,A} \tag{4.17}$$

Where:

- $A = 0, \ldots, 95$: one year age index.

- $s = 1, 2$: index for sex.

- $z = 1, \ldots, zt$: index for disease.

- zt : total number of diseases involved.

- $j = 0, 1$: index for reference (0) or intervention population (1).

- $M^{s,A}$: constant overall mortality quotient.

- $M_t^{j,s,A}$: adjusted overall mortality quotient.

- $M^{z,s,A}$: disease specific mortality quotient.

---

[5]We have used the following classification (ICD ninth revision): lung cancer, ICD 162; breast cancer, ICD 174;ischemic heart disease, ICD 410-414; cerebrovascular accident, ICD 430-438; COLD, ICD 490-496; cirrhosis of the liver, ICD 571;traffic accidents, ICD E810-E819; accidental fall, ICD E880-E888.

The overall mortality quotient is in one year age groups, and the disease specific quotients, TIF's and PIF's in five year age- groups.

The resulting two sets of mortality quotients are used to calculate next year's reference and intervention population by the following equations:

$$POP_{t+1}^{j,1,0} = 0.515B_t(1 - M_t^{j,1,0}) \tag{4.18}$$

$$POP_{t+1}^{j,2,0} = 0.485B_t(1 - M_t^{j,2,0}) \tag{4.19}$$

$$POP_{t+1}^{j,s,A} = POP_t^{j,s,A-1}(1 - M_t^{j,s,A-1}) \tag{4.20}$$

$$POP_{t+1}^{j,s,95} = POP_t^{j,s,95}(1 - M_t^{j,s,95}) + POP_t^{j,s,94}(1 - M_t^{j,s,94}) \tag{4.21}$$

Where:

- $A = 1, \ldots, 94$: one year age index.

- $s = 1, 2$: index for sex.

- $j = 0, 1$: index for reference (0) and intervention population (1).

- B_t : number of births.

- $M_t^{j,s,A}, j = 0, 1$: adjusted overall mortality quotient.

Remarks:

- Births are divided into male (.515) and female (.485), (cf. eq. 4.18 and 4.19).

- Eq. 4.21 describes the age group of 95 and over.

- Migration is assumed not to occur.

In the population model several output measures (as defined in the previous chapter) are calculated, all based on mortality.

- Disease specific mortality: calculated for both the reference and the intervention population by multiplying disease, age and sex specific mortality quotients with the one year age groups and summing over age.

- Disease specific mortality difference: calculated by subtracting the disease specific mortality of the intervention population from the reference population.

- Overall mortality: calculated for reference and intervention population and summed over age.

- Mortality difference: calculated by subtracting overall mortality of the intervention population from that of the reference population.

- Potential years of life gained: calculated by multiplying age specific mortality difference with the current life expectancy of that particular one-year age group, and then summing over age.

- Actual years of life gained: this is calculated by each year, subtracting the intervention population from the reference population.

- Survival curve. This is simulation year specific and is calculated by applying the adjusted total mortality quotients of the specified year to an initial population of 100,000 newborns.

- Life expectancy at birth. This is simulation year specific and is calculated by applying the adjusted total mortality quotients to an initial population of 100,000 newborns, and dividing the resulting total number of years lived by 100,000. The value for 1985 comes from the Central Bureau of Statistics (CBS).

Apart from these output measures the PIF's, TIF's and EF's are available for output as well.

4.3 Some general remarks on the implementation

One of the objectives of the project was that Prevent could be used directly by policy makers. Special care was taken to make the model easy to use: Prevent is interactive, menu driven, the user is asked to input as few data as possible, and usually default values are available. Output is available in both graphic and tabular form. It runs on most IBM PC compatibles.

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Part III

THE INPUT DATA FOR PREVENT

Introduction and summary

During the work on the Dutch health policy paper "The Health 2000 Report" a health model was developed with major emphasis on the determinants of health, paving the way for more interest in policy measures in the preventive and intersectoral field. During this exercise an attempt was made to estimate the relative contribution of each of the health determinants, to the health status of the Dutch population. The problems encountered during this quantification effort have been reported elsewhere (1,2). A direct result of these quantification problems was the research proposal on which this project has been based. This entailed that the methodology that would be developed should also be applied to Dutch data.

In the previous section the main emphasis has been on the conceptual and methodological aspects of this project. In this section we shall look at the data collection necessary to apply the Prevent model to policy making for the Dutch population in order to achieve the second objective stated in chapter 1: "To distill from existing epidemiologic studies the data necessary to apply the Prevent tool to policy making in the Netherlands."

Since the results are primarily intended for policy making the choice of the disease categories to include in the project was determined by criteria, relevant to public health policies:

1. the disease had to contribute significantly to the ill health of the Dutch population,

2. the disease should have known risk factors upon which interventions can reasonably be applied.

The research proposal specified that the project should concentrate on three main categories of disease that contribute significantly to premature mortality, morbidity and invalidity in the Netherlands. These three main groups were: cardiovascular disease, cancers and accidents.

Together they represent:

- 76% of total mortality (average '76-'80)

- 72% of potential years of life lost (average '76-'80)

- 25.7% of hospital admissions (1982)

- 17.1% of invalidity pensions (1983)

Within these three main categories the following eight diagnostic entities (ICD, ninth revision) were specified:

-Ischemic Heart Disease (IHD)	(ICD 410-414)
-Cerebrovascular Diseases (CVA)	(ICD 430-438)
-Cancer of the lung (Lungca.)	(ICD 162)
-Cancer of the breast (Brstca.)	(ICD 174)
-Cancer of the colon (Colonca.)	(ICD 153)
-Cancer of the stomach (Stomachca.)	(ICD 151)
-Traffic accidents (Tr. acc.)	(ICDE800-E848)
-Other accidents (Oth. acc.)	(ICDE849-E999 except
(except suicide and homicide)	E950-E969)

Table 5.1 shows the burden of ill health occasioned by these eight disease categories in more detail. They are a logical starting point for a risk factor intervention study.

First the risk factors, generally accepted and well documented, for each of these disease categories were identified. In the following phase we searched in the opposite direction and tried to identify the most important diseases known to be (partly) influenced by the risk factors identified in the first phase. Both steps will be summarized in the chapter 5. The necessary quantification of these relationships will be made explicit in chapter 6.

In the search for the risk factor-disease combinations to include in the current version of the Prevent model, preference was given to those for which there is sufficient evidence of the causality of the relationship. Not only in the sense that exposure to the risk factor influences disease incidence but also the fact that that influence is reversed once exposure ceases. This meant that for certain diseases such as stomach cancer the evidence on the etiology was as yet insufficient to include the disease in the model. For other diseases such as colon cancer there appears to be a causal relationship with exposure to certain risk factors but there is not yet a consensus about the quantification of the relationship is still uncertain. In that case the particular risk factor-disease combination was not included in the current version of the model.

Table 5.1: Burden of disease in 1985 for major diagnoses

	Incidence per100,000		Mortality per 100,000		Hospital Adm. per 100,000		Hospital days	
	M	F	M	F	M	F	M	F
Cardiovascular Disease	-	-	391	340	1474	1010	14.8	18.2
myocardial infarct	370	390	171	107	280	113	16.0	17.2
ischem. heart disease	-	-	39	27	322	139	9.7	12.8
cerebrovasc.acc.	-	-	71	93	178	161	23.5	29.5
Cancers	335	329	266	187	821	996	17.5	16.6
larynx, lung	95	11	105	12	196	24	18.9	21.5
breast	1	97	-	40	1	144	19.0	18.7
cervix	-	30	-	4	-	47	-	11.5
colon	22	27	18	21	29	34	26.5	30.9
stomach	23	13	22	13	35	18	23.1	28.3
liver, gallbladder	4	8	5	8	-	-	-	-
Accidents	-	-	35	24	847	628	14.0	20.6
occupational	908	73	1	-	39	2	-	-
traffic	489	266	18	7	212	110	17.2	18.9
other	2210	2340	16	17	-	-	-	-

Source: 234

For the calculations in Prevent three types of data are needed: data on IDR for all exposure categories, data on the prevalence of risk factors in the Dutch population and data on the time dimensions.

The IDR data proved to be abundant and for most risk factors relatively consistent once corrected for different characteristics of the population studied. This supports the hypothesis that the relative risk is a biological constant. In the previous section it was shown that given the assumption of an independent distribution of risk factors and multiplicative relative risks, the existence of unknown confounders in the population of the study will not affect the relative risk found. Thus relative risk estimates can indeed be transferred from one population to another as long as they are stratified by age, sex, and exposure category. This stratification of the relative risks is an essential element for the causality of the Prevent model, so IDR values were used with as much detail as possible. In some cases additional dimensions were only available without for instance age stratification, in those cases precedence was given to the dimensions age, sex and exposure category.

The most difficult IDR value to determine was the remnant IDR after cessation of exposure. Although many studies examine the effect of exposure on disease incidence, cessation of exposure, especially in the general population, is far less frequently studied. Since the time between first ex-

posure and mortality is often very long in chronic disease epidemiology, a preventive policy that aims at health benefits in the near future, will have to concentrate on both prevention and cessation of exposure. The extent to which the relative risk is reduced after cessation of exposure is therefore of great importance in policy making. For some risk factors we had to rely on expert judgement to determine the remnant IDR.

The second category of required data is on the prevalence in the Dutch population of the risk factors for which IDR data existed. Those were usually available, although such data are often collected only after evidence of a risk factor-disease relationship has been found in other countries. This was one of the reasons why the risk factors finally incorporated in the Prevent model are by necessity the more obvious ones. Most of the prevalence data were stratified by age, sex and exposure category and where the exact categories did not coincide with those used for the IDR data, the data were converted. Only in a few cases data were available over a number of years so that trends in prevalence could be deduced.

For some risk factors the prevalence data do not stem from a representative sample of the Dutch population. In chapter 8 several initial prevalence input data were applied to see whether the model is very sensitive to small variations in the initial risk factor distribution.

Finally data are needed concerning the time dimensions LAG and LAT. For some risk factors these could be deduced from the longitudinal studies with sufficient length of follow up, for others these data could not be found and again had to be supplied by expert judgement.

The following chapters will give a brief overview of the epidemiologic literature from which the data were derived. In the appendix C a short summary of the values of the input data is given and some of the summary tables of trials published elsewhere are included in appendix B.

Chapter 5

The choice of variables

5.1 Diseases and their risk factors

Two criteria were applied to decide which risk factors to include in this version of the model: the availability of good quantitative data, and the magnitude of the effect of the risk factor on the populations health.

1. Quality of the evidence

   Since the quantification in this model is primarily meant for policy making rather than for hypothesis generation, those risk factors for which a reasonable consensus exists about their influence on disease incidence, were most interesting. In most reviews the traditional epidemiological criteria such as consistency, strength, specificity, coherence and temporal relationship of the association, were applied to determine causality. However the quantity and the quality of the evidence varied considerably. This meant that for some disease categories or risk factors the quantitative evidence was as yet insufficient to include them in the current version of the model.

2. Magnitude of the influence

   The magnitude of the overall influence of a risk factor on the health of a population was the second important criterion. Several variables determine the magnitude of the influence of a risk factor (intervention) on the health of a population.

   - The relative risk, which quantifies the extent to which a certain exposure will increase the individuals absolute risk of getting a specific disease.

- The prevalence of the risk factor in the population, which, together with the relative risk, will determine the influence of a risk factor on the incidence of a specific disease at the population level.

- The relative importance of the disease category in question for the health benefit measure used.

Risk factors that have a low relative risk such as hypertension will be included because of the high prevalence of hypertension in the population and because of the importance of IHD in the mortality of the Dutch population, while a risk factor such as asbestos with a very high relative risk will be omitted even though lung cancer is an important cause of death, simply because so few people are exposed to asbestos nowadays.

5.1.1 Ischemic Heart Disease

Figure 5.1: The risk factors for Ischemic Heart Disease
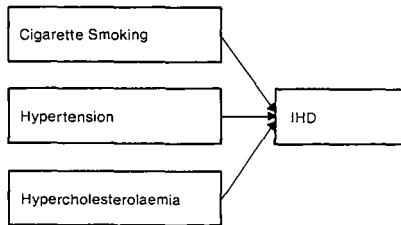
Cardiovascular disease, with special emphasis on acute myocardial infarction and other ischemic heart disease, has received considerable attention in recent decades: the epidemic of premature death due to ischemic heart disease among middle-aged men in the 1950's and 1960's did indeed warrant such attention (3-11).

Initially epidemiological research concentrated on identifying the risk factors in that epidemic. The Framingham Study (4, 12, 13) in the US, is maybe the best known of the many prospective studies that have identified subgroups in the population that were apparently at a greater risk of developing ischemic heart disease (5, 11, 13, 15-35). They were followed by an even larger number of studies attempting to measure the effect of interventions on these risk factors (36-69).

Many different risk factors were hypothesized: serum cholesterol levels, hypertension (systolic and diastolic), cigarette smoking, level of physical activity, Type A personality, lipoproteins LDL and HDL (70), diabetes, etc. The final conclusion from the literature has been that there are three independent, major risk factors identified that are important in the occurrence of ischemic heart disease (71-75)

- Hypertension

- Hyperlipidemia (serum cholesterol, LDL and the protective influence of HDL)

- Cigarette smoking

On the relative importance of these three risk factors authors may still disagree. Goldman (76) claims that changes in serum cholesterol and smoking habits are responsible for more than half of the considerable decline in IHD mortality rates in the US between 1968-76, while Pell (77) in the DuPont Company Study, identifies "improved control of hypertension as a major factor in the declining incidence of coronary heart disease".

The intervention studies, of which the MRFIT (40) study attracted much interest, have not yielded the expected positive results. Although in theory it was easy to identify "the right thing to do" (78, 79), the effect of the risk factor intervention is not yet conclusively agreed upon (37, 41, 80-86).

These disappointing effects have generated a discussion on the possibility and the acceptability of different preventive interventions, such as population versus high risk approach or lifestyle changes versus medication (36, 42, 45, 62, 69, 87-92).

5.1.2 Cerebrovascular Disease

Figure 5.2: The risk factor for cerebrovascular disease

Although cerebrovascular disease encompasses a number of different disease processes (for instance ischemic cerebrovascular disease, and hemorrhages), these distinctions are not always correctly made in mortality statistics. In most epidemiological studies therefore, the diagnoses are considered at an aggregated level.

Contrary to the ischemic heart disease, there has been a reduction in cerebrovascular disease mortality both for men and for women for some decades. The most important risk factor identified in CVA remains hypertension. In some instances it is suggested that hypertension is only an intermediate risk factor, which itself can be influenced by diet, (47, 93), oral contraceptives (94) or alcohol (95). Intervention trials have shown a marked improvement in CVA mortality. Randomized trials on the treatment of mild hypertension pooled together (87) seem to indicate that even a small lowering (7 mm Hg) of blood pressure over longer periods of time could result in large gains in preventing premature mortality due to stroke.

5.1.3   Lung cancer

Figure 5.3: The risk factors for lung cancer
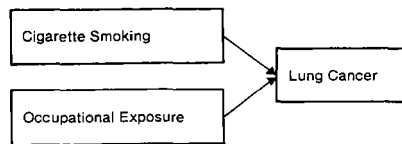
Lung cancer may perhaps be viewed as the prime example of the contribution that epidemiological research can provide towards the understanding of a chronic disease epidemic in a population. Although Doll and Hill's publication in 1950 (96) is often viewed as the first study presenting reliable data on the relationship between cigarette smoking and lung cancer, some skepticism continued to exist even after its wide acclaim (97, 98). Many similar studies were set up to find correlations between cigarette smoking and lung cancer. They all confirmed the relationship found by Doll (99-105). The result was among others that governments took an interest in smoking as a major threat to the populations health.

As early as 1964 the US Department of Health published the first of what would prove to be a long succession of reports from the Surgeon General on Smoking and Health. The British DHSS and the WHO also produced reports on the subject.

Nowadays there is little doubt about the strong causal relationship between cigarette smoking and lung cancer. The causal nature of the relationship has recently been further reinforced by reports of a falling lung cancer mortality rate, presumably due to a drop in the prevalence of cigarette

smoking (106-109).

Probably several factors are involved that ultimately decide which individual will develop lung cancer: for instance a genetic component (110) or an excess risk in those exposed to occupational hazards such as asbestos or ionizing radiation. But even within these subcategories smoking will greatly enhance the risk of ultimately developing lung cancer.

5.1.4 Breast cancer

Figure 5.4: The risk factors for breast cancer
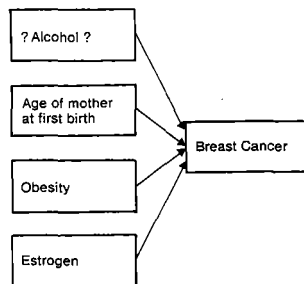
The incidence of breast cancer is of particular importance in industrialized countries where it usually is the most frequent cause of cancer mortality in women. The Netherlands are no exception, in fact their age adjusted death rate for this disease is one of the highest in the world.

Some interesting hypotheses for possible risk factors have been postulated by epidemiologists (review by Kelsey 111). It appears beyond doubt that there is a genetic predisposition to breast cancer that is important: in general a 2 to 3 fold increase in risk has been reported in women with a first degree relative affected. In a few situations there appear to be even higher associated risks.

Because of the nature of the organ involved it is not surprising that some of the hypotheses explored have been in the field of the reproductive variables. It now seems well established that an early first birth (i.e. full-term pregnancy) can be considered a protective factor. There is some suggestion that high parity also has a protective effect, independent of the age at first birth. Breast feeding, once thought to reduce the risk, appears to be unimportant once a correction for parity has been made. Age of menarche however remains of importance.

A logical sequence to the interest in reproductive variables, was the investigation of the role of hormones in the risk pattern of human breast cancer. Both endogenous hormones and exogenous estrogen were reviewed (112-119). There has been consistent evidence that estrogen increases the risk of breast cancer, resulting among others in a suggestion at one point to adopt tamoxifen (an anti-estrogen drug) as a preventive measure (120). The latest results of the "nurses study" in the US, reported by Lipnick (121), however suggest only a very slightly elevated risk in pre-menopausal women who currently use oral contraceptives.

The other large field of hypotheses lies in the direction of diet, obesity and body build (122-125). Intercountry studies have shown a very strong association between total dietary fat intake and age adjusted breast cancer death rates.

Even differences within countries, regionally as seen in England (126) or between sub populations such as the Seventh day Adventists in the US population, have shown positive correlations between fat intake and breast cancer mortality. However these studies are not considered definite proof of a direct causal relationship. One of the hypotheses postulated has been that obesity is the intervening variable explaining the relationship (127). Measures of body build such as weight, weight/height ratio's, height and total body mass have been explored among others by de Waard (125, 128, 172).

Recently alcohol consumption has been implicated in the occurrence of breast cancer. The results of different studies (129-131) remain contradictory but the hypothesis deserves to be explored more fully since even a very weak association would be of considerable importance because of the widespread consumption of alcohol in industrialized countries.

Finally, one interesting finding of the epidemiological studies on breast cancer, has been the distribution of cases over socioeconomic classes. Contrary to most other causes of death the risk of breast cancer is higher among the higher socioeconomic classes (22, 132). Whether this is due to an uneven distribution of the above mentioned risk factors over the socioeconomic classes has not yet been fully established.

5.1.5   Colon cancer

In recent reviews of the literature concerning possible explanations for the variation in the occurrence of colon cancer (125, 133, 134) the suggestion was made that the reported incidence is greatly influenced by diagnostic traditions. The correlation between the incidence of colon cancer and rectal cancer suggests that there is no clear distinction between the two categories (135).

Figure 5.5: The risk factors for colon cancer
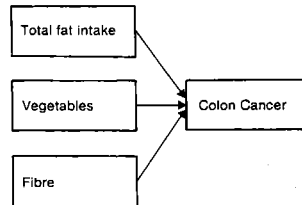
In both instances, but particularly in the case of colon cancer, dietary variables have been suggested as possible risk factors (136). In their intercountry study Armstrong and Doll (137) identified a strong correlation between total fat intake and meat consumption or animal protein content in the regular diet, and the occurrence of colon cancer. Phillips (138) found an association, within the Seventh day Adventist population, of several more specific food items such as coffee, meat, dairy products and green salad. Total weight was also negatively implicated, not only in persons who are overweight as would be expected, but also in those who are more than 10% underweight. It has been suggested that the underlying mechanism of the influence of dietary factors is represented by the endogenous production of bile acids, and that one of the important intervening variables is the speed of passage of the stool through the colon. Factors that appear to be of interest in this respect are fibre content of the diet (139), which increases stool bulk and helps dilute bile acids, and physical activity which tends to stimulate colon peristalsis (140-142). Another protective agent against bile acids and hence against colon cancer, appears to be the presence of calcium salts.

In Millers review article for the IARC (125), two additional factors are discussed: the apparent protection provided by cruciferous vegetables and the still unresolved controversy over the relationship between serum cholesterol and colon cancer. Results from preventive intervention trials for cardiovascular disease (for instance the MRFIT and the WHO clofibrate trials) revealed an increased mortality from cancer in the intervention group, with a supposedly lowered serum cholesterol. However other studies have shown contradictory results, even implicating high dietary cholesterol levels as a risk factor in colon cancer (143-148).

Cambien (149) proposes as an explanation, that the lowered serum cholesterol is not a risk factor in colon cancer but that on the contrary

it is the direct result of the cancer disease process. Miller on the other hand suggests: "that high fat (and/or cholesterol) levels in the diet of individuals with a metabolism that maintains a low serum cholesterol, result in a high excretion of cholesterol breakdown products in the intestine....".

There have also been occupational factors implicated in the occurrence of colon cancer. Spiegelman (150) reports a large number of possible exposure effects most notably solvents, fuel oil and abrasives for men and solvents for women. She also reports a strong correlation with occupational stress especially with regard to "high demand low control" jobs.

5.1.6   Stomach cancer

Figure 5.6: The risk factors for stomach cancer
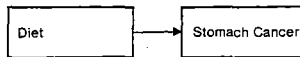
The point of interest in this particular type of cancer, to epidemiologists and health planners lies in the fact that the age specific incidence (and mortality) rates have been steadily going down in most countries for both men and women since the 1960's. The Netherlands form no exception as can be seen in from the CBS adjusted death rates, figure 5.7.

Figure 5.7: Mortality from stomach cancer in the Netherlands, indices of adjusted death rates, 1960=100
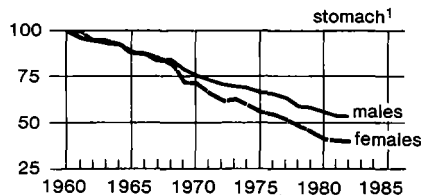
1960-1968 I.C.D. 1955 nrs.	[1]	151
1969-1978 I.C.D. 1965 nrs.		151
vanaf 1979 I.C.D. 1975 nrs.		151

Although several suggestions about possible causes for this decline have been put forward, for instance that of an improvement in the storage of food (due to refrigeration possibilities) and a subsequent decrease in the

contamination by micro organisms (135), no agreement has been reached beyond the fact that it seems to be the nutrition in childhood and early adult life that determines the incidence of stomach cancer.

Armstrong and Doll (137) have reported a negative correlation with total fat consumption as the strongest intercountry association with stomach cancer. Other dietary factors have been investigated. A recent case-control study, reported by Risch et al (151) found results that did not differ markedly from what they found in a review of the literature: it implicates nitrite, chocolate and carbohydrates as risk factors in stomach cancer, while dietary fiber, and citrus fruit intake (Vit.C. to a lesser extent) provided a protection against stomach cancer. At this moment we feel the quantitative evidence is not sufficient to include risk factors for stomach cancer in the model.

Accidents

Accidents in general, form an important cause of mortality and of use of medical services as a result of injury. Contrary to the other disease categories however, the risks involved are largely dependent on man made products and on individual behavior. Even the environmental variables that may influence exposure risk or injury risk are often created by man. The result is that types of accidents and injuries are very much culturally and geographically determined: what is considered dangerous driving on the crowded highway between Amsterdam and The Hague, is virtually without risk on lonely stretches of road for instance in Alaska, traditions of child rearing will make medicines and cleaning products a hazard in some countries, but much less so elsewhere.

Contrary to other disease categories there is no direct simple relationship between prevalence of risk factors and incidence of injuries. Some risk factors may influence the risk of accidents, while others will influence the risk of injuries as a result of the accident.

At both levels, risk factors and preventive interventions can be considered. Factors influencing the risk of exposure are mostly determined by the availability of the "object" containing a risk of accidents. Availability is the result of general socioeconomic developments and fluctuations outside the health field: new technological developments such as the invention of the automobile, postwar prosperity bringing the automobile within financial reach of many, the oil crisis of 1973 followed by a sharp reduction in the use of the automobile etc. Sometimes it is possible to intervene at this level for instance by strictly regulating the sales of dangerous products. However most often factors other than the health risks take priority. Exposure rates are often unavailable at population level.

The risk of accidents among the exposed is better quantified, in statistics about the number of automobile accidents per km. travelled or per hour exposed to traffic. These can be of interest for comparative studies over time or between countries, but since they are based on population averages there are no distinct exposure categories. Furthermore many accidents are not recorded either because they were too unimportant to involve the police or the insurance companies, or there were no personal injuries. The risk of accidents to the exposed therefore is likely to be under recorded. Risk factors of importance on this level concern the safety of the product and the behavior of the individual. In the latter we are not only concerned with "risk seeking behavior" or "accident proneness" but also for instance with the use of alcohol.

At a third level the number of injuries among all accidents is of interest. Here again the relevant statistics are often not available, since the total number of accidents is not known and there is often no connection between the registration of accidents on the one hand and the number and type of injuries on the other hand. Data are available on the type of activity or product involved per number of injured and type of injury. They do give an idea of the most frequently involved products or situations but they are not incidence rates.

The effect on mortality due to accidents is known for certain preventive interventions in the past, for instance on the use of motorcycle helmets. The changes in certain host characteristics, considered as risk factors, and the concurrent changes in the severity or lethality of certain injuries have sometimes been explored, such as osteoporosis for fractures of the lower extremities in the elderly (153).

In the following paragraph some risk factors at the individual level and some estimates of the preventive effect of certain regulations in the past will be presented, based on the available literature.

5.1.7   Traffic Accidents

Traffic accidents have been included in this study because of their importance as a cause of death. What makes them particularly relevant for a policy based on prevention is the fact that the victims are often young so that traffic accidents contribute substantially to premature mortality and to potential years of life lost. They are also responsible for a large category of the severely handicapped patients.

Looking at the age adjusted mortality due to of motor vehicle accidents over the last 35 years in the Netherlands, there is a rapid rise in the first two decades, followed by the equally rapid decline in the subsequent years.

Some of this trend may be due to the experience gained as a nation

Figure 5.8: The risk factors for traffic accidents
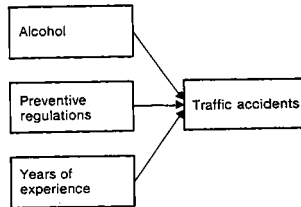
Figure 5.9: Hospital admissions by age and by type of vehicle 1982-83
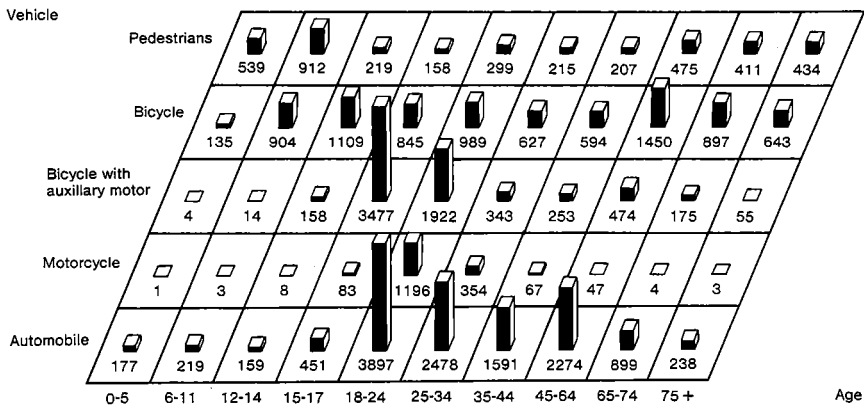
Source: 152

becomes motorized and used to the presence of automobiles. However some of the decline can be attributed directly to preventive measures (154). This does not only apply to motor vehicle accidents but also to motorcycle and bicycle accidents. Some of the measures mentioned have been: speed limits, compulsory seat belts, child restraints, motorcycle helmets, safety of the roads, visibility of cyclists etc.

Figure 5.9, the hospital admissions by age and by vehicle involved in the accident, shows a very distinct pattern, which has been confirmed in other countries. It appears that the age groups that just start participating in a certain type of traffic situation are most often victims of an accident. Young children (6-11 years) first walking to school alone, the 12-14 year olds first riding their bicycles alone, the 16 year olds allowed to ride a bicycle with auxiliary engine and the 18 year olds with their new drivers licence. As they gain experience with their particular vehicle the accident rate drops sharply, only to rise again when old age makes traffic participants vulnerable. The first element is interesting since it has nothing to do with increasing incidence with age often encountered in other disease categories, but is the result of a distinct influx of inexperienced first users at a certain age. As such this risk factor will be influenced by regulations determining age limits as well as by demography. The third risk factor to be included is the use of alcohol.

5.1.8 "Other" accidents

In the Dutch statistics other accidents are called "accidents in private life" to distinguish them from occupational and traffic accidents. It also makes them a very diverse rest group. They include: drownings, poisoning, accidental falls, sports accidents and all the cuts, fractures and other injuries that are serious enough to warrant medical attention. Some of them seem to be the inevitable consequence of living and especially of growing up. Not all of them can be prevented, although serious efforts are made, for instance through health education at the well baby clinics, to limit the more serious accidents. Because they are such a diverse group it is difficult to identify important risk factors,

We have therefore chosen to limit ourselves to the accidental fall, for two reasons: the elderly are most often seriously injured by an accidental fall, and it is an important cause of death but an even more important cause of disability and of dependency and institutionalization, especially for elderly women. With the increasing demographic shift towards the older ages it is therefore bound to be an important health problem in the years to come.

The other reason for this choice was the evidence of recent shifts in the incidence, particularly of hip fractures following accidental falls suggesting

an influence of exogenous risk factors possibly amenable to prevention (155).

The most likely hypotheses at the moment concentrate on the role of alcohol and osteoporosis.

Alcohol is involved in the *risk of accidents* while osteoporosis is a factor that influences the *risk of injury* following an accidental fall. Osteoporosis has received considerable attention in epidemiology lately (156), partly because statistics show a sharp concurrent increase of osteoporosis and of hip fractures (157, 158). Hoogendoorn (153) has shown that there is a sharp increase in hip fractures in the Netherlands and Duursma (157) has used data on trends in osteoporosis and hip fractures to estimate incidence in the future. It should be kept in mind however that these are based on hospital admission data and as such may not necessarily illustrate a rise in incidence.

Cummings (156) shows that osteoporosis is primarily a risk factor for post menopausal women. Estrogen has been identified as a protective factor for osteoporosis and post menopausal estrogen has been shown to be beneficial. Continuous (sometimes cyclical) use of estrogens for at least 5 years after menopause appears to reduce the risk of hip fractures by 50%. Other reproductive factors such as age at menarche and age at first full term pregnancy do not appear to be important.

Other risk factors investigated are in the dietary field. Obesity seems to protect against bone loss, possibly by increasing the amount of available estrogen. The evidence on calcium intake is controversial. Probably the diets of most western women contain insufficient calcium to prevent persistent net loss of calcium, especially after menopause, however the efficacy of calcium in the prevention of osteoporotic fractures is not proven. The recent consensus meeting on osteoporosis in the Netherlands (159) suggested an increase in the recommended daily calcium intake, not only for post menopausal women but also for children and young adults in an effort to increase the peak bone mass. Other dietary hypotheses such as the negative effect of our western levels of protein intake, and its influence on the phos-

Figure 5.10: The risk factors for accidental fall
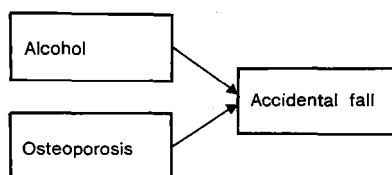
phorus/calcium balance (159, 160) are not yet sufficiently agreed upon to warrant interventions, except in an experimental setting. The same applies to fluoride therapy (161).

Physical activity appears to have some influence on peak bone mass in youth and on bone loss in the elderly. The Dutch consensus meeting has advised to include regular exercise in any therapeutic regimen (159).

Conclusions

From a survey of the existing evidence it is evident that often the same risk factors are implicated. There are several possible explanations for this phenomenon. It is quite conceivable that the strong correlation found between a risk factor and a disease inspires epidemiologists to investigate the same risk factor in relation to other diseases as well. This was certainly the case for cigarette smoking. Following its "discovery" by Doll it was tested for a large array of other diseases, some of which did indeed show a relationship.

It is in itself not surprising that concurrent changes in incidence such as IHD and lung cancer are explained by the same risk factors. After all those risk factors represent the most significant changes in the "macro & micro environment" during that same period and may well be responsible for several different diseases processes.

One of the theories suggested as an explanation in this context has been that of the free radicals and excited oxygen. For the time being this issue has not yet been resolved, but the phenomenon of the concurrent risk factors remains and in fact is a major point of interest in this study. In the following paragraphs the relationships described so far will be presented from the risk factor i.e. the preventive policy point of view.

5.2   Risk factors and diseases

5.2.1   Cigarette smoking

Smoking, and in particular cigarette smoking, is the most widely studied risk factor in epidemiology (25, 26, 74, 103, 105, 162-164). Although several trials have shown correlations with a large number of disease categories, we shall concentrate on the three most important ones.

The relationship between cigarette smoking and lung cancer and ischemic heart disease has already been extensively discussed in the previous pages. We have added here the category of Chronic Obstructive Lung Disease (COLD) which is now "the best understood of all the diseases caused

Figure 5.11: Diseases influenced by smoking
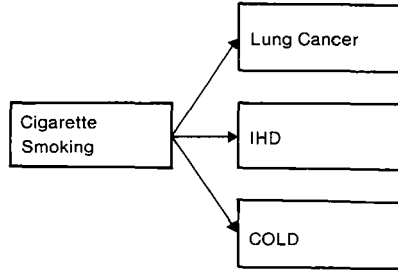
by smoking" (165).

Important variables in the relationship between smoking and these disease categories are:

- the amount smoked

- the age at which smoking was first started

- filter versus non-filter cigarettes and inhalation habits or more generally the tar and nicotine contents of cigarettes for lung cancer and the CO contents of the smoke inhaled for ischemic heart disease (19, 58, 166)

- the number of years that elapsed since smoking cessation

5.2.2   Hypertension

Figure 5.12: Diseases influenced by hypertension
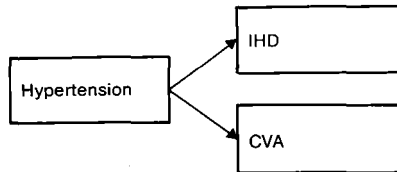
Hypertension, or more realistically blood pressure level, is a strong predictor for ischemic heart disease and cerebrovascular accidents (167). Originally it was thought that only "malignant" hypertension, that is blood pressures

of > 160 mmHg (systolic) and/or > 105 mmHg (diastolic), was dangerous. Now there is evidence that the risk of IHD and of CVA simply increases with the higher blood pressures measured. There is no real cut-off point below which there is no increased risk.

For the purpose of this exercise the WHO classification in mild and severe hypertension is used, with the albeit arbitrary cut-off-points of:

Normotensive	DBP <90 and SBP <140
Mild hypertensive	DBP 90-94 and/or SBP 140-159
Severe hypertensive	DBP ≥95 and/or SBP ≥160

In this classification the lowest category is considered the reference population against which the relative risks are measured. We are well aware that this artificial segmentation becomes especially troublesome in populations where blood pressure increases with age. There has been discussion about whether one should consider that age related risk as pathological or not. Given the fact that there are populations where this increasing blood pressure with age is not observed, we will assume that even for elderly people a higher blood pressure is a pathological though common phenomenon. However the relative risk for the elderly is lower than for younger people with the same level of hypertension.

5.2.3   Diet

As has been discussed in the analysis of the disease categories, many dietary elements seem to be important in the etiology of diseases. Some are very specific and well documented, for others the evidence is still controversial. Although it may be interesting at a later stage to run the model for some of these more controversial food items, to get an impression of their possible impact, we have decided to limit ourselves in this first exercise to two major diet related elements:

- Serum cholesterol

- Measure of obesity

Serum cholesterol has since long been identified as a risk factor in the occurrence of atherosclerotic disease and its clinical manifestation of cardiovascular disease (168). Intervention trials, set up to reduce cardiovascular risk factors (45, 88, 169), have successfully managed to lower serum cholesterol levels, resulting in a decreased number of cardiovascular deaths in the intervention groups. However, investigators discovered that these health benefits were accompanied by an increased number of cancer deaths, most notably from colon cancer. Since then several studies were started to test

the hypotheses that a high or a low serum cholesterol level may be a risk factor for cancer of the large bowel. As has been discussed earlier, the question is still controversial.

Obesity in itself appears to be both a direct and an indirect risk factor (123, 170, 171). It influences conditions like hypertension (and diabetes) which, although themselves causes of illness and death, are also important as risk factors in other disease categories. The same applies to the estrogen levels: it has been hypothesized that estrogen products are produced in fat cells and that as such obesity increases the levels of available estrogens, especially in post menopausal women. There is strong evidence from studies like those from de Waard c.s. (172) that obesity is correlated directly to the risk of breast cancer for post menopausal women.

Direct evidence is available and recognized as important by a.o. the Committee on Diet, Nutrition and Cancer (173), for the cancer sites of breast and colon. There also appears to be a relationship between the dietary fat intake and the level of serum cholesterol, although the influence on disease incidence (f.i. IHD) then becomes indirect. The same applies to obesity: a high fat intake is often associated with a high total caloric intake and hence with obesity. High fat is therefore not considered separately.

5.2.4 Alcohol

Figure 5.13: Diseases influenced by alcohol
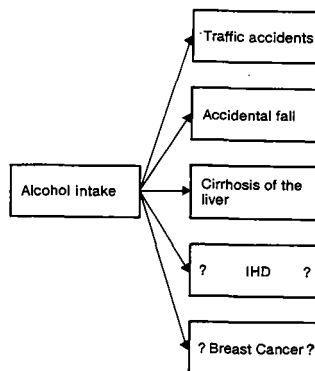
Alcohol abuse has long been recognized as a major cause of disease (174). Prevention of excessive drinking has been tried in different periods of his-

Figure 5.14: Alcohol consumption (in liters alcohol ad 100%) in the Dutch
population 1960-83
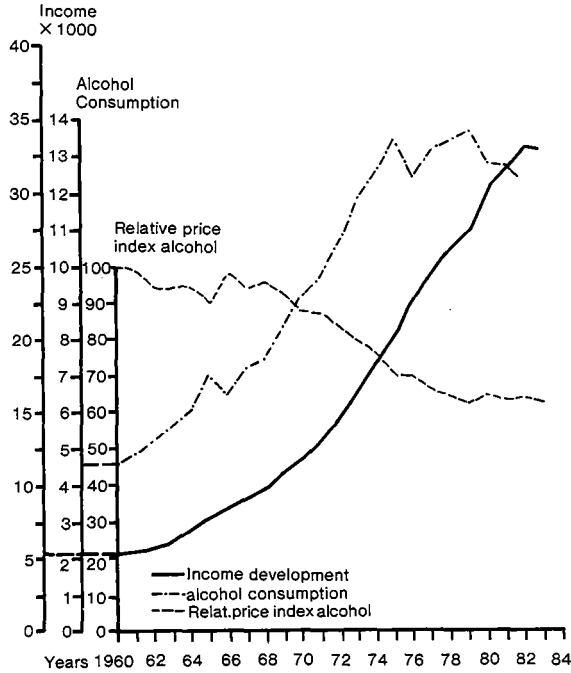
Source: 234

tory. Now, with the increasing financial possibilities of most families in
Western European countries, there has been an important increase in the
prevalence of drinking. Figure 5.14 shows the average amount of alcohol
consumed by the Dutch population since the Second World War.

Much of this drinking is so called "social drinking" and not generally
classified as alcohol abuse. However recent epidemiologic literature has
shown that even such "moderate" amounts of alcohol intake influence a
persons health (28, 130, 131, 175-177), for certain diseases it is a risk factor,
for others there appears to be a protective influence.

Liver cirrhosis is included in this version since it so directly related to
alcohol abuse.

5.2.5   Reproductive variables

From the hypothesis that apart from lifestyle differences (178,179), hormonal factors may be partly responsible for the differences in life expectancy between men and women (180), studies evolved within the female population comparing pre- and post menopausal disease. From these studies estrogen has come forward as an important factor influencing health.

For osteoporosis and IHD, estrogen is a protective factor, and the risks increase sharply after menopause. In the case of breast cancer and cancer of the corpus uteri (63, 119, 181-183), estrogen has to be considered a risk factor. Women with an early menarche and a late menopause (therefore a long exposure to estrogen) have an increased risk for breast cancer (184). The evidence on oral contraceptives and an increase in risk of IHD, cancers and CVA remains controversial and mostly seems to affect pre menopausal women (94, 185, 186).

There is a direct link between the risk of breast cancer and the mothers age at first full-term pregnancy. A mother under 20 years will have 1/3 the risk of a mother over 35 (187).

Conclusion

Although the health model used in the Health 2000 Report includes a wide range of determinants of health, not only individual lifestyles but social and physical environmental factors as well, these last risk factors have proved to be much more elusive in epidemiological research than the so-called lifestyle factors.

This lack of suitable data on the relationship between risk factors present in our physical environment, was already mentioned in the Health 2000 Report. Proposals were made for scenario studies, especially on the possible long term toxic effects of chemical products. As soon as reliable data on the relationship between these risk factors and specific disease entities become known they can be incorporated in the present model.

Chapter 6

Data used in the model

In this chapter the quantitative data both for the prevalence of the risk factor in the Dutch population and for the relative risk ratio's that apply to these risk factors and each specific disease category will be discussed. These data were used in the runs with this basic version of the model described in the following chapters.

Prevalence data

The prevalence data on risk factors in the Netherlands are scarce. There have been a number of surveys in the first half of the 1970's (COPIH, CB project, KRIS, ONNO, Boot, etc.) in which some prevalences were measured. These were primarily geared towards cardiovascular risk factors, and covered rather different populations, none of which was really a representative sample of the Dutch population. There has been one health survey since, which is more general in scope but which is restricted to one residential area, Zoetermeer (188). The results of that survey tend to differ somewhat from the earlier surveys.

For alcohol and smoking the data are more complete: there have been continuous surveys on smoking behavior in the general population since 1970 and they are considered reliable, especially on the total percentage of smokers. They are less reliable on the amount smoked, when compared to figures on the tobacco taxes administered by the National government and the statistics issued by the industry. It is generally assumed that the under reporting of the number of cigarettes consumed is merely an under reporting by smokers, not an under reporting of the number of people who smoke. It amounts to an average of 6-7 cigarettes a day per smoker. The

data on the amount smoked have therefore to be used with caution.

The same applies to the available statistics on alcohol consumption. Again the data come from two different sources: surveys of drinking habits in the general population (a very recent survey was conducted in the preparatory phase of the recent national anti-alcohol campaign) and the statistics of the alcohol industry. The estimated under reporting of the amounts of alcohol consumed is 40% in the general surveys and 20% in the surveys done for the industry. As with smoking, the general impression is that there is primarily an under reporting of the amount consumed rather than an under reporting of the number of people who drink alcohol.

A third source of information on the prevalence of risk factors comes from the routinely collected data by the Central Bureau of Statistics (CBS). These include household surveys on food consumption and data on the age of mothers at the birth of their first child.

Criteria applied to the choice of prevalence data:

- Representativity of the Dutch population. Some studies only include certain age groups or selective sub populations. Where there was not a representative sample of the Dutch population, data were combined from different sources to achieve a coverage as representative as possible.

- The reliability of the data.

- The subcategories presented. Risk factor influence depends very much on variables such as age, sex and exposure dose. In most of the surveys, such subcategories were used. Preference was given to data sources where the subcategories coincided with those used for the relative risk ratio's.

- Time trends. When data on the development of prevalence over time were available from the same source, these were used to estimate a trend in risk factor prevalence, when data were available on only one point in time, trends were estimated based on circumstantial evidence.

Relative risks

The data on the relative risk ratio's associated with risk factors, that were used in this study, stem mostly from longitudinal trials in the USA or the UK. Use was also made of secondary sources such as the Health Consequences of Smoking reports of the Surgeon General in the US or similar documents from the UK and the Netherlands. For certain risk factors very good and comprehensive review articles in leading journals exist. Although

these review documents give a good overview of the studies done, they usually do not draw quantitative conclusions from the articles reviewed. We combined these review articles with recent publications on the major risk factor trials and selected which relative risk ratio's to include in the basic runs with the Prevent model.

Criteria applied to the choice of relative risks:

- Type of study population. Relative risk data came from non-Dutch populations. To be able to transfer them to the Netherlands, data were selected on white populations, in western industrialized countries, if possible specified according to age and sex and exposure category, and corrected for known confounders.

- Follow up period. The lag period between risk factor cessation and diminished relative risk obviously are more fully appreciated in studies with a long follow up period. The one disadvantage to long follow up periods, is the impossibility to control for the cohort effect. The recent hypotheses about infant nutrition and the subsequent risks of cardiovascular disease and breast cancer (126, 189) would be such an example. However these factors mainly influence the absolute risk and the evidence is controversial whether such factors will also influence the relative risk ratio.

- Extreme values. When comparing such a large number of study results it is inevitable that some differences remain even after adjusting for differences in study design. Differences between dose-related categories or age groups were only used if the differences were large.

The choice of data, used in the basic runs of the Prevent model, will be presented by risk factor.

6.1 Cigarette smoking

6.1.1 Prevalence data

There are two major sources on the smoking habits of the Dutch population: survey data and the yearly statistics of the government taxes on tobacco. These last ones are available and have been analyzed (190) since 1946. They show a steady increase in tobacco sales and assuming that relatively few cigarettes are left unsmoked, therefore a steady increase in the consumption of tobacco from 1 kg per person in 1946 to 2 kg in 1950 and more than 3 kg in 1981.

Survey data are available in the Netherlands since 1958. Several independent surveys were conducted since then, for research purposes and for marketing. In 1970 continuous surveys were started. These data are from a large sample (currently 22000 respondents per year) and can be considered representative for the Dutch population. The data are reported among others by age, sex, level of education, and recently also by the amount smoked.

Unfortunately when the results of the surveys are compared with the statistics on the taxes paid by manufacturers there appears to be a severe under reporting. The total amount smoked as reported by smokers in the surveys would need to be augmented by some 6 to 7 cigarettes per smoker to achieve the total consumption as can be deduced from taxes. Earlier studies have attempted to correct for the under reporting (191) with the assumption that the under reporting is distributed evenly over the different categories. It has been suggested (Baan, personal communication) that the under reporting may be primarily in the categories of smokers who smoke more than 13 cigarettes a day, partly because it is much more difficult to make a mistake about 2-5 cigarettes a day than it is when one smokes as many as 20. There is also a hypothesis that the under reporting, which did not exist in the 1958 survey, is due to the prevailing social anti-smoking climate. Although aware of this discussion on under reporting, we decided to use the data on amounts smoked, as an indication of dose, without further correction (table 6.1) In the historic testing on smoking and lung cancer (in chapter 8) a variable IDRfac is introduced to correct for the discrepancy between sales taxes and survey data. In table I.1 we did correct for an over reporting of the number of never smokers. From the earlier survey's the cohort data were used to find the more realistic number of never smokers.

Table 6.1 shows that there has been a major trend in smoking cessation for males since 1958. In the 1950's almost all men over 20 years smoked, this was reduced to less than 70% in the early 1970's and reached levels just over 40% by 1982. For women there is a different trend. After the second world war less than a third of all women smoked. In the following years, smoking habits became more pervasive in women, and by 1970 more adolescent girls started to smoke than adolescent boys. However older women smoke far less than the men in the same age group do. The other major difference between men and women is the percentage of the population that has never smoked: except for the youngest cohorts this is consistently much higher for women than for men. Looking at time trends in smoking cessation, there appears to be a sudden decrease in the number of smokers between 1979 and 1982, which is subsequently followed by a stabilization or very slow further downward trend. These trends were used for the historic cohort data on smoking cessation.

Table 6.1: Percentage of smokers by sex and age in the Netherlands from 1958-1982

	1958	1963	1967	1970	1975	1979	1981	1982
Males:								
15 - 19	–	–	58	55	46	29	27	18
20 - 34	91	78	79	77	68	56	49	45
35 - 49	91	85	80	77	69	58	50	44
50 - 64	89	81	82	78	68	61	51	45
65+	88	76	83	74	66	57	51	43
All ages	90	82	78	75	66	52	47	41
Females:								
15 - 19	–	–	57	57	48	39	30	27
20 - 34	46	45	58	57	58	52	48	45
35 - 49	32	38	46	48	47	40	39	36
50 - 64	18	20	26	27	29	30	28	27
65+	5	3	13	13	12	13	13	13
All ages	29	32	42	42	40	38	36	33

Age-groups for 1958: 21-40, 41-50, 51-70, 71+
Source 191

6.1.2 IDR data by disease category

Smoking and lung cancer

In 1982 the USDHHS published the cancer volume in the series of reports on the Health Consequences of Smoking (193). This volume was a follow up report whereby the evidence collected since the landmark report of 1964 (194), is reviewed using the same criteria necessary for a causal relationship as established by the Advisory Committee in 1964:

1. The consistency of the association

2. The strength of the association

3. The specificity of the association

4. The temporal relationship of the association

5. The coherence of the association

The report covers a great many cancer sites all of which are affected by smoking. The lung cancer data are used in this project.

In table B.1 (Appendix B) the results of the 8 major prospective studies on smoking and lung cancer are shown as they have been summarized for this report. It is obvious that smokers have a much higher risk of lung

Table 6.2: Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day (prospective studies).

| | Men | | Women | |
Population	Cigarettes smoked per day	Mortality ratio	Cigarettes smoked per day	Mortality ratio
ACS 25-State	Nonsmoker	1.00	Nonsmoker	1.00
Study	1-9	4.62	1-9	1.30
	10-19	8.62	10-19	2.40
	20-39	14.69	20-39	4.90
	40+	18.71	40+	7.50
British	Nonsmoker	1.00	Nonsmoker	1.00
Physicians	1-14	7.80	1-14	1.28
Study	15-24	12.70	15-24	6.41
	25+	25.10	25+	29.71
Swedish Study	Nonsmoker	1.00	Nonsmoker	1.00
.	1-7	2.30	1-7	1.80
	8-15	8.80	8-15	11.30
	16+	13.70	16+	-
Japanese Study	Nonsmoker	1.00	Nonsmoker	1.00
All ages	1-19	3.49	<20	1.90
	20-39	5.69	20-29	4.20
	40+	6.45		
U.S. Veterans	Nonsmoker	1.00		
Study	1-9	3.89		
	10-20	9.63		
	21-39	16.70		
	$\geq$40	23.70		
ACS 9-State	Nonsmoker	1.00		
Study	1-9	8.00		
	10-20	10.50		
	20+	23.40		
Canadian	Nonsmoker	1.00		
Veterans	1-9	9.50		
	10-20	15.80		
	20+	17.30		
California	Nonsmoker	1.00		
males in 9	about $\frac{1}{2}$ pk	3.72		
occupations	about 1 pk	9.05		
	about $1\frac{1}{2}$ pk	9.56		

Source: 193

Table 6.3: Reduction in relative risk (lung cancer) after smoking cessation, by number of years since cessation

Study	Years	Mortality ratio	
British Physicians	1-4	16.0	
	5-9	5.9	
	10-14	5.3	
	15+	2.0	
	Current smokers	14.0	
U.S. Veterans[1]	1-4	18.83	
	5-9	7.73	
	10-14	4.71	
	15-19	4.81	
	20+	2.10	
	Current smokers	11.28	
Japanese Males	1-4	4.65	
	5-9	2.50	
	10+	1.35	
	Current smokers	3.76	
		Number of cigarettes smoked per day	
		1-19	20+
ACS 25-State Study			
(males 50-69)	<1	7.20	29.13
	1-4	4.60	12.00
	5-9	1.00	7.20
	10+	0.40	1.06
	Current smokers	6.47	13.67

1 Includes data only for ex-cigarette smokers who stopped for other than physicians' orders
Source: 193

cancer mortality than nonsmokers. However the level of relative risk varies considerably between studies. This is probably due to the different mix of the amount smokers smoke. The data in table 6.2 show that this greatly influences the relative risks found. There is also a difference in the relative risks found for men and for women. The hypothesis is that this is not so much due to a different influence of smoking on women but more likely a consequence of the period in which these studies were done: most studies were started in the 1950's and early 60's (all except for Japan and these data differ markedly from the other studies). In that period few women smoked and more importantly women smoked less and inhaled less than men did. The development of lung cancer mortality in the US for women now is remarkably similar to that for men 25 years ago. From these data one could conclude that lung cancer mortality for women may unfortunately have to reach the peak levels of males before it will decrease.

In 1983 the Royal College of Physicians in Britain published a report: Health or Smoking? (195) in which essentially the same data were discussed. Particular attention is given to the fact that lung cancer rates for males are now falling in the UK. The report suggests that this is due to the falling levels of tar and nicotine in cigarettes in recent years. No such falling of mortality rates have yet been noted for women. This is one reason why it was eventually decided that women in Prevent are assigned the same IDR's as men.

Since this USDHSS report there has been a number of new publications on smoking and lung cancer (99, 103, 104) but all are case control studies and although they differ somewhat on the relative risks reported they do not present data that make the results of the earlier prospective studies obsolete. In table 6.2 a dose related response is found in all prospective studies, although the exact relative risk may vary.

Four of the eight prospective studies have reported data on what will happen to lung cancer mortality risk ratio's after smoking cessation (see table 6.3).

Nothing happens to the risk ratio's in the first 4 years after cessation, if anything they are slightly higher than those of current smokers. This phenomenon can be explained by the fact that those who already feel, or have been diagnosed, ill will very often quit smoking, so a relatively high mortality is to be expected among recent quitters. After that period the risk ratio's diminish over a period of approximately 10 years to reach a stable, low level, but still not that of lifelong nonsmokers (197). From the data we assume a LAT of 4 years and a LAG of 10 years to reach the remnant IDR of 2.

Smoking and IHD (Ischemic Heart Disease)

There have been innumerable studies on the major risk factors for cardiovascular disease and it is now common knowledge that cigarette smoking is an important and independent risk factor. The USDHHS has reviewed the quantitative evidence in 1979 (196) and again in 1983 (73) and the Royal College of Physicians has also reported on these study results in 1983 (195). Since then several major intervention trials (MRFIT, WHO collaborative, Gothenburg) have published their final results. In 1979 USDHHS reports the results of 14 major prospective studies. All but one have concentrated on men, which is understandable considering the period in which these studies were started. Most of the results as shown in table B.2 (Appendix B) are similar except for the Japanese data (just as in lung cancer). All report a higher relative risk for the younger age groups and contrary to the lung cancer data there appears to be very little difference between men and women.

As with lung cancer we are also interested in the development of the risk ratio's after smoking cessation (12, 52, 82). There appear to be two distinct mechanisms whereby smoking increases the risk of IHD: it promotes and accelerates the development of atherosclerotic disease but it also affects the clotting mechanism. This dual mechanism would account for the very rapid reduction of risk in the first year followed by a slower risk reduction in the next five years. Table 6.4 shows the data on 4 major studies, all of which show a reduction of risk following smoking cessation.

Contrary to lung cancer this reduction is already apparent in the first year and approaches a maximum after 5 years. Some studies report a lower relative risk for ex smokers as compared to lifelong non smokers, but this is not supported by evidence from the intervention trials. We shall assume that the risk of IHD diminishes immediately upon smoking cessation and linearly reaches its lowest level of 1.2 for both men and women in 5 years (57).

Smoking and COLD (chronic obstructive lung disease)

In 1964 the Advisory Committee to the Surgeon General acknowledged the relationship between smoking and chronic bronchitis and emphysema although they had to conclude that the causal nature of the relationship had not yet been established. In 1984 no such doubts remain and the USDHHS report states: "Cigarette smoking is the major cause of chronic obstructive lung disease in the US for both men and women. The contribution of cigarette smoking to COLD morbidity and mortality far outweighs all other factors."(165). It has even been said that COLD rarely exists among non

Table 6.4: The effect of the cessation of cigarette smoking on the incidence of CHD. (Incidence ratios - actual number of cases or events are shown in parentheses)

Author, year, country		Mortality ratio	
		CHD	myocardial infarction
Jenkins, et al., 1968 USA	Never smoked	1.00 (30)	1.00 (21)
	Current cigarette smokers	2.36 (84)	2.78 (68)
	Former cigarette smokers	2.15 (19)	2.47 (15)
		CHD by cigarettes/day	
		1-19	>20
Hammond and Garfinkel 1969, USA	Never smoked regularly	1.00 (1,81)	1.00 (1,81)[1]
	Current cigarette smokers	1.90 (1,063)	2.55 (2,822)
	Stopped <1 year	1.62 (29)	1.61 (62)
	1-4	1.22 (57)	1.51 (154)
	5-9	1.26 (55)	1.16 (135)
	10-19	0.96 (52)	1.25 (133)
	>20	1.08 (70)	1.05 (80)
	All ex-cigarette smokers	1.16 (253)	1.28 (564)
		myocardial infarction	
Shapiro, et al., 1969, USA	Never smoked	1.00	
	Current cigarette smokers	1.87	
	Stopped ≤5 years	0.76	
		All CHD deaths	First major coronary events
Pooling Project American Heart Association 1970, USA	Never smoked	1.00 (27)	1.00 (53)
	> ½ pack/day	1.65 (34)	1.65 (72)
	1 pack/day	1.70 (86)	2.08 (205)
	>1 pack/day	3.00 (68)	3.28 (154)
	Ex-smokers	0.80 (19)	1.25 (51)

1 Male data only
Source: 196

Table 6.5: COLD mortality ratios for men and women, by number of cigarettes smoked per day (prospective studies)

Study	Cigarettes per day	Mortality ratio		COLD disease classification
		M	F	
British physicians	Nonsmoker	1.00	1.00	Chronic bronchi- tis, emphysema or both
	1-14	17.00	10.50	
	15-24	26.00	28.50	
	25+	38.00	32.00	
US veterans	Nonsmoker	1.00		Chronic bronchi- tis
	1-9	3.63		
	10-20	4.51		
	21-39	4.57		
	40+	8.31		
	Nonsmoker	1.00		Emphysema
	1-9	5.33		
	10-19	14.04		
	21-39	17.04		
	40+	25.34		
	Nonsmoker	1.00		Chronic bronchi- tis and emphysema
	1-9	4.84		
	10-19	11.23		
	21-39	17.45		
	40+	21.98		
Canadian veterans	Nonsmoker	1.00		Chronic bronchi- tis
	1-9	7.02		
	10-20	13.65		
	21+	14.63		
	Nonsmoker	1.00		Emphysema
	1-9	4.81		
	10-20	6.12		
	21+	6.93		
Japanese	Nonsmoker	1.00	1.00	Emphysema
	<100,000[1]	0.51	2.28	
	<200,000	2.57	3.14	
	>300,000	1.93	10.93	
California men in various oc- cupations	Nonsmoker[2]	1.00		Emphysema
	About $\frac{1}{2}$ pk	8.18		
	About 1 pk	11.80		
	About $1\frac{1}{2}$ pk	20.86		
American Cancer Society 9-State	Nonsmoker	1.00		All pulmonary diseases other than cancer[3]
	1-9	1.67		
	10-20	3.00		
	20+	3.64		

1 Data for the Japanese study are for lifetime exposure by total number of cigarettes consumed

2 Nonsmoker in the California occupations study also includes smokers of pipes and cigars

3 Pneumonia, influenza, TB, asthma, bronchitis, lung abscess, etc.

Source: 165

smokers.

Contrary to the disease categories discussed above (lung cancer and IHD) COLD is a much more important cause of morbidity than of mortality. Most COLD patients die "with COLD not of COLD". This means that the disease burden caused by COLD is much larger than would be expected from the mortality statistics. However there is no evidence that the relative risk ratio differs when looking at the mortality risk rather than the incidence risk.

There have been a great number of cross sectional studies. However these cross sectional studies usually record lung function levels instead of diagnosed morbidity. For instance the Dutch longitudinal study measuring lung functions regularly in the populations of Vlagtwedde and Vlaardingen (198,199), which reports a severely restricted lung capacity in heavy smokers. For our IDR values we looked at the mortality ratio's for emphysema, chronic bronchitis or both from the prospective studies available.

As can be seen from table 6.5, 6 of the 8 studies report dose related data on COLD mortality among smokers and non smokers. The Swedish and the ACS 25 state study have only more general risk ratio's. The latter is important because it is the only one to report risk ratio's by age category. Contrary to the previous disease categories there appears to be an increase in relative risk with older age. It is obvious from the data that the risk ratio's increase sharply with the amount smoked to reach values that are even higher than those found for lung cancer. The IDR values selected are based on the British doctors study and the US veterans study.

Although there tend to be marked differences in the mortality ratio's found in the prospective studies, these are likely to be due to the length of follow up. COLD mortality occurs most often after the age of 65, and considering the long latency periods before COLD results in death, studies with a short follow up or a population mostly under 65 years of age will tend to severely underestimate the relative risk of COLD. From the American Cancer Society 25 state study we know that the IDR's sharply increase with age. However these data only concerned emphysema and more importantly did not differentiate by the amount smoked. Because of the nature of the damage done to the lungs, that result in COLD symptoms, the effect of smoking cessation is less impressive on COLD than on lung cancer mortality. Two of the prospective studies have reported on the effect of smoking cessation.

Table 6.6 shows that the first four years after quitting the mortality risk ratio barely changes, after which it becomes higher than for current smokers. This is probably the result of the higher rate of smoking cessation among people diagnosed as COLD patients. During the next 9 years the ratio slowly falls. However even at its lowest point, the risk of COLD mor-

Table 6.6: Mortality ratios for bronchitis and emphysema in nonsmokers and in ex-smokers and current smokers by number of cigarettes smoked daily and number of years of cessation, US veterans study

Smoking status		Cigarettes/day				
		0	<10	10-20	21-39	>39
Nonsmoker		1.00	-	-	-	-
Ex-smoker		-	1.64	5.35	7.68	9.91
Current smoker		-	4.84	11.23	17.45	21.98
		Years of cessation				
	Current					
Nonsmoker	smoker	<5	5-9	10-14	15-20	>20
1.00	12.07	11.66	14.35	10.19	5.66	2.64

Source: 165

tality remains much higher for ex-smokers than for life long non smokers. We assume that COLD mortality ratio's will not change for the first 10 years after smoking cessation, after that they will slowly diminish over the next 10 years to reach the remnant IDR of 2.6 for both men and women.

6.2 Hypertension

6.2.1 Prevalence data

In 1983 the Health Council in the Netherlands published a report with recommendations concerning Hypertension (200). It contains an overview of the surveys done in the Netherlands between 1960 and 1977 in which population data were collected on blood pressure (table 6.7). None of these population surveys are truly representative of the Dutch population, however when the average blood pressure levels found in all these different studies for the different age groups are compared, they do not differ substantially. As can be seen the largest survey is the COPIH. This also has the advantage of being spread over the country so as to minimize the effect of regional variations. A major drawback however is the fact that it looked at employees only, which in 1971 certainly did not represent the female population in that age group in the Netherlands. Furthermore it has recorded only the first blood pressure measurement, which may over report hypertension. In an effort to see whether the above mentioned drawbacks really affected the data, the Health Council committee asked investigators of the different studies to publish their results for the common age group of 35-44 according to the model used by the COPIH project (see table B.3

Table 6.7: Population Studies in which blood pressure data were collected
in the Netherlands

Study	Starting year	Age	N	Sex	Location
1. Zutphen	1960	40-59	900	m	Zutphen
2. Vlagtwedde-Vlaardingen	1970	20-50	1400	m/f	Vlagtwedde-Vlaardingen
3. COPIH	1971	35-64	21600	m	Several
4. CB	1971	20-50	8000	m/f	Rotterdam Tilburg Doetinchem
5. K.R.I.S.	1972	45-59	3400	m	Rotterdam
6. Voedingsraad	1973	8	900	m/f	National
7. EPOZ	1975	5-75	3500	m/f	Zoetermeer
8. Voedingsraad	1976	15-16	1000	m/f	National
9. Boot	1976	5-75	2000	m/f	Den Haag
10.Milit.keur-lingen	1976	18-19	3100	m	National
11.Cordon	1976	40-65	7000	f	Utrecht e.o.
12.NIP	1977	20-50	4500	m/f	Regio Nijmegen

N: Population size
Source: 200

in appendix B). There are some differences between the percentages found:
EPOZ reports a significantly lower percentage of hypertensives both for
men and women while COPIH has very high values for women. We have
attempted to look at the results of these surveys for the other age groups in
a similar way (for the detailed tables see appendix B). Three categories of
blood pressure were applied following the WHO guidelines: a reference pop-
ulation of normotensives, a group with mild hypertension (Diastolic blood
pressure, DBP, 90-94 and/or systolic blood pressure, SBP, 140-159) and a
group with "severe" hypertension (DBP$\geq$95 and/or SBP$\geq$160). In the sur-
veys from which these data have been extracted some subjects were known
to have hypertension and an, albeit small (13%) percentage was treated
by their family physician. Therefore the initial percentage of hypertensives
in the population may be higher, but since the increased risk is related to
the current blood pressure rather than to the initial blood pressure these
treated hypertensives are inserted in the risk category of the blood pressure
as measured at the time of the survey.

Looking at table 6.8 one is struck by the rapid rise in the prevalence of
high blood pressure in the age group 45-49. To a certain extent this is due to
the fact that in the higher age group the most reliable and complete source
of information is the COPIH survey. As seen earlier this is characterized by

Table 6.8: Prevalence of hypertension in the Dutch population by age and sex category, 1976

	35-44		45-49		50-54		55-59		60-64	
	M	F	M	F	M	F	M	F	M	F
Normotensive	58.4	78.4	45	49	41	45	34	35	28	25
Hypertensive										
Mild	24.6	13.3	27	26	26	26	29	30	29	31
Severe	17	8.3	29	25	32	29	37	35	43	44

Table 6.9: Prevalence of hypertension in the Dutch population by age and sex category, based on the EPOZ data

	5-19		20-34		35-49		50-64		65+	
	M	F	M	F	M	F	M	F	M	F
Normotensive	92.7	96.4	76.3	89.1	68.2	68.5	44.2	33.1	27.8	.8
Hypertensive										
Mild	6.5	3.2	17.8	6.1	18.2	13.7	29.5	25.9	26.6	35.2
Severe	0.8	0.4	5.0	2.6	10.2	9.1	18.9	24.0	29.6	34.5
Ex			.9	2.2	3.4	8.7	7.4	17.0	16.0	31.1

a relatively high overall prevalence of hypertension especially for women. There are no population data on the prevalence of hypertension in the very old. The Health council report however assumes that there is no further rise in blood pressure after the age of 70. The age group over 65 years will be assigned the same prevalence data as the age category 60-64.

Little is known about the trend in the incidence or prevalence of hypertension. The awareness of family practitioners of the importance of regular blood pressure measurements and subsequent treatment of hypertensives has probably increased over the last ten years. The lower prevalence of hypertension found in the more recent EPOZ study also points in the direction of a reduction in incidence. We assume a 1% yearly increase in the number of hypertensives being successfully treated before major disease symptoms have been diagnosed. These will not be returned however to the pool of normotensives but will remain in the category ex hypertensives. The data in table 6.8, in 1976, result in an estimated prevalence of hypertension in 1985 shown in table C.5.

Since the EPOZ data are so different from the other surveys, while they come from a population sample, some special runs with the Prevent model using the EPOZ material, were done to see whether it made much

difference. For the hypertension prevalence data we have gone back to the
raw data and regrouped the categories as shown in table 6.9.

As said earlier, the EPOZ prevalence data suggest a lower incidence of
hypertension, especially of severe hypertension. However it is striking to
see that almost no woman over 65 years of age appears to be normotensive
without antihypertensive medication.

6.2.2   IDR data by disease category

Hypertension and IHD

The interest in the risk factors of IHD in the postwar years has resulted
in a number of prospective studies concerning the relative risks associated
with hypertension in the population. There have also been a fair number
of intervention trials that produced data on the reduction of risk following
treatment of hypertension. It is important for the interpretation of the
results of the model to keep in mind that there are two ways of prevention
of the adverse effects of hypertension: primary prevention at a population
level, which will mostly concentrate on what is commonly called a "prudent
life style", and the possibility of secondary prevention by screening and
subsequent treatment of diagnosed hypertensives. For the latter type of
prevention the opinions on the benefits to be expected of the treatment of
mild hypertension still differ.

Table 6.10 summarizes the results of the major longitudinal studies in
the US. The best known and the one with the longest follow up period is
undoubtedly the Framingham study. There seems to be a dose response
relationship. The Framingham study has found the SBP to be the better
predictor of risk, but other surveys the DBP. For men there seems to be
a decrease of risk ratio in the older age groups. This is less obvious for
women. The rise in risk ratio for women in the 40-49 age group in the
Framingham study is probably an artifact. It does seem however, that
women with severe hypertension have higher relative risks for IHD then
men. The risk ratio's that were applied in the basic runs are presented in
table C.6.

For the category of ex-hypertensives the intervention trials report a re-
duction of risk in the order of 10-20%. However these trials are mostly multi
factorial and it is therefore sometimes difficult to assess the influence of the
individual risk factors. Collins c.s (87) have combined a great number of
intervention trials on moderate hypertension and report a significant effect
even of a reduction of blood pressure by as little as 7mm. We will assume
that hypertension controlled by medication will result in an immediate re-
duction of the IHD mortality ratio. After 2 years the remnant IDR will be

Table 6.10: Mortality ratios for IHD from the major prospective studies

Study	N	Years of follow up		Reported IHD mortality risk ratio's			
Evans	3102	7 yrs		35-44	45-54	55-64	65+
County	Males		SBP Mild	2.52	1.54	1.37	1.78
			SBP Severe	1.43	1.61	2.02	2.34
			DBP Mild	-	.36	1.88	1.46
			DBP Severe	2.26	1.73	1.63	1.95
				30-39	40-49	50-59	
Framing-	5209	26 yrs	Mild M	1.88	1.32	1.65	
ham			Mild F	1.63	1.78	1.60	
			Severe M	2.34	1.76	1.88	
			Severe F	2.95	2.69	2.71	
Nat.Coop	7342	10 yrs	DBP				
pooling			85-94	1.7			
project			95-104	1.9			
			105+	3.6			

1.6. For the mild hypertensives a complete elimination of the excess risk is assumed.

Hypertension and cerebrovascular accident (CVA)

There are only a few population studies concerning the relationship between hypertension and CVA. The most reliable data come from the Framingham study (see table 6.11).

Table 6.11: CVA Mortality ratios as reported in the Framingham study, by age and sex.

	30-39		40-49		50-59	
	Men	Women	Men	Women	Men	Women
Hypertension						
Mild	3.86	2.06	1.78	1.96	2.02	1.49
Severe	10.20	3.38	3.27	3.46	2.98	2.70

The dose response relationship is apparent, as well as the increased risk for the younger age groups. Men seem to be affected more severely by mild hypertension than women are, which is not so obvious for severe hypertensives. The very high value found for men in the age group 30-39 is most likely the result of the very small numbers of death in this age category. The IDR's assumed are reported in table C.7.

The intervention trials by the HDFP and the pooled results of Collins report a much larger impact of blood pressure reduction on CVA mortality than on IHD mortality. Risk reductions of as much as 50% have been found. We assume that hypertensives who are effectively treated will have an immediate reduction in the risk of CVA mortality, but the remnant IDR remains 1.5.

6.3 Serum cholesterol

6.3.1 Prevalence data

The same population surveys that measured the level of hypertension in the Netherlands have also included data on the serum cholesterol levels (201). In the investigations on serum cholesterol the cutoff points appear to be even more arbitrary than was the case with blood pressure. Some investigators consider levels of 240-280 mg% to be a mild hypercholesterolemia, others consider any level above 200 mg% to be elevated. Some put the cutoff point for severe hypercholesterolemia at 300 while others consider this to be 260 or 280. In 1983 the Nutrition Council in the Netherlands published an overview on diet in relation to coronary heart disease (202), in which the available literature on both the prevalence and relative risk data were reviewed. In table 6.12 the results of the data on the prevalence of hypercholesterolemia as found in the different Dutch population studies are summarized.

The prevalence of hypercholesterolemia appears to increase with age for both men and women. While initially women have much lower rates than men, this changes after the age of 50. The COPIH project, the largest survey but with the drawbacks discussed earlier, shows this for both mild and severe hypercholesterolemia (table 6.13). These results are corroborated by the findings of Boot in a sample of the general population. The absolute numbers vary considerably between investigators. We are inclined to use the COPIH data because of the continuous data on all age groups.

The serum cholesterol level appears to be influenced by the dietary fat intake in a population. Evidence for this relationship is mostly found in cross cultural studies, although recently intra population correlations have been reported as well. The Dutch diet and the distribution of macro nutrients that can be distilled from this, does not differ from other Western diets in that it contains a relatively high fat intake (some 40%) and a ratio between polyunsaturated and saturated fats of .36, which can both be considered risk factors for atherosclerotic disease.

From table 6.14 can be seen that the percentage of fat in the diet has

Table 6.12: Prevalence of elevated total serum cholesterol[1] from different studies in the Netherlands

Study	Age	Sex	Threshold level	Prevalence
COPIH	35-64	m	7,8 mmol/l	22%
(1974-1976)			(300 mg %)	
CB	35-49	m	7,3 mmol/l	16%
(1973)			(280 mg %)	
		f	idem	10%
KRIS	45-59	m	6,7 mmol/l	26%
(1972)			(260 mg %)	
Vlagtwedde	20-49	m	6,7 mmol/l	45%
(1970)			(260 mg %)	
Westland	9-12	m	5,7 mmol/l	14%
(1974)			(220 mg %)	
		f	idem	16%
Heerenveen	4-13	m	5,6 mmol/l	19%
Roermond			(215 mg %)	
Harderwijk		f	idem	25%
		m	6,1 mmol/l	7%
(1974-1976)			(236 mg %)	
		f	idem	10%
Den Haag	30-59	m	6,1 mmol/l	67%
(1979)		f	(236 mg %)	27%

1: according to Huang
Source: 202

Table 6.13: Prevalence of mild and severe hypercholesterolemia in the Dutch population, 1976.

serumcholesterol	35-39 M	35-39 F	40-44 M	40-44 F	45-49 M	45-49 F	50-54 M	50-54 F	55-59 M	55-59 F	60+ M	60+ F
<240 mg %	66	76	59	72	56	64	54	46	52	38	53	35
240-300 mg %	23	18	27	21	28	26	30	34	31	32	30	38
>300 mg %	11	6	14	7	16	10	16	20	17	30	17	27

Table 6.14: Macro nutrients in the Dutch diet in 1936/38 and 1973

Year	1936/38		1973	
Total energy (excl. alcohol)	11,4 MJ	(2714 kcal)	12,5 MJ	(2978 kcal)
	g	energy%	g	energy%
Animal protein	39	6	54	7
Vegetable protein	42	6	31	4
Total protein	81	12	85	11
Saturated fat	49	16	62	19
Monounsaturated fat	36	12	53	16
Polyunsaturated fat	13	4	23	7
Total fat	102	34	138	42
Oligosaccharides	137	20	192	26
Polysaccharides	231	34	157	21
Total carbohydrates	268	54	349	47
Cholesterol (mg/4200 kJ)		116		137
Fibre (g/4200 kJ)		11.8		8.9
Alcohol (kJ)		113		563

Source: 202

Table 6.15: Prevalence of mild and severe hyper cholesterolaemia in the Dutch population based on EPOZ data

serum cholesterol	30-44 M	F	45-49 M	F	50-54 M	F	55-59 M	F	60+ M	F
<240	53.8	68.4	49.7	39.0	44.4	34.1	47.4	30.4	60.8	43.4
240-270	24.0	18.6	25.0	28.0	22.9	26.5	30.1	27.7	23.8	26.3
270+	22.2	13.0	25.3	33.0	32.7	39.4	22.5	41.9	15.4	30.3
IDRs										
Mild	3.5	3.0	2.0	1.7	2.0	1.7	1.3	-	1.3	-
Severe	5.5	5.0	13.0	2.0	3.0	2.0	1.9	-	1.9	-

gone up in the postwar years. However more detailed analyses of recent dietary changes show some more positive developments in nutritional habits since 1970 (202).

The COPIH data also show a reduction in hypercholesterolemia in the subsequent years of the study. A 1% yearly reduction in the prevalence of hypercholesterolemia was applied to the prevalence data in table 6.13 to arrive at the 1985 values used in the basic runs (see table C.8).

As with hypertension, the prevalence data on serum cholesterol levels found in the EPOZ study differ from the COPIH data. From the raw EPOZ data two tables were constructed. One (table 6.15) with the same categories as the COPIH data and one according to the criteria of the recently released MRFIT analysis (table 6.16). These data were used in the sensitivity analysis (chapter 8) to see the effect of a change in the initial input data. In the analysis, the effects of elevated serum cholesterol on IHD mortality were found to be more pronounced than assumed earlier (203, 204). Since the exposure categories differed as well as the relative risks reported, the IDR's found in the MRFIT study were used only in the sensitivity runs. These are shown in table 6.16 as well.

6.3.2   IDR data by disease category

Serum cholesterol and IHD

The same prospective studies that have yielded the data on the influence of smoking and hypertension on IHD also included serum cholesterol (205-208). The mortality risk ratios found in the different prospective studies are summarized in table 6.17.

The most striking finding is the wide range of reference populations used by the different studies, which accounts for the differences between values reported. The relative risk rapidly diminishes in the older age groups, to become virtually non existent for the elderly women. This is of interest because of the high prevalence of severe hypercholesterolemia found for that age group.

The multi factorial intervention trials on IHD risk factors that were reported in the hypertension paragraph have often included interventions on dietary factors as well. Besides those, a number of mono factorial intervention trials were set up. The Nutritional Council concluded in 1983 that the results of these trials were not always statistically significant but all pointed in the direction of a reduced IHD risk following dietary changes that lowered serum cholesterol. The dietary changes included both a reduction of total fat intake and an increase in the P/S ratio of the fat intake. It is estimated that an 8% reduction in the saturated fat intake in the Netherlands would

Table 6.16: Prevalence of serum cholesterol levels according to Mr.Fit, in the Dutch population based on EPOZ data, with corresponding IDR's

Prevalence	35-39		40-44		45-49		50-54		55-59	
(mg %)	M	F	M	F	M	F	M	F	M	F
A <181	6.2	9.2	3.7	10.8	3.3	3.8	3.7	0.9	7.5	2.2
B 181-195	19.7	28.0	14.4	30.0	12.5	13.1	13.1	7.6	8.1	8.2
C 210-225	28.2	20.6	26.5	15.8	33.9	22.1	27.6	25.6	31.8	20.1
D 226-240	10.4	13.3	17.5	12.1	12.5	13.1	13.5	12.6	18.5	16.3
E 240+	35.5	28.9	37.9	31.3	37.8	47.9	42.1	53.4	34.0	53.3
IDR's										
A	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
B	1.14	1.14	1.79	1.79	1.26	1.26	1.28	1.28	1.20	1.20
C	2.32	2.32	2.63	2.63	1.79	1.79	1.43	1.43	1.74	1.74
D	2.44	2.44	3.69	3.69	2.36	2.36	1.96	1.96	1.93	1.93
E	7.75	7.75	5.79	5.79	3.88	3.88	2.93	2.93	2.40	2.40

Table 6.17: Mortality ratios for coronary heart disease according to serum cholesterol level

Study	Age	Total serum cholesterol (mg %)	Relative risk ratio M	F
Framingham	35-44	≥265 versus <220	5,5	5,0
	45-54	"	2,4	1,5
	55-64	"	1,7	1,3
	all ages	"	2,5	1,5
Pooling project	40-64	≥240 versus <218	2,0	
Whitehall Study	40-62	≥ 234[1] versus < 159[2]	2,0	
Western Colla-borative Study	39-49	≥260 versus 260	2,9	
	50-59	≥260 versus <260	1,7	
Stockholm Pros-pective Study	35-39	≥280 versus <280	2,1	
Evans County Study	15-75+	≥260 versus <220	1,3	

1 P_{80}
2 P_{20}
Source: 202

lead to an average reduction of serum cholesterol of 22mg%. In the basic runs we shall assume that a reduction in serum cholesterol as the result of dietary changes will indeed lead to a lowered risk ratio. The remnant IDR will be considered 3 for the younger age groups and 1.5 for those over 45. This level will be achieved over a period of 3 years (202).

6.4 Obesity

6.4.1 Prevalence data

Obesity has long been considered an important risk factor for premature mortality (209, 210). This was first noted by the life insurance companies in the USA. Since then there has been a lively debate about the validity of the data. Part of the problem appears to be the measurement of obesity. Weight as a simple index soon proved to be relatively poorly correlated with excess body fat. Other measures were introduced of which the QI, Quetelet index (weight/height^2) seems to be the least dependent on the variation in height. Better still are the skinfold measurements or the direct body fat measurements but these are usually too elaborate to be of practical use for large scale population studies. In the Netherlands several studies were done to determine the level of obesity in the population. The most important of these are listed in table B.4 (appendix B). In the recent report by the Dutch Health Council (211) the cut off point for obesity was put at a QI of 30 or more. This is a change from earlier cut off points which were in the range of a QI of 26-27 (123, 127). This change reflects the general trend in the opinion that overweight is not as harmful as was long thought. The choice of cut off point will however greatly influence the perceived prevalence of obesity in the population.

Table B.4 shows that the percentage of the population that can be considered obese increases with age and is slightly higher for women than for men.

6.4.2 IDR data by disease category

Obesity and IHD

In many of the prospective IHD studies obesity was investigated as a possible risk factor. The results are not conclusive. In the Pooling Project a positive correlation was found between obesity and the incidence of IHD for the younger men(<50) but an inverse relationship was found for the older men. The same results were found in the Manitoba study. In the Seven Country study no relationship was found, however when the Dutch data

were analyzed separately a positive relationship was found between skinfold measurements and IHD mortality. We shall adhere to the conclusions of the Dutch reports of the Health Council and the Nutrition Board that there is as yet no conclusive evidence that obesity contributes to IHD mortality.

Obesity and cancer

The relationship between obesity and cancer incidence dates back to animal experiments in the 1940's. Tannenbaum reported that rats fed on a very low calory diet lived much longer. However the diet used by Tannenbaum (135) was so extreme that it could never be tried out on humans. The results of the large ACS (American Cancer Study) trial that have already been referred to elsewhere, have yielded some mortality ratio's by weight categories. These are listed in table 6.18. Unfortunately they did not use the Quetelet index but the simple weight/height measure.

Doll and Peto (135) conclude that there appears to be some correlation between obesity and cancer mortality especially in women. This effect is most pronounced for endometrial cancer which could be explained by the increased level of estrogen found in obese post menopausal women. De Waard has found a correlation between body mass indices and breast cancer (212), whereby a QI of >29 was associated with a relative risk of 1.3. There is a continuing debate whether this really constitutes a causal relationship or whether body mass is simply a risk indicator masking a true risk factor such as for instance early menarche, high consumption of milk fat or body surface index. In the current version of the model, obesity in post menopausal women is a risk factor for breast cancer, with a relative risk ratio of 1.3 for all women over 50 years of age with a QI of more than 30. After weight reduction the relative risk ratio return to 1 over a period of 1 year. The LAT for obesity and breast cancer will be set at 5 years.

The effect of obesity on the incidence of colon cancer is still controversial. It has been measured in the Seventh day Adventist studies by Philips (138). He found a U-shaped curve and reports a relative risk of 1.6 for all those outside the "normal" weight range. These values will only be available in a special run and will not be used in the basic runs.

6.4.3   Relationship to other risk factors

Obesity also affects some of the more traditional risk factors which makes it difficult to discern between direct and indirect effects of body weight. In the research on this subject it is often easier to find a relationship between the reduction of overweight and a reduction of risk than a direct relationship

Table 6.18: Mortality ratios from various types of cancer, by weight index[1]

Cancer	Sex	Mortality ratio for weight index[2] in ranges:						
		<0.80	0.80-0.89	0.90-1.09	1.10.-1.19	1.20-1.29	1.30-1.39	≥1.40
Endometrium	f	0.89	1.04	1.00	1.36	1.85	2.30[3]	5.42
Gallbladder, plus biliary passages	f	0.68[3]	0.74	1.00	1.59	1.74	1.80	3.58
Cervix	f	0.76	0.77	1.00	1.24	1.51	1.42[3]	2.39
Kidney	f	1.12	0.70	1.00	1.09	1.30	1.85	2.03
Stomach	m	1.34	0.61	1.00	1.22	0.97	0.73[3]	1.88[3]
	f	0.74	0.95	1.00	1.07	1.28	1.26	1.03
Colon, rectum	m	0.90	0.86	1.00	1.26	1.23	1.53	1.73
	f	0.93	0.84	1.00	0.96	1.10	1.30	1.22
Lymphoma	f	0.83	1.14	1.00	1.06	1.00	0.92	1.13
Brain	f	0.86	0.89	1.00	0.95	1.52	0.69[3]	1.10
Leukemia	f	0.73	1.00	1.00	1.01	0.88	0.85	1.24
Breast	f	0.82	0.86	1.00	1.19	1.16	1.22	1.53
Prostate	m	1.02	0.92	1.00	0.90	1.37	1.33	1.29
Lung	m	1.78	1.38	1.00	0.85	1.04	1.00	1.27
	f	1.49	1.20	1.00	1.10	1.06	1.06	1.22
Ovary	f	0.86	0.98	1.00	1.15	0.99	0.88	1.63
Pancreas	m	1.20	0.82	1.00	0.91	0.88	0.76[3]	1.63
	f	1.17	1.06	1.00	1.36	1.43	1.18	0.61
All cancers	f	0.96	0.92	1.00	1.10	1.19	1.23	1.55
	m	1.33	1.13	1.00	1.02	1.09	1.14	1.33

1 Based on report by Lew and Garfinkel (1979) of data from ACS study of one million U.S. men and women during the 1960's. The tabulated ratio's, all of which are standardized for age and sex a few crude categories of tobacco usage, compare cancer death rates with cancer death rate among people whose weight index was 0.90-1.09.

2 Actual weight divided by the average weight for people of similar height and sex. Values in the range 0.90-1.09 are close to average weight.

3 Ratio based on only 5-9 deaths.

Source: 135.

between the prevalence of obesity in the population and the prevalence of
the other risk factors.

- Serum cholesterol level: In the Zutphen study in the Netherlands a
  reduction in weight by one Kg was found to be associated with a
  reduction of serum cholesterol by 0.05 mmol/liter.

- Hypertension: The prevalence of hypertension has been found to be
  positively associated with the prevalence of obesity. In the Fram-
  ingham study a 10% weight increase resulted on average in a 6mm
  increase in systolic blood pressure and a 4mm Hg increase in diastolic
  blood pressure. Although the exact mechanism whereby bodyweight
  affects blood pressure has not yet been fully understood it is com-
  monly accepted that a weight reduction is accompanied by a decrease
  in blood pressure and as such is one of the first steps in treating mild
  hypertensives.

- Estrogen: There appears to be a positive correlation between the
  amount of body fat and the level of estrogen in post menopausal
  women. However we were not able to find data on the quantitative
  estimates of this relationship.

These relationships will not be present in the Prevent model, but will be
considered when formulating preventive policy measures.

6.5   Fruit and vegetables

In the continuing search for dietary carcinogens an protective agents in
the diet, fresh fruit and vegetables are found to be protective against all
cancers, but especially colon cancer. Two hypotheses are put forward to
explain this relationship. The fibre hypothesis assumes that it reduces the
length of time stools remain in the bowel and that it decreases the concen-
tration of carcinogens in the stools (by increasing their bulk). The other
hypothesis concerns the as yet unexplained protective effect of a high intake
of cruciferous vegetables and possibly also of vitamin C on the incidence of
colon cancer.

6.5.1   Prevalence data

In table 6.19 we can see that the consumption of vegetables but especially
of fresh fruit has increased in the last thirty years. If an effect is to be
expected it would therefore be quite large. However at this point we do
not feel that the quantitative evidence is sufficient to incorporate fruit and
vegetable consumption in the basic runs of the Prevent model.

Table 6.19: Trends in nutritional intake during 1950-78 (in kg. or liters)

	1950	1955	1960	1965	1970	1975	1978
Flour	86.6	81.9	74.9	67.1	60.3	58.3	56.2
Potatoes	128.5	91.0	100.0	90.3	84.4	79.9	82.1
Sugar & Glucose	39.1	42.0	47.8	46.5	51.4	50.5	47.1
Fresh vegetables	40.2	41.1	42.1	41.4	45.6	48.4	51.2
Fruit	42.1	46.5	53.6	60.1	70.0	69.0	72.6
Nuts	2.2	2.0	2.7	3.2	3.9	5.4	5.2
Milk	187.9	174.1	145.0	120.1	96.7	73.1	61.4
Lowfat milk	-	-	-	-	4.2	17.8	25.5
Cheese	4.6	6.2	7.4	7.9	8.2	10.2	11.6
Butter	2.6	3.0	4.7	4.3	2.8	2.6	3.2
Margarine	17.0	19.2	19.9	19.6	17.7	13.5	12.9
Lowfat margarine	-	-	-	-	0.6	3.1	2.8
Oil	5.0	5.2	5.3	6.8	8.1	9.6	9.9
Beef	12.2	16.2	16.3	17.4	19.0	20.1	19.6
Pork	14.0	15.1	18.2	21.1	26.5	31.7	35.0
Chicken	0.2	0.5	2.1	4.4	6.0	7.0	8.2
Eggs	4.7	8.0	11.8	12.1	11.9	11.1	11.1
Fish	10.3	8.7	9.2	10.7	11.7	13.4	13.8
Coffee	1.3	2.4	3.6	4.9	6.0	7.1	6.5
Tea	0.8	0.7	0.8	0.6	0.6	0.7	0.6
Soft drinks	-	-	-	32.0	55.5	58.9	60.4
Beer	10.6	16.2	23.8	37.2	57.4	79.0	85.2
Liquor (100%)	1.5	1.2	1.1	1.9	2.0	3.4	3.0
Wine	0.5	1.2	1.9	3.4	5.1	10.3	12.2

Source: 202

Table 6.20: Prevalence of alcohol consumption, in glasses per week by age and sex

number of glasses of alcohol/week	total (n=324)	15-24 (n=147)	25-34 (n= 68)	35-44 (n= 61)	45-60 (n= 48)
Men					
0-1	16	20	17	11	15
2-5	21	27	24	14	20
6-10	23	20	18	25	31
11-20	25	18	26	27	23
21-30	8	5	3	12	11
30+	7	10	12	11	0
total	100%	100%	100%	100%	100%
Women	(n=418)	(n=189)	(n= 68)	(n= 73)	(n=88)
0-1	28	37	22	16	35
2-5	34	30	36	39	30
6-10	24	16	30	29	23
11-20	11	12	10	11	11
21-30	2	4	0	5	1
30+	1	1	2	0	0
total	100%	100%	100%	100%	100%

Source: 218

6.6 Alcohol intake

6.6.1 Prevalence data

As with smoking data the major problem with the prevalence of alcohol intake in the Dutch population is not the lack of data but more the abundance of data both from industry and from surveys and the discrepancy between the two (213-217). Again there is evidence of severe under reporting. The three major population surveys of 1958, 1970 and 1981 all show an approximate under reporting when compared to the industrial statistics of that same period, of 40-50%. In carefully analyzing these data Knibbe (216) concludes that much can be explained by unintentional misjudgment of the amount consumed. We will therefore not correct the data for under reporting (table 6.20).

The data in table 6.21 show an increase in the number of heavy drinkers in the population. This is corroborated by the data from the industry that show an increase in the total consumption of alcohol in the Dutch population of some 300% over that same period. This has resulted in an overall increase of heavy drinkers from 2% in 1958 to more than 15% for men in 1981.

Table 6.21: Alcohol consumption (glasses per week) of different subpopulations in 1958, 1970 and 1981, in percentages

	1958					1970					1981				
	Abst.	≤3gl.	4-12	13-31	≥22	Abst.	≤3gl.	4-12	13-21	≥2 2	Abst.	≤3gl.	4-12	13-21	≥22
Men	11.6	62.1[1]	19.3[1]	5.0[1]	2.0[1]	13.7	28.2[2]	33.5	13.9[2]	10.7[2]	13.2	20.3[3]	32.4[3]	18.3[3]	15.7[3]
Women	25.8[3]	65.2[1]	7.1[1]	1.8[1]	0.2[1]	31.3	42.2[2]	19.0[2]	5.[2]	0.7[2]	30.3	32.6[3]	26.1[3]	8.6[3]	2.4[3]
Men															
21-40	11.1	58.8[1]	22.1[1]	5.7[1]	2.3[1]	8.8	23.6	33.7	19.4	14.5	11.3	18.4[3]	35.3[3]	18.4[3]	16.6[3]
≥41	12.1[1]	65.1[1]	16.7[1]	4.3[1]	1.8[1]	19.8	33.3[2]	31.6	8.4[2]	6.9[2]	15.2	22.2[3]	29.5[3]	18.1[3]	14.9[3]
Women															
21-40	19.5	68.8[1]	10.3[1]	1.4[1]	-	22.8	42.4	27.6	6.2	1.0[2]	27.1[3]	36.7[3]	23.6[3]	9.0[3]	3.5[3]
≥41	30.7[1]	62.3[1]	4.6[1]	2.2	0.3	38.2	43.3[2]	13.6[2]	4.4[2]	0.5	33.7	28.2[3]	28.8[3]	8.0[3]	1.2
Men															
(total 2035)	63	337	27	11	5	117	242	287	119	92	84	129	206	116	100
Women															
(total 2095)	171	433	47	12	1	238	338	145	39	5	202	217	174	57	15

1: Significant difference between 1958 and 1970
2: Significant difference between 1970 and 1981
3: Significant difference between 1958 and 1981
Two sided t-test sign at ≤0.05
Source: 216

However in recent years the total percentage of abstainers does not change much. The major shift is away from the light drinkers (less than 4 drinks per week) towards the category of moderate and heavy drinkers.

6.6.2   IDR data by disease category

Alcohol and IHD

In 1979 an article in the Lancet (in 219) generated considerable interest because the suggestion was made that moderate alcohol consumption, and especially wine, could be a protective factor in IHD. This was not the first time that such hypotheses were launched. Since then several authors have reported similar results (28, 219, 220, 221).

Marmot in his review article (222) on the subject concluded that although there are several hypotheses about the biomedical mechanism by which alcohol protects, there is not yet conclusive evidence that the relationship between moderate alcohol consumption and IHD is indeed causal. Nevertheless he concludes that, given the results of both case-control and longitudinal studies, one can assume that moderate alcohol consumption (less than 4 drinks a day) reduces the risk of IHD.

Based on the data in table 6.22, which include very diverse populations, we will assume that moderate drinkers have the lowest IHD mortality. The relative risks reported by the different studies are not completely consistent and do not give data on different age groups nor do they agree on the dose-effect relationship. Because the relationship is still controversial a moderate risk ratio of 2 for abstainers as well as excessive drinkers was assumed. In both cases the excess risk will disappear upon cessation.

Alcohol and cirrhosis

It has long been recognized that in most cases, cirrhosis of the liver is a disease that is caused directly by excessive alcohol consumption. Very few cirrhosis deaths are recorded in abstainers or moderate drinkers. Most are found in alcoholics. As with the definition of moderate drinkers there is a confusion in the literature about who is to be considered an alcoholic. We have few data on the prevalence of real alcoholism in the Netherlands since data are limited to those seeking treatment. Compared to surrounding countries there still is a low incidence of liver cirrhosis in the Netherlands, given the current alcohol consumption. One explanation proposed, has been a leadtime, before the rapid increase in consumption results in noticeable increase in liver cirrhosis. This expected mortality increase has in the meantime already been noted by Hoogendoorn (215). Another explanation

could be that although the absolute alcohol consumption has gone up since the second World War, this may be the result of a cohort effect. In that case the younger cohorts, as they age, will have a different "alcohol history" and the incidence of liver cirrhosis may increase even more sharply.

There are detailed case control studies (223-225) available but to fit cirrhosis of the liver in the model with the other disease categories we have had to use a more general relative risk based on the same categories of alcohol consumption used for other diseases. The data come from a longitudinal study by Klatsky (221) on the Kaiser-Permanente population (see table 6.22).

This will apply for all age categories and both sexes, for the heaviest drinkers only. The remnant IDR of 3 will be reached after 1 year with a LAT of 4 years.

Alcohol and accidents

Although alcohol is important in accidental deaths, both accidental falls and traffic accidents, it is extremely difficult to obtain data on relative risk ratio's. In the previous chapter it was shown that there are data on the number or proportion of accidents in which alcohol is implicated but that there are few data on the prevalence of alcohol use in the total population at risk. One could rely on the percentages found in the alcohol traffic controls but these are obviously not a representative sample of the automobilists nor of the hours in which autokilometers are covered (226).

Again we relied on the data collected by Klatsky on the Kaiser-Permanente population where he also recorded the number of deaths classified as due to accidents. Since he made no distinction between traffic accidents and accidental fall we shall use the relative risk ratio of 2 for both causes of death. This relative risk will apply only to the heavy drinkers and will be identical for men, women and both age groups. This excess risk disappears completely, immediately after cessation.

Alcohol and breast cancer

Although there have recently been suggestions (129, 131) that there is an increased risk for breast cancer in women who habitually drink even moderate amounts of alcohol, we feel that at the moment the evidence is not yet sufficient to include this relationship in the current version of the model.

Table 6.22: Death by cause[1] according to alcohol consumption

Cause of death[2]	Usual Number of Drinks/Day[3] (n=2015, Each Group)			
	0	$\leq$2	3-5	6+
	n (%) mortality			
All malignant neoplasms, (140-209)	45 (2.2)	42 (2.1)	53 (2.6)	75 (3.7)
Oral cavity and esophagus (140-150)	2 (0.1)	0 (0.0)	5 (0.2)	8 (0.4)
Stomach (151)	3 (0.2)	3 (0.2)	3 (0.2)	4 (0.2)
Colon and rectum (153-154)	3 (0.2)	7 (0.4)	5 (0.3)	4 (0.2)
Pancreas (157)	2 (0.1)	5 (0.3)	3 (0.2)	6 (0.3)
Lung (162)	15 (0.7)	7 (0.4)	16 (0.8)	24 (1.2)
Breast (174)	4 (0.2)	1 (0.1)	3 (0.2)	3 (0.2)
Genitourinary (180-189)	3 (0.2)	8 (0.4)	7 (0.4)	4 (0.2)
Central nervous system (191-192)	2 (0.1)	3 (0.2)	3 (0.2)	4 (0.2)
Lymphatic and hemato-poietic (200-209)	7 (0.4)	7 (0.4)	3 (0.2)	7 (0.4)
Primary site unspeci-fied (196-199)	2 (0.1)	0 (0.0)	3 (0.2)	7 (0.4)
Other specified site	2 (0.1)	1 (0.1)	2 (0.1)	4 (0.2)
All cardiovascular (390-458)	88 (4.4)	64 (3.2)	82 (4.1)	77 (3.8)
All coronary disease (410-414)	66 (3.3)	40 (2.0)	47 (2.3)	55 (2.7)
Acute myocardial in-farction (410)	36 (1.8)	22 (1.1)	29 (1.4)	22 (1.1)
Other coronary (411-414)	30 (1.5)	18 (0.9)	18 (0.9)	33 (1.6)
Stroke (430-438)	10 (0.5)	15 (0.7)	16 (0.8)	9 (0.5)
Other cardiovascular (390-409, 415-429, 439-458)	12 (0.6)	9 (0.4)	19 (1.1)	13 (0.6)
Respiratory (460-519)	7 (0.4)	3 (0.2)	12 (0.6)	18 (0.9)
Cirrhosis (571)	5 (0.3)	0 (0.0)	12 (0.6)	33 (1.6)
Accidents (800-959; E800-919)	16 (0.8)	8 (0.4)	19 (0.9)	39 (1.9)
Other causes	16 (0.8)	9 (0.4)	9 (0.4)	13 (0.6)
Total deaths	177 (8.8)	126 (6.3)	187 (9.3)	255 (12.7)

1 In California from time of entry into study (1965 to 1968; mean dates = July 1966 through 31 December 1976)
2 Numbers in parentheses indicate code numbers of the International Classification of Diseases Adapted, 8th revision
3 Comparisons between groups were significant at $p<0.05$. Source: 221

Table 6.23: Differences in the prevalence of hypertension between groups
with a high or a low alcohol consumption

Authors	Definition hypertension[1]	P1/P2[2]
Liam	?	4.0
Klatsky et al	160 and/or 95	1.5-2.4
Arkwright et al	140 (syst.)	4.0
D'Alonzo et al	160 and/or 95	2.3
Dyer et al	160 and/or 95	1.8
Kannel et al	160 and/or 95	2.0
Mathews	>120 (pressure average)	2,7

1 Systolic and diastolic blood pressure in mmHg
2 P1 = high alcohol consumption, prevalence of hypertension
  P2 = low alcohol consumption, prevalence of hypertension
Source: 231

6.6.3 Relationship to other risk factors

The most important relationship of alcohol to other risk factors is the
effect of heavy drinking on the prevalence of hypertension (227-230). This
correlation has been noted by a number of investigators. The shape of
the curve is not linear, it has been described as J shaped. As with the
data on IHD deaths there are problems with the definition of moderate and
heavy drinkers. In table 6.23 an overview of the relative risks found by the
different investigators is summarized by Grobbee (231, 232). These are not
yet routinely included in the current version of the Prevent model.

6.7 Age of the mother at time of the first birth

6.7.1 Prevalence data

In the Netherlands data on the age of the mother at the time she gives birth
to her first child, are available for all women born after 1932. Contrary to
other risk factors, this variable can not change over a persons lifetime. Once
a woman has had her first child, she is assigned to a risk category which
will remain unchanged as she grows older. This means that the data are
presented in a different way. Each age group represents a cohort of women
of which a certain percentage has had a first child. As time proceeds this
cohort will move to an older age group and will take the distribution of
ages at first birth along. For the cohorts now over forty, few births will be
added as they grow older but in the younger age group the percentage of
women that has never had a child will continue to decrease over time.

Figure 6.1: Cumulative percentage of women who have had a first child in 1984, by age at birth and by birth cohort
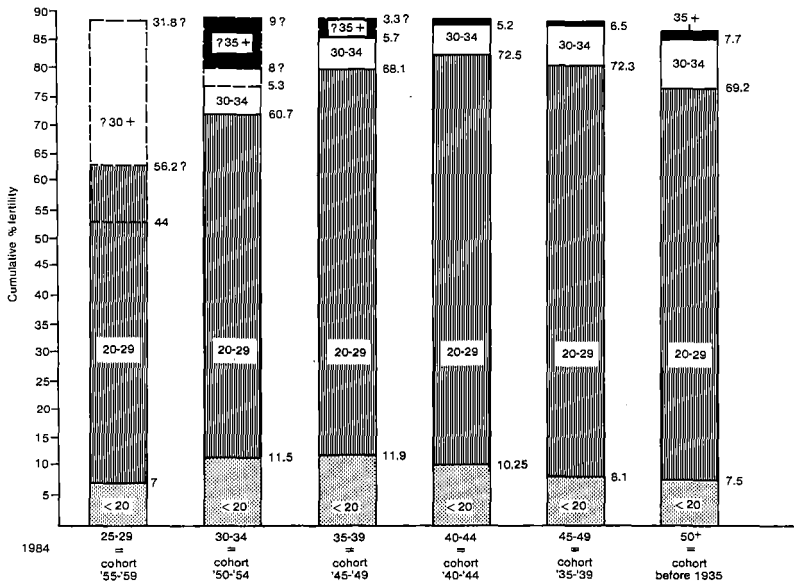
Figure 6.1 shows the distribution of age specific fertility in 1984 for women born after 1932. Unfortunately no comparable data exist for older cohorts. Obviously the younger women will continue to have baby's and for the age group 25-29 we do not know how many will have had their first child before the age of 30. For the other age groups it is easier since we only need to make assumptions about the total "first fertility rate" that each cohort will achieve to calculate the percentage of first births occurring after the age of 30 and 35. We assume that this first fertility rate will remain at 89% . More women may remain childless in the younger cohorts (although the current wave of "quick before its too late pregnancies" seems to belie this hypothesis) but misclassifications between women who have their first

Table 6.24: First fertility rate by age of the mother for different birth cohorts in 1984

	<20	20-29	30-34	35+	Never
25-29	7	56.2?	31.8?		11
30-34	11.5	60.7	8?	9?	11
35-39	11.9	68.1	5.7	3.3?	11
40-44	10.25	72.5	5.2	1	11.05
45-49	8.1	72.3	6.5	1.2	11.9
50-53	7.5	69.2	7.7	1.6	14

child after the age of 30 and women who never have any children should not give rise to considerable error, since both have an increased risk for breast cancer.

In table 6.24 the percentages by age group which were not available, were derived by assuming that each cohort would have a yearly fertility rate equivalent to that of the year before. This method was only used for the categories with partially complete data. The assumption was made that total first fertility remains constant and the remaining percentages are thus calculated. All data arrived at by these assumptions are marked with a question mark.

As can be seen from these data there has been an important shift in the age at which women have their first child. After an initial rise in the percentage of women who had a child under the age of twenty in the fifties and sixties, there is a sharp drop after the early seventies which is probably related to the increasing availability of effective contraceptives. Most women have their children between the ages of 20 and 29. However this percentage starts to drop for the cohorts born after 1944. At the same time there is a rise in the percentage of first time mothers over 30 and increasingly over 35.

6.7.2   IDR by disease category

Age of mother at first birth and breast cancer

It has been shown in many different populations, that the risk of breast cancer is related to childbearing. In fact the age at which the first child is born is the most important determinant in the relationship between fertility and breast cancer. McMahon et al (233) in their international collaborative study in the 1960's were able to quantify this relationship. They found a linear increase in the risk with the rising age of the mother as is shown in figure 6.2.

Figure 6.2:

Relative risk[a] of breast cancer according to age at first birth; data for all centres combined

Age at first birth
(years)
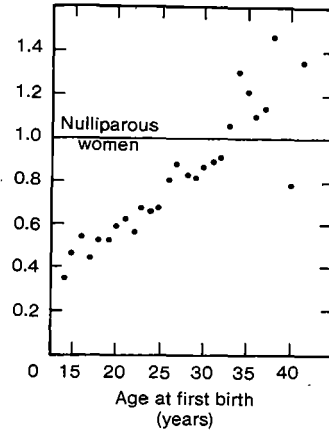
Source: 233   [a]Relative to a risk of 1.0 for nulliparous women.

Women who never bore children are the reference category and the birth of a child protects if the child is born before the mother reaches the age of 35. These same results are given in table 6.25.

The data on risk ratios presented by MacMahon were adjusted to fit the prevalence data (table C.13).

Conclusion

From this chapter it becomes obvious that although many relationships between risk factors and disease incidence/mortality rates are accepted as causal (see chapter 5), the exact quantification of that relationship in terms of risk ratios is often problematic. Where possible the empirical data were used. In some cases, as for instance with obesity and breast cancer, no trials are available on the effects of interventions, so that values for the remnant risk ratio for the ex-exposed and the lag and latency periods were estimated (prof. de Waard, personal communication).

The current input data are a deliberate choice, necessary to illustrate the use of the Prevent model in the following chapters. Other users may prefer other values, but this will not change the type of data necessary, nor the type of results produced by Prevent (see also chapter 8 on the sensitivity

Table 6.25: Estimates of relative risk of breast cancer by age at delivery, for women of parity 1 only

Centre	Relative risks[1], age at delivery being:						No. of:	
	<20	20-24	25-29	30-34	≥35	Any age	Cases	Controls
Boston	19	72	60	107	118	76	77	233
Glamorgan	(50)	29	100	55	106	68	117	345
Athens	44	64	65	120	81	76	129	433
Slovenia	123	81	83	126	88	93	136	399
Sao Paulo	66	70	102	(74)	(175)	78	63	165
Taipei	(92)	(61)	(121)	(50)	(81)	74	22	48
Tokyo	52	61	67	119	152	82	135	302
All centres	58	62	77	98	104	78	679	1925

1 Relative risks are expressed relative to a risk of 100 for non-parous women.
Estimates are based on direct comparison of cases and controls, without adjustment.
Values for cells containing less than 20 controls are shown in parentheses.
Source: 233

runs).

This chapter is meant to show where we derived our data from. Since the reader may wish to have an overview of the input data files they are brought together in appendix C.

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Part IV

SOME RESULTS OF THE MODEL

Introduction and summary

In this section we shall show and analyze some of the results produced with the Prevent model. For this purpose a basic version of the model is used as an example. It is obvious that different opinions may exist on the choices made about input data and on past and future trends. Prevent offers the methodology, other users may eventually adjust input data to suit their population or specific interests.

Using a very simple and straightforward intervention as an example, we shall show in the first chapter what kind of results Prevent produces and how the information they provide could be used to weigh policy decisions. Two important outcome measures will be discussed: total mortality reduction and Actual Years of Life Gained (AYLG). In the total mortality reduction the different disease specific mortality reductions are reflected in the evolution of the curve over time. Both its peak value and the development over time are important. The AYLG is the best overall outcome measure since it not only reflects the total mortality reduction but also the length of survival after a death avoided. For both benefit measures it is of interest to look not only at the total value but also at the distribution of health benefit in the population, for instance between men and women.

To show the level of confidence that can be attached to the results of a model, it is often subjected to a form of testing. This can be *sensitivity testing* to see how sensitive the model is to the choice of the initial input data, or a *historic reconstruction* using the model to check whether, given the right data, the model will yield the correct results. In chapter 8 the results of the testing done with Prevent are presented. The sensitivity testing shows that the initial input data for IDR's and prevalence sometimes affect the level of outcome of the model but that it is the time dimension and the remnant IDR which really determine the characteristic shape of the result curves. In the historic testing an attempt was made to simulate

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the development of lung cancer mortality in the Netherlands between 1970 and 1985, using historic data on smoking. The final conclusion must be that the available data leave some interesting questions unanswered, which may be worth additional research in the future, but which at present are outside the scope of Prevent.

Chapter 7

A basic Prevent run

In the current version of the Prevent model, used in this example, the risk factors and disease categories included are shown in table 7.1.

When considering risk factors and disease incidence, the first question to ask is to what extent these risk factors can explain the variance in disease specific incidence and mortality. The outcome measure of interest is the Etiologic Fraction at time 0. In the Prevent model the Etiologic Fraction is an age and sex specific value. Table 7.2 shows the Etiologic Fraction for the age group 60-64, for all the risk factor-disease combinations considered in the model, separately for men and women.

The etiologic fraction not only gives an indication of the amount of variance in disease specific mortality that can be explained by the known risk factors, but it also sets the limits for the potential mortality reduction that can be achieved by an intervention on this risk factor. In table 7.2 cigarette smoking can be held responsible for 86% of lung cancer mortality

Table 7.1: Risk factors and diseases in the basic runs

Risk factors	Disease categories
Cigarette smoking (Cig.Smoking)	Ischemic heart disease
Hypertension	Cerebrovascular accident
Hypercholesterolemia (Serumchol)	Chronic Obstructive Lung
Alcohol consumption	Disease
Obesity	Lung cancer
Age of mother at first birth (AMFB)	Breast cancer
	Traffic accidents
	Accidental fall
	Liver cirrhosis

Table 7.2: Etiologic fractions in the Dutch population 1985

	Cig. smoking		Hyper- tension		Serum- chol.		Alcohol		Obesity	AMFB
	M	F	M	F	M	F	M	F	F	F
IHD	36	23	33	47	19	-	34	39	-	-
CVA	-	-	51	49	-	-	-	-	-	-
Lungca.	86	41	-	-	-	-	-	-	-	-
Breastca.	-	-	-	-	-	-	-	-	4.3	23.5
COLD	92	72	-	-	-	-	-	-	-	-
Traffic accidents	-	-	-	-	-	-	13	1.2	-	-
Accidental fall	-	-	-	-	-	-	13	1.2	-	-
Cirrhosis	-	-	-	-	-	-	54	9	-	-

and 92% of COLD mortality in 60-64 year old men and a lower but still impressive percentage in women. The EF for IHD is much lower. However although lung cancer is an important cause of mortality for men it is not nearly as important as ischaemic heart disease. A small percentage of IHD mortality prevented may still constitute a larger mortality reduction than a large percentage of lung cancer mortality prevented. This is the reason why it is also important to look at absolute measures of benefit.

What is of interest in the etiologic fractions, is that these can give an impression of the extent to which disease categories are preventable. The above results show for instance that COLD could largely be eliminated through primary prevention, but not breast cancer.

The following examples will show how the different variables in Prevent affect the health benefit estimates, both in proportional and in absolute terms. To show how the different variables interact they will be introduced one by one and the effect on outcome measures will be shown for one risk factor only, smoking. The other risk factors will only be used to illustrate specific interactions. Finally the health benefits of a 50% prevalence reduction on each risk factor, will be presented to compare the potential impact of primary prevention for the different risk factors.

7.1 Smoking and health

In the Prevent model cigarette smoking affects the following diseases: IHD, lung cancer and COLD. The input data are summarized in appendix C, and a future autonomous trend of a 1% reduction per year is assumed for all age, sex and exposure categories.

Figure 7.1:

Lung cancer mortality for men, three alternatives
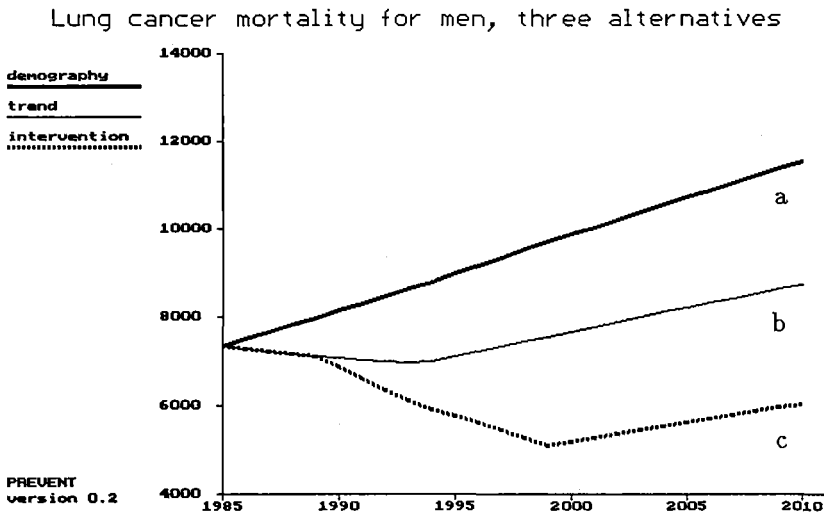
As intervention, an immediate reduction by 50% of the prevalence of smokers in 1985 is assumed, in all age, sex and exposure categories. This highly unrealistic assumption of an immediate reduction is chosen because it allows us to illustrate the effect of the different time variables in Prevent.

7.1.1 Time dimensions

In figure 7.1 the estimated development of total lung cancer mortality over time is shown under three different assumptions. Curve "a" represents the so called "null" scenario in which only the demographic aging of the population affects the total lung cancer mortality. This is what would be expected if the effects of smoking cessation were immediate and there were no changes in smoking prevalence in the future.

Curve "b" shows the effect of adding a time variable and assuming a moderate future autonomous reduction in smoking prevalence (-1%), based on the past trends. This is the reference or trend scenario as it will be used in these example runs. The initial dip in the lung cancer mortality is the result of the substantial reduction in smoking prevalence in the years before the simulation started. Because of the LAG and LAT variables this reduction continues to affect lung cancer mortality in the future. After

the effect of this past reduction wears off, the influence of demography and
of the trend determine the evolution of the mortality. The negative trend
in smoking prevalence makes the rise in lung cancer mortality due to the
aging of the population, less steep than in the "null" scenario. Otherwise
the curves "a" and "b" would have been parallel.

Finally curve "c" shows the effect of an intervention in 1985. Lung
cancer mortality is not affected by that intervention until after LAT years,
until 1989 the mortality evolves as it did in the reference scenario (the LAT
for smoking and lung cancer is assumed to be four years). After 1989 the
mortality starts to decrease slowly over LAG years. This is the lag time
(ten years) necessary for the complete risk reduction of the ex-smokers, and
thus also the time period necessary to see the full effect of the intervention.
After LAG+LAT years, in 1999, the trend and the demography take over
again and the mortality evolves parallel to the reference scenario. The pro-
portional reduction of lung cancer mortality due to the intervention remains
the same but the absolute level of mortality increases due to demographic
changes, although it does not again reach the 1985 level in this 25 year
simulation.

7.1.2   Multi factorial model

Smoking does not only affect lung cancer mortality. Figures 7.2 and 7.3
show the trend and the intervention scenario for IHD and COLD mortality,
under the same assumptions as before. IHD has a short LAG+LAT period
so that the effect of the intervention reaches a maximum already after 6
years.

For that same reason the effect of past reductions in smoking prevalence
are not very marked. In the case of IHD mortality the effect of the aging of
the population is so pronounced that despite the lowering of the age specific
mortality due to the intervention, the absolute mortality exceeds the 1985
level after approximately 10 years.

For COLD on the other hand the LAG+LAT is extremely long (20
years) so that past reductions in smoking continue to have a visible effect
on mortality until 1995. After 1995 the demography and the assumed
future trend in smoking cessation determine the COLD mortality in the
trend scenario. In the intervention scenario, the effect of the intervention
starts to be visible in 1995, but continues to affect the COLD mortality
until 2005. However, there is also an initial rise in COLD mortality. This
is the result of the long LAT period, in which COLD mortality is not yet
affected by the intervention while IHD age specific mortality has already
been markedly reduced: COLD mortality is in a sense substituted for IHD
mortality. This is noticeable only for men, since the reduction in IHD

Figure 7.2:

Disease Specific Mortality (numbers) from IHD

men, trend

men, interv.

women, trend

women, interv.

PREVENT
version 0.2

Figure 7.3:

Disease Specific Mortality (numbers) from COLD

men, trend

men, interv.

women, trend

women, interv.

PREVENT
version 0.2
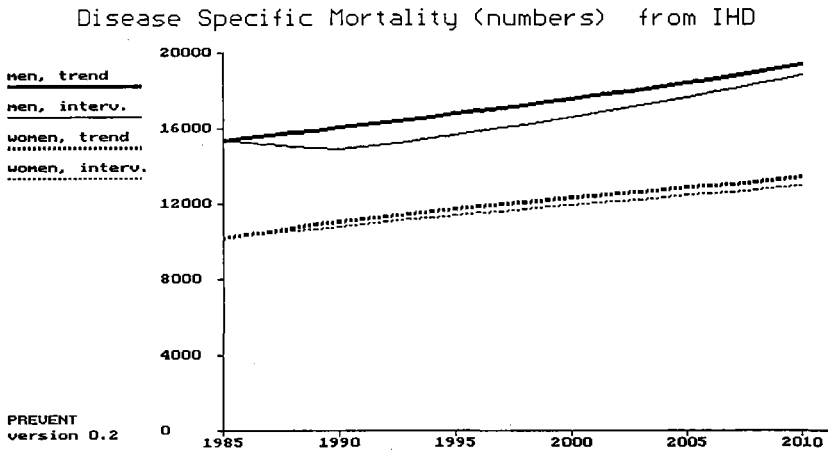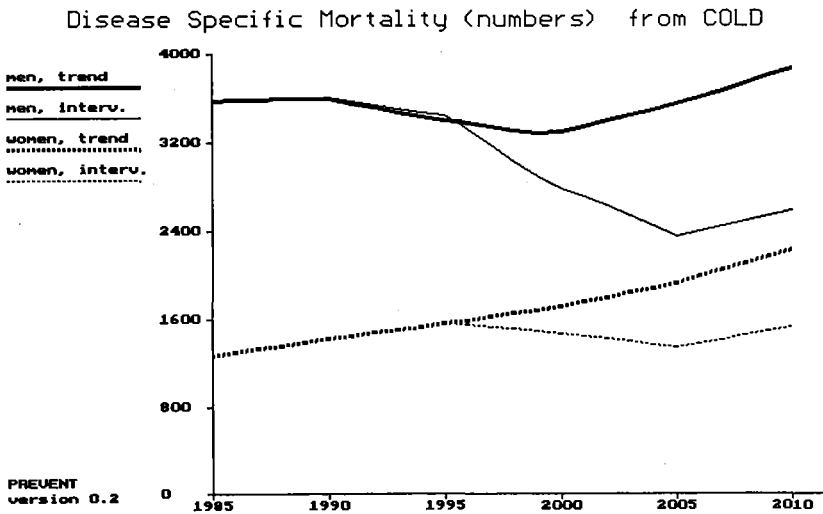
Table 7.3: Total PIF and mortality reduction in 2000, by disease, after a 50% reduction in smoking prevalence in 1985

	Lung cancer		IHD		COLD	
	M	F	M	F	M	F
PIF (%)	33	29	5	3	16	14
Mortality reduction	2501	383	954	376	533	248

mortality is so much larger for men than for women.

To illustrate the difference between the proportional and the absolute level of health benefit table 7.3 shows the PIF (proportional reduction in mortality) for all age groups and the absolute disease specific mortality reduction in the year 2000 for IHD, lung cancer and COLD after a 50% reduction in smoking in 1985.

For men lung cancer represents both the highest proportional and absolute mortality reduction. For women lung cancer also represents the highest proportional reduction but the absolute mortality reduction for IHD is almost as large.

7.1.3 Demography

Ultimately it is the total health benefit to be derived from this hypothetical intervention, which is of interest. Figure 7.4 shows the total mortality reduction for men as well as the mortality reduction in each of the three disease categories affected by smoking. The total mortality reduction represents the absolute number of deaths prevented each year for the full simulation period, as a result of the intervention. The effect of the different time dimensions of the three disease categories is easily recognized in the different slopes of the top curve. It reaches its maximum after all the LAG+LAT years have passed. After that the mortality reduction starts to diminish. This is not because of the diminishing effect of the intervention on these three causes of death, but a result of the increase in mortality from other causes that is bound to occur in an aging population.

The maximum mortality reduction in each disease category is reached after LAG+LAT years and then remains approximately constant while the total mortality reduction starts to go down. The fact that the disease specific mortality reduction is not completely constant is the result of the fact that the PIF is a proportional reduction in mortality. If the disease specific mortality changes considerably over the simulation period, for instance as a result of the aging of the population, the absolute mortality reduction

Figure 7.4:

Total and disease specific mortality reduction, men
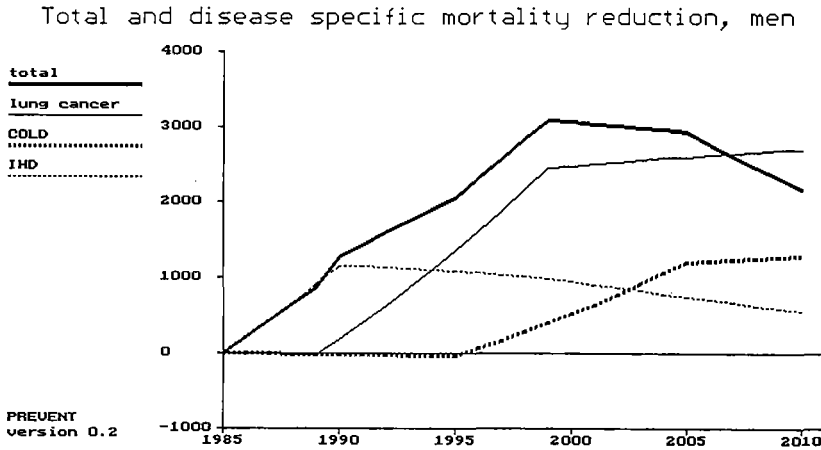
resulting from a constant proportional reduction, will not be constant.

The two other composite outcome measures are the PYLG (potential years of life gained) and AYLG (actual years of life gained). Figures 7.5 and 7.6 show the PYLG and the AYLG resulting from the above intervention.

PYLG in figure 7.5 shows very clearly that this measure is nothing but a mortality reduction weighed for the age at which death occurs. Since for the above diseases the age of death does not vary very much, the shape of the PYLG curve is basically identical to that of the total mortality reduction, with a slight extra emphasis on the effect caused by IHD mortality, which tends to occur at a slightly younger age than lung cancer or COLD.

By contrast the actual years of life gained, which shows how the "saved" individual remains part of the total population until he dies from another cause of death, develops in a very different way. It slowly builds up as more and more cases of death are prevented and accumulate in the population before dying. For the period of 25 years for which we have simulated in this run, the measure of AYLG continues to rise. This measure is maybe the best indication of the health benefit of an intervention since it shows the increase in the population over time, due to the intervention, a true cumulation of the year by year effect of the intervention.

Figure 7.5: Potential Years of Life Gained after smoking cessation
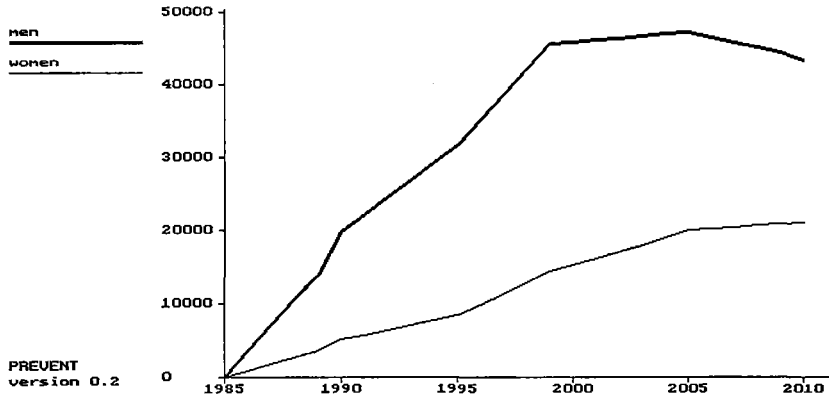
Figure 7.6: Actual Years of Life Gained after smoking cessation
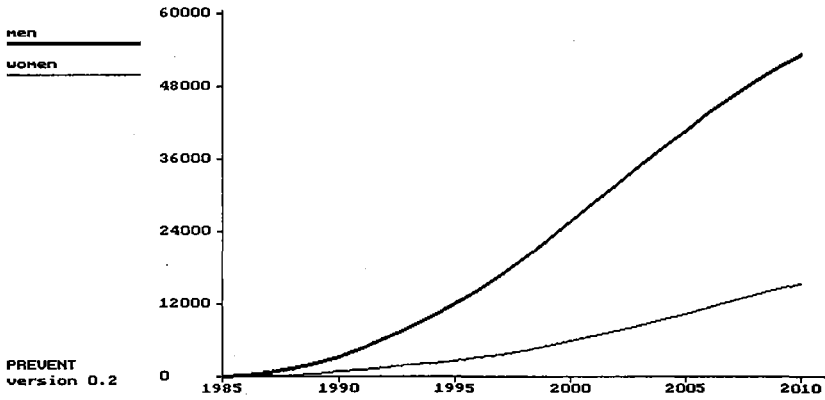
7.2 Other risk factors

7.2.1 Hypertension

The effects of a 50% reduction in hypertension in all age, sex and exposure categories in the Dutch population is shown in figure 7.7.

Hypertension affects both IHD and CVA. In both cases the effect of the intervention is proportionally small. The short LAG and LAT times are clearly apparent by the immediate effect of the intervention and the short period after which both populations evolve in a parallel way again.

However the total mortality reduction shows that the relatively small proportional change in disease specific mortality does lead to a sizable reduction in total mortality. The peak level is comparable to the peak level achieved by the smoking intervention but both the evolution over time and the individual contribution of female and male mortality reduction differ greatly.

The male/female contribution to the health benefit is interesting. For IHD we see that although the level of mortality is lower for women than for men, the effect of a reduction in hypertension prevalence is greater for women than for men, due to the higher prevalence of hypertension especially among older women and the higher IDR values for women. In the case of CVA women have higher initial mortality rates, and the effect of the intervention is almost identical for men and for women. Together the effect on IHD and CVA is initially higher for women than for men but after approximately 20 years this is reversed. Probably this crossover is the result of the fact that the aging of the population seems to affect the male IHD mortality much more than the female IHD mortality. This is an illustration of the difference between proportional and absolute mortality reduction mentioned earlier: after a certain number of years the same proportional reduction in mortality means a larger number of deaths prevented for men, while the number for women barely increases over the years.

If we compare the effect of a 50% reduction in smoking and a 50% reduction in the prevalence hypertension (see figure 7.4 and 7.8), an important difference is the fact that the mortality reduction in the case of smoking is almost entirely in the male population while in the case of hypertension both men and women benefit from the intervention. The peak mortality reduction achieved by a 50% reduction in hypertension is only slightly lower than in smoking, but the mortality reduction as a result of smoking cessation persists for a longer period, therefore the total benefit (the area under the curve) is much greater in the case of the smoking intervention.

This example illustrates two points that should be considered when comparing benefits. In the first place the total benefit may be identical but

Figure 7.7:

Disease Specific Mortality (numbers) from IHD

Disease Specific Mortality (numbers) from CVA
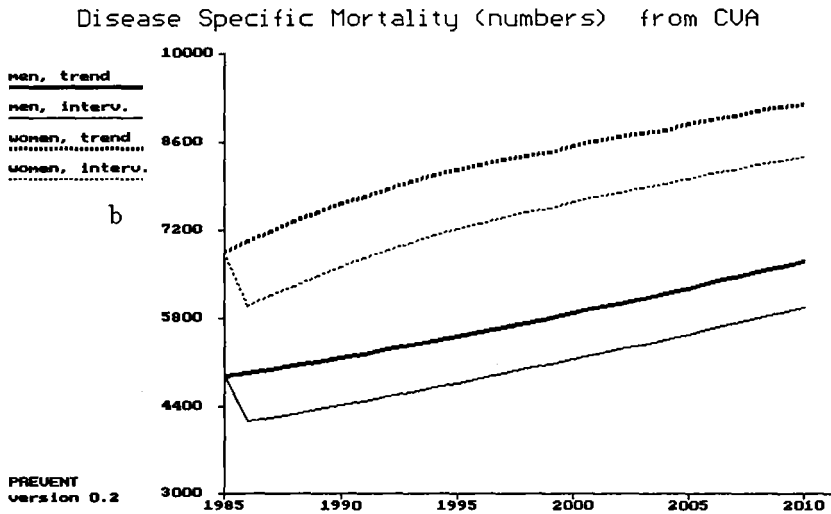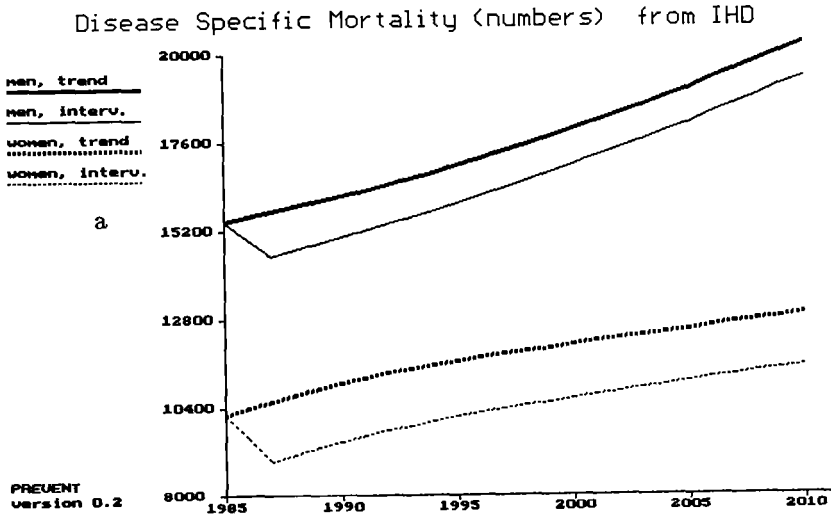
Figure 7.8:

Total Mortality Reduction (numbers)
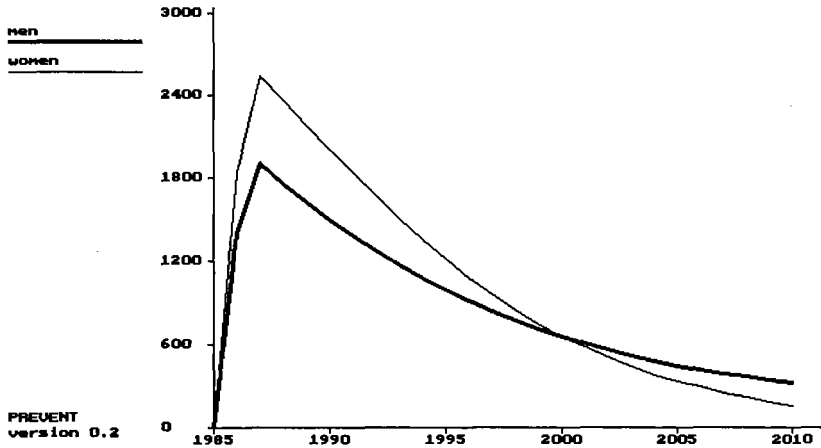
the distribution of the benefit over sub populations may differ. In this case it concerned the male/female distribution but similar differences may arise between age groups or between socioeconomic groups. Secondly the peak mortality reduction is not the best measure of effect since the persistence over time may vary. The AYLG measure of effect is therefore more reliable as comparative measure since this shows the cumulative effect. Figure 7.9 shows the AYLG for the intervention on smoking and hypertension and clearly illustrates the difference of the effect on population growth of both interventions.

7.2.2 Alcohol

An intervention on alcohol is used here to illustrate the importance of looking at all the disease categories affected by a risk factor. In prevention there is always a lively debate on the *population* versus the *high risk group* approach. The point is whether more benefits can be achieved by slightly reducing the risk of many versus considerably reducing the risk of a few. In the prevention of alcohol related death another dimension is added to this debate by the Ledermann theory which states that the number of excessive drinkers is directly related to the total number of drinkers in a population.

Figure 7.9: Actual Years of Life Gained after smoking cessation or reduction
in hypertension
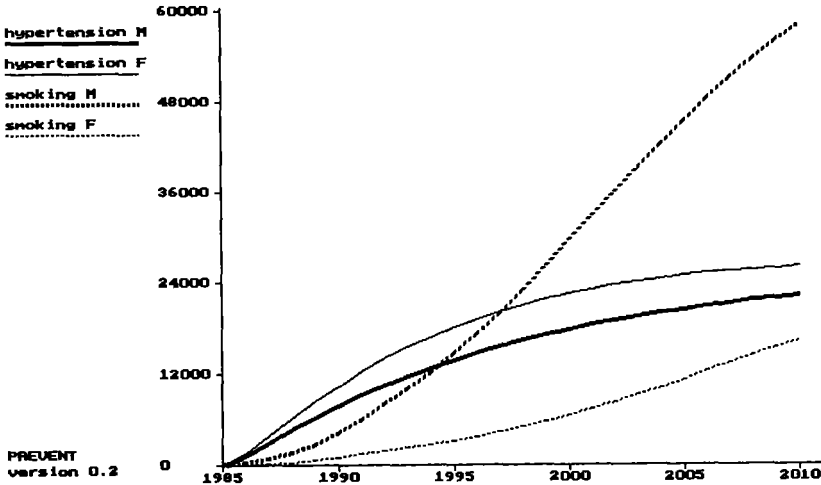
The question then becomes whether one should reduce the number of ex-
cessive drinkers by reducing the total number of drinkers in a population
or whether one should exclusively lower the number of excessive drinkers
without affecting the number of moderate drinkers. Both strategies are
analyzed here.

Lets assume for a moment that the effect of moderate alcohol consump-
tion on IHD mortality is indeed causal and that a shift from moderate
alcohol consumption to total abstinence, will indeed result in an increase
in IHD mortality. An alcohol campaign aimed at reducing the number of
alcohol related accidents or the number of cases of cirrhosis of the liver, by
an approach aimed at the excessive drinkers only can be compared with
the strategy of the reduction of total alcohol consumption in the popula-
tion. Figure 7.10 shows the effect on mortality reduction of a 50% reduction
of the proportion of drinkers in all exposure categories (a) and the effect
if the preventive intervention would affect only excessive drinkers in the
population (b).

As with smoking, the mortality reduction is the result of changes in
several diseases each with different time dimensions. In the case of ex-

Figure 7.10:

Total mortality reduction, two alternative interventions on alcohol consumption
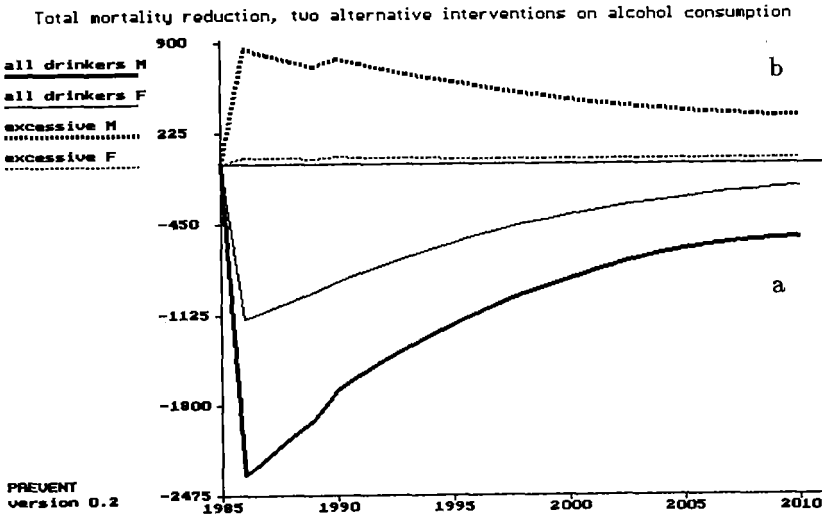
<cessive drinkers only (b), there is a second peak caused by the reduction
in mortality due to liver cirrhosis, after the initial effect due to IHD and
traffic accidents. Men benefit more from the intervention, which is logical
given that very few women drink excessively and that the diseases affected
by alcohol, except accidental fall, are a more important cause of death for
men.

Although the effect on accidents may be the same for both interventions,
the total mortality reduction is very different. Since a shift from moder-
ate drinking to total abstinence increases the risk of IHD, an intervention
aimed at the total population has a negative effect on total mortality. The
small proportional negative effect on the most important cause of death,
IHD, far outweighs the positive effects on the mortality due to accidents or
cirrhosis. This example illustrates that the health policy maker needs to
weigh the advantages and disadvantages of alternative interventions for the
total health of the population and not just the disease specific benefit.

Table 7.4: Total mortality reduction and AYLG in 2000 and 2010, after a 50% reduction of different risk factors and a combined intervention

| | Mortality reduction | | | | AYLG | | | |
| | 2000 | | 2010 | | 2000 | | 2010 | |
	M	F	M	F	M	F	M	F
Smoking	3087	793	2159	992	25687	5808	53006	15443
Cholesterol	436	35	204	32	9777	384	12678	739
Hypertension	814	808	916	269	18547	23476	26477	28164
Alcohol	475	34	346	40	9756	607	13636	963
Obesity	-	28	-	12	-	595	-	782
Combination	1783	640	1294	477	22675	11953	38027	17551

7.3   Comparing risk factors

Although the actual levels of disease specific mortality in the future will differ from those calculated by the Prevent model, if only because curative care is assumed static, interventions all of which are of a preventive nature, can be compared by assuming that all other circumstances remain unchanged.

From the runs presented in this chapter, it is apparent that the height of the effect curve (for instance mortality reduction), its evolution over time and its shape vary considerably depending on the risk factor studied.

Table 7.5 presents the proportional changes in disease specific mortality in the year 2000, for all the disease categories in Prevent, after a 50% reduction in the prevalence of each of the different risk factors in 1985. Again the intervention is presumed to be immediate and identical for all age, sex and exposure categories. Finally the effects of a simultaneous reduction by 20% of the prevalence of smoking, hypertension and elevated serum cholesterol are shown. The range of the effect of a 50% prevalence reduction for the different risk factors varies considerably and to a certain extent is accompanied by a substitution of causes of death.

In order to compare the ultimate health benefits, table 7.4 shows the total mortality reduction and the AYLG in the year 2000 and 2010 of each of these interventions.

Smoking will affect mortality to a far greater extent than any of the other risk factors. In 2000 the AYLG of men and women combined may still be greater for hypertension, in 2010 AYLG is much greater in the case of smoking.

Table 7.5: % changes in disease specific mortality in 2000, after a 50% reduction in risk factor prevalence in 1985.

	IHD		CVA		Lung cancer		COLD		Traffic accidents		Accidental fall		Cirrhosis of the liver		Breast cancer
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	F
Smoking	-5%	-3%	+2%	-	-33%	-29%	-16%	-14%	+1%	-	+2%	-	+1%	-	-
Cholesterol	-6%	-	+1%	-	-	-	+1%	-	-	-	+1%	-	-	-	-
Hypertension	-5%	-12%	-12%	-11%	+1%	+1%	+2%	+3%	-	-	+3%	+4%	-	-	+1%
Alcohol (exces.only)	-4%	-	+1%	-	-	-	+1%	-	-5%	-1%	-5%	-	-20%	-4%	-
Obesity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-2%
-20% smoking+ -20%hypert.+ -20% chol.	-7%	-7%	-4%	-4%	-13%	-8%	-5%	-5%	-	-	+3%	+2%	-	-	-

7.4   Comparing health benefits

Because of the different outcome measures used, the ranking of interventions is not always straightforward. Three aspects need to be addressed in order to be able to use quantitative data to set priorities.

7.4.1   Distribution of health versus maximizing health benefit

The majority of the risk factors included in Prevent affect male mortality to a much greater extent than female mortality, with the exception of hypertension. Considering that the male population has lagged behind in the increase in life expectancy this century and that cardiovascular disease, which has started non communicable disease epidemiology mainly affects men this is not surprising. The diseases studied and the risk factors identified have concentrated on the male population, and hence in the Prevent model it is male mortality that is most affected by preventive interventions.

If the general health goal is to achieve an equal distribution of effect between men and women, the choice of an intervention might be different than when the goal is simply a maximum mortality reduction. On the other hand women currently have a longer life expectancy than men. If the health goal is to achieve a more equal distribution of mortality these risk factors offer a good starting point since most of the proposed policy measures will tend to reduce the mortality gap between men and women.

7.4.2   Short term versus long term benefits

In some cases preventive investments will immediately yield effect such as in the case of alcohol and accidents, in other cases it will take almost twenty years to see the maximum level of benefit, as in smoking and Chronic Obstructive Lung Disease. The introduction of a time lag creates the danger that preventive measures will not be attractive (especially politically) because the promised benefits are so far ahead. If using even a small discount rate this may make prevention in general seem less attractive than curative interventions.

There are two things to keep in mind when considering the distribution of effects over time:

- The effect of an intervention on a risk factor for the disease being considered may take many years to become visible, such as in smoking and lung cancer but other benefits of the intervention may already be apparent earlier. This is illustrated in the Cancer scenario report

(1). An intervention on smoking is much more attractive when the effects of a smoking cessation program are not only considered for lung cancer but also for IHD, since these benefits will be apparent much sooner.

- The long LAG times mean that a long simulation period may be necessary to show the full effect of a measure. Given the relatively short planning horizon for most governments, this will negatively influence the perceived benefits of prevention. Very often the benefits considered when discussing alternative interventions are only a small fraction of the total benefits because the time span considered is too short. In table 7.5 it was clear that, when comparing the AYLG benefits in 2000, the choice of intervention might have been different than when looking at the estimates for 2010. This illustrates the importance of considering at least the full LAG+LAT period to assess the benefits of interventions.

7.4.3 The health indicator chosen

The outcome measures that are considered in these analyses are based on mortality only. However it has rightly been argued that mortality is often but a poor indicator of health in industrialized countries. Some diseases with a considerable burden of disease, such as COLD, cause relatively little mortality. A ranking of priorities by mortality outcome measures will tend to give insufficient weight to these diseases. It would therefore be useful in a further elaboration of Prevent to also add a measure of morbidity. However when several outcome measures are available, the ranking of priorities may depend on the health outcome chosen. Already now, the different benefit measures in the Prevent model may lead to different decisions.

Rather than using composite measures (with different objective dimensions and sometimes with subjective value weights) to arrive at one dimension on which alternatives are compared, we would suggest the use of many different concurrent outcome variables: when all agree on the same ranking of alternative interventions, it will reinforce the decision, when they do not agree, it will force an open discussion of the general health goals pursued. A quantification of effects will then not only show the health benefits to be expected from the proposed intervention but also the benefits foregone because of interventions not taken.

7.4.4   Conclusions

In this chapter we have shown how the different features of Prevent affect
the benefit estimates of risk factor interventions. The ranking of risk factors
by maximum effect, differs when looking at proportional or at absolute
disease specific mortality reductions, when comparing mortality reductions
or actual years of life gained, and according to the time horizon used. When
using effect estimates for priority setting, choices will have to be made about
the dimensions on which to maximize effect, such as the distribution versus
the total health benefits, short- versus longterm effects, and simple versus
weighed indicators. The interpretation of the results will depend on the
above choices as well as on the estimates of the "costs" to achieve these
reductions in risk factor prevalence.

Chapter 8

Testing the model

Once a model is operational the question remains how valid the results are. The most basic check, that of the correct performance of the calculations can be done by tedious handwork, but the more difficult problem of the value of the results remains to be addressed. The validity of the results will depend on both the credibility of the data put into the model and on the methodology used. Consequently, two main categories of checks were performed: a number of sensitivity runs to see how sensitive the model was to variations in the initial input data, and a historical analysis to see whether the model would have accurately simulated the actual lung cancer incidence from the historic prevalence data on cigarette smoking. Both will be discussed in this chapter.

8.1   Sensitivity runs

In chapter 5 and 6 the choice of IDR values and data on the prevalence of risk factors in the Dutch population have been discussed. The values used as input in the basic runs done with this version of the Prevent model, are shown in appendix C. However these input data remain a choice and it is important to see whether this choice by itself will greatly determine the results of the model.

The variables used in the model can be divided into four categories:

- The demographic data on the Dutch population and the disease related mortality rates. These are not estimates but simply recorded data, and as such are not really amenable to sensitivity runs. The only check performed on these data was to see whether the population, and the mortality rates, after a long simulation period would

yield a population comparable to the one predicted by the Central Bureau of Statistics. The results of the model closely followed the CBS predictions. These variables were not investigated further.

- The data on the Incidence Density Ratio for risk factors and certain causes of death. These variables obviously are the backbone of the model. The values found in different studies vary, sometimes slightly, sometimes considerably. Furthermore these data usually come from populations other than the Dutch population. Although we tried to select data coming from populations as similar as possible, it remains a possibility that the relative risks used are not really suitable for the population in the model. To check whether our choice greatly influenced the results of different simulation runs both lowest and highest values found in literature were applied for each disease category, as well as combined for several disease categories simultaneously. Finally the remnant IDR was tested, which is the lowest value the IDR will attain for the "ex" level, by assuming that the IDR will never be lower than the IDR of the lowest exposure category.

- The different time dimensions incorporated in the model. The LAG time between the intervention and the moment when the remnant IDR is reached is especially important since this determines in what order and to what extent the incidence reduction will affect the health benefit measure chosen. By eliminating both LAG and LAT the results should in fact resemble those that are obtained in the traditional epidemiologic calculations. The risk factor prevalence trends in the past will then be of no importance.

- The data on the prevalence of risk factors in the Dutch population. These data were derived from studies on samples of the population and as such open to sampling errors. Different initial input of prevalence data were tested by using the EPOZ data as prevalence data for the Dutch population.

8.1.1   IDR's

Smoking

The first and most important risk factor tested for different IDR values was smoking. To make the results of different runs comparable the same intervention was applied in all runs, an immediate reduction of 50% in smoking prevalence in all age, sex and exposure categories, with a simulation period of 25 years.

Table 8.1: IDR values for smoking/lung cancer

| | 20-64 | | | 65+ | | |
	Prevent	highest	lowest	Prevent	highest	lowest
1-12 cig.	7	16.2	4	7	8.6	4
13-22 cig.	12	27.6	4	12	12.3	4
23+cig	20	89.3	4	20	24.3	4

Table 8.2: IDR values for smoking/COLD

	Prevent	highest	lowest
1-12 cig.	12	17	5
13-22 cig.	25	26	11
23+ cig.	30	38	19

Table 8.3: Percentage difference for mortality without and with intervention and mortality reduction in 2010, for the highest and the lowest IDR values for smoking

| | Highest IDR value | | Lowest IDR value | |
	M	F	M	F
Lung cancer				
Mort. trend	-3	8	5	-9
Mort. intervention	-9	-13	33	-4
Mort. reduction	10	73	-57	-22
IHD				
Mort. trend	7	19		
Mort.intervention	-5	6		
Mort. reduction	224	470		
COLD				
Mort. trend	-3	9	10	-5
Mort.intervention	-6	-4	27	12
Mort. reduction	4	10	-25	-41
Total mort. reduction	29	67	-44	-38

Figure 8.1:

Total mortality reduction, men, three alternative IDR's smoking
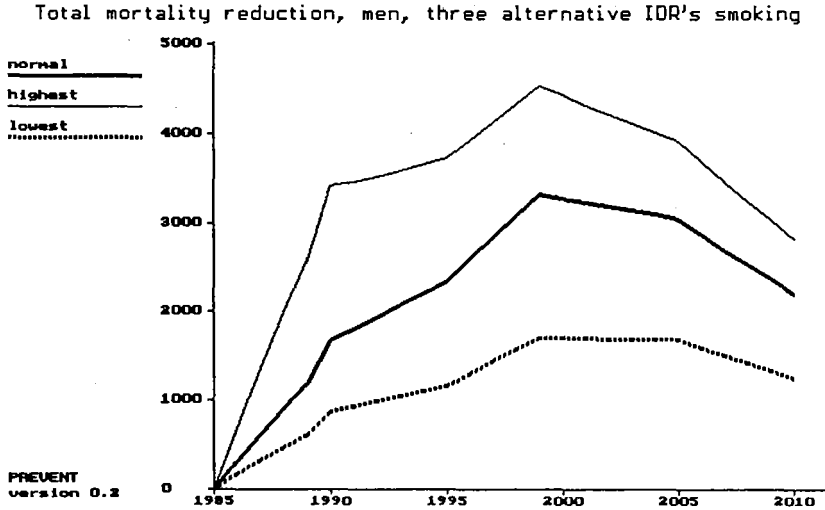
The highest values used for the IDR smoking/lung cancer were those reported by Pathak for a New Mexico population (2). The biggest difference is in the lowest smoking exposure category and in the younger age groups. The lowest IDR values used were those found in Levins study (3).

In the literature there is little variation in the IDR's found for smoking/IHD. When applying the higher values found in the youngest age groups to the total population, the effect of the intervention on IHD is more pronounced. As a highest IDR value for COLD Doll's (4) data for all age and sex categories were used.

In table 8.3 the effects of the different IDR values are presented as the percentage of the outcome values compared to those found in the standard Prevent runs.

That the effect of an intervention would vary with the initial IDR value was to be expected, since the difference between the IDR and the remnant IDR determine the extent to which a change in prevalence of a risk factor will affect the disease specific mortality. What is interesting however in table 8.3 is that the mortality as simulated without an intervention is also affected by the initial IDR value. This is because both past and assumed future trends in risk factor prevalence will affect mortality to a different

extent and will thus interact with demography in a different way. For smoking this is best illustrated by the difference in the effect of a higher or lower IDR value for smoking related diseases, between men and women. A higher IDR value will in general result in a lower mortality in the trend or reference population for men. This is the result of the fact that the substantial decrease in smoking prevalence in the last decades will have more effect on future mortality. Women on the other hand have a number of birth cohorts moving into the vulnerable age groups which have a very different smoking history than the current elderly women. More smokers will result in a higher trend mortality when the IDR's are higher. For both men and women the effect of an intervention will be greater if the IDR's are higher, but because of the higher trend mortality, the mortality reduction as a result of the intervention will increase more for women than for men with a higher initial IDR.

An important point is illustrated by the large percentage differences for the highest IHD IDR values. The large possible risk reductions when the higher IDR's are applied, mostly affect the older age groups in which the IHD mortality is concentrated, in other words in those groups for which the absolute mortality is greatest. IHD mortality is therefore much more sensitive to initial input data than the less important causes of death.

When the highest and the lowest IDR value for all the diseases affected by smoking were combined, the total mortality reductions found, are shown in figure 8.1. The differences in overall mortality benefits are considerable. IHD is again shown to play a major role in the overall mortality (see the difference in slope in the first 5-10 years of the simulation period).

Hypertension

Table 8.4: IDR values for hypertension/IHD (males).

	normal <45	normal >45	highest	lowest
mild	1.9	1.6	1.9	1
severe	2.3	1.8	2.9	1.8

Hypertension not only influences IHD but also CVA. Again we compared the same intervention, an immediate 50% reduction in the prevalence of hypertension, for all age sex and exposure categories, with a simulation time of 25 years, under different assumptions of IDR's. This time the highest IDR values applied for IHD, were those reported for young women

(severe) and young men (mild), and the lowest those reported for older men (severe).

The crossover between male and female mortality benefit discussed earlier, disappears as soon as the higher IDR hypertension/IHD values are assigned (see table 8.4 and fig.8.2). The proportional effect on mortality of the intervention is now much higher, especially for the elderly women and the advantage of men is not any longer sufficient to create a crossover. The crossover reappears however with the lowest IDR values.

Alcohol

Alcohol affects four causes of death in the Prevent model, whereby abstainers are given a higher risk for IHD than moderate drinkers. The IDR values found are more controversial than those discussed above, it is therefore more important to see how the results are influenced by the values chosen. As earlier we applied an immediate 50% reduction to "excessive" drinkers in all age and sex categories.

Little is known about the effects of alcohol in comparison to the other risk factors mentioned so far. Few real intervention trials on population level have been attempted and few relative risk ratio's reported. We tested the hypothesis that alcohol is a much more important risk factor and experimentally assigned the highest IDR values shown in table 8.5.

Table 8.5: IDR values for excessive alcohol consumption and related diseases.

	normal	highest	lowest
IHD	2	4	1
cirrhosis	9	20	9
traffic accidents	2	10	2
accidental fall	2	5	2

With the higher IDR values the total mortality reduction in 2010, after an intervention in 1985, went up by 61 % for men and only 16 % for women. Much of the health benefit came from traffic accidents (where men are more often killed than women), which was to be expected given the high increase in IDR alcohol/traffic accidents used in this run.

Finally a run was made whereby alcohol was assumed to have no effect on ischemic heart disease neither as a risk factor nor as a protective factor in small quantities. The remaining effect of an intervention is minimal, and completely due to accidents and cirrhosis. The total mortality reduction is reduced by 78 % for men and 81 % for women.

Figure 8.2: Variation in expected mortality reduction with standard (a), high (b) and low (c) IDR
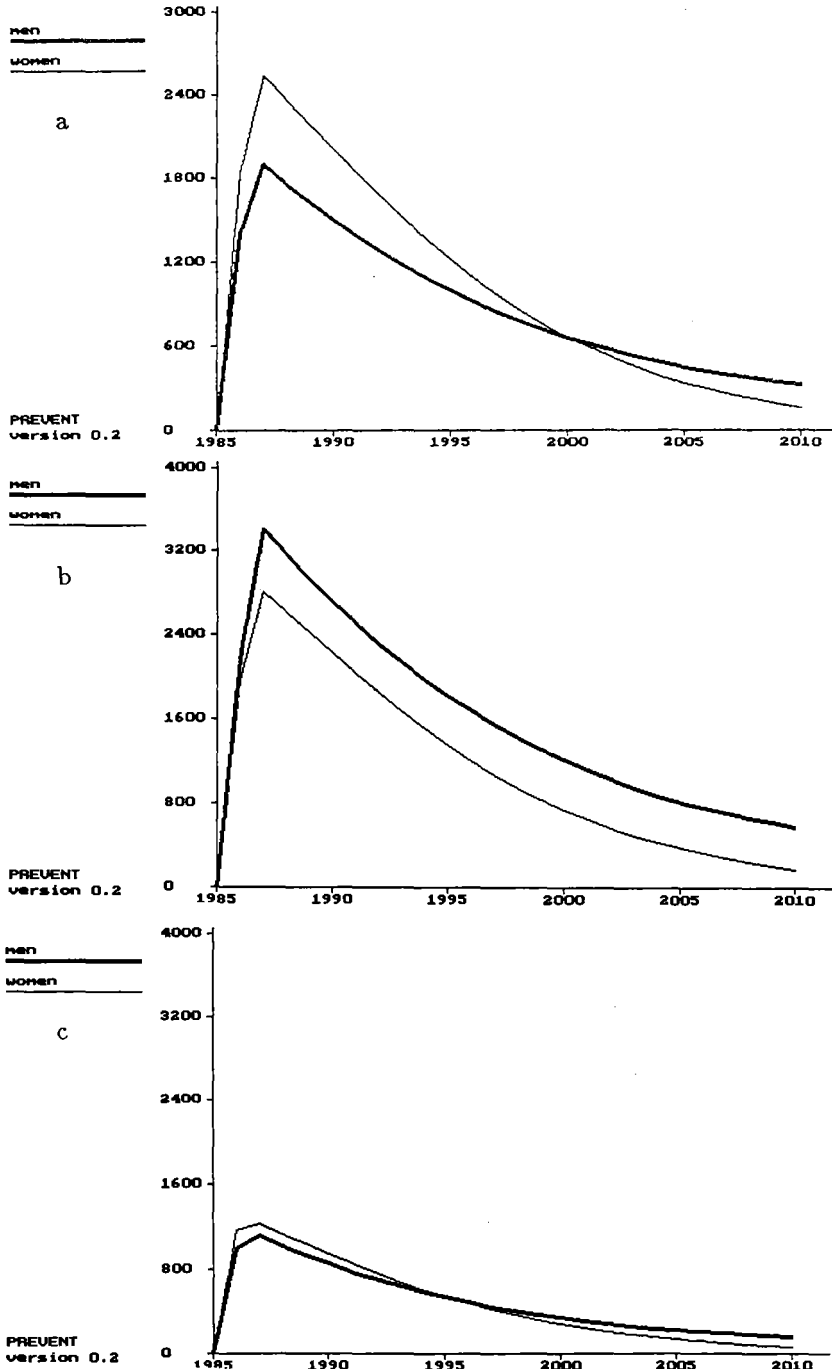
This last finding illustrates the importance of IHD on the quantitative effects of interventions. It is such a common cause of death that IHD mortality changes due to the varying IDR values, overshadow most other intervention effects. It is therefore clear that the uncertainty of the effects of alcohol consumption on IHD (see 5, the recent article from the Honolulu heart study) poses a major difficulty in estimating the potential health benefits of an anti-alcohol campaign.

Remnant IDR

In the final IDR sensitivity run it was assumed that interventions on risk factor prevalence through cessation programs are less successful than expected, because the final risk reduction of the "ex" category is not as great as assumed. We assumed that the remnant IDR's for ex-smokers were no lower than the IDR of the lowest exposure category. As expected the diseases with a high IDR and a large difference between lowest exposure IDR and final remnant IDR, such as lung cancer and COLD, are most affected. Again as with the initial lower IDR it is the difference between the IDR and the remnant IDR which determines the range of the effect of an intervention.

8.1.2   Time dimensions

The time dimensions play an important role in the Prevent model. In previous chapters it was argued, that the lack of a time dimension in earlier epidemiologic effect estimates of risk factor interventions, may have been responsible for the disappointing results: too much was expected too soon. Three time dimensions were introduced: the LAG, the LAT and the possibility to spread an intervention over a number of years. Only the first two assumptions need to be tested.

The risk factor most affected by the LAG and the LAT is smoking, because of the very long time lags involved in both lung cancer and COLD. As a test we assumed there was no time lag (which in the model means setting LAG=1 and LAT=0) and looked what the effect would be yet again of a 50% reduction of all age, sex and exposure categories in a 25 year simulation run.

Fig. 8.3 show a sharp contrast with the traditional Prevent runs. Apart from the obvious difference in the tall and narrow peak early on, because all disease specific mortality gains occur at the same moment, it is interesting to see how the absence of a long LAG/LAT period reduces the importance of past prevalences. The disease specific mortality shows that immediately after the intervention the demography takes over again.

Figure 8.3: Health effects of smoking cessation with minimal time lags

Disease Specific Mortality (numbers) from lung cancer

Disease Specific Mortality (numbers) from IHD

Figure 8.3: continued

Disease Specific Mortality (numbers)   from COLD

Total Mortality Reduction (numbers)
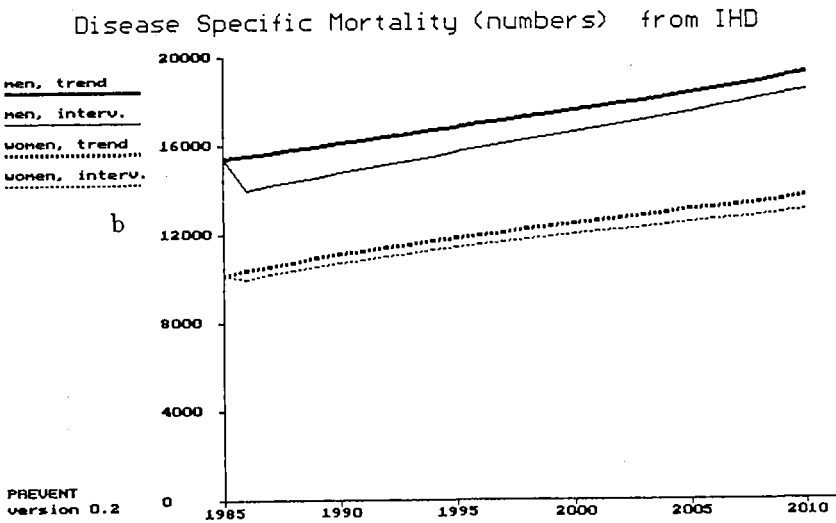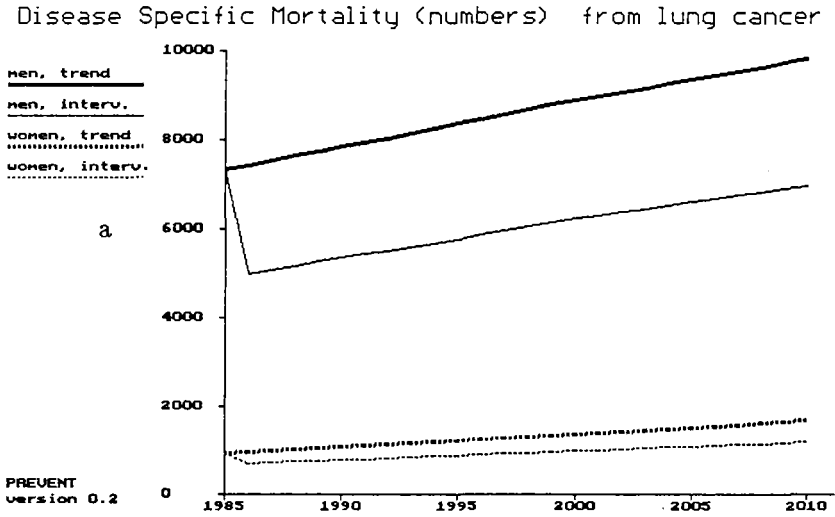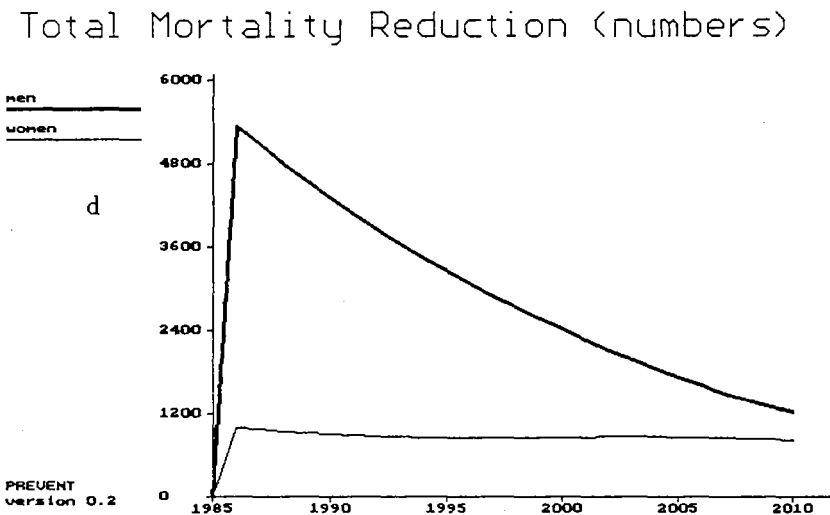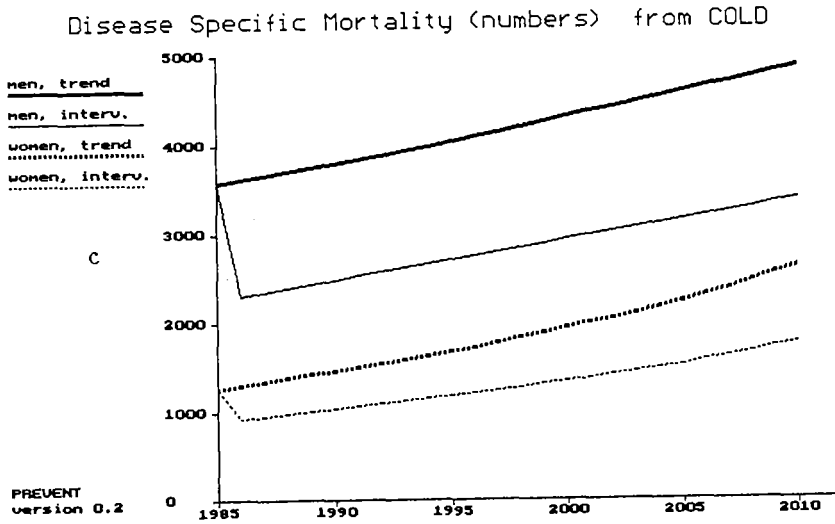
Figure 8.4: Variation in expected mortality reductions with varying initial hypertension prevalence data
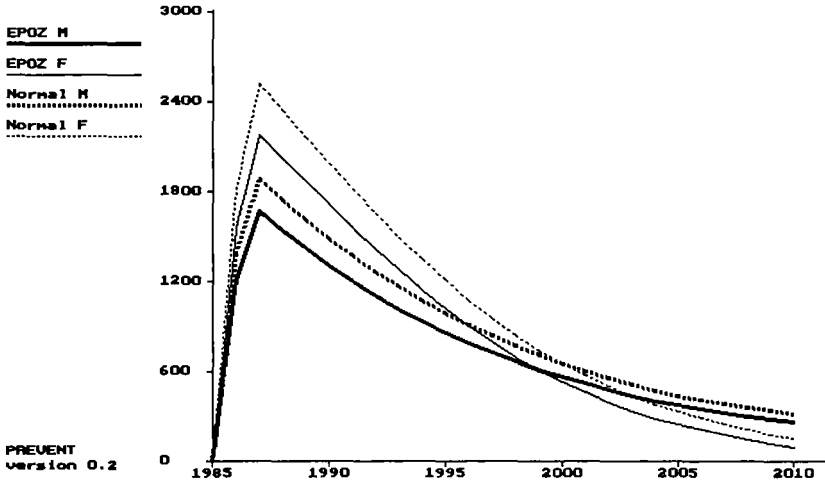
8.1.3 Prevalence data

Finally we looked at the possible effect of variation of initial prevalence data on the results of the model. Two risk factors were considered, hypertension and serum cholesterol, for which alternative prevalence data exist for the Dutch population from the EPOZ survey. In all trial runs the prevalence was again reduced by 50% for all age, sex and exposure categories.

Fig. 8.4 show the combined results of the traditional Prevent run and the EPOZ run on hypertension and shows relatively little difference.

Fig. 8.5 does the same thing for serum cholesterol. The differences this time are sizable. This is understandable, considering that EPOZ has a cutoff point of severe hypercholesterolemia of 270mg%. Consequently there is a far larger percentage of the population at high risk. The same effect is seen with the more recent MRFIT data. The EPOZ data were used to estimate the effect of lowering serum cholesterol when using the recent MRFIT data on exposure level and corresponding IDR values.

Both runs show how sensitive Prevent is to such differences in initial prevalence data. In the standard run, interventions on serum cholesterol will have little effect on total mortality. But as soon as the EPOZ or MRFIT

Figure 8.5: Variation in expected mortality reductions with varying initial serum cholesterol prevalence data
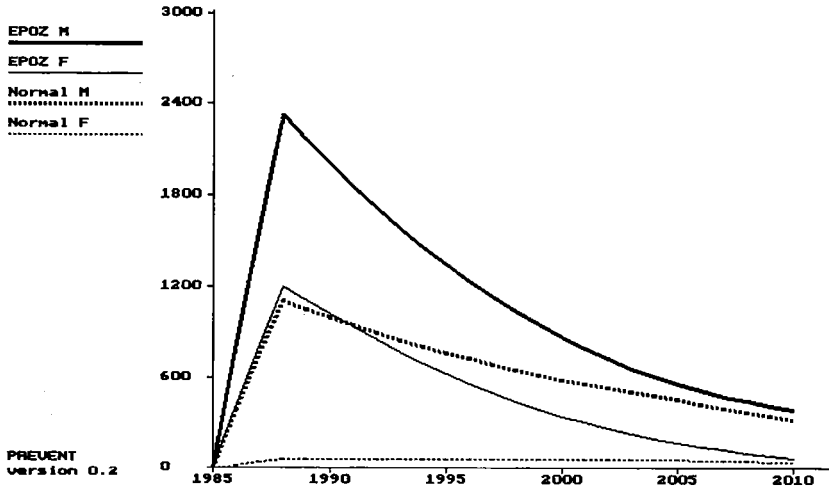
Figure 8.6: Variation in expected mortality reduction with the MrFit exposure categories
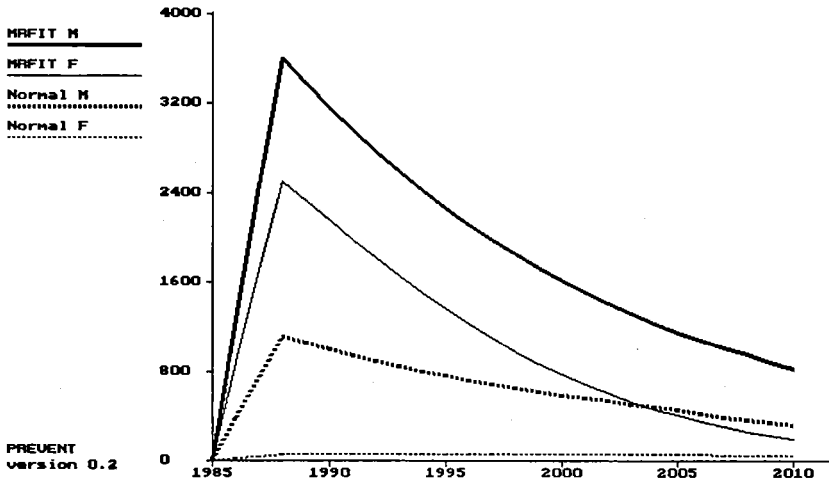
Table 8.6: Smoking habits by age, sex and amount smoked in 1958.

Age	20-30		31-50		51+	
sex	M	F	M	F	M	F
non-smokers	14.3	54.1	9.6	68.9	15.3	85.2
2-17 cig	54.9	40.9	48.4	27.1	39.6	12.7
18+ cig	30.8	5.0	42.0	4.0	45.1	2.1

data are used, the total mortality reductions are comparable to those found with interventions on smoking and hypertension.

8.1.4 Conclusions

The above examples have shown that the results of a model such as Prevent, depend on the input data. The height of the mortality reduction curve is most influenced by the different assumptions about the IDR's, but the shape of the curve is primarily determined by the time variables included. In the basic runs discussed in this book, assumptions were made about the input data. This section illustrates that if other values are selected for policy purposes, it will always be necessary to explore to which extent these different assumptions influence the priority setting.

8.2 Historical testing

Models used to simulate future developments are often tested by applying them to historical data. In the case of Prevent a historical testing was done by looking at the development of lung cancer mortality in the Netherlands between 1970 and 1984. Lung cancer is a disease for which the case fatality and the survival period have not changed significantly for the period studied, the assumption of ceteris paribus is thus realistic. Furthermore lung cancer is influenced mainly by smoking and smoking is one of the few risk factors for which there are relatively detailed historical prevalence data.

8.2.1 The Prevent estimate

The first survey on smoking habits in the Netherlands was done by Gadourek in 1958. He interviewed 1300 individuals about their lifestyles and published these data in 1963 (6). He did not report smoking habits and the amount smoked by age but did provide information by birth cohort.

Table 8.7: Smoking habits by age, sex and amount smoked in 1970.

Age	20-24		25-34		35-49		50-64		65+	
Sex	M	F	M	F	M	F	M	F	M	F
Smokers										
1-12 cig	55.9	45.7	49.4	39.9	46.1	32.8	49.9	20.4	54.4	10.7
13-22 cig	14.7	10.3	18.3	9.1	20.0	8.8	18.8	3.8	14.1	1.1
23+ cig	6.4	4.2	9.3	3.9	10.9	3.2	9.3	1.8	6.8	1.2
Ex-smokers										
1-12 cig	-	-	-	-	-	-	-	5	-	2.0
13-22 cig	-	-	12	-	11	-	10	-	7	-
23+ cig	-	-	6	-	7	-	8	-	5.2	-
Non-smokers	23	39.8	5	47.1	5	55.2	6	69	12.5	85.2

These data show that in 1958 virtually all men smoked and that especially in the older age groups they smoked heavily. The women show a different smoking pattern, few older women smoked but younger women were starting in larger numbers. However there are very few heavy smokers among women. These data were used to reconstruct the number of ex-smokers in 1970.

The NOP survey of 1970 reported the prevalence of smoking and asked about the amount smoked. Using the raw material data by age, sex and amount smoked were extracted (table 8.7).[1]

These prevalence data were used with a future trend to fit the real development in smoking prevalences. The number of ex-smokers was adjusted to fit the cohort data reported by Gadourek.

The population data used were the CBS 1970 Dutch population with the corresponding mortality quotients. With these data the Prevent model was used to estimate the Dutch lung cancer mortality during the period 1970-84.

Figure 8.7 shows that the lung cancer mortality, as predicted by Prevent, is substantially lower than the observed mortality in both men and women. It is not surprising that Prevent expects a reduction in age specific lung cancer mortality after the early 1970's, since smoking prevalences had been going down since 1958. The observed lung cancer mortality shows an increase in the age specific lung cancer mortality and the difference be-

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[1] To get data comparable to the 1985 input, the assumption had to be made that the amount smoked increased in a linear fashion. A second assumption was that those, who omitted to answer the question about the amount smoked, represented a unbiased sample of the population of smokers and could be distributed proportionally over the exposure categories.

Figure 8.7: Observed and predicted lung cancer mortality 1970-1985

Observed and predicted lung cancer mortality in men, 1970-1985

Observed and predicted lung cancer mortality in women, 1970-1985
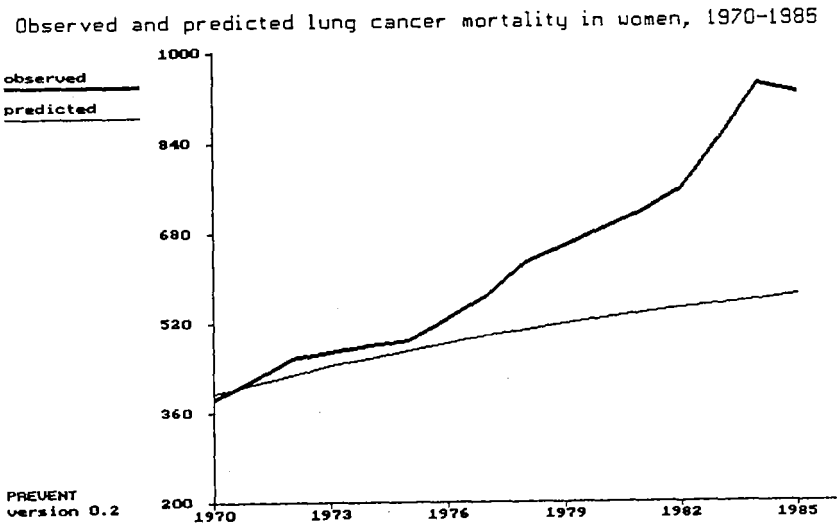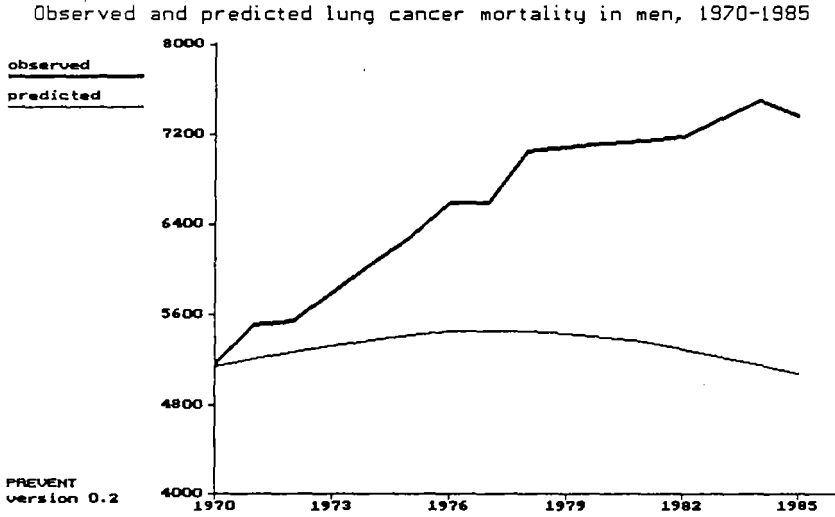
tween observed and predicted mortality poses questions about the validity
of the input data or the parameters used to predict the lung cancer mortal-
ity. Both will be explored in the following paragraphs, to see whether the
cause for the under estimate by Prevent can be found and more importantly
whether this will affect the use of Prevent for future estimates.

8.2.2 Parameters

The nature of models like Prevent is that they use quantitative evidence of
causal relationships from empirical studies to explain changes in an outcome
variable such as lung cancer mortality. Another approach is to hypothesize
a causal relationship in a mathematical model because certain variables
correctly predict the variation in the outcome measure. For lung cancer
mortality both approaches have been used (7, 8).

Because of the choice in this project to start from the observed rela-
tionship between risk factors and disease mortality in epidemiology, it is
not likely that the causal relationship between lung cancer and smoking as
such will not be correct. One possibility for the under estimation is that
the parameters used to predict the lung cancer mortality are not sufficient.
It is possible that the exposure categories in the Prevent model are not the
only relevant exposure dimensions that should be taken into account or that
other risk factors than cigarette smoking determine lung cancer mortality.

Townsend (7) and Peto (9) show for instance, that the age of first ex-
posure and the length of exposure may be important variables. Although
the smoking prevalence data for the Netherlands are not as detailed as the
British ones, the effect of these dimensions on the lung cancer mortality
predictions by Prevent were explored.

The data used to reconstruct the smoking history of the different cohorts
are memory recall data on the age at which smoking was started, from
Gadourek. Figure 8.8 and 8.9 show the percentage of each cohort that
smoked over the years.

Men in the early birth cohorts started to smoke as children, many before
they were ten years old and by the age of 20 more than 90% of a cohort
smoked. These men continued to smoke until the general downward trend
in smoking prevalence started in the late 50's. However these data do not
suggest that the age at which smoking started ever increased to over 20.
It shows no indication that this parameter, if included, would result in an
increase in age specific lung cancer mortality over time.

Cumulative exposure in a situation where exposure starts approximately
at the same age, as smoking did in men, can be expressed in an increase in
relative risk for older age groups or can be related to the remnant IDR at the
age of cessation. It may be realistic to assume that because of cumulative

8.2. HISTORICAL TESTING

Figure 8.8: Prevalence of smokers by birth cohort for men from 1887-1984
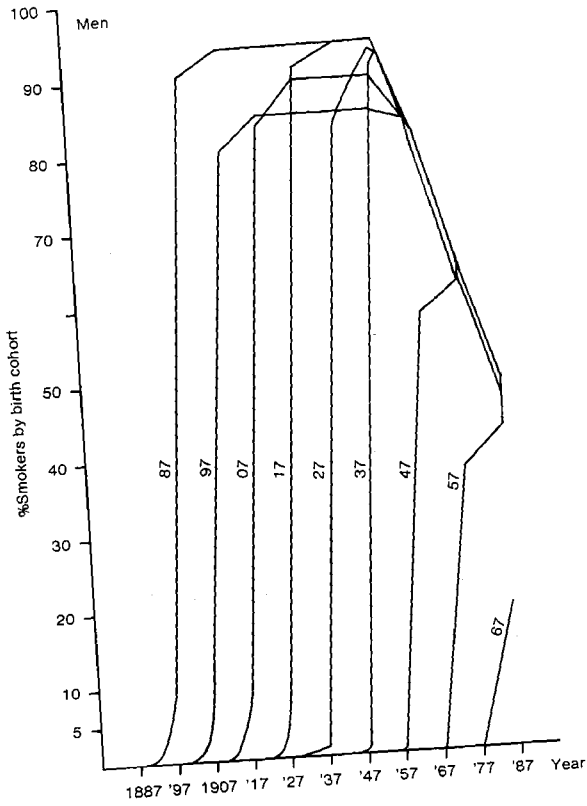
Figure 8.9: Prevalence of smokers by birth cohort for women from 1887-1984
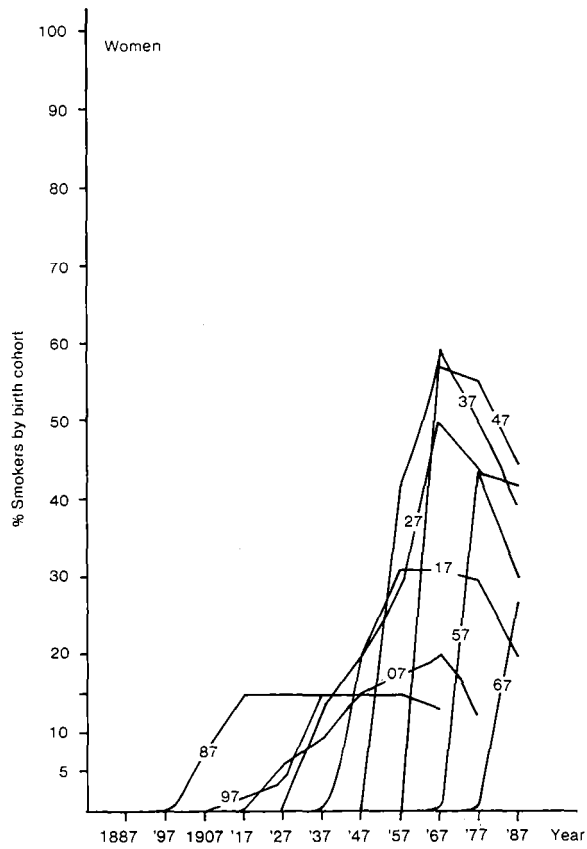
Table 8.8: Adjusted smoking/ lung cancer IDR's.

	20-34		35-49		50-64		65+	
	IDR	Remn.	IDR	Remn.	IDR	Remn.	IDR	Remn.
1-12 cig.	1.5	1.2	6	2	13.5	6	13.5	13.5
13-22 cig.	3	1.2	12	2	27	12	27	27
23+ cig.	4	1.2	16	2	36	16	36	36

exposure, the effect of smoking cessation is not as great in the older age groups, and may even be non existent after a certain age. A run was done in which we assumed that smoking cessation after 50 years would only result in a limited reduction in risk and after 65 in no risk reduction. In the last case the remnant IDR remains identical to the IDR of the exposure category from which the ex-smoker comes. There is a rise in the mortality especially for men, but it is not sufficient to achieve a satisfactory fit.

The above cohort smoking figures are not detailed enough to make a careful analysis of exposure history as done by Townsend but a rough estimate of the length of exposure can be added to the model, by increasing the IDR with age.

In table 8.8 the IDR's were adjusted for the different age categories to show an increase with age as well as a high remnant IDR in the older age groups to simulate the irreversible damage of very long exposure.

Although the above IDR adjustments result in a small increase in mortality it is not sufficient to correctly predict the observed mortality increase.

8.2.3   The input data

The lung cancer mortality as modeled by Prevent, is determined by the following variables:

- demography

- age specific mortality in 1970 for lung cancer and for the total mortality due to other causes.

- smoking prevalence data by age, sex and exposure category

- the time dimensions LAG and LAT

- IDR's by exposure and the remnant IDR for ex-smokers

For all of these variables choices were made for the initial input data. It is possible that these choices are responsible for the under estimates.

Demography

Data on the real population in 1970 were used and the demographic development in the model closely follows the development of the real population, so that this can not be an explanation for the absence of the rise in mortality in the predicted values.

Age specific mortality

Age specific mortality quotients used, are the observed numbers in the Dutch population in 1970. In the Prevent model changes in mortality quotients are assumed to occur as a result of changes in risk factor prevalence. For smoking related causes of mortality this indeed happens in this historic reconstruction. However for the other causes of death no change is assumed. If there were an important reduction in these causes of death this may account for a rise in absolute lung cancer mortality quite apart from trends in age specific lung cancer mortality due to the change in smoking behavior.

When a trend in these mortality quotients was applied simulating the real development over that period this did result in an increase in lung cancer mortality. The increase however, was not sufficient to achieve a good fit.

Prevalence data

The crude prevalence of smoking in the population reportedly decreased since the first survey by Gadourek. Therefore a simple increase in the prevalence of smoking can not be the explanation for Prevent's under estimation. However within the group of smokers a shift in the amount smoked could possibly explain the increase in incidence, either because there is an absolute increase in heavy smokers or because all smokers have increased the amount they smoke over time.

Although the age and exposure categories do not quite correspond, table 8.9 shows that the number of light smokers has diminished more than the number of heavy smokers. In a relative sense the prevalence of heavy smokers among smokers has increased. However the data do not show an increase in the absolute proportion of heavy smokers in the population.

The reported increase in the sales of cigarettes until the late 1970's does not agree with the reported reduction in the number of smokers even when the shift to more heavy smokers is taken into account. This under reporting has already been discussed elsewhere. It indicates a general under reporting of amounts smoked, which may have increased over time due to the changing public attitude towards smoking. A general increase in the

Table 8.9: Proportion of the male population who smoke, by amount smoked and age for 1958, 1970 and 1985.

Age	20-24			25-34			35-49			50-64			65+		
Year	58	70	85	58	70	85	58	70	85	58	70	85	58	70	85
Cig.															
1-12		56	22		49	21		46	20		50	22		54	23
2-17	55			55			48			40			40		
13-22		15	14		18	19		20	17		19	16		14	12
18+	31			31			42			45			45		
23+		6	4		9	7		11	10		9	10		7	6

amount smoked over the period studied for all exposure categories could be expressed as an increase over that period of the IDR's associated with the different exposure categories.

The time dimensions

The LAG period of 10 years for smoking/ lung cancer was reported in the intervention trials. It may be that in reality the reduction of risk takes much longer and that a LAG of, for instance, 20 years may be more realistic. When tried it does result in an increase in mortality. There is also a postponement of the moment when the absolute mortality starts to go down. But it is not sufficient to achieve a realistic estimate of lung cancer mortality.

An increase in LAT makes virtually no difference if it does not exceed 12 years since the reduction in smoking after 1958 is almost linear. Further postponing the year in which changes in incidence become visible as changes in mortality, will not affect the absolute mortality results sufficiently as there was no proportional increase in smoking prevalence in the past.

The IDR's

The IDR's used as input in the Prevent model form a selection, as has already been discussed extensively in the previous pages. A higher IDR however, for instance because smoking affects lung cancer even more than thought until now, will not result in a sufficient increase in predicted mortality. What is needed is an increase in IDR over time.

If the development of the sales of cigarettes over time are a better indicator of the amount smoked than the self reported exposure category, one would expect that the IDR associated with each exposure category would increase proportionally with the increase in cigarette sales. This increase

has to be calculated relative to the 1970 level, since it will result in proportional changes in mortality relative to the 1970 mortality figures.

An estimate of the lung cancer mortality after such a correction is made results in an acceptable fit between the lung cancer mortality as predicted by Prevent and the observed lung cancer mortality from 1970-84. This suggests that a correction in the reported amount smoked may be necessary to arrive at the correct prevalence data. Obviously the above correction is a very crude one: neither the distribution of the under reporting over different age, sex and exposure categories is considered nor the fact that the average tar and nicotine level of cigarettes has gone down in most western countries over that period (10). However it is remarkable that this simple correction not only achieves an acceptable fit but also correctly predicts the moment when the absolute lung cancer mortality for men reaches its highest level.

From the above we must conclude that for the input data only a correction for the under reporting of cigarette consumption will result in an acceptable fit for the lung cancer mortality (see figure 8.10). To allow for such a correction, an IDRfac was introduced in the Prevent model. In the case of the relative sales of cigarettes, the IDRfac can be said to act as a period factor.

8.2.4   A cohort effect

The correction factor suggested above does not allow for a differentiation of effect by birth cohort. However if an IDR changes over time this could also be explained by changing susceptibility of the cohorts underlying the age specific prevalence data. To explore this hypothesis changes in lung cancer mortality should be described by birth cohort.

One way to look at the differences by cohort is to show the percentage increase in age specific lung cancer mortality rate for men, in five year age group when one birth cohort is compared to the preceding birth cohort (see table 8.10). The rows are birth cohorts, the columns are years and the diagonals represent the same age groups. The 1950 mortality rates are the base line data. It shows for instance that the cohort, born in 1883 consistently in each age group, had a lung cancer mortality rate 40% higher than the cohort born in 1878.

Although table 8.10 is but a crude description, it does suggest that there is a strong cohort factor in the development of the lung cancer mortality. The fact that the percentage increases are so constant over the years for each birth cohort is highly suggestive. Our data on smoking or on the sales of cigarettes in no way explain the sharp increase for each successive birth cohort until 1900 or the abrupt levelling off after that. The reductions after the 1913 cohort are accurately predicted by Prevent, and are therefore

Figure 8.10: Lung cancer mortality with correction for cigarette sales

Observed and corrected predicted lung cancer mortality in men, 1970-1985

observed
predicted

PREVENT
version 0.2

Observed and corrected predicted lung cancer mortality in women, 1970-1985

observed
predicted

PREVENT
version 0.2
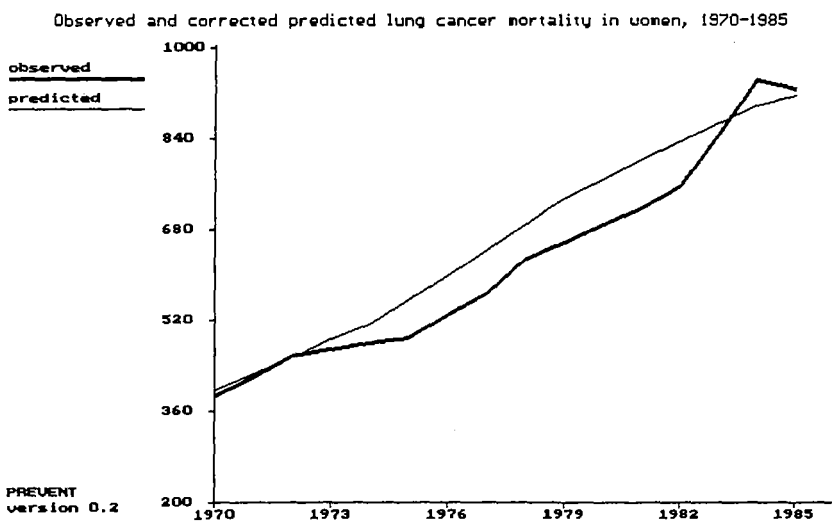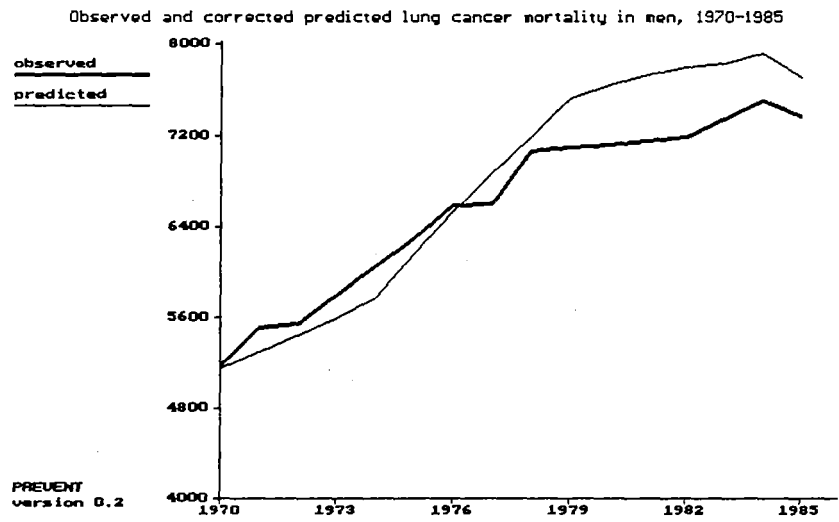
Table 8.10: % increase in age specific lung cancer mortality /100.000, for each five year cohort compared to the previous cohort in that same age group, 1960, '65, '70, '75, '80.

	1960	1965	1970	1975	1980
1873	30				
1878	50	47			
1883	40	40	40		
1888	50	40	40	47	
1893	60	50	50	60	40
1898	40	50	40	40	30
1903	20	20	20	20	20
1908	20	20	20	14	20
1913	1	5	2	2	0
1918	8	8	5	3	1
1923	-30	-7	-2	-9	-10

probably the result of the reduction in smoking prevalence.

The hypothesis of a cohort effect in the history of smoking and lung cancer is not a new idea. For the Netherlands it was already found and quantified by van der Hoff in 1977 (11). He made an analysis of the available mortality figures and concluded that he could extract a cohort factor, an age factor and a correction factor (which could be considered a period effect). The value of the cohort risk factor increases for all birth cohorts born before 1900, remains constant for those born between 1900-30. He predicts a sharp reduction of the cohort factor for later birth cohorts but in 1977 this was based on very few deaths. A problem with this cohort factor for our analysis is, that it represents both the effect of the differences in smoking prevalence between the cohorts and the additional cohort factor which may explain the sharp increase in lung cancer mortality for the early birth cohorts.

Hoogendoorn (12) has shown that the trends in lung cancer mortality for men between 1950-1980 differ by age group. Although this is not an analysis by birth cohort his data suggest a change in trends occurring at different moments for different age groups. Finally Verbeek et al.(13) recently performed an analysis of the lung cancer mortality by period and by birth cohort. For men they found a levelling off of the increase in age specific mortality for the younger birth cohorts (those born after 1910), while the women continue to show a increase in age specific mortality rates for each new birth cohort.

It is clear from these analyses that different birth cohorts have a different age specific lung cancer mortality and that after years of rising rates

for men there appears to be a slight decrease, heralding the peak of the epidemic. Our original assumption was that these cohort specific lung cancer mortality rates would be explained by the differences in the prevalence of smoking among those cohorts. The Prevent runs in figure 8.7 show that the differences in smoking prevalences now and in the recent past can not adequately predict the evolution of lung cancer mortality. If there is indeed another cohort factor that influenced lung cancer mortality for the older birth cohorts, there should be a difference in how accurately Prevent predicts lung cancer mortality for the different birth cohorts.

Figure 8.11 shows the age specific mortality rates for lung cancer for three different years. In each figure the observed mortality is shown as well as the original estimate of the Prevent model. The third line is the mortality as it is predicted by Prevent if the correction for the sale of cigarettes suggested earlier, is applied.

It shows that the original underestimation by Prevent is especially important in the oldest birth cohorts. These seem to be the cohorts for which the smoking history does not correctly predict the lung cancer mortality. The lung cancer mortality of the younger birth cohorts is correctly estimated by Prevent and in fact the correction as suggested earlier, certainly does not improve the fit for these cohorts. Our conclusion is therefore that there is indeed another cohort factor which influences the lung cancer mortality in the older birth cohorts.

Many hypotheses can be put forward to explain this cohort effect, for instance the possibility that environmental factors known to affect lung cancer incidence, such as coal fumes or housing conditions or harmful exposure in the working environment, account either directly for the rise in lung cancer mortality or for the increased susceptibility for the dangers of cigarette smoke in the earlier birth cohorts. At this moment there is insufficient data to corroborate any of these hypotheses.

Prevent can however, through the introduction of the IDRfac, calculate the value of this extra cohort factor necessary to fit the lung cancer mortality between 1970 and 1985. This was only done for men and for the birth cohorts born between 1906 and 1927 since those were the only groups for which sufficient deaths were recorded to do a useful analysis. We used the lung cancer mortality quotients by age, cohort and year of death as produced by CBS. For the years 1972, 75, 78 and 81 these were compared to the values predicted by Prevent and the necessary corrective IDRfac for that year was assigned to the respective cohorts. The IDRfac then represents the correction factor necessary for each birth cohort, in each year to achieve a predicted mortality that equals the observed lung cancer mortality. In figure 8.12 the resulting IDRfacs are shown. Although they all concern the same period (1970-85) the cohorts have been pulled

Figure 8.11: Age specific lung cancer mortality /100,000 observed and predicted 1975, 1978, 1984 (log scale)

●———● = Observed lung cancer mortality/1000
△----△ = Predicted lung cancer mortality/1000
▲——▲ = Predicted lung cancer mortality/1000 after correction
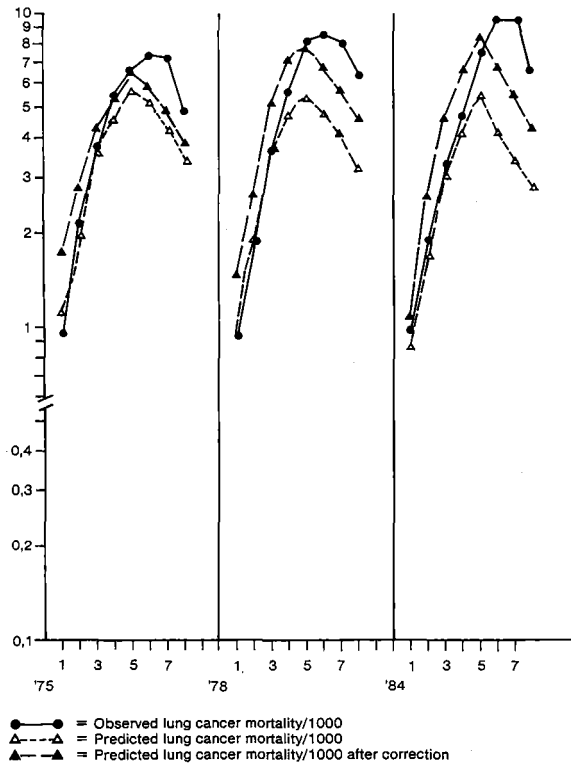
Figure 8.12: IDRfac for men for the cohorts born from 1906-1927
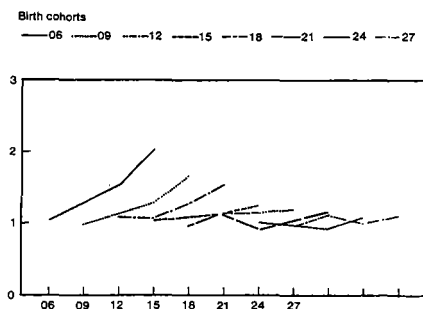
apart to facilitate the interpretation. They show that the correction factor necessary diminishes for the younger birth cohorts, stabilising around 1 for those born after 1918.

The results correspond with table 8.10: a correction is necessary for the older cohorts while the lung cancer mortality for the younger cohorts is predicted fairly well by the smoking history and thus by Prevent. These results suggest that whatever the factor may be that caused the sharp increase in lung cancer mortality for the early birth cohorts, it does not appear to affect the younger birth cohorts. Since these younger birth cohorts will be important for the future estimates made with Prevent there is no indication that a similar under estimation will also occur in those future runs.

8.2.5 Conclusions

Although the initial estimation of the historic development of lung cancer mortality by Prevent was disappointing, the subsequent search for explanations makes the following conclusions possible.

Prevent and the simple epidemiologic model of risk factors and relative risks do not always describe reality adequately. An adjustment in the initial input data can not achieve a satisfactory fit. The introduction of the IDRfac correcting for the under reporting of the consumption of cigarettes did achieve an acceptable overall fit, but when shown by age group it resulted in an over estimate in the younger birth cohorts and a remaining under estimate for the older birth cohorts.

Different dimensions of exposure may be needed which are not always routinely available. The cohort development of lung cancer mortality suggests that it may be very useful or even necessary to have exposure data by birth cohort.

Even when the effect of a change in risk factor prevalence is correctly estimated, the confounding effect of other risk factors may distort the final results. As long as we do not know which factors those are, we will have to use the assumption of ceteris paribus for effect estimates into the future. It does mean that absolute numbers as predicted by Prevent have to be used cautiously.

Two corrective factors were introduced in this chapter, a period IDRfac representing the proportional change in the sale of cigarettes, and the cohort IDRfac, for which we do not know at present what it represents. The fact that the latter appears to be only necessary for the birth cohorts born before 1920, makes it possible to assume that it will not be important for the cohorts determining the lung cancer mortality after 1985. The former allows for a correction based on expected sales of cigarettes. The availability of the IDRfac in the Prevent model however, allows users to make different assumptions.

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Part V

DISCUSSION AND CONCLUSION

Chapter 9

Policy making with Prevent

So far it was shown how Prevent works, what data are incorporated and how the outcomes should be interpreted and valued. In this last section we discuss some illustrations of the possible uses of the model, and the results of the project in general.

Prevent was initiated to translate known epidemiologic data on the relationship between risk factors and disease incidence, into measures that could be used in health policy decisions. The ability to quantify the health effects of changing risk factor prevalence in a population can be of use for different aspects of health policy making. The following three implementations will be demonstrated in this chapter:

- a straightforward quantification exercise of the health status changes in the population as a result of (autonomous) changes in risk factor prevalence,

- the ability to quantify (realistic) disease specific targets and the changes of risk factor prevalence necessary to achieve these,

- and finally the use of effect estimates in formal priority setting such as cost-effectiveness analysis.

The ability of Prevent to calculate the effect of a change in risk factor prevalence, on the incidence of disease over and above the changes already occurring because of autonomous trends in risk factor prevalence, demographic changes or competing death risks, allows for a quantitative estimate of the

net benefit to be derived from that intervention, in a situation where all other circumstances are assumed to remain unchanged.

As such the use of Prevent may be a tool in health planning as proposed by WHO. In this chapter we shall show some examples of the way Prevent could be used, using existing policy documents in the Netherlands. Obviously the assumptions about future trends and time spread of interventions, as well as the initial input data are choices we made. What is demonstrated here is the tool, the results are but illustrations.

9.1   Health effects of risk factors

The first example will concern itself with scenario's. In the Netherlands a number of expert committees has recently advised the government on possible and probable future development in certain fields of health and health care. These future developments are not presented as predictions but rather as alternative scenario's based on a combination of autonomous determinants and deliberate changes in relevant policy areas. Two of these scenario reports will be discussed here, the Lifestyle scenario (1) and the Cancer scenario report (2).

9.1.1   Lifestyle scenario's

The first is a scenario committee concerned with future development of lifestyles. The scenario committee did not have an easy task since they set out to analyze and if possible quantify a very broad range of lifestyle and socio cultural determinants of health. The outcome of that study was a number of alternative developments in the prevalence of certain risk factors, in the form of a reference scenario, as the most likely development if all circumstances remain equal, and several alternative scenario's resulting from varying assumptions about autonomous or deliberate changes in society. In this example we shall look only at the smoking scenario's as they were presented by the committee, showing the changes in health outcomes that would result from these different smoking scenario's.

The Lifestyle committee assumes that in a realistic (reference) scenario there will be a continuing downward trend in the prevalence of smoking resulting in 25% smokers for men and 24% for women in 2000. Offset against that is the pessimistic development, in which smoking prevalence remains unchanged and the optimistic scenario in which only 7% of the population will smoke in 2000. We have spread the percentage smokers over the exposure categories proportionally to match the current distribution.

Figure 9.1: The health effects of the three smoking scenario's of the Lifestyle scenario committee. (realistic, optimistic, pessimistic)

Lung cancer mortality, men, three smoking scenario's

pessimistic M

realistic M

optimistic M

PREVENT
version 0.2

Lung cancer mortality, women, three smoking scenario's

pessimistic F

realistic F

optimistic F

PREVENT
version 0.2
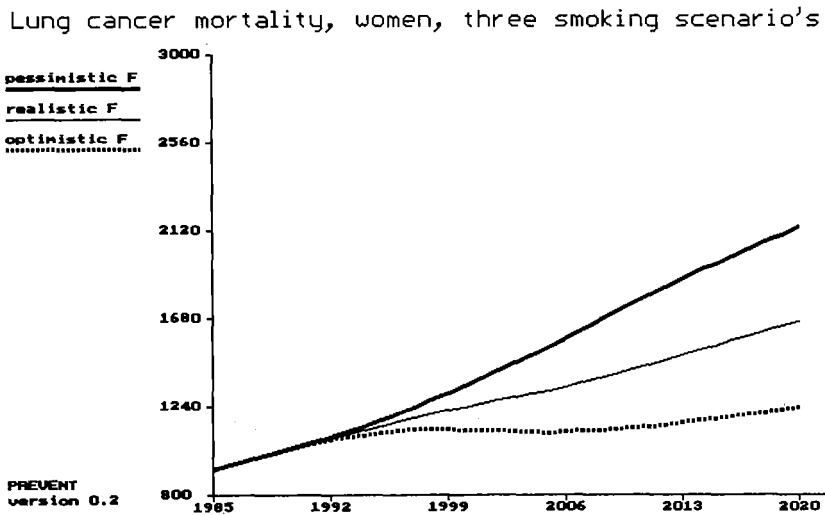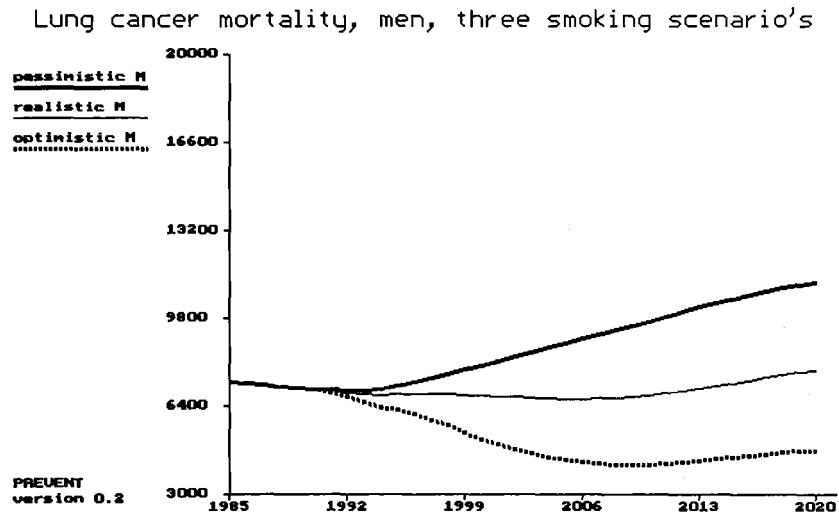
In the realistic scenario the continuing reduction in smoking prevalence is able to counteract the aging of the population and the absolute mortality for lung cancer remains fairly constant for men (see figure 9.1). For women however an increase occurs as the older, (virtually) non-smoking cohorts are replaced by younger women with a smoking history. The same was seen for COLD mortality. In IHD mortality a proportional reduction is achieved but demographic changes are so important that absolute mortality increases even in the realistic scenario. This illustrates the importance of showing absolute measures of health as well as proportional health benefits, since only the optimistic scenario's, which would mean sizable reductions in smoking prevalence, will result in a real reduction of the future case load. In the above figures the intervention is spread over many years, so as to have reached the full effect in the year 2000, as was indicated by the committee. This means that the full health benefit will not be apparent until 2020.

In these scenario's it is not specified whether the smoking cessation is concentrated in certain age or exposure categories. Just to illustrate how much difference this will make, the total mortality reduction (for men) achieved by the intervention of the optimistic scenario is shown, based on different assumptions about the groups in the population, the intervention is aimed at. In the first case the original spread of the prevalence over exposure categories is assumed, in the second case the remaining 7% smokers are all assumed to be light smokers, in the third case on the contrary the intervention is only successful for light smokers so that all the remaining smokers are the heavy smokers. The results are shown in figure 9.2.

Finally the results are shown when the intervention reaches different age groups. The original age distribution is compared with alternatives in which the intervention affects only older or younger smokers.

Figure 9.2 shows that these specifications of the same scenario produce very different results, and show the necessity of not only proposing global interventions but of also specifying their distribution in the population.

9.1.2   Cancer scenario's

The second illustration of a straightforward quantification of health benefits from risk factor prevalence changes is one of the intervention scenario's from the scenario committee on cancers. The committee analyzed the effect of a smoking cessation program for middle-aged men, in which smokers in the age groups under 35 quit for 50 % and in the age group 35-59 for 40%.

Figure 9.3 illustrates that the reduction of smoking prevalence in middle aged men over a period of 15 years, will not lead to very sizable health benefits in the near future. We need to simulate for a rather long period to allow the intervention on middle-aged men to take full effect in the age

Figure 9.2: Optimistic scenario's with light smokers only, heavy smokers only, young smokers only and only old smokers
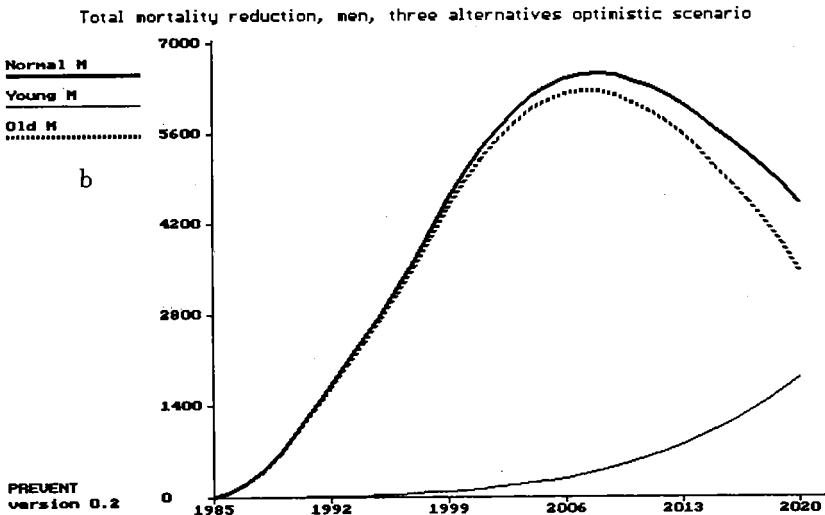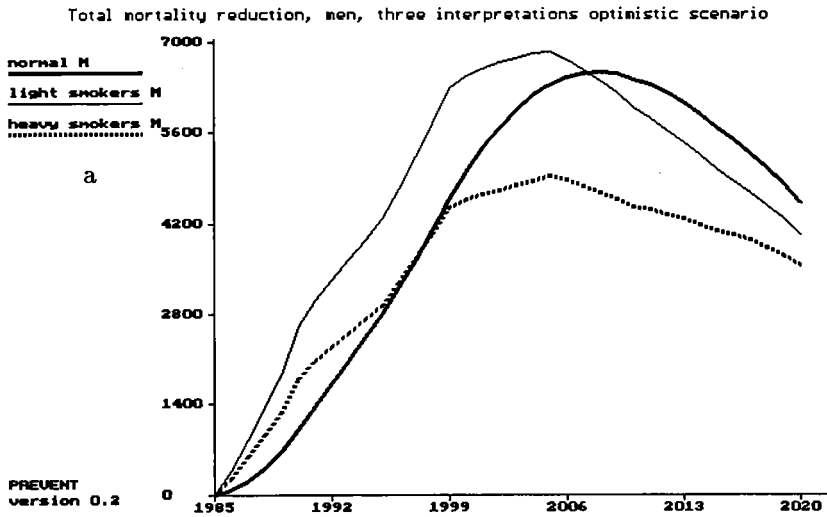
Figure 9.3: The effect of a reduction in smoking prevalence on lung cancer mortality as quantified by the Cancer scenario committee and by Prevent
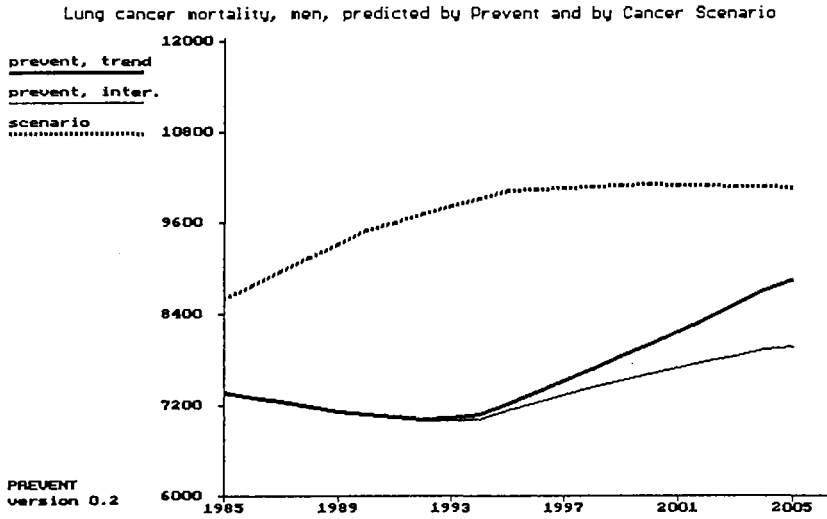
Figure 9.4: Lung cancer and total mortality reduction after smoking cessation
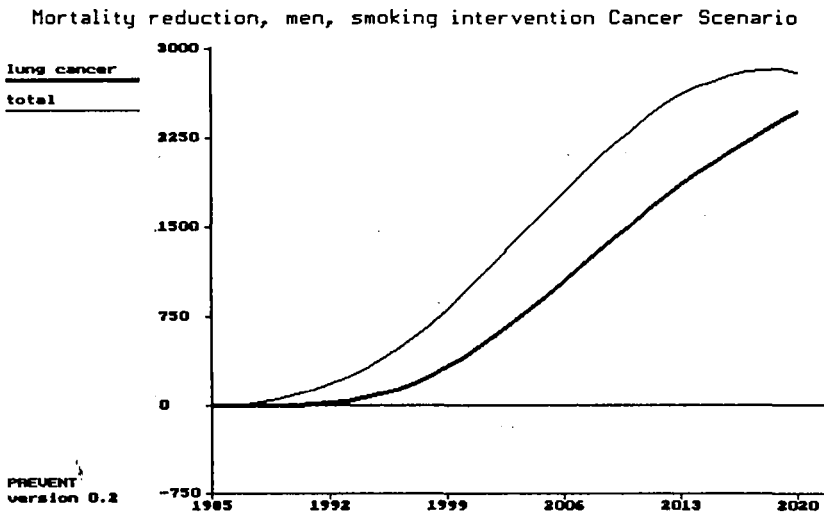
groups where the mortality rates are high. The difference between Prevent and the Cancer scenario is not so much due to the quantification of the effect of the intervention, since the Cancer scenario's also incorporate a certain lag time before an effect becomes apparent, but to the development of the reference lung cancer mortality. Prevent incorporates the continuing effect of the very sizable change in smoking behavior seen in the last decades.

A final conclusion of the Cancer scenario study was that smoking is the one risk factor on which an intervention needs to be directed immediately, however it predicted that even if a sizable reduction in smoking prevalence were achieved immediately, the lung cancer mortality would not start to diminish until the turn of the millennium. This may be an unnecessarily pessimistic conclusion since it may underestimate the effects of health policy measures against smoking in the past, of which we will reap the benefits in the years to come, and furthermore it fails to acknowledge that although the effects on lung cancer mortality may take many years to become apparent, the effects on IHD mortality will result in important health benefits in the mean time. Figure 9.4 shows the mortality reduction expected from the smoking intervention proposed by the committee, from lung cancer only and the total mortality reduction.

This last point illustrates the importance of looking at all the health benefits resulting from a risk factor intervention. Since the diseases have different time dimensions, the multi factorial approach in this case will present a much more optimistic effect estimate of an intervention on smoking than would be the case if only lung cancer were considered, and this may be very important politically.

9.2 Quantification of disease specific targets

A recent development in health policy making was initiated by WHO in its Health for All campaign in the European region. The introduction of health targets as quantitative measures both of the intentions and of the results of health policy, has forced national governments to question the general goals of their public health policy and to quantify the present and future health status of their populations.

The project of which Prevent is the result, is a direct consequence of this change of orientation in policy making. The use of quantitative targets was first practiced in the Dutch Health 2000 Report and has been further elaborated in the recent policy document on the Prevention of Cardiovascular disease (3). In that last document, targets are expressed in terms of proportional reductions in cardiovascular mortality in those under 65 years of age, over and above what would be expected from the autonomous

trends.

More recently the Dutch government has designed "Target flow charts" for the three most important disease categories from the Health 2000 Report. In these flow charts the disease specific targets are quantified and the risk factors on which interventions would need to achieve changes are indicated as well.

In the case of the cardiovascular prevention program the target is quantified as well as the proposed intervention on smoking. Prevent can only add to that the quantification of the necessary prevalence changes in the other risk factors to achieve the targets. With the target flow charts single versus multi factorial intervention strategies and the importance of combining preventive strategies for several disease categories are explored.

9.2.1   Cardiovascular prevention

In the Nota Preventie Hart en Vaatziekten (the health policy document on the prevention of cardiovascular disease) the target is defined as follows:

> "Around the year 2000 the mortality caused by diseases of the circulatory system, in persons under 65 years of age, will be reduced by at least 15 % over and above what could be expected based on extrapolations of the past. This will be achieved by a reduction in smoking prevalence to 20% as well as a reduction of total tobacco consumption by 50%, and a reduction in the prevalence of elevated serum cholesterol and blood pressure by a reduction of total fat intake from 40% to 30-35% and a reduction in salt intake."

In the discussion on the possible interpretations of this target we shall limit ourselves to ischemic heart disease (IHD). In the policy document it is interpreted in a broader sense but the inclusion of other disease categories will make it more difficult to understand the results. The effects of interventions will be overestimated in our example since more risk factors are known for IHD than for the other diseases (CVA and peripheral vascular disease) included in the policy paper. The limitation to IHD will not affect any of the discussion points.

Three possible interpretations of the above target will be examined as well as the changes in the prevalence of hypertension and hypercholesterolemia necessary to achieve that target, given a reduction in smoking prevalence to 20%. We have assumed an autonomous future trend in the prevalence of hypertension and hypercholesterolemia of -1% yearly.

In the definition of the target it is not clear whether the 15 % reduction in mortality due to Ischemic Heart Disease in the population under 65 years,

Table 9.1: Alternative changes in risk factor prevalence necessary to achieve target 1 in the prevention of cardiovascular disease.

	M<65 men achieved	M<65 women achieved	M<65 total	all PIF <65
Smoking −50%	−	−	−	−
Smoking −75%	+	+	+	−
Hypertension −60%	−	+	−	−
Cholesterol −100%	+	−	−	−
Smoking −50% +Bldpr. −25% all cat.	+	+	+	−
Smoking −50% +Chol. −50% all cat.	+	−	+	−
Smoking −50% +Bldpr. −10% all cat. +Chol. −25% all cat.	+	−	−	−
Smoking −50% +exc.alcohol −50%	+	−	−	−

Key:−=target not achieved, +=target achieved

means an average reduction in the population (M<65 total) or that a 15 % reduction will be achieved for both men and women or for each age group under 65 (all PIF <65). These three alternatives will be discussed.

In the quantification the smoking prevalence is assumed to reach 20% over 15 years and the prevalence of smoking is spread over exposure categories to reduce the total tobacco consumption by 50%. We experimented with the lowest reduction in the prevalence of hypertension, of hypercholesterolemia or of a combination of both, necessary to achieve the target. The results are shown in table 9.1.

The most interesting feature of the above list of possible interventions is that the reduction in smoking, as proposed, alone will not achieve the IHD target. Quite sizable reductions in the prevalence of hypertension will achieve the target for women but a reduction in hypercholesterolemia alone, will achieve the desired effect for men only with a complete elimination of hypercholesterolemia. Even in combination with the reduction in smoking proposed in the policy paper the reductions in the prevalence of hypertension or hypercholesterolemia will have to be large. These reductions will not be easy to achieve and it is unlikely that they will be achieved with lifestyle changes only. This illustrates a dilemma in preventive policy which is often disregarded when discussing preventive interventions at population level. Obviously reductions in hypertension will produce health benefits at the population levels, but when, such as in this analysis, no mention is made of the way in which these reductions are achieved, it is not possible to

weigh the health benefits achieved by the reduction in hypertension against the possible side effects of the preventive intervention. This point has been extensively discussed when the "prudent diet" was proposed in the USA, for the possible long term noxious effects for children of a reduced fat intake. The discussion becomes even more important when the intervention proposed involves long term medication.

Another feature in the above table is that, although the overall target of M<65 may be reached, this does not necessarily mean that the PIF target is reached in every age group. So we may need more stringent interventions if the target indeed means that the PIF<65 is reduced by 15% in all age groups. This also applies for the sex differentiated target. Targets for health policy making that are not differentiated by sub population will be easier to achieve.

The conclusions from the above exercise must be that, if quantitative targets are really to be used in health planning, it is important that they are formulated in great detail, however tedious this may seem, since the different interpretations lead to different policy measures necessary to achieve the target. For each interpretation of the target however we can formulate alternative preventive strategies, some of which are more realistic or acceptable than others. In this particular situation there was the restriction of the already formulated reduction in smoking prevalence and tobacco consumption. In the next paragraph we will look at a situation where the alternatives can vary with respect to all risk factors.

9.2.2   Target flow charts

Figure 9.5 shows some flow charts as proposed for the Dutch Department of Public Health. They concern quantitative, disease specific, targets as formulated in the Health 2000 Report, on ischemic heart disease and lung cancer. Other cancers or accidents are not considered here since the risk factors at present incorporated in Prevent do not correspond with those used by the Ministry of Health for target setting in these areas. In this example it is assumed that the targets concern mortality reductions for the entire population.

The purpose of this exercise is not to actually quantify the target flow charts, but to show how Prevent can be used in such a situation and which questions remain to be answered before priorities can really be set.

Table 9.2 shows the smallest change in the prevalence of each risk factor individually, necessary to achieve each disease specific target. As can be seen immediately some of the intervention alternatives are clearly impossible.

It is obvious that single risk factor interventions, which are realistic, will

Figure 9.5: "Target flow charts" for IHD and lung cancer
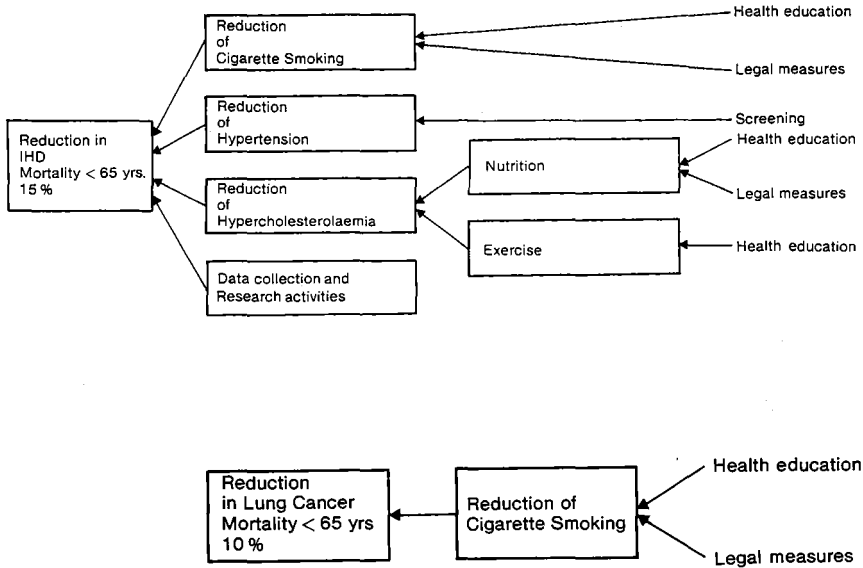
Table 9.2: Alternative changes in risk factor prevalence necessary to achieve the targets on IHD and lung cancer in the year 2000.

	IHD M<65=−15%	Lung cancer M<65=−10%
Smoking −17.5%	−	+
Smoking −75%	+	+
Hypertension −70%	+	−
Hyper chol. −100%	−	−
Exc.Alc. −100%	−	−

never be able to achieve the targets for multi factorial diseases. If the IHD
target is to be achieved, multi factorial interventions (as shown earlier in
table 9.1) will be needed.

The second point of interest is the fact that smoking influences both
IHD and lung cancer mortality. The reduction in smoking prevalence nec-
essary to achieve the IHD target will automatically achieve the lung cancer
target without any additional investment. This means that it is important
in an organization concerned with preventive interventions to achieve dis-
ease specific targets, to avoid too strict a separation of policy decisions by
disease category, but on the contrary to encourage the cooperation and co-
ordination in setting disease specific targets and priorities for interventions.

9.3   Priority setting

As mentioned in the introduction the effect estimates of preventive inter-
ventions as produced by Prevent can not be used directly to set priorities.
There is no indication of the intervention mode used to achieve the change
in risk factor prevalence nor is there an estimate of the costs involved. All
Prevent does is to quantify the health benefits in such a way that they can
be used in a cost-effectiveness analysis.

When comparing alternative preventive interventions to achieve disease
specific targets as illustrated in the previous paragraph there are two points
to keep in mind: the time horizon of the effect estimates on which the
decision is based and the total mortality reduction achieved together with
the disease specific target.

Both elements have been discussed already in chapter 7. To illustrate
these, information for some of the intervention alternatives discussed in the
previous paragraph is assembled in table 9.3. It shows the total mortality
reduction and the actual years of life gained for each intervention both in
the year 2000 and in the year 2020. The effect measure of total mortality
reduction at one point in time is of course not only dependent on the size of
the mortality reduction achieved but also on the time dimension of the risk
factor disease combination. The difference between the level of mortality
reduction in 2000 and 2020 illustrates how the year in which effects are
compared, may arbitrarily influence the priority setting. A better measure
on which to compare health benefits is the Actual Years of Life Gained,
which shows the cumulation of effect over the years.

The conclusion that can be drawn from this exercise is that it is unwise
to look at the health benefits achieved by a risk factor intervention only in
terms of disease specific mortality. If we look at the mortality reduction
(as an example of more general measures of health benefit) of the differ-

Table 9.3: Total mortality reduction and AYLG in 2000 and in 2020 for alternative interventions.

| | Total mortality reduction | | AYLG | |
	2000	2020	2000	2020
Smoking −75%	4087	4049	24568	128845
Smoking −50% +Bldpr. −25% all cat.	3858	3278	27489	111325
Smoking −50% +Chol. −50% all cat.	3105	2971	20275	96253
Smoking −50% +Bldpr. −10% all cat. +Chol. −25% all cat.	3349	3020	22240	100450
Smoking −50% +exc.alcohol −50%	3200	3272	20994	100781

ent alternatives we see that, although they may achieve approximately the same effect on IHD mortality, their effect on total mortality is strikingly different. In the setting of priorities in preventive interventions, it seems important not only to look at the effect on the disease specific target but to consider also the side effects of the measure on total health. This is the type of information which can be crucial in choosing the most cost-effective intervention.

It also shows that some intervention alternatives will not achieve their full benefit until many years after the intervention. If the time horizon for which benefits are compared is too short the real benefits may be obscured and priority setting ineffective. Or the time horizon of your target may in itself influence the perceived benefits of alternative interventions and thus the priority setting.

9.4 Conclusion

With the above examples of the use of Prevent it was shown how the quantification of the health benefits of alternative risk factor interventions can help in health policy making. It must be clear however that Prevent will not dictate the priorities. Prevent only quantifies one step in the whole process of policy making.

In the illustrations in this chapter certain choices were made. As always when the real decisions are made, other circumstances may dictate other choices. It is for this reason that Prevent is designed as a tool: an interactive model that can be used directly in policy making. Only after experimentation with the effects of alternative interventions can a feeling

be acquired for the important dimensions that will influence the outcome and for which political choices may need to be made.

The goals of the user will determine the outcome measure chosen to rank the priorities and furthermore the proposed interventions will have to be assigned an estimate of cost, not only financially but also politically. The cost-health benefit equation that results from such analyses will determine the political decision. However in a careful analysis of costs and benefits of an intervention, it is crucial that the estimates of benefits are calculated with as much precision as the costs. This is the area in which Prevent can make a contribution.

Chapter 10

Conclusions

The policy implications that can be deduced from the results of the model have been discussed in the previous chapter. In this chapter the emphasis is on whether the project was able to achieve its objectives and what recommendations can be made from the experience with the project. The general goal of the project was subdivided into three objectives:

- To adjust existing epidemiologic measures to suit a multifactorial model with a time dimension

- To collect the necessary input data from the existing epidemiological literature on relative risks and risk factor prevalence

- To develop a policy making tool which could be used for effect estimates of prevention, and as such be useful for priority setting.

The conclusions will be presented along those same lines.

10.1 The methodology

It proved possible to adapt an existing epidemiologic measure of effect, the potential impact fraction, to incorporate both the multi factorial nature of the relationship between risk factors and diseases, and a time dimension to simulate slow risk reduction after cessation of exposure.

It was also possible to express the health benefits in terms of absolute numbers for general health indicators, as well as proportional changes in disease specific incidence rates, by the incorporation of a dynamic population model. This allowed for the influence of competing death risks and demography to be taken into account.

The resulting Prevent model was programmed for use with a micro computer and can be used in an interactive manner by policy makers. The model is best suited for estimating the effects of preventive interventions. It does not readily allow for the incorporation of changes in curative care.

However in order to achieve this objective certain assumptions and certain simplifications had to be made.

- To incorporate several risk factors and several diseases in one model, a certain simplification of the stratification dimensions of the input data was necessary. This implies that to be able to fit together the data about different risk factors in a consistent manner, important extra information was sometimes lost.

- To simulate the effect of several risk factors on one disease it was assumed that risk factors are independently distributed in the population and that the effect of a simultaneous exposure to more than one risk factor is a multiplication of the relative risks without interaction.

- The assumption was made that whatever interaction may exist between different causes of death, was explained by a joint risk factor. When none was known, causes of death were assumed to be independent.

- The translation of proportional changes in incidence into absolute health benefits over the long simulation period dictated by the time dimensions, necessitated the assumption that over the simulation period, the effect of curative care on the case fatality rate and the survival period remained unchanged.

These assumptions are necessary because insufficient knowledge and data exist to allow a more detailed modelling of a multi disease model. The results produced with this multi factorial approach show that taking several diseases into account simultaneously, does alter the estimated benefits from an intervention. To improve such a model in the future, the following elements should be added: the interaction both between diseases and between risk factors, estimates of the effects of changing curative care on survival and case fatality and an estimate of both the costs of interventions and of the utilization of health services avoided by the intervention.

10.2   The data for Prevent

The objective of this project was to see if the available epidemiological data could be used more effectively for health policy decisions. Although

there is a large body of knowledge about risk factors and their influence on disease incidence, some problems were encountered when using the data for prospective effect estimates.

Relative risks had to represent a causal relationship. This meant that only those risk factors were included for which a consensus was reached. With alcohol in relation to IHD, which is still controversial, it was shown how much estimates about the effects of an alcohol reduction program, could differ under different assumptions about this relationship. In general data on the effect of cessation of exposure are scarce. The remnant relative risk as well as the time dimensions are not reported consistently, while this information is especially important when interventions will be directed at cessation as well as prevention of exposure.

Data on the prevalence of risk factors in the Dutch population were available. However the stratification by exposure category did not always correspond with the available stratification in relative risk. Few time trends of exposure prevalence are available. This made assumptions about the past changes in prevalence necessary. With the historical testing on smoking and lung cancer it proved essential to link certain exposure characteristics to birth cohorts. When prevalence data are available from one point in time only it is impossible to differentiate between age specific and cohort specific factors.

As mentioned in the previous paragraph, limitations of available data made certain simplifications of the model necessary. These simplifications obviously will affect the results of the model as was shown with the historic testing. If epidemiologic information is to be of use in setting priorities for prevention, it will be necessary to include certain variables such as remnant relative risks, time dimensions and cohort characteristics, in the empirical epidemiologic studies.

10.3 Prevent as a tool

To evaluate the utility of such a model in health policy making, it seems useful to see whether the inclusion of

- several diseases

- a time dimension

- the possibility to express benefits both in proportional and in absolute terms,

significantly changes the expected health benefits.

The time dimension is the Prevent feature of which the effect is most easily perceived. The long time lags between an intervention on exposure and changes in mortality which can be seen in some diseases greatly affect the results. The inclusion of the time dimension not only emphasizes that in some cases results of preventive measures will not be noticeable immediately but it also shows that such a measure will continue to affect the populations health long after the intervention has ceased. To present the expected effects over too short a period may lead to serious underestimation of the ultimate benefits.

In the current version of Prevent all outcome measures are based on mortality. The cause of death which still dominates the health profile of the Dutch population, ischemic heart disease, is so much more important than other diseases, that even small proportional changes in the IHD mortality will greatly affect the ultimate health benefit. This illustrates why effects of risk factor interventions should not be measured in proportional changes of disease specific mortality only. Often the cardiovascular risk factors have not been considered worth intervening upon, because reducing them would only marginally affect the IHD mortality rate. Interventions on risk factors for other diseases however, have been discussed based on high proportional effects without realizing that in absolute terms it would result in far fewer deaths prevented.

The main interest in the multi factorial approach of the Prevent model lies in the fact that not all diseases affect a health indicator expressed in absolute numbers to the same extent, and that the important time variables differ by disease. This means that a risk factor intervention will reduce total mortality through several disease specific mortalities, each to a different extent and at different moments. This can be seen in the mortality reduction curve of a reduction in smoking prevalence, in which the contribution of the different diseases can be clearly discerned.

It does make a difference whether the effects of an intervention are evaluated in a single disease model or a multi disease model. However the multi factorial approach also dispels another commonly held belief: that competing death risks in our aging population will eliminate all mortality reduction from one disease by substituting another cause of death. To a certain extent such a substitution occurs as was illustrated earlier, with the initial increase in COLD mortality after smoking cessation due to the decrease in IHD mortality. However the expected total mortality reduction of that same intervention shows that despite the initial extra mortality, the ultimate health benefit remains impressive. Although there is an increase in causes of death not affected by the risk factor intervened upon, there nevertheless is a large overall mortality reduction. When looking at the actual years of life gained by this intervention, one can conclude that the

deaths prevented have indeed resulted in substantially extended lives. It is a fallacy to think that prevention will achieve an important mortality reduction only in a young population. Even in our aging population we can achieve sizable mortality benefits.

The aggregation of health benefits and the introduction of a dynamic population, simulating the demographic evolution of the Dutch population is essential to the second step of the model. When looking at the disease specific mortality, even without an intervention, it is obvious that demographic changes in the coming years, will greatly increase the absolute mortality for the diseases included in Prevent. In some cases even far reaching reductions in risk factor prevalence will not prevent that the total number of cases in the future will be higher than they are today. In the introduction it was stated that prevention is often difficult to sell politically since its effects take so long to become apparent. After the Prevent exercise we have to conclude it is even worse: effects will seldom be apparent as real reductions in disease. This conclusion should not be interpreted to mean that prevention will not have any beneficial effect in an aging population. On the contrary it can result in a sizable mortality reduction despite competing death risks. It does mean however, that to be able to appreciate the effects it is important to show what would happen without the preventive intervention and not compare it to the current level of mortality.

10.4 Recommendations

Epidemiology has sometimes claimed to be a basic science for public health. Results from theoretical and empirical epidemiologic work can indeed be used in providing information essential to public health decisions. Global modelling for policy purposes with epidemiologic data is possible and useful. However to make future results more realistic further research will be necessary along the lines mentioned above, especially concerning the inclusion of possible changes in curative care in a more comprehensive public health model.

This project was a first step on the road from etiologic and intervention research to the implementation of these results in health policy making. It shows that the health benefits of preventive interventions may differ from what would be expected from the traditional effect measures. Health policy making with such public health models can improve priority setting by providing more precise quantification of effect estimates, however it will also require precise target setting and an investment in the collection of data which are essential to such an exercise.

References Part V

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Part VI

APPENDICES

Appendix A

EF and PIF in a multi factorial model[1]

The interest in EF as a measure of the importance of a risk factor has greatly increased in recent years. This has generated a large methodological literature on the computation of EF in different situations. One of the complications which has recently received considerable attention is the calculation of EF in a population where more than one risk factor for the disease considered, is present (1-12). Most of these deal with the problems of epidemiological analysis in which the joint distribution of several risk factors in the population and the ensuing IDR's are known. Walters paper in 1983 (8) acknowledges the parallel problems of the use of the traditional EF formula's when trying to estimate the effect of preventive interventions in the general population, where data on the joint distribution of more than one risk factor are seldom available.

In the field of Health Risk Appraisal a similar discussion on the relative risk associated with joint exposure has evolved. Spasoff (12) showed how both the additive and the multiplicative (as well as a logistic) model could be used to calculate the effect of joint exposure. Their ultimate choice, based on expert opinion, was to assume a multiplicative model for most causes of death.

For the Prevent model the problem is whether EF's and PIF's can be calculated for diseases which are affected by several risk factors, without knowing the joint distribution or the IDR's, and secondly whether this can be done sequentially for each risk factor or whether they need to be

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[1] This appendix would have been incomprehensible without the valuable help of Gerrit van Oortmarssen, who simplified the equations despite his aversion to PIFs and TIFs.

Figure A.1: Distribution of risk factor A and B in a population
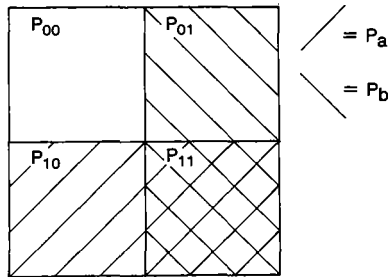
considered simultaneously.

In the following paragraphs it will be shown that the equation for the marginal attributable risk, the EF assuming no other risk factors are present, can be used to estimate the etiologic fraction of a risk factor when more than one risk factor is known. This can be done without knowledge of joint distribution, under two different assumptions of the IDR associated with joint exposure. The two assumptions do result in different equations.

In a situation where two risk factors A and B exist, with only a dichotomous exposure, (no time lags or remnant IDR's are considered), the distribution of exposure can be depicted as in figure A:1.

If P stands for the proportion of the population exposed to a certain risk factor and IDR for the relative risk associated with that exposure,

Let:

$$
\begin{aligned}
P_{00} &= \text{non exposed} \\
P_{10} &= \text{exposed to A only} \\
P_{01} &= \text{exposed to B only} \\
P_{11} &= \text{exposed to both A and B} \\
P_a &= P_{10} + P_{11} \\
P_b &= P_{01} + P_{11} \\
IDR_a &= IDR_{10} \\
IDR_b &= IDR_{01} \\
IDR_{00} &= 1 \text{ (by definition)}
\end{aligned}
$$

The IDR_{11} now can be defined in two ways:

1. Multiplicative model: $IDR_{11} = IDR_{10}IDR_{01}$ or

2. Additive model: $(IDR_{11} - 1) = (IDR_{10} - 1) + (IDR_{01} - 1)$

We are interested to see whether $EF_a = EF_{10,11}$ and $PIF_a = PIF_{10,11}$.

A.1 Multiplicative model

Let EF_a be the etiological fraction in a situation where only risk factor A exists. Then:

$$EF_a = \frac{P_a(IDR_a - 1)}{P_a(IDR_a - 1) + 1}$$
$$= \frac{IDR_a - 1}{IDR_a + \frac{1-P_a}{P_a}} \tag{A.1}$$

Let $EF_{10,11}$ be the etiological fraction for risk factor A in a situation where both risk factor A and B are present and because of the multiplicative model $IDR_{11} = IDR_{10}IDR_{01}$. Then:

$$EF_{11} = \frac{P_{10}(IDR_a - 1) + P_{11}(IDR_{11} - IDR_b)}{P_{10}IDR_a + P_{11}IDR_{11} + P_{01}IDR_b + P_{00}}$$
$$= \frac{P_{10}(IDR_a - 1) + P_{11}IDR_b(IDR_a - 1)}{P_{10}IDR_a + P_{11}IDR_aIDR_b + P_{01}IDR_b + P_{00}}$$

Dividing numerator and denominator by $P_{10} + P_{11}IDR_b$:

$$= \frac{IDR_a - 1}{IDR_a + \frac{P_{01}IDR_b + P_{00}}{P_{10} + P_{11}IDR_b}}$$
$$= \frac{IDR_a - 1}{IDR_a + \frac{P_{01}(IDR_b - 1) + (1 - P_a)}{P_{11}(IDR_b - 1) + P_a}} \tag{A.2}$$

We assume both risk factors are indeed present and each have an IDR$>$1. If the two risk factors A and B are distributed independently in the population then: $\frac{P_{11}}{P_{01}} = \frac{P_{10}}{P_{00}} = \frac{P_a}{1-P_a}$ *and* $IDR_{11} = IDR_{10}IDR_{01}$. Equation A2 = A1. This implies that:

$$EF_{10,11} = EF_a$$

EF_a in a one risk factor situation is identical to $EF_{10,11}$, the etiological fraction of risk factor A in the presence of a second risk factor. The same can be done for multiple risk factors. A similar proof applies to PIF_a and $PIF_{10,11}$.

This means that if a multiplicative model of relative risk *and* independence of the distribution of risk factors can be assumed, EF's and PIF's can be calculated sequentially for each risk factor without necessary knowledge of joint distribution.

A.2 Additive model

Again let EF_a be the etiological fraction of risk factor A in a situation where only A exists, and PIF_a the potential impact fraction in a one risk factor situation. Then:

$$
\begin{aligned}
EF_a &= \frac{P_a(IDR_a - 1)}{P_a(IDR_a - 1) + 1} \\
&= \frac{IDR_a - 1}{IDR_a + \frac{1 - P_a}{P_a}}
\end{aligned}
$$

and

$$
PIF_a = \frac{(P_a IDR_{10} + 1 - P_a) - (P'_a IDR_{10} + 1 - P'_a)}{P_a IDR_{10} + 1 - P_a}
$$

Now let $EF_{10,11}$ be the same etiological fraction for risk factor A in a situation where both A and B are present *and*

$$
(IDR_{11} - 1) = (IDR_a - 1) + (IDR_b - 1) \tag{A.3}
$$

or equivalently:

$$
IDR_{11} - IDR_b = IDR_a - 1 \tag{A.4}
$$

Then:

$$
EF_{10,11} = \frac{(P_{10}(IDR_a - 1) + (P_{11}(IDR_{11} - IDR_b))}{P_{10}(IDR_a - 1) + P_{11}(IDR_{11} - 1) + (P_{01}(IDR_b - 1) + 1}
$$

Or applying (A.4) to denominator and (A.3) to numerator :

$$
\begin{aligned}
&= \frac{(P_{10} + P_{11})(IDR_a - 1)}{(P_{10} + P_{11}(IDR_a - 1) + P_{01} + P_{11}(IDR_b - 1) + 1} \\
&= \frac{P_a(IDR_a - 1)}{P_a(IDR_a - 1) + P_b(IDR_b - 1) + 1} \tag{A.5} \\
&\neq EF_a
\end{aligned}
$$

In a similar way one can prove:

$$
\begin{aligned}
PIF_{10,11} \;=\; & \frac{P_a(IDR_{10} - 1) + P_b(IDR_{01} - 1)}{P_a(IDR_{10} - 1) + P_b(IDR_{01} - 1) + 1} \\
& - \frac{(P'_a(IDR_{10} - 1) + P'_b(IDR_{01} - 1))}{P_a(IDR_{10} - 1) + P_b(IDR_{01} - 1) + 1} \\
\neq \;\; & PIF_a
\end{aligned}
\tag{A.6}
$$

With the assumption of additivity, the equations for EF and PIF will have to be adjusted. However no assumptions need to be made about the independent distribution of risk factors. One implicit condition in the equation used is that all the relevant risk factors are known since all must be included in the denominator. In the case of an as yet unknown confounder the attributable fraction may be overestimated.

A.3 Conclusion

For most diseases there is no consensus on the effect of joint risk exposure. Spasoff concluded from his search that except for accidents (which experts assumed were best described by an additive model) and IHD for which he applied a logistic model, all other diseases were best described by a multiplicative model.

In the Prevent model this problem is further complicated because so few prevalence data on joint exposure exist. In the absence of such data we shall assume a multiplicative model of IDR for joint exposure as well as independence of the distribution of risk factors. Then the single risk factor equations for EF and PIF can be used.

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Appendix B

Background tables

In this appendix some of the overview tables will be presented on which the
input data are based. They have been published previously and the sources
mentioned can be found in the references after part III. Only the data on
the prevalence of hypertension by age group have not been published in this
form before, however they have been constructed from published material.
They contain the percentage of the Dutch population in each age group,
in a certain range of blood pressure, according to the different available
surveys in the Netherlands. In the final column a population estimate is
given, based on these data.

Table B.1: Outline of eight major prospective studies.

Authors	Doll Hill Peto Pike	Hammond	Dorn Kahn Rogot	Hirayama	Best Josie Walker	Hammond Horn	Weir Dunn Linden Breslow	Cederlof Friberg Hrubec Lorich
Subjects	British doctors	Males and Females in 25 States	U.S. veterans	Total population of 29 health districts in Japan	Canadian pensioners	White males in 9 States	California males in various occupations	Probability sample of the Swedish population
Population size Females	40,000 6,000	1,000,000 562,671	290,000 <1%	265,000 142,857	92,000 14,000	187,000	68,000	55,000 27,700
Age range	20-85+	35-84	35-84	40 and up	30-90	50-69	33-64	18-69
Year of enrollment	1951	1960	1954 1957	1966	1955	1952	1954	1963
Years of follow-up years reported	20-22	12 years	16 years	13 years	6 years	4 years	5-8 years	10 years
Number of deaths	11,166	150,000	107,500	39,100	11,000	12,000	4,700	4,500
Person years of experience	800,000	8,000,000	3,500,000	3,000,000	500,000	670,000	480,000	550,000
Mortality ratio's	M14 F5	M8.5 F3.6	M11.3	M3.8 2		M10.7	M7.6	M7.0 F4.5

Source: 196

Table B.2: Coronary heart disease mortality ratios related to smoking - some prospective studies (Actual number of deaths shown in parentheses)[1]

Author year country	Number and type of population	Data collection	Follow-up (yrs)	Number of deaths	Cigarettes/day		Age variation				Comments
Hammond and Horn, 1958, U.S.A.	187,783 white males in 9 states 50-69 yrs of age	Question-naire and follow-up of death certificate	3.5	5,297	NS All smokers <10 10-20 20-40 40+	1.00 (709) 1.70 (3361) 1.29 (192) 1.89 (864) 2.20 (604) 2.41 (118)	50-54 1.93 (765) 1.38 (35) 2.00 (213) 2.51 (203)	55-59 1.85 (962) 1.38 (50) 2.04 (258) 2.47 (199)	60-64 1.66 (921) 1.17 (49) 1.91 (235) 1.92 (129)	65-69 1.41 (713) 1.27 (58) 1.58 (158) 1.56 (73)	
Doyle et al. 1964, U.S.A.	2,282 males Framing-ham, 30-62 yrs of age 1,913 males Albany 30-35 yrs of age	Detailed medical examination and follow-up	10 8	93	NS All smokers <20 20 >20	1.00 (2) 2.40 (73) 2.00 (17) 1.70 (20) 3.50 (36)					Data apply only to aged 40-49 and free of CHD at entry, NS include pipe,cigar and ex-smokers
Doll and Hill 1964, Great Britain	Approxi-mately 41,000 male Bri-tish phy-	Question-naire and follow-up of death certificate	10	1,376	NS All smokers 1-14 15-24 >25	1.00 1.35 1.29 1.27 1.43	35-44 3.73 4.45 1.36	45-64 1.40 1.73 1.92	65-84 1.71 1.27 1.58		
Strobel and Gsell 1965 Switzer-land	3,749 male Swiss phy-cisians	Question-naire and follow-up of death certificate	9	162	NS ≤20 >20	1.00 1.48 1.76					
Best 1966, Canada	Approxima-tely 78,000 male Cana-dian veterans	Question-naire and follow-up of death certificate	6	2,000	NS All smokers <10 10-20 >20	1.00 1.60 (1380) 1.55 (327) 1.58 (766) 1.78 (277)	30-49 0.97 (18) 1.45 (115) 1.85 (65)	50-69 1.56 (230) 1.67 (557) 1.76 (184)	70 and over 1.71 (99) 1.29 (94) 1.73 (28)		

Table B.2: Continued

Author year country	Number and type of population	Data collection	Follow-up (yrs)	Number of deaths	Cigarettes/day		Age variation				Comments
Kahn 1966, U.S.A.	US male veterans 2,265,674 person years	Question-naire and follow-up of death certificate	8.5	10,890	NS All smokers 1-9 10-20 21-39 >39	1.00 (2997) 1.74 (4150) 1.39 (439) 1.78 (2102) 1.84 (1292) 2.00 (266)					
Hirayama 1967, Japan	265,118 Japanese adults over age 40	Trained in-terviewers and follow-up of death certificate	1	96	NS 1.24 >25	1.00 (17) 1.13 (69) 1.00 (5)					Prelimi-report
Kannel et al. 1968,	5,127 males and females age 30-59	Medical ex-amination and follow-up	12	52	NS >20	1.00 (27) 2.20 (25)					
Hammond and Garfinkel 1969, USA	358,534 males 445,875 females age 40-79 at entry	Question-naire and follow-up of death certificate	6	14,819	Males NS 1-9 10-19 20-30 >40	1.00 1.27 1.60 1.73 1.77	40-49 1.60 2.59 3.76 5.51	50-59 1.59 2.13 2.40 2.79	60-69 1.48 1.82 1.91 1.79	70-79 1.14 1.41 1.49 1.47	
					Females NS 1-9 10-19 20-30 >40	1.00 0.84 1.22 1.52 0.61	40-49 1.31 2.08 3.62 3.31*	50-59 1.15 2.37 2.68 3.73	60-69 1.04 1.79 2.08 2.02*	70-79 0.76 0.98 1.27	* Based on 5-9 deaths

1 NS = Nonsmokers
Source: 193

Table B.3: Overview of the prevalence of hypertension in four categories by study and sex

			Blood pressure in MmHg[1]							
Study	Men N	<140/90	≥140/90 and <160/95	≥160/95 and <180/105	≥180/105	Women N	<140	≥140/90 and <160/95	≥160/95 and <180/105	≥180/105
Consulta-tiebureaus together (1977-78)	9812	63.4	20.4	12.2	4.0	10675	78.4	13.3	6.3	2.0
Tilburg	1792	66.7	19.2	10.7	3.2	1805	78.3	14.4	5.8	1.5
Maastricht	1862	67.3	16.7	11.9	4.0	1944	84.9	9.0	4.6	1.4
Doetinchem	1176	62.7	23.3	10.7	3.2	1271	73.8	16.4	7.8	2.0
Amsterdam	1478	73.6	14.3	9.3	2.8	1876	80.7	10.3	7.1	1.9
Leiden	1469	60.4	19.9	14.4	5.3	1670	78.4	12.8	6.3	2.2
Rotterdam	2035	51.9	27.9	15.1	5.1	2109	73.1	17.3	6.8	2.7
COPIH ('74)	5803	53.4	28.7	12.9	4.9	1622	65.0	20.7	11.0	3.3
EPOZ (1975-78)	765	77.6	15.8	5.2	1.3	825	81.9	11.4	5.4	1.2
Vlaardingen (1975-76)	201	64.2	23.9	11.4	0.5	184	72.8	15.8	6.0	5.4
Vlagtwedde (1976)	314	51.6	36.3	9.2	2.9	-	-	-	-	-
Bedum (1972)	-	-	-	-	-	371	52.3	33.7	10.2	3.8

1 this concerns first measurement
N = population size
Source: 200

Table B.4: Prevalence of obesity according to the Quetelet Index (QI) in the Netherlands

Men

Study	Vlagtwedde		COPIH		Den Haag (N=139)	Zeist		Ede		Zutphen	
	N	QI>27 %	N	QI>27 %	QI>27 %	N	QI>27 %	N	QI>27 %	N	QI>27 %
Age:											
20-24	209	12						648	5		
25-29	147	31			8			559	12		
30-34	147	27						558	14		
35-39	170	39	178	16	20						
40-44	205	36	1207	18		101	20				
45-49	163	35	1328	22	30						
50-54			1408	24		131	35			816	11
55-59			1410	28	25						
60-64			923	25		198	38				
65-69					31	140	30				
70-75					41						

Women

Study	Utrecht (Overvecht, N=6000)		Den Haag (N=269)	Zeist		Ede	
	QI>26 %	QI>29 %	QI>26 %	N	QI>26 %	N	QI>26 %
Age:							
20-24						729	6
25-29			10			653	10
30-34	±10	±5				710	12
35-39			22				
40-44	±10-25	±5-10					
45-49			33				
50-54	±25-45	±15		116	40		
55-59			42				
60-64	±45-55	±20-30		101	57		
65-69			57	104	56		
70-75			50				

N: populationsize
Source: 202

In the following tables only published material was used. Sometimes the categories of hypertension did not agree. Since these tables are background material no adjustment was made but all available categories were reported. This may make tables somewhat cumbersome to read. Each time a survey was first introduced the sample size is given as well as the age groups on which the reported data are based. The population estimate given in the last column are the choice data on which prevalence data for input in the Prevent model were based. The EPOZ data were later reconstructed for the purpose of testing the sensibility of the model for the initial input data (see chapter 8).

Table B.5: Prevalence of hypertension, age group 35-44

Bld pr.	S	CB	COPIH	EPOZ	Vlaar.	Vlach.	Bed.	Est.pop
DBP<90	M	63.4	53.4	77.6	64.2	51.6	-	58.4
SBP<140	F	78.4	65.0	81.9	72.8	-	52.3	78.4
DBP 90-94	M	20.4	28.7	15.8	23.9	36.3	-	24.6
+SBP 140-159	F	13.3	20.7	11.4	15.8	-	33.7	13.3
DBP 95 -104	M	12.2	12.9	5.2	11.4	9.2	-	12.6
+SBP 160 -179	F	6.3	11.0	5.4	6.0	-	7.8	6.3
DBP≥105	M	4.0	4.9	1.3	.5	2.9	-	4.4
+SBP≥180	F	2.0	3.3	1.2	5.4	-	3.8	2.0
DBP ≥90	M	21.4	31.0	13.3	12.9	15.3	-	26.2
	F	12.3	22.9	12.6	13.6	-	11.0	13.3
SBP ≥140	M	32.0	38.9	17.6	32.8	45.5	-	35.5
	F	18.8	20.1	12	24.5	-	45.5	18.8
N	M	9812	5803	765	201	314	-	
	F	10675	1622	825	184	-	371	
Period		'77-'78	'74	'75-78	'75-76	'76	'72	

Table B.6: Prevalence of hypertension, age group 45-49

Bld.pr.	S	CB project	Copih	KRIS	Est.pop.
DBP<90	M		45		45
+SBP<140	F		49		49
DBP 90-94	M		27		27
+SBP 140-159	F		26		26
DBP ≥95	M		29	19	29
+SBP ≥160	F		25		25
DBP<95	M	95.0			
	F	92.1			
DBP 95-104	M	4.2			
	F	6.7			
DBP ≥105	M	.9			
	F	1.1			
SBP<140	M	68.6			
	F	90.1			
SBP 140-159	M	25.2			
	F	4.3			
SBP≥180	M	6.2			
	F	5.5			
N	M	338		3364	
	F	416			

Table B.7: Prevalence of hypertension, age group 50-54

Bld.Pr.	S	Copih	EPOZ	KRIS	Est.pop.
DBP<90	M	41	29.1	-	41
+SBP<140	F	45	19.5	-	45
DBP 90-94	M	26	48.4	-	26
+SBP 140-159	F	26	49.9	-	26
DBP 95-104	M	-	18.9	-	-
+SBP 160-179	F	-	24.0	-	-
DBP ≥105	M	-	3.6	-	-
+SBP≥180	F	-	6.6	-	-
DBP ≥95	M	32	-	19	32
+SBP ≥160	F	29	-	-	29
N			10355 based on agegroup 50-64	3364 based on agegroup 45-59	

Table B.8: Prevalence of hypertension, age group 55-59

Bld.pr.	S	Copih	EPOZ	Boot	Est.pop.
DBP<90	M	34	29.1	-	34
+SBP<140	F	35	19.5	-	35
DBP 90-94	M	29	48.4	44	29
+SBP 140-159	F	30	49.9	34	30
DBP 95-104	M	-	18.9	-	-
+SBP 160-179	F	-	24.0	-	-
DBP$\geq$105	M	-	3.6	-	-
+SBP$\geq$180	F	-	6.6	-	-
DBP$\geq$95	M	37	-	20	37
+SBP$\geq$160	F	35	-	15	35
N			10355 based on agegroup 50-64	M=733 F=910 30-59	

Table B.9: Prevalence of hypertension, age group 60-64

Bld.pr.	S	Copih	EPOZ	Boot	Est.pop.
DBP<90	M	28	29.1	-	28
+SBP<140	F	25	19.5	-	25
DBP 90-94	M	29	48.4	69	29
+SBP 140-159	F	31	49.9	76	31
DBP 95-104	M	-	18.9	-	-
+SBP 160-179	F	-	24.0	-	-
DBP$\geq$105	M	-	3.6	-	-
+SBP$\geq$180	F	-	6.6	-	-
DBP $\geq$95	M	43	-	26	43
+SBP$\geq$160	F	44	-	41	44
N			based on agegroup 50-64	based on agegroup 60-74	

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Appendix C

Input data

In this appendix the input data on prevalences and IDR's are presented as they have been used in the Prevent runs in this publication.

Table C.1: Prevalence of cigarette smoking by age, sex, exposure category and exposure level, 1985

Age	20-24		25-34		35-49		50-64		65+	
Sex	M	F	M	F	M	F	M	F	M	F
Smokers										
1-12	22	24	21	24	18	21	22	19	23	9
13-22	14	14	19	15	17	11	16	8	12	3
23+	4	4	7	5	10	5	10	4	6	1
Non-smokers	56	52	40	41	36	48	30	56	34	78
ex-smokers										
<1 yr.	2	2	3	2	1	2	2	1	2	1
1-2yr.	1	2	3	2	1	1	2	1	2	1
3-4yr.	.5	2	3	3	3	2	2	1	2	1
5-9yr.	.4	1	4	5	5	4	4	3	4	1
10+yr.	.1	.2	2	2	6	5	12	7	16	5

Source: NIPO in opdracht van Stichting Volksgezondheid en Roken, Continu onderzoek, Rookgewoonten, periode 85 II t/m 86 I Oct 15, mei 1986.

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Table C.2: Lung cancer IDR's for men and women by current number of cigarettes smoked

	Males	Females
1-12 cig	7	7
13-22 cig	12	12
23+ cig	20	20

Table C.3: IHD IDR's for men and women by age and by current number of cigarettes smoked

	<35		35-49		50-64		65+	
	M	F	M	F	M	F	M	F
1-12 cig	-	-	3	3	1.7	1.7	1.5	1.5
13-22 cig	-	-	4	4	2	2	1.5	1.5
23+ cig	-	-	4	4	2.4	2.4	1.7	1.7

Table C.4: COLD IDR's for men and women by amount smoked

	males	females
1-12 cig	12	12
13-22 cig	25	25
23+ cig	30	30

Table C.5: Prevalence of hypertension by age, sex, exposure category, 1985

age	35-44		45-49		50-54		55-59		60+	
sex	M	F	M	F	M	F	M	F	M	F
Hypertensive										
Mild	22	12	24	24	24	24	26	27	26	28
Severe	15	8	26	23	29	26	33	32	39	40
Normotensive	58	78	45	49	42	45	34	35	28	25
Ex-hypertensive										
Mild	2	1	2	2	2	2	3	3	3	3
Severe	2	1	3	2	3	3	4	3	4	4

Table C.6: IHD IDR's for men and women with mild and severe hypertension in the Netherlands, by age and sex

	<45 yrs		≥45 yrs	
	Men	Women	Men	Women
Mild	1.9	1.7	1.6	1.6
Severe	2.3	2.9	1.8	2.7

Table C.7: CVA IDR's for men and women with mild and severe hypertension in the Netherlands, by age and sex

	<45		≥45	
	Men	Women	Men	Women
Hypertension				
Mild	3.5	2	1.8	1.5
Severe	5	3.5	3	3

Table C.8: Prevalence of elevated serum cholesterol by age, sex, exposure category, 1985

Age	35-39		40-40		45-49		50-54		55-59		60+	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Elevated												
Mild	20	16	24	19	25	24	27	31	28	29	27	34
Severe	10	5	13	6	9	9	14	18	15	27	15	24
Normal	66	76	59	72	62	64	54	46	52	38	53	35
Ex-elevated												
Mild	2	2	3	2	3	2	3	3	3	3	3	4
Severe	1	1	1	1	1	1	2	2	2	3	2	3

Table C.9: IHD IDR's for men and women by serum cholesterol level

	<45		45-54		55+	
	M	F	M	F	M	F
mild elevated serumchol	3.5	3	2	1.7	1.3	-
severe elevated serumchol	5.5	5	3	2	1.9	-

Table C.10: Prevalence of obesity[1] in the Dutch population by age and sex, 1985

	Men		Women
<30	2		3
31-40	5		4
41-50	5		10
>50	10		15

1 Obesity is defined as a QI of >30 for men and >30 for women.

Table C.11: Percentage of drinkers in the Dutch population by age,sex and number of glasses of alcoholic beverages per week

	21-40 yrs		40+	
	M	F	M	F
Ref.pop. (4-21 drinks/ week)	54	33	43	37
Excessive drink- ers 22+ drinks/ week	17	4	15	1
Abstainers <4 drinks/week	30	64	37	62

Table C.12: Alcohol IDR's for men and women, for abstainers and excessive drinkers

	abstainers	excessive drinkers
IHD	2	2
cirrhosis	1	9
traffic accidents	1	2
accidental fall	1	2

Table C.13: Prevalence of age mother at first birth, by age group in the Dutch population, 1985

	25-29	30-34	35-39	40-44	45-49	50+
Ref.pop. (<20 yrs)	7	11	12	10	8	8
20-29	56	61	68	73	73	69
30+	32	17	9	6	8	9
No children	11	11	11	11	12	14

Table C.14: Breast cancer IDR's by age of mother at first birth

	IDR
Ref.pop.	1
20-29	1.20
30+	1.74
No children	1.72

Summary

Introduction

In 1986 the Health 2000 Report, a long term health policy document, was presented to the Dutch parliament. This document is part of shift in interest in public health towards *health* rather than *health services* planning. There are two interesting features in this shift. The one is the tendency to measure the effectiveness of a policy, an intervention or a technology in terms of health, the outcome rather than the input, output or process. The other is the acceptance that political choices need to be made, since however large the budget for health is, it will always be limited.

One of the choices to make will be whether or not to invest in preventive interventions. Preventive interventions can be defined as deliberate changes in the prevalence of risk factors in a population. To be able to weigh the costs and the benefits of such preventive interventions, an estimate will have to be made of their effect on the health of the population. Furthermore changes in risk factor prevalence may also occur autonomously. An estimate of the changes in the health status of the population as a result of these shifts in risk factor prevalence, will be important for the planning of health services and for the setting of realistic targets, as proposed by WHO.

Prevent is a tool that will estimate the health effects of changes in risk factor prevalence in a population, as a result of trends or interventions. Its results can either be used directly in health policy making to formulate targets or quantify different scenario's on changes in risk factor prevalence in the future, or its results can be used as input for formal decision making processes such as for instance cost effectiveness studies.

The Prevent model

In epidemiology an analysis of the distribution of disease incidence and risk factor prevalence in different populations is used to confirm the hypothesis

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of a causal relationship between risk factor and disease. The strength of the relationship is often expressed as the ratio of incidence between exposed and non exposed, the Incidence Density Ratio (IDR). The importance of a risk factor for the incidence of a certain disease in a population is usually expressed as the Etiologic Fraction (EF), the proportion of the total incidence of the disease that can be attributed to the prevalence of that risk factor in the population. The EF is sometimes used as an indication of the proportion of incidence that could be prevented by the total elimination of that risk factor in the population.

However, since most often prevention will not eliminate but merely reduce the prevalence of a risk factor, a measure was developed to estimate the impact of a change in prevalence of a risk factor on the incidence of a disease, the Potential Impact Fraction (PIF). It stands for the incidence that is avoided by a preventive intervention as a proportion of the incidence that would have occurred in that population without the intervention.

Prevent estimates the effect of changes in risk factor prevalence in a population in terms of health benefit. It is based on the epidemiologic effect measure the Potential Impact Fraction. To achieve the objectives of the project it has incorporated the following three requirements in the methodology:

- the possibility that one risk factor affects several diseases, and that one disease is affected by several risk factors,

- a time dimension to simulate the reduction in excess risk after cessation of exposure to the risk factor,

- the interaction between the effect of the intervention and the demographic evolution in the population.

The model will simulate the development, over time, of two populations: one as a result of trends in risk factor prevalence and demography, and the other which incorporates both trends and interventions on risk factors and the demography. Differences between these two populations are the effect of the intervention. In the current version of Prevent all measures of health benefit are based on mortality.

Results

Since the results are primarily intended for policy making the choice of the disease categories to include in the project was determined by criteria, relevant to public health policies:

- the disease had to contribute significantly to the ill health of the Dutch population,

- the disease should have known risk factors upon which interventions could reasonably be applied.

The availability of reliable data both on the relationship between risk factor and disease incidence and on the prevalence of the risk factor in the Dutch population, determined which risk factors and diseases were included in the current version of the model. Sensitivity testing on the input data and a historical reconstruction of lung cancer mortality in the Netherlands were done to provide an indication of the robustness of the model.

With the Prevent model a number of risk factor interventions were simulated and the results analyzed. The interventions show that there is a considerable difference in the outcome measured as a proportional mortality reduction as with the Potential Impact Fraction and an outcome measure in absolute terms such as mortality reduction. Especially for a common cause of death such as Ischemic Heart Disease even a small proportional reduction may represent a large number of deaths prevented.

Interventions on the prevalence of smoking in the population illustrate both the importance of a multifactorial approach and of the time dimension. If only one disease is considered much of the effect of the intervention is missed. In order to evaluate the effect of a risk factor intervention the total (aggregated) health benefit should be considered. This also includes the possible increase in causes of death not related to the risk factor considered, as a result of the intervention.

The timelag between smoking cessation and the ultimate effect on lung cancer mortality illustrates the consequences of the introduction of a time dimension. Not only does a considerable period elapse before the full effect of a reduction in smoking prevalence can be appreciated, but it also means that the quite sizable reductions in smoking prevalence in the recent years will be noticeable in an initial reduction in lung cancer mortality in the near future in both the trend and the intervention population. With the introduction of a time dimension changes in risk factor prevalence in the past will continue to affect health in the future.

In the Dutch population which can expect a large increase in the proportion of elderly in the coming years, the absolute number of cases of diseases which occur mostly in old age, will increase sharply in the future. For some diseases even considerable reductions in risk factor prevalence will not be able to counteract this increase. This means that even with a successful preventive policy the need for certain curative services will continue to increase. If demography is not taken into account reductions in mortal-

ity rates as a result of a preventive intervention may create the erroneous
impression that the absolute number of cases will also go down.

When comparing the effect of different risk factor interventions it is
important to keep the following items in mind:

- Not only the total health benefit should be compared but also the
  distribution over sub groups in the population.

- The simulation time over which interventions are compared should be
  sufficiently long to show the full effect of each intervention.

- The choice of benefit measure will influence the priority setting.

Of all the risk factors in the Prevent model, the greatest health benefits are
to be expected from a reduction in smoking prevalence. Not only a new
generation of non smokers will greatly improve the populations health, a
program of smoking cessation will also result in sizable mortality reductions,
although mostly for men.

Finally the Prevent model was applied to a number of recent Dutch
policy documents to show how it can provide useful quantitative informa-
tion for policy making. The alternative smoking scenario's of the Dutch
Lifestyle Scenario project were simulated with different assumptions of the
population groups affected by the intervention. It shows that the health
benefits will greatly differ depending on the group in the population in-
tervened upon. A similar quantification of the hypothetical smoking inter-
vention analyzed in the Dutch Cancer Scenario, illustrates why it is useful
to look at risk factor interventions in a multifactorial model since the ex-
pected benefits are much higher if other diseases affected are also taken into
account.

The alternative risk factor reductions necessary to achieve the targets
as stated in the Health 2000 Report and the more recent policy document
on the Prevention of Cardiovascular Disease, were calculated. For Ischemic
Heart Disease it will be impossible to achieve the target with an interven-
tion on one risk factor only. Even in a multifactorial intervention large
reductions in risk factor prevalence in the near future, will be necessary if
the target is to be achieved before the year 2000.

Prevent shows a positive aspect of the interrelationship of risk factors
and diseases. Some interventions proposed to achieve one disease specific
target may automatically achieve another disease target. This is the case
in all interventions suggested for the reduction in Ischemic Heart Disease:
the inherent reduction in smoking prevalence ensures that the lung cancer
target is achieved without additional interventions. This illustrates the
necessity to apply targets in a comprehensive health policy, and not only
by disease category.

Conclusions

The results of hypothetical interventions simulated by Prevent show that a multifactorial model with a time dimension will yield different estimates of the effects of risk factor intervention than the traditional epidemiological measures. The use of a dynamic population model makes it easier to visualize the interaction between changes in age specific mortality (as a result of changes in risk factor prevalences) and demography. This is especially important for policy making since it helps to show that despite a possible increase in absolute disease specific mortality, the mortality reduction due to a preventive intervention can be quite large.

Prevent only expresses health benefits in outcome measures based on mortality. In the future it would be useful to extend this to morbidity measures also. This will only be possible if curative care is not assumed static over time. The model should therefore be extended into a public health model which not only looks at preventive interventions but also at interventions on curative care. It will then be possible to also express effects in terms of changes in the utilization of services or even costs.

Samenvatting

Inleiding

In 1986 werd de Nota 2000 aangeboden aan de Tweede Kamer. De nota bevat een lange termijn visie op de ontwikkelingen van gezondheidsbeleid en illustreert de verschuivende belangstelling van *gezondheidszorg*beleid naar *gezondheids*beleid. Deze verschuiving is om twee redenen interessant. Ten eerste omdat in gezondheidsbeleid de effectiviteit van een beleidsmaatregel, een interventie of een technologie beoordeeld wordt in termen van het gezondheidseffect voor de gehele bevolking en ten tweede omdat met het stellen van prioriteiten voor een gezondheidsbeleid, impliciet aanvaard wordt dat er keuzes gemaakt zullen moeten worden, ongeacht het uiteindelijk te besteden budget voor Volksgezondheid.

Een van de keuzes die gemaakt zal moeten worden is of er wel of niet in preventie moet worden geïnvesteerd. Primaire preventie maatregelen kunnen interventies omvatten op het vóórkomen van risicofactoren in de bevolking. Om de kosten en de baten van dergelijke maatregelen tegen elkaar te kunnen afwegen, zal een schatting van de effecten op de gezondheid van de bevolking van groot belang zijn. Bovendien kunnen er ook autonome veranderingen in risicofactor prevalentie optreden die de gezondheidstoestand van de bevolking zullen beïnvloeden. De daaruit voortvloeiende verandering in de vraag naar zorg zal van belang zijn voor het vaststellen van het benodigde voorzieningenniveau. Dus zowel voor het beleid ten aanzien van preventie als voor het voorzieningenbeleid is het schatten van de gezondheidseffecten van verschuivingen in risicofactor prevalentie nuttig.

Prevent is een simulatie model waarmee dergelijke gezondheidseffecten geschat kunnen worden. De resultaten kunnen of rechtstreeks in het beleid gebruikt worden, bijv. om doelstellingen te kwantificeren, of om de effecten van verschillende leefwijze scenario's te simuleren, of gebruikt worden als effect schatting in meer formele besluitvormingsprocessen zoals kosten effectiviteits analyses.

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Het Prevent model

In de epidemiologie staat de analyse van de incidentie van ziekten in relatie tot de prevalentie van risicofactoren in een bevolking centraal. De mate waarin een risicofactor de kans op het krijgen van een ziekte beïnvloedt, wordt meestal uitgedrukt als de verhouding tussen de incidentie bij geëxposeerden en bij niet-geëxposeerden, het relatief risico. Het belang van de risicofactor voor de totale incidentie in een bevolking wordt meestal uitgedrukt als het attributieve risico, dat deel van de totale incidentie dat toegeschreven kan worden aan het voorkomen van de risicofactor in de bevolking. Dit attributieve risico wordt soms ook gebruikt om aan te geven welk deel van de incidentie voorkomen zou kunnen worden wanneer de risicofactor in de bevolking geheel geëlimineerd werd.

Over het algemeen is een preventieve maatregel niet in staat om een risicofactor geheel uit te schakelen. Om het effect op de incidentie te schatten van een vermindering in het voorkomen van een risicofactor, werd de Potential Impact Fraction geïntroduceerd. Deze PIF geeft de proportionele reductie in de toekomstige incidentie aan, die het gevolg is van een vermindering in de prevalentie van de risicofactor.

Prevent schat de gezondheidseffecten van een verandering in de prevalentie van een risicofactor gebaseerd op de Potential Impact Fraction, maar heeft daar de volgende elementen aan toegevoegd:

- de mogelijkheid dat één risicofactor meer dan één ziekte beïnvloedt en dat de incidentie van één ziekte door meerdere risicofactoren wordt bepaald,

- een tijdsdimensie waarmee de geleidelijke afname in relatief risico wordt gesimuleerd die optreedt na het beëindigen van expositie aan een risicofactor,

- de interactie tussen de proportionele verandering in incidentie en de absolute sterfte en de demografie.

Het model simuleert de ontwikkeling in de loop der jaren van twee populaties: de *referentie* bevolking onder invloed van trends in risicofactor prevalentie en demografie, en de *interventie* populatie waarbij rekening wordt gehouden met zowel trends in, als de effecten van interventies op de prevalentie van risicofactoren en de demografie. Het verschil tussen deze beide populaties is het effect van de interventie. In de huidige versie van het Prevent model worden alle effectmaten op sterfte gebaseerd.

Resultaten

Aangezien de resultaten van het model in eerste instantie voor beleidsdoeleinden bedoeld zijn, is de keuze van de ziektecategorieën die in het model zijn opgenomen gebaseerd op de volgende overwegingen:

- de mate waarin de ziektecategorie bijdraagt tot de algemene sterfte in de Nederlands bevolking,

- de mate waarin risicofactoren voor de ziekte bekend zijn, waarop redelijkerwijs zou kunnen worden geïntervenieerd.

De beschikbaarheid van betrouwbare gegevens zowel voor de relatieve risico's als voor de prevalentie van de risicofactor in de Nederlandse bevolking bepaalde uiteindelijk welke risicofactoren en welke ziektecategorieën in de huidige versie van het model werden opgenomen. Het model werd vervolgens getoetst op het effect van de keuze van de invoer variabelen op de resultaten via gevoeligheidsanalyses. Er werd ook een historische toetsing uitgevoerd door de ontwikkeling van de sterfte aan longkanker in Nederland tussen 1970 en 1985 te schatten op grond van het aantal rokers.

Met het Prevent model worden vervolgens een aantal hypothetische interventies gesimuleerd waarvan de resultaten worden besproken. Zoals te verwachten verschilt de beoordeling van interventies soms aanzienlijk wanneer het proportionele effect, zoals de PIF, of het absolute effect, zoals bijv. het sterfteverschil, wordt vergeleken. Voor belangrijke doodsoorzaken zoals ischemische hartziekten, kan zelfs een kleine procentuele afname een belangrijke sterftereductie in absolute aantallen betekenen.

Het effect van een vermindering van het aantal rokers in de bevolking illustreert zowel het belang van een multifactorieel model als van de tijdsdimensie. Wanneer slechts naar de gezondheidswinst in termen van één ziekte gekeken wordt, wordt het potentiële effect sterk onderschat. Om het totale effect van een interventie te kunnen beoordelen dient het verschil in sterfte geäggregeerd over alle ziektecategorieën beschouwd te worden inclusief die doodsoorzaken die ten gevolge van de verschuiving in ziekteincidentie zullen toenemen.

De tijd die verstrijkt tussen het stoppen met roken en de uiteindelijke daling in risico op bijv. longkanker, illustreert de consequenties van het invoeren van een tijdsdimensie. Niet alleen zullen de uiteindelijk effecten van een interventie pas na vele jaren merkbaar zijn, maar bovendien zal de niet onaanzienlijke daling in het aantal rokers van de afgelopen tien jaar in de eerstkomende jaren, ongeacht het te voeren beleid, nog aanleiding zijn tot een daling in leeftijdspecifieke longkankersterfte bij mannen. Bij vrouwen zal eerst nog merkbaar zijn dat er een aantal geboortecohorten

aankomen die in tegenstelling tot de oudere cohorten, wel degelijk in het
verleden veel gerookt hebben. Met het invoeren van een tijdsdimensie wordt
zichtbaar gemaakt hoe verschuivingen in risicofactor prevalentie uit het
verleden ook in de toekomst nog de gezondheidstoestand van de bevolking
blijven bepalen.

In Nederland zal in de komende jaren het percentage ouderen maar
vooral ook het absolute aantal ouderen in de bevolking nog sterk blijven
toenemen. Omdat de gezondheidsproblemen in onze bevolking vooral op
oudere leeftijd optreden, zal het absolute aantal gevallen (en ook sterfge-
vallen) voor de belangrijkste doodsoorzaken in de komende jaren scherp
toenemen. Voor een aantal doodsoorzaken zullen zelfs heel drastische ver-
minderingen in de prevalentie van risicofactoren niet in staat zijn om die
stijging te niet te doen. Dit heeft tot gevolg dat zelfs met een zeer suc-
cesvol preventie beleid, de behoefte aan sommige gezondheidszorg voor-
zieningen zal blijven toenemen. Dit betekent niet dat het preventiebeleid
niets uitricht, want zonder die preventie maatregelen zou de behoefte aan
voorzieningen nog veel sterker toenemen.

Het gebruik van de resultaten

Wanneer de effecten van verschillende interventies met elkaar vergeleken
worden moeten de volgende aspecten daarin meegenomen worden:

- niet alleen de totale gezondheidswinst voor de bevolking moet vergele-
  ken worden maar ook de verdeling over groepen binnen die populatie,

- de tijdspanne waarop interventies met elkaar worden vergeleken moet
  lang genoeg zijn om voor alle risicofactoren het maximale effect te
  bereiken,

- de keuze van de uitkomstmaat waarop vergeleken wordt zal mede de
  prioriteitenstelling beïnvloeden.

Van alle risicofactoren die in Prevent zijn opgenomen, is de grootste ge-
zondheidswinst te verwachten van een interventie op het roken. Een nieu-
we generatie niet rokers zal de gezondheidstoestand van de bevolking sterk
verbeteren. Maar een beleid gericht op het doen stoppen met roken zal op
een veel kortere termijn, een aanzienlijke sterftereductie opleveren.

Tot slot werd Prevent gebruikt om een aantal recente beleidsdocumenten
te kwantificeren. De alternatieve rookscenario's zoals zij door de Scenario
Commissie Leefwijzen werden gepubliceerd, en de hypothetische interventie
op roken die werd voorgesteld door de Scenario Commissie Kanker werden

gekwantificeerd. Deze simulaties laten zien dat de geschatte gezondheids-winst van dergelijke interventies sterk afhangt van de subgroepen in de populatie op wie de interventie betrekking heeft en dat het te verwachten effect toeneemt wanneer in een multifactorieel model de belangrijkste door roken beïnvloedde ziektecategorieën worden meeberekend.

De alternatieve risicofactor interventies die in staat zouden zijn om de Targets uit de Nota 2000 of de Beleidsnota Preventie Hart en Vaatziekten te bereiken geven aan dat het onmogelijk zal zijn om de beoogde reduc-tie in sterfte ten gevolge van ischemische hartziekten te bereiken wanneer slechts op een risicofactor wordt geïntervenieerd. Maatregelen zullen ge-richt moeten zijn op het tegelijkertijd terugdringen van de prevalentie van de verschillende risicofactoren.

Een multifactorieel model van risicofactoren en ziekten laat ook zien dat sommige interventies bedoeld om één van de ziektetargets te bewerkstelli-gen, soms automatisch ook een target voor een andere ziekte bereiken. Dit is bijvoorbeeld het geval voor de interventies die worden voorgesteld om het target voor de ischemische hartziekte te bereiken die, vanwege de interventie op roken, automatisch ook de gewenste daling in longkankersterfte teweeg brengen. Dit illustreert het belang van een algeheel gezondheidsbeleid en niet alleen een ziektegerichte aanpak.

Conclusies

De resultaten van de simulaties die met Prevent zijn uitgevoerd tonen aan dat effectschattingen van veranderingen in risicofactor prevalentie, aanzien-lijk anders zijn wanneer een multifactorieel model met een tijdsdimensie gebruikt wordt. Het gebruik van een dynamisch populatie model waarmee ook absolute verschuivingen in de gezondheidstoestand van de bevolking kunnen worden gesimuleerd, maakt het gemakkelijker om de interacties tussen veranderingen in leeftijdspecifieke sterfte (als gevolg van een daling in risicofactor prevalentie) en de demografie zichtbaar te maken. Dit is vooral van belang voor het beleid omdat het laat zien hoe groot de gezond-heidswinst van een preventieve maatregel kan zijn zelfs wanneer de absolute sterfte toeneemt vergeleken met het huidige niveau.

Prevent berekent uitsluitend gezondheidswinst gebaseerd op sterfte. In de toekomst zou een dergelijk model moeten worden uitgebouwd om ook morbiditeits maten te bevatten. Daarvoor moet echter de invloed van de curatieve zorg ook gemodelleerd worden. Een dergelijk volksgezondheids model zou het dan ook mogelijk maken om effecten uit te drukken in termen van het gebruik van voorzieningen en zelfs kosten.

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Curriculum Vitae

1-7-1951	Geboren te Amsterdam
1969	Eindexamen Gymnasium Beta, Stedelijk Lyceum Maastricht
1969-70	AFS, Studenten uitwisseling in de Verenigde Staten
1973	Kandidaats examen medicijnen, RU Groningen
1973-75	Planned Parenthood, Washington DC, USA
1975-79	Johns Hopkins School of Public Health, Baltimore, USA, Masters of Science International Health
1980-81	Wetenschappelijk medewerker, Centre d'Etudes Socio Economiques de la Santé, Université Catholique de Louvain, Brussel, België
1982-85	Beleidsmedewerker, Stafbureau Beleidsontwikkeling, Ministerie van WVC
1985-	Wetenschappelijk medewerker, Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, Rotterdam

Dankwoord

Bij het maken van een proefschrift, ben je je meer dan met andere werkstukken, bewust van hen die je geholpen hebben. Het is dan ook een goede gewoonte om hen schriftelijk te bedanken. Toen ik naging welke mensen in ieder geval in zo'n dankwoord genoemd zouden moeten worden, viel mij op dat zij die mij gesteund hebben in deze periode in twee groepen uiteen vallen, twee groepen die denk ik beide onontbeerlijk zijn geweest. Allereerst zou ik hen willen danken die mij daadwerkelijk geholpen hebben. Als eerste wil ik daarbij Jan Barendregt noemen zonder wie Prevent niets meer dan een hersenspinsel zou zijn gebleven. Hij heeft wonderen van programmeerwerk verricht om het model op een micro computer te houden. Hoewel hij bij elk nieuw verzinsel mijnerzijds begon met bedenkelijk te kijken vanwege de nog beschikbare geheugen ruimte, bleek na enige dagen toch telkens weer een nieuwe, voor mij geheel onbegrijpelijk truc om de computer te misleiden, het plan mogelijk te maken. Ook de introductie en het gebruik van LaTeX zou zonder Jans enthousiasme nooit mogelijk geweest zijn.

Zonder de inhoudelijke bijdragen van andere collegae van het Instituut Maatschappelijke Gezondheidszorg zou het schrijven van dit proefschrift heel wat moeilijker geweest zijn. Met name wil ik hier alleen Johan Mackenbach, Dik Habbema, Caspar Looman en Ed van Beeck noemen. Een bijzondere plaats neemt Gerrit van Oortmarssen in die veel van zijn heel kostbare tijd in het lezen en becommentarieren van eerdere versies van de tekst heeft gestoken.

Ook andere medewerkers van het instituut hebben mij veel werk uit handen genomen o.a.: Arry de Bruyn met het documentatiemateriaal, Theresa v.d Starre-Bout voor het invoeren van de literatuur en Atie Vogelenzang de Jong voor alle secretariaatswerkzaamheden.

De leden van de promotie commissie Prof. Dr. F. Surmans, Prof. Dr. F.H. Rutten en Prof. Dr. A. Hofman wil ik het bijzonder danken voor het feit dat ze ondanks de vakantieperiode zo snel en zo enthousiast in hun commentaar waren.

Maar hulp voor een proefschrift komt niet alleen van collegae, ook thuis

moet zo nu en dan echt geholpen worden. Voor die hulp ben ik Adrie Coljee en Liesbeth Pleyster veel dank verschuldigd.

De andere groep mensen die bij een promotieonderzoek belangrijk is, zijn zij die je de ruimte geven. In de eerste plaats wil ik op deze manier Prof. D. Deliège bedanken die mij indertijd, ondanks de afwezigheid van financiële middelen, de ruimte gaf om aan de UCL in Brussel ruimschoots onderzoekservaring op te doen. Zonder een dergelijke startruimte was dit onderzoek er nooit gekomen. Ik wil het Stafbureau Beleidsontwikkeling van het Ministerie van WVC bedanken voor de financiële ruimte die ze voor dit onderzoek geschapen hebben, en het Instituut Maatschappelijke Gezondheidszorg omdat ze mij de ruimte gegeven hebben om me uitsluitend met dit onderzoek bezig te houden.

Paul van der Maas neemt in deze rij een bijzondere plaats in, niet alleen omdat hij mijn promotor is, maar vooral omdat zijn steun in de afgelopen jaren in beide categorieën viel. Allereerst wil ik hem bedanken omdat hij me de ruimte heeft gegeven om eigenwijs mijn eigen gang te gaan, maar daarnaast ook omdat hij me desondanks door de opzet van de voortgangs- besprekingen ook vele malen daadwerkelijk geholpen heeft.