3

A multistate life table analysis of cardiovascular disease life history

Abstract

We demonstrate a method for producing occurrence-exposure rates from micro data and for using occurrence-exposure rates to construct a multistate life table (MSLT). Using epidemiological data, we measure the burden of cardiovascular disease and its sub-types in terms of life course indicators such as lifetime probability of cardiovascular disease, life expectancy free of cardiovascular disease and life expectancy with cardiovascular disease. We use the 48 year cardiovascular life history of the original Framingham Heart Study (FHS) population, aged 28-62 at study onset, and followed up between 1948 and 1998. We construct the life table for the total population and for males and females separately, to analyze sex differences in the cardiovascular disease life history. We found that at age 40, a FHS participant can expect to live an average of another 38.5 years, of which 84 percent free of cardiovascular disease. At age 50, a male can expect to spend 25 percent of his remaining life expectancy with the disease; a female, 18 percent. The lifetime probability of developing CVD is 67 percent for males and 55 percent for females (60 percent for total population). The number of years lived with disease after age 80 is higher for females compared to males. There is a disparity in the life trajectory of cardiovascular disease between males and females. Although middle-aged males spend more time with CVD, the burden of CVD at later ages of life is higher for females. The method and results we present here are simple and transparent to enable meaningful conclusions to be drawn about the potential burden of cardiovascular disease life history on both total population and male-female separately.

3.1 Introduction

The previous chapter provided a theoretical and mathematical description of the multistate life table and its potential utility in public health. In the present chapter, we have constructed a multistate life table to analyze the life history of cardiovascular disease. The epidemiology of cardiovascular disease has been comprehensively investigated and described during the past half century. Many prospective studies have enabled researchers to identify and quantify the major risk factors for cardiovascular disease (Dawber et al., 1957; Doyle et al., 1957; Chapman et al., 1957; Drake et al., 1957). Numerous studies have confirmed that altering these risk factors causes a reduction of event rates (Pignone et al., 2000; Chalmers, 1999; Hooper, 2000; Wilson, 2000; Yusuf et al., 2001). A recent study using 50 years of follow-up in the Framingham Heart Study (FHS) has found that the incidence of heart failure has declined among females but not among males and that survival after the onset of heart failure has improved in both sexes (Levy et al., 2002). Cardiovascular disease has been identified as a leading cause of disability and premature mortality (Murray and Lopez, 1996). Despite the recognition of cardiovascular disease (CVD) as a paramount health problem in public health, surprisingly little evidence is available on trajectories of CVD and its different manifestations.

Over the past few years, interest in conceptualizing the disease etiology within a life course framework has grown (Kuh, 1997; WHO, 2002). A recent review study by Ben-Shlomo and Kuh (2002) concludes that 'A *life course approach is paradoxical as on the one hand it is intuitively obvious (do we really need research to demonstrate risk accumulation?), and yet on the other hand is empirically complex (do we really have much evidence in support of these models?)'*. In this chapter, in which demographic techniques are applied to the epidemiologic information, an initial attempt is made to measure the burden of chronic disease, more specifically cardiovascular disease history, on human life course.

Demographic models of cardiovascular disease morbidity and mortality are very limited at best. Most of the demographic models have combined both morbidity and mortality by focusing on so-called health expectancy (e.g. active life expectancy) (Rogers et al., 1989; Crimmins et al., 1994). The underlying cardiovascular disease etiology of active life has been largely ignored by demographers in general (for exceptions see Hayward et al., 1998; Barendregt and Bonneux, 1998). However, Manton and Stallard (1988) proposed what may be the first demographic model of chronic morbidity and mortality. Much like the model developed here, Manton and Stallard's approach began by following individuals who are free of (cardiovascular) disease. They were thus able to observe the onset of a given fatal chronic disease, perhaps the onset of another fatal disease and the ending of the disease experience,

which is was death. The substantive aspect of our study is directly based on Manton and Stallard's conceptual work. We followed individuals as they experienced cardiovascular disease and its subtypes, and observed subsequent disease mortality and morbidity experience. The backbone of such a model is the age schedule at death and disease. Parsimonious models estimating life histories from the age schedules of various events (such as migration, or entry in the labour market) are a time-honored tradition in demography, laid down in the multi-state life table. We present the cardiovascular life history of the 4998 subjects making up the population of the original Framingham Heart Study cohort. This population was aged 28-62 at study onset and followed up between 1948 and 1998.

The objectives of this chapter are two-fold. First, we present a method to obtain observed occurrence-exposure rates from micro data. The observed occurrence-exposure rates are the basic input to construct a MSLT. Second, applying this demographic technique to the FHS cohort, we have derived several life course indicators, such as- lifetime risk of CVD, the expected number of years lived with CVD, the expected number of years lived without CVD and the differences in the number of years lived with and without CVD. These population measures, derived from a health-based life history, are essential both for precise assessment of changing health care needs and for intervention preferences.

This chapter is an extension of our previous study (Mamun, 2001; Peeters et al., 2002). From the methodological point of view, there are three basic differences between this chapter and previous works. First, in our previous study, multistate life tables were constructed based on the direct transition probabilities estimated from the micro data. We relied in that study on the concept of risk set. In the present study, the multistate life table is constructed based on the exact occurrence-exposure rates, which give a more accurate estimation of the life table parameters compared to the risk set approach. We demonstrate a method to estimate occurrence-exposure rates using micro data. The novelties of the latter approach are that the exact risk period is counted and left censoring is controlled. Second, the mortality and disease incidence used here were taken from the first 48 years of follow-up of the Framingham cohort; in the previous study we used the first 40 years of follow-up of the same cohort. We calculate the life table for the total population and also estimate the differences in cardiovascular life history between male and female participants of the Framingham Heart Study. Third, we provide a step-by-step demonstration of the multistate methods and estimation procedures.

This chapter is organized as follows. Section 3.2 offers a general overview of the approach that is used in this chapter. Section 3.3 describes the data and methods that are used to describe the life trajectory of cardiovascular disease. In this section, we have provided an overview of the original Framingham Heart Study cohort, after which we go on to distinguish between states and events, to specify different state space and transitions occurring with cardiovascular disease. We

illustrate how occurrence-exposure rates are estimated and finally, show how an MSLT is constructed. The results are described in Section 3.4, where mainly the cardiovascular disease history for the total FHS cohort is described. Finally, we explore the differences in cardiovascular disease life trajectory between males and females based on the life table implied prevalence, the proportion surviving, the proportion of time spent in a particular state, the lifetime probability of events and number of years lived. Section 3.5 closes this chapter with a discussion and conclusion.

3.2 The general approach

In this chapter, we used multistate life table techniques to describe the life history of cardiovascular disease. First, however, a brief description of the cardiovascular disease process and the modeling framework is given.

Cardiovascular disease process

Much information has been disseminated in the past half century regarding the cardiovascular disease process. Cardiovascular disease is a general term for diseases of the *heart* and *blood vessels*. Cardiovascular disease typically includes coronary heart disease (heart attack or myocardial infraction and angina pectoris), stroke, congestive heart failure, rheumatic fever and rheumatic heart disease, and congenital cardiovascular defects (American Heart Association, 2002). Heart disease, or coronary heart disease, is a disease caused by atherosclerosis, which leads to the narrowing of the lumen of arteries in the heart (American Heart Association, 2002). It is likely to produce angina pectoris (heart-related chest pain) or a heart attack. A stroke occurs when an artery supplying blood to the brain is blocked causing cells, or even an entire area of the brain to die. The damage resulting from an insufficient supply of blood may include a loss of mental function, muscle function, vision, sensation, or speech, depending on the area of the brain affected (National Stroke Association 2002). A heart attack occurs when an artery feeding the heart is blocked, allowing the cells in the part of the heart usually supplied with oxygen and nutrients by that artery to be damaged and even die. Heart attacks are most often caused by the blockage of an artery already narrowed by atherosclerosis; it can also result from an artery that is blocked because of contractions, i.e. the artery goes into spasm (American Heart Association, 2002).

Cardiovascular disease is of multifactoral etiology. Genetic susceptibility, risky behaviors and age play a primary role in the etiology of CVD (Center for Disease Control, 2002). Modifiable risk factors include high blood pressure, high blood cholesterol, obesity, smoking, diabetes, and physical inactivity and irremediable risk factors are age, genes and family history. The etiology of some of the risk factors is

complex and still unknown. For example, genetic factors and cardiovascular disease etiology are still unresolved (WHO, 2002). For details of cardiovascular disease etiology we refer to WHO (2002); American Heart Association (2002), National Stroke Association (2002); Center for Disease Control (2002).

The modeling framework

Useful public health measures of CVD occurrences are (WHO 1980; 1984): disease free survival, disease free life expectancy or healthy life expectancy, years of life saved or lost, disability adjusted years of life saved and so on. In the public health literature, the life table method is one of the best-known models to measure all these indicators. The life table method is an illustration of duration analysis (Willekens, 1991) where the time clock could be individual time (age), process or sojourn time and calendar or historical time. For chronic disease modeling, individual age is the most important time clock. The life table is based on age-specific *occurrence-exposure rates.*

The construction of a life table requires information on the dates of some basic variables: time of entry into the study, observation window, date of experiencing the event of interest or failure date, date of censoring or last follow-up or cutoff date. Theoretically, the date of entry marks the beginning of the exposure of an individual or unit under study to the risk of experiencing the event of interest (Namboodiri and Suchindran, 1987). For instance, the first examination date of the FHS original cohort marks the beginning of the risk of cardiovascular disease (provided there is no left censoring present). The observation of an individual ends with occurrence of the event of interest, competing event or the discontinuation of observation. The occurrence of an event unrelated to the event of interest or the discontinuation is known as right censoring.

In the single decrement life table, the attrition is due to a single cause, namely death (Namboodiri and Suchindran, 1987). If censoring exists, attrition can be either the result of having experienced the event of interest or censoring. For the application of life table techniques in the FHS, censoring concerns the right end of the observation window. The occurrence-exposure approach can easily control for censoring.

We have constructed a number of different life tables. In the standard life table, an individual moves from alive to dead. In the multi-state disease model, an individual may exit through death but may also move from "no cardiovascular disease" to disease to death. We use the Russian Doll model or Matrioshka model for a series of life tables of increased complexity. The different models divide the disease states up further into more specific disease states, but all states are hierarchically related. Transition into a disease state represents the entry into a disease. In this way, we created a series of multi-state models of the cardiovascular disease process.

To extract the input data for the construction of the life tables using FHS, we made three assumptions:

i. The FHS population is assumed to be homogeneous within each age and sex category.
ii. Censoring is independent of the event of interest.
iii. Exact age at the time of event or censoring is known.

3.3 Data and methods

3.3.1 Overview of the Framingham Heart Study

The Framingham Heart Study (FHS) is considered as the pioneer study into the cardiovascular disease process. At the time the FHS started in September 1948, doctors and even researchers had no idea why 1 in 4 men aged 55 or older developed heart disease (Brink, 2001). William Kannel, senior investigator and director of the FHS from 1966 to 1979 mentioned that "*when we started, we were getting death certificates saying that patients had died of acute indigestion*". At the time, , the FHS started with one main aim and two subsidiary aims (Dawber and Moore, 1952). The main aim was to secure epidemiological data on arteriosclerotic and hypertensive cardiovascular disease. The two subsidiary aims were (i) to secure data on the prevalence of all forms of cardiovascular disease in a representative population sample and (ii) to test the efficiency of various diagnostic procedures. The first aim was the major thrust of the study, the other two were viewed as by-products.

Under the direction of the National Heart Institute (NHI), in 1948, the Framingham Heart Study (FHS) embarked on an ambitious project in public health research. Now the institute is known as the National Heart, Lung, and Blood Institute (NHLBI). The Framingham Heart Study is now conducted in collaboration with Boston University.

The researchers in this study recruited 5,209 men and women between the ages of 28 and 62, from the town of Framingham, Massachusetts, and began the first round of extensive physical examinations and lifestyle interviews that they would later analyze for common patterns related to CVD development. The original study cohort consisted of respondents of a sample of 2 out of 3 adults, 28 to 62 years of age, who were residing in Framingham, Massachusetts in 1948 (Dawber and Moore, 1952). Of the original cohort of 5209 men and women, 1095 known were alive as of February 1998. Table 3.1 represents the age and sex distribution of the original cohort of the FHS at entry time in 1948 and as of February 1998, respectively.

The subjects have continued to return to the study every two years since 1948, for a detailed medical history, physical examination, and laboratory tests. For those participants who have moved out of the Framingham area and have not come back

for examinations, there is no clinical exam data available. However, telephone and/or mail contact data is maintained on nearly everyone, as a result of which morbidity and mortality information is available. Hospital records and death certificates are obtained. Family and doctors are queried. Event information is therefore quite complete. Also, many persons do come back for examinations even though they have moved out of the area. The participants are so committed to the study that when they come to the Boston area for a visit, they will often call the study to schedule an examination (Paul Sorlie, Personal communication, FHS, 2003).

In 1971, the study enrolled a second-generation group consisting of 5,124 individuals of the original participants' adult children and their spouses. They participated in similar examinations, and are known as the offspring cohort. This landmark study has even started recruiting a third generation since 2001 (National Institute of Health, 2001). In our analysis, we considered the original cohort.

Although the Framingham cohort is primarily white, the importance of the major CVD risk factors identified in this group have been shown in other studies to apply to other racial and ethnic groups, even though the patterns of distribution may vary from group to group (Leaverton et al., 1987). In the past 50 years, the study has produced approximately 1,000 articles in leading medical journals. Until recently, no demographic model has ever been applied, however. The concept of CVD risk factors has become an integral part of the modern medical curriculum and has led to the development of effective treatment and preventive strategies in clinical practice. The Framingham Heart Study continues to make important scientific contributions to public health, especially regarding diseases related to CVD by enhancing research capabilities and capitalizing on the inherent resources of this study. New medical innovations are evaluated and incorporated into ongoing protocols.

Table 3.1 Framingham Heart Study original cohort: age-sex distribution

At Entry (1948)			As of February 1998		
Age	Men	Women	Age	Men	Women
29-39	835	1042	70-79	75	124
40-49	779	962	80-89	243	500
50-62	722	869	90-99	34	114
			100+	1	4
Total	2336	2873	Total	353	742

Source: (http://www.nhlbi.nih.gov/ about/framingham/design.htm)

In the FHS, the following diseases were examined (Shurtleff, 1971): Cardiovascular disease (CVD) incorporating all the types of cardiovascular disease listed below:

- Coronary heart disease (CHD): myocardial infarction (MI), Angina pectoris (AP), and Coronary insufficiency (CI).
- Cerebrovascular accident (CA): Stroke (ABI, embolism, haemorrhage and other cerebrovascular accident), and Transient ischaemic attack (TIA).
- Congestive heart failure (CHF).
- Intermittent claudication (IC).

A brief definition of all these diseases is given in Technical Appendix 3.1.

In this study we refer to those who are free of cardiovascular disease as "NO-CVD". We exclude the subjects with pre-existing CVD at 1st examination (139 respondents) from the population at risk of developing CVD and those who were lost to follow-up (72 respondents). The pre-existing CVD at 1st examination was identified by any one of the following diagnoses at examination 1: *definite angina pectoris*, *definite history of myocardial infarction*, *definite myocardial infraction by electrocardiogram*, *doubtful myocardial infarction by electrocardiogram*, *definite coronary insufficiency by electrocardiogram* and history. After excluding 211 (139+72) cases, we found a total of 4998 subjects in the original FHS cohort. Details of the criteria for the original cohort are described in the data manual of the FHS (Cupples et al., 1987; Shurtleff, 1971).

3.3.2 States and events

The life history of an individual is viewed as a sequence of *states*. *Events* signify the transitions from one state to another (Willekens, 2002). A state is defined as a specific attribute of an individual. At each age, a person has particular attributes and occupies a particular state. For instance, if a person has no CVD at exact age 32 he occupies the state "NO-CVD" at that age. The number of states a person may occupy is finite. Hence the state variable is a discrete variable. All possible states constitute the state space. The number of persons in a given state is referred to as the state occupancy. State occupancy is a stock variable.

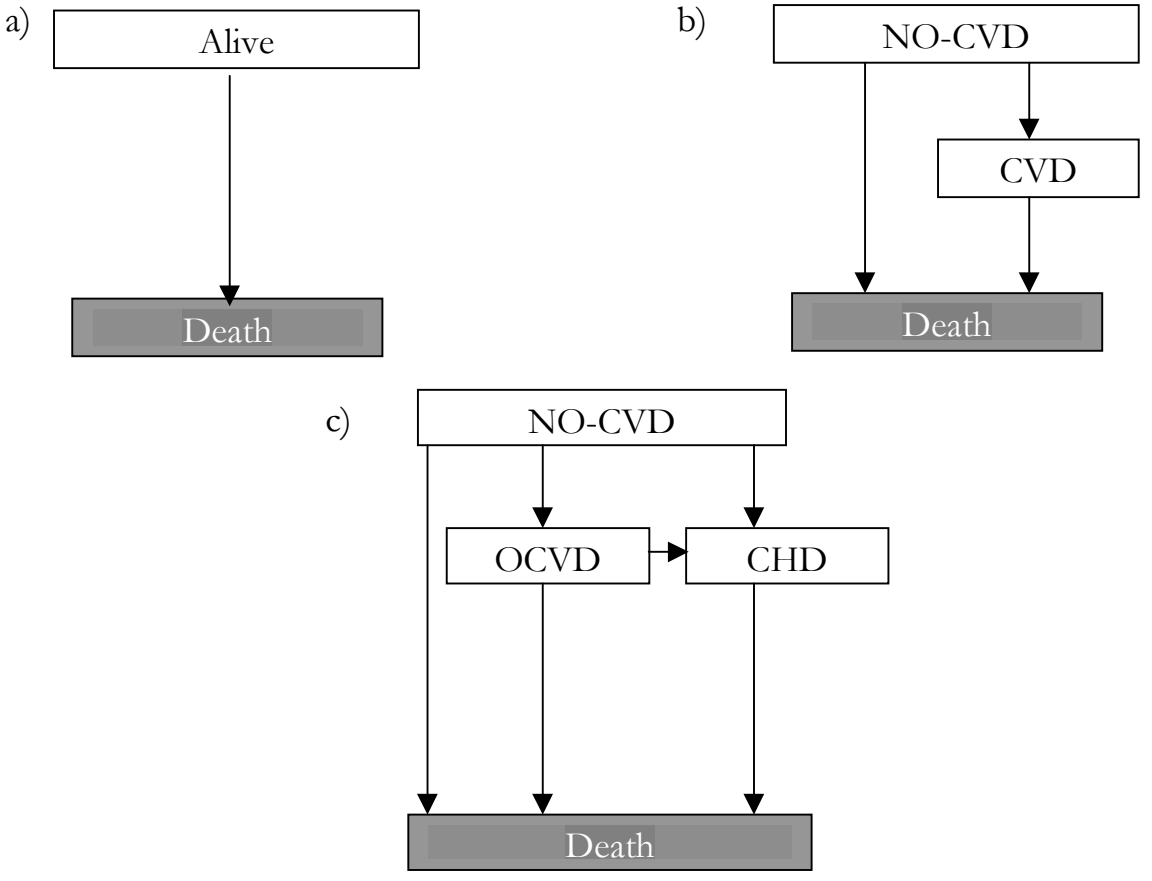
A change of attribute (state) is defined as an event. An event implies a transition between states in the state space. For example, if an individual is healthy at exact age 34 and suffers an MI before exact age 35, the change of attribute from healthy to MI is an event. The types of events depend on the state space. We consider the different state spaces separately. The number of events or transitions during a given interval is a flow variable.

We specified different state spaces and transitions, starting from a simple state space and ending with a complex one. Some of the state spaces and the associated transitions are presented in Figure 3.1. Others are given in Technical Appendix 3.2. We constructed life tables for all the specified models in Figure 3.1. The models

specified in Technical Appendix 3.2 demonstrate the more complex state space and associated transitions. For their application, we needed a large sample population. The FHS was too short.

The first state space is a simple two-state model: the state space is {alive, dead}(Figure 3.1(a)). The second state space consists of three states (Figure 3.1 (b)). In the three-state model, we divided the state of alive into two states: NO-CVD (i.e. alive without CVD) and CVD (i.e. alive with CVD). The third state is death, which is an absorbing state. The state space is {NO-CVD, CVD, Dead}. Individuals could pass from NO-CVD to death, spending no time in the state cardiovascular disease, or they could first transit through this state. We assumed that there would be no back transition from CVD to NO-CVD i.e. no recovery. In the third model, we decomposed the state of CVD into two states: CHD and other CVD (OCVD). The state space is: {NO-CVD, CHD, OCVD, Dead} (Figure 3.1(c)). In this model, OCVD is CVD other than CHD. While back transition could occur in the population this was not taken into consideration for the purpose of our analysis. Three other models were constructed with the same design except with myocardial infarction, congestive heart failure and stroke instead of coronary heart disease.

Figure 3.1 Multistate life table model of cardiovascular disease



3.3.3 Estimation of *occurrence-exposure* rates

As we discussed earlier (Section 2.4.3 in Chapter 2) there are two approaches to estimating the transition probabilities. There is the *risk set approach* that provides direct transition probability and the *occurrence-exposure rates*. The occurrence-exposure rates are also known as event rates, hazard rates, transition rates or instantaneous rates, depending on the field of study. Occurrence and exposure i.e. cumulative waiting time at risk are two key concepts in rate calculation. This method, according to which a key position is assigned to occurrence-exposure rate, is sometimes referred to as the person-years approach. This person-years approach is widely used in the field of demography to analyze event history data. In the field of epidemiology, Breslow and Day (1987) have used the person-years approach to describe incidence rates. In this approach, the clock begins for each individual at the start of an episode or time of the onset of risk for a specified transition. Both the fixed and time varying variables could be incorporated in this data file. The construction is best introduced by an example using the observational plan depicted in Figure 3.2.

In previous studies calculating MSLTs (Mamun, 2001; Peeters et al., 2002), we estimated transition probabilities directly from the micro data based on the risk set, where the risk set was the number of people who were at the risk of experiencing an event of interest (Namboodiri and Suchindran, 1987). This risk approach is an approximation of the occurrence-exposure rate approach since the denominator is the population at risk (i.e. risk set) instead of the exact risk period of the event of interest., Using the rate method, we can calculate the transition probabilities more accurately. The use of occurrence-exposure rates is a guarantee for the correct estimation of probabilities (Willekens, 2002). Therefore, instead of a risk set, we calculated the occurrence-exposure rate using the observational plan shown in Figure 3.2. Since the transition probabilities are calculated from occurrence/exposure rates, and not from a risk set, the estimated outcomes in this study could be different compared to our previous study.

The Framingham Study has maintained continual follow-up of the participants. In the data available to us, the follow-up is for 48 years, from mid-1948 to mid-1998. We have the exact time (in number of days) of survival or censoring time for each participant from exam 1 until exam 24[1]. There were 72 respondents who were lost to follow-up at different points in time. We excluded these from our analysis. In the end we were left with 4998 (5209-139-72=4998) respondents. To estimate the occurrence-exposure or occurrence-risk set, we needed to define the

[1] Days are transformed into exact years using the equations-
Year=Exam1+Survtime/365.25, where 'Year' is the exact year of survival or censored, 'Exam1' is exact year of first exam and 'Survtime' is the number of days (survived or censored) since Exam1.

observational plan. The observational plan gave us a clear picture of the starting, and ending times of a follow-up. We calculated the occurrence-exposure rates based on the observational plan for 48 years of follow-up in the FHS, as illustrated in Figure 3.2.

To depict the timing of the occurrences of an event or censoring and the number of exact person-years contributed from entry to exit time, 4 hypothetical participants entering into the study at the exact time of 1948.7*y*[2] were taken as an example. These were followed until they experienced events or were censored at the end of the observation time in 1996.5*y*. We have shown the occurrence-exposure rates and risk set in two time scales: (A) calendar period and (B) age. Since life table estimation uses age as the time scale, we estimated occurrence-exposures rates by age.

Consider individual *I*. He entered the study at age 60.7y at the first exam held in 1948.7y. He died at exact age 75.0y, which was in 1961.0*y*. Individual *II* entered the survey at age 35.3y in 1948.7y, experienced cardiovascular disease at age 52.2y (i.e. the age of entry into the CVD state) in 1965.6y and died at age 66.6y in 1980.0y. Individual *III* entered the study at age 41.5y and experienced no event of any kind during 47.8y of follow-up. He is defined as right censored at age 89.3y in 1996.5y.Lastly, individual *IV* entered the study at age 28.9y, experienced CVD at age 48.6y in 1968.4y and died at age 70.2y in 1990y. All four individuals contribute a total of 98.7 years (14.3y+16.9+47.8y+19.7y= 98.7y) to the NO-CVD state before making the transition to CVD or death (i.e. considering a multiple exit to CVD or death) and spend 36.0 years (14.4y+21.6y=36.0y) in the CVD state before making the transition to death.

As age-specific occurrence-exposure rates were required as input for the MSLT, we used age as the time scale. For the construction of the life table, we used a one-year age band. In Figure 3.2 (B), however, we used a 10-year age band for illustrative purposes. Individual *II* and individual *IV* together contributed 13.6y (individual *II,* 3.6y and individual *IV,* 10.0y) of exposure time to the age band 28.9y-38.9y. Similarly, individual *II, III* and *IV* contributed a total of 27.1y *(II* 10y, *III* 7.4y and *IV 9.7y).* Individual *IV* experienced CVD at age 48.6y and contributed 0.3y to age group 38.8y-48.9y. The person-years of observation obtained on these participants (in this case 98.8y for being in NO-CVD state and 36.0y for CVD) were the same regardless of whether calendar period or age was used as the time scale.

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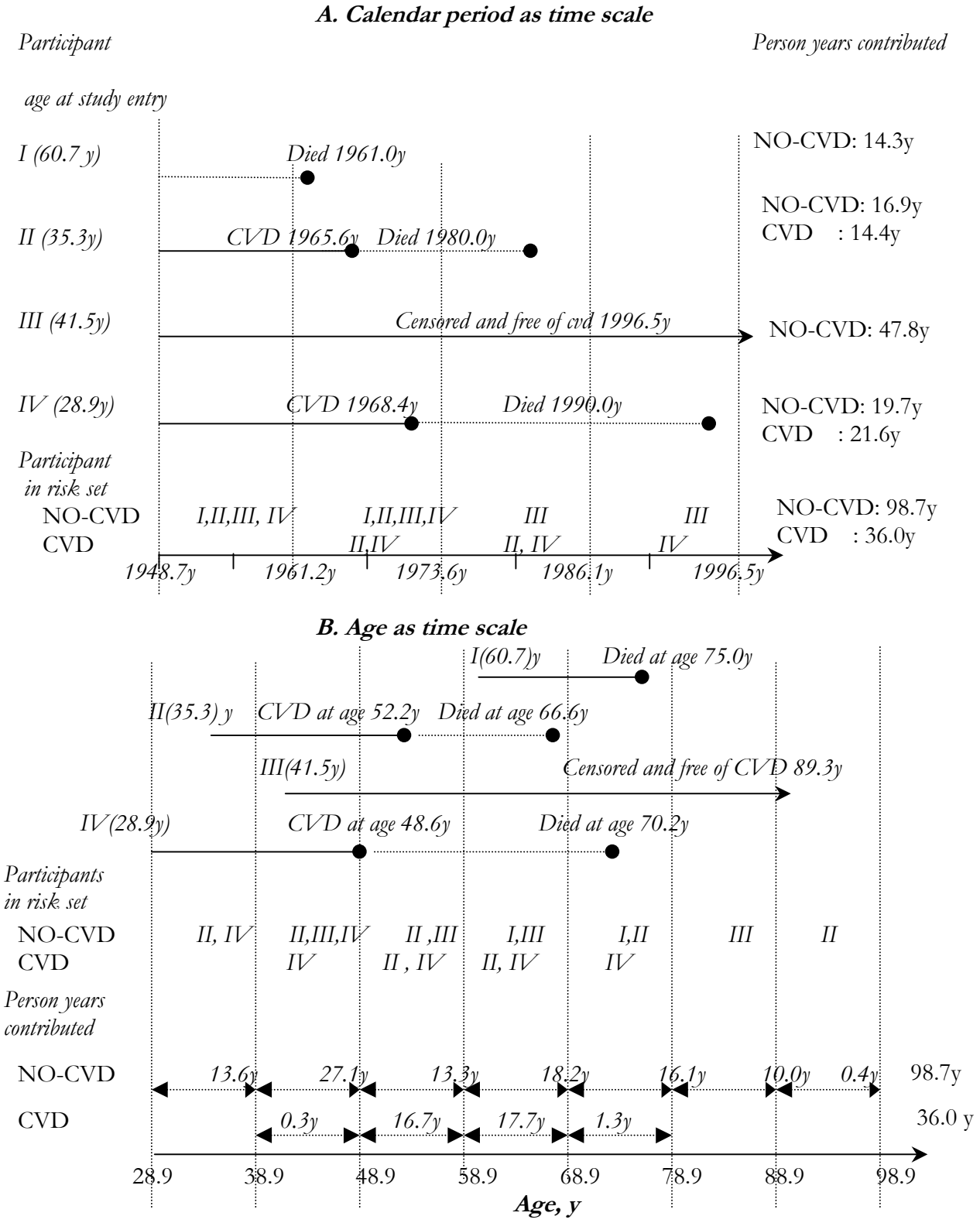
[2] The day, month and year can be calculated from the date in exact years. For instance, 1948.7y can be transferred to day, year and month as follows:
Calendar Year = trunc(1948)=1948
Month =trunc(0.7*12)+1=9
Day = TRUNC((0.7*12+1-TRUNC(0.7*12+1))*30.347)+1=13
i.e. 1948.7y = September 13, 1948 (for details we refer to Mamun, 2001)

Figure 3.2 Estimation of occurrence-exposure based on the observational plan



This age-specific person-years information can be used to blend the aggregate-level occurrence (i.e. event-count) and exposure (person-years) into aggregate contingency tables. In order to clarify the multistate life table calculation using occurrence-exposure rates, the basic algorithms are described here. A 3-state CVD model of the FHS original cohort was chosen as an example, as this was the simplest MSLT among those presented in this chapter. The calculation of observed occurrence-exposure rates using SPSS syntax is presented in Technical Appendix 3.3. The observed occurrences, exposures and occurrence/exposure rates for the basic cardiovascular disease model (Figure 3.1(b)) are presented in Technical Appendix 3.4.

In the FHS, some transitions could occur simultaneously. For example, some persons experienced CVD and death on the same day. We assumed that they had experienced two events at the same time. The first event was then the transition to CVD and the second was death. For the first event, the exposure time ran from entry into observation to the event. For the second event, the exposure time was zero.

How to obtain the input data from the micro data set to actually produce the multistate life table is something that is rarely discussed in the published literature. The basic data matrices contain two types of information: the first is the number of events or transitions from each origin state to the destination state, the second is the exposure time. The advantage of this input data is that it is simple to calculate the MSLT using Excel worksheet.

3.3.4 Multistate life table construction

We constructed a multistate life table that starts at age 40. At age 40, everyone was in the NO-CVD state. As the multistate life tables that we constructed were hierarchical, the life table equations presented here are in simple equations instead of the matrix notation that we described in Chapter 2 of this study. A step-by-step description of the construction of the life table is described in the following.

Transition probabilities

When constructing the MSLT, the first step was to estimate the age-specific transition rates or probabilities from the data. The empirical transition rate was estimated by dividing the number of occurrences by the duration of exposure during the age interval x to x+1. The occurrence-exposure rate from state i to state j was calculated using equation 2.7 in Chapter 2.2. The occurrence-exposure rates were converted to probabilities by assuming that the occurrence-exposure rates remained constant within an age interval (Schoen, 1988a). The total probability of leaving the NO-CVD state ($q_{no\text{-}cvd}$) in a unit interval (one year) was calculated from the death rate ($M_{no\text{-}cvd,d}$) and the transition from NO-CVD to CVD ($M_{no\text{-}cvd,cvd}$) using:

$$q_{no-cvd}[x, x+1) = 1 - \exp\left(-M_{no-cvd,d}[x, x+1) - M_{no-cvd,cvd}[x, x+1)\right)$$

The probability of transit from the NO-CVD state to the CVD state ($q_{no-cvd,cvd}[x,x+1)$) while taking the competing risk into account (Manton and Stallard, 1988) was calculated by:

$$q_{no-cvd,cvd}[x, x+1) = q_{no-cvd}[x, x+1)\left(\frac{M_{no-cvd,cvd}[x, x+1)}{M_{no-cvd,cvd}[x, x+1) + M_{no-cvd,d}[x, x+1)}\right)$$

Similarly, the probability of transit from the NO-CVD state to death ($q_{no-cvd,d}[x,x+1)$ was calculated by:

$$q_{no-cvd,d}[x, x+1) = q_{no-cvd}[x, x+1)\left(\frac{M_{no-cvd,d}[x, x+1)}{M_{no-cvd,cvd}[x, x+1) + M_{no-cvd,d}[x, x+1)}\right)$$

The transition probability to death from CVD was estimated by:

$$q_{cvd,d}[x, x+1) = 1 - \exp(-M_{cvd,d}[x, x+1))$$

Survival probability at exact age x

The total survival probability at age x is denoted by $l(x)$ (see Section 2.4.3). We used radix 1 at age 40. We assumed that at age 40, everybody was free of CVD, therefore, $l_{no-cvd}(40)=1$ and $l_{cvd}(40)=0$. The sum is the total probability of surviving at age 40 i.e. $l(40)=l_{no-cvd}(40)+l_{cvd}(40)=1+0=1$. The probability of surviving in state NO-CVD and CVD at age $x+1$ was calculated by:

$$l_{no-cvd}(x+1)=l_{no-cvd}(x)*[1-q_{no-cvd}[x,x+1)]$$

and $$l_{cvd}(x+1)=l_{cvd}(x)[1- q_{cvd,d}[x,x+1)]+l_{no-cvd}(x)*q_{no-cvd,cvd}[x,x+1)$$

Person years lived or exposure time

The number of person years or duration at risk between the ages of x and $x+1$ in the state NO-CVD or CVD was calculated using equation 2.14 in Chapter 2. Schoen (1988a) discusses the advantages of the exponential approach. However, if a cell frequency is empty (i.e. $l_{cvd}(x)=0$ or successive values of two cells are equal (i.e. $l_{cvd}(x)=l_{cvd}(x+1)$) , application of this method is problematic. In the first case, the denominator remains undefined and in the second case both numerator and denominator become zero. As a result, the person-years value in that age interval remains undefined. Therefore, in that extreme situation, we assume the uniform

distribution of the events and apply the linear formula given in equation 2.13 of Chapter 2.

In our application, $L_{cvd}[40, 41)$ was estimated using linear approximation instead of exponential. Life tables are constructed from age 40 onwards. They were closed at age 90 using the Massachusetts life expectancy at age 90 for 1989-91 (males 3.93 years, females 4.76 years, total population 4.55 years) (Centers for Disease Control and Prevention, 1989-91). We assumed that $M_{no\text{-}cvd}[90+)=M_{\text{cvd}}[90+)=1/e(90+)$. For males, for instance, $e(90+)= 3.93$; $M_{no\text{-}cvd}[90+)=M_{cvd}[90+)=1/3.93=0.25$; $L_{no\text{-}cvd}[90+)=l_{no\text{-}cvd}(90+)/0.25$ and $L_{cvd}[90+)=l_{cvd}(90+)/0.25$. We assumed that mortality rates beyond age 90 were same for CVD and NO-CVD subjects.

Total person years lived

The total number of person years lived in the state NO-CVD and CVD beyond age x was calculated taking the sum of the values of person years lived or exposure time beyond age x. The formula is:

$$T_{no\text{-}cvd}(x)=\sum_{t=40}^{90} L_{no-cvd}(t,t+1) \text{ and } T_{cvd}(x)=\sum_{t=40}^{90} L_{cvd}(t,t+1).$$

Life expectancy

The population-based life expectancy was calculated using the following formula:

$$\text{Free of cardiovascular disease, } e_{no\text{-}cvd}(\text{x})=T_{no\text{-}cvd}(x)/l(x)$$
$$\text{and with cardiovascular disease, } e_{cvd}(x)=T_{cvd}(x)/l(x),$$

where $l(x)=l_{no\text{-}cvd}(\text{x})+l_{cvd}(x)$. This is the average number of years an individual who is alive at age x may expect to stay in a state beyond age x.

In Technical Appendix 3.5, a basic cardiovascular multistate life table for the FHS cohort is given.

3.4 Results

The cardiovascular disease histories are presented in three Sections. In Section 3.5.1, the observed event occurrences in the FHS are given. In Section 3.5.2, the cardiovascular life history of the FHS cohort (males and females combined) is described and in Section 3.5.3, the differences in the cardiovascular disease history of males and females are explored. The last two Sections contain the results of the life table calculation. We have mainly presented the implied prevalence, survival probability, life expectancy free of disease and with disease, and the differences in the years spent with disease.

3.4.1 Observed event occurrences in the FHS

At the onset of the study, the 4998 cardiovascular disease-free Framingham Heart Study members ranged between the ages of 28 and 62; 45 percent were male. Over 48 years of follow-up, 57 percent (64 percent male and 52 percent female) of this cohort developed cardiovascular disease and 77 percent (83 percent male and 72 percent female) died (Table 3.2). Of the original cohort, 37 percent developed coronary heart disease (male 47 percent and female 30 percent), 22 percent suffered an acute myocardial infarction (30 percent male and 16 percent female), 17 percent developed congestive heart failure (18 percent male and 17 percent female) and 16 percent suffered a stroke (15 percent male and 17 percent female). It is a well-established fact that cardiovascular disease mortality and incidence probabilities increase with increasing age, as does mortality from other causes. The quantification of the population burden of different diseases or determination of how this is distributed across age groups is not intuitive. The creation of multistate tables enables analyses to be made of the lifetime probabilities of disease, proportion of survival and expected sojourn times in the various health states.

Table 3.2 Number of outcomes studied in FHS

A Total number of deaths, and number of deaths from cardiovascular disease during period of observation

	All deaths	NO-CVD to death	CVD to death	CHD to death	MI to death	CHF to death	Stroke to death
Males	1847 (83%)	615(28%)	1232(55%)	915(41%)	596(27%)	373(17%)	301(14%)
Females	1982 (72%)	832(30%)	1150(42%)	678(24%)	370(13%)	400(14%)	400(14%)
Total	3829(77%)	1447(29%)	2382 (48%)	1592(32%)	966(19%)	773(15%)	701(14%)

B Transition from NO-CVD to CVD and its subtypes states

	CVD	CHD	MI	CHF	Stroke
Male	1415(64%)	1036(47%)	672 (30%)	402(18%)	334(15%)
Female	1428(52%)	838(30%)	439(16%)	469(17%)	465(17%)
Total	2843 (57%)	1874(37%)	1111(22%)	871(17%)	799(16%)

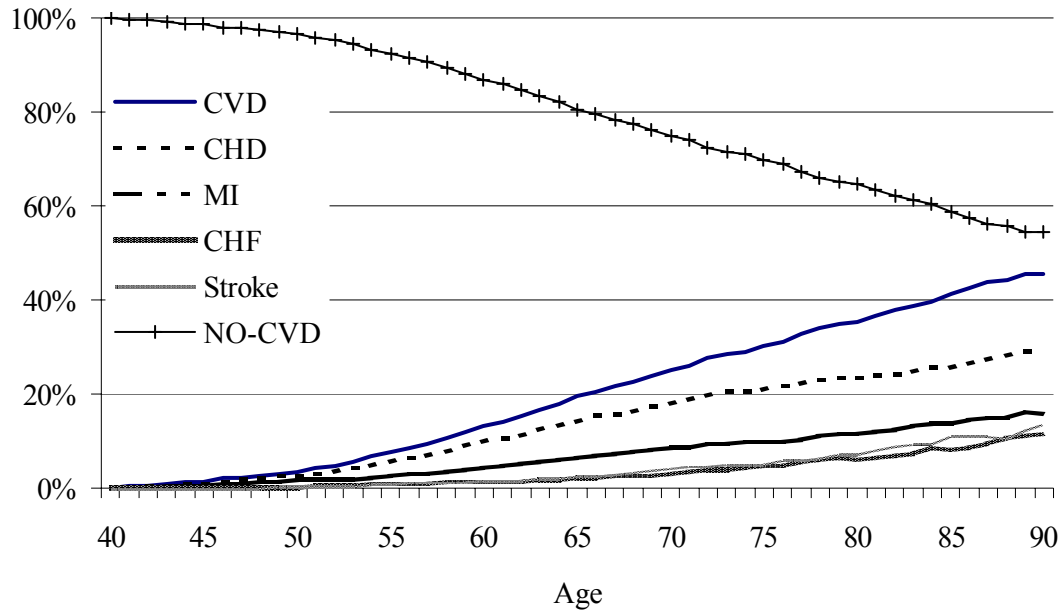
3.4.2 Males and females combined

Implied prevalence

The implied prevalence (IP) or state probability of the synthetic cohort in terms of life table notation was defined in equation (2.21) in Chapter 2. The implied prevalence at different ages reveals how different states evolve over the life course. They relate to the synthetic biography generated by the multistate life table. The prevalence of the life table population in each of the disease states is shown in Figure 3.3. This simple measure has intuitive appeal. The proportion of respondents in various states at each exact age illustrates how survivors who are not in the disease state (i.e. NO-CVD) at exact age 40 in the original cohort of FHS would be distributed over the state space at successive one-year intervals.

The proportion of the life table survivors in the disease states increases regularly with age, while the proportion with NO-CVD decreases sharply after middle age, either by death or by making the transition to CVD. Some 54 percent of the 90 year-old life table survivors were found to have experienced cardiovascular disease, more than half of which was coronary heart disease, the rest being other cardiovascular disease. Figure 3.3 illustrates the steady progression from NO-CVD to CVD.

Figure 3.3 Implied prevalence of disease in the life table population



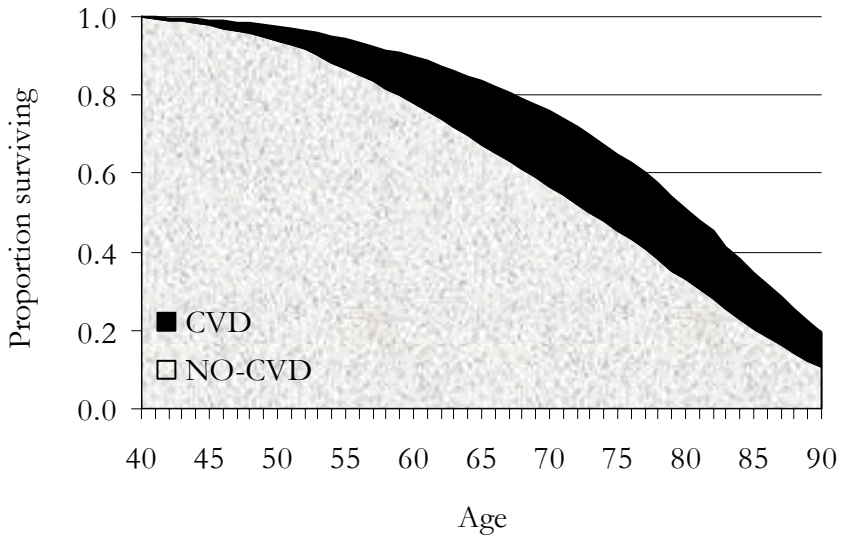
Survival probability

The survival probability of a cohort of cardiovascular disease-free 40 year-old persons is demonstrated in Figure 3.4. The light area represents the proportion of a cohort that is alive at x and free of cardiovascular disease and dark area represents the proportion that has a history of cardiovascular disease (Figure 3.4(a)). Cardiovascular disease states are differentiated in Figure 3.4(b) (using Figure 3.1(c)), into history of coronary heart disease (dark area) and other cardiovascular disease (patterned area). Similarly, three other figures (Figures 3.4(c), 3.4(d), 3.4(e)) demonstrate the proportion of the cohort surviving with myocardial infarction, congestive heart failure and stroke.

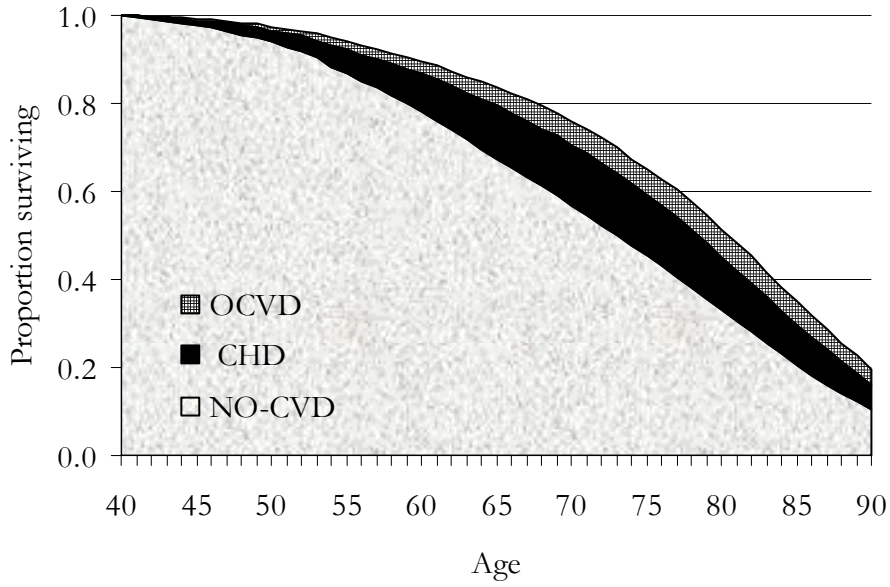
These survival curves indicate survival with and without cardiovascular disease and its different subtypes, given that the cohort population was free of cardiovascular disease at age 40. As expected, the survival of both the NO-CVD and CVD life table proportion decreases as age increases. For instance, of the people free of CVD at age 40, nearly 50 percent will survive until age 80, and at age 80, one third will have cardiovascular disease.

Figure 3.4 Survival of a cohort of cardiovascular disease-free 40-year-old population

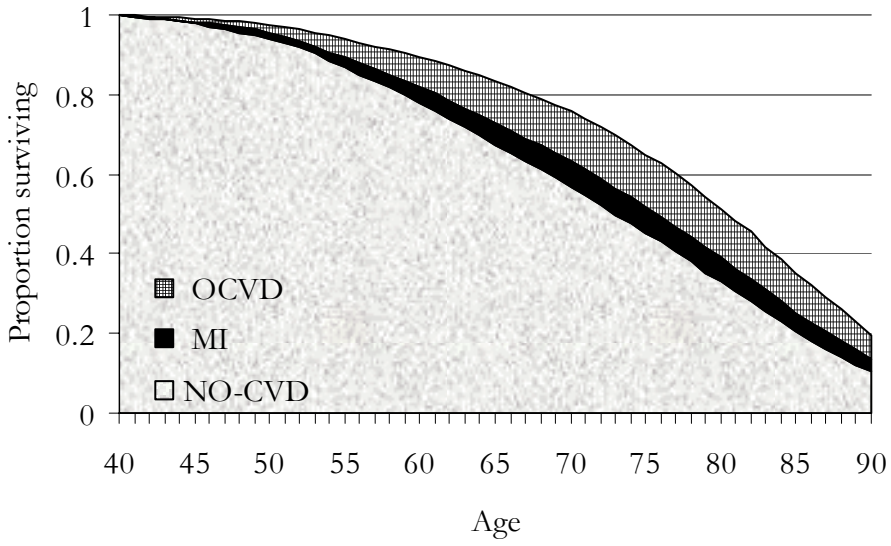
(a) CVD



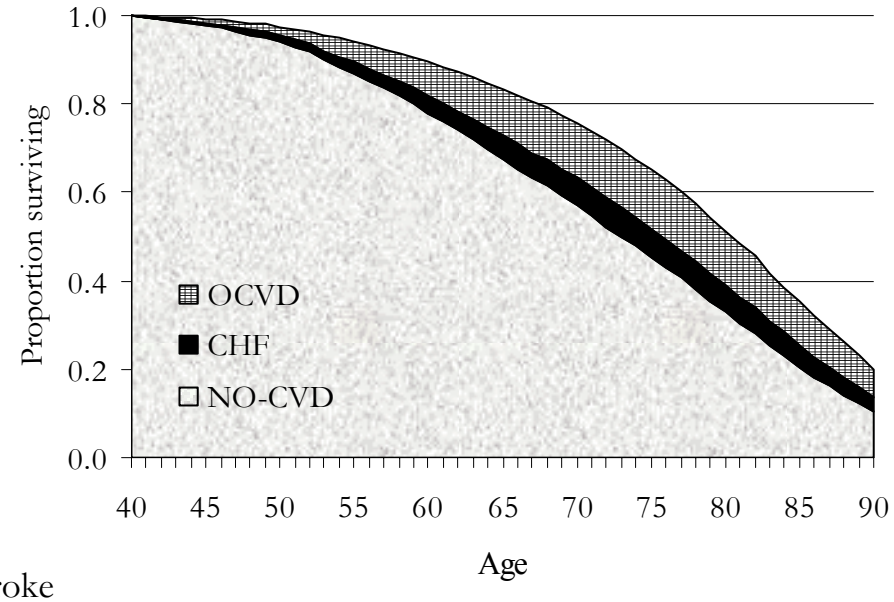
(b) CHD


1.0
0.8
0.6
0.4
0.2
0.0
Proportion surviving
OCVD
CHD
NO-CVD
40
45
50
55
60
65
70
75
80
85
90
Age

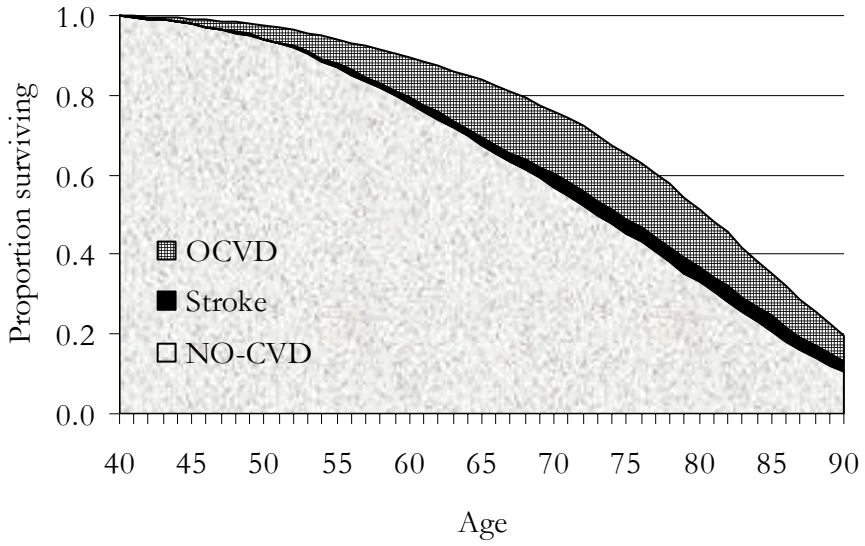
(c) MI


1
0.8
0.6
0.4
0.2
0
Proportion surviving
OCVD
MI
NO-CVD
40
45
50
55
60
65
70
75
80
85
90
Age

(d) CHF



(e) Stroke



Life expectancy

The added value of the multi-state life table lies in its ability to synthesize the consequences of age-specific incidence rates and to calculate life expectancies in specific disease states. This is achieved by adding up the measure of years lived without a history of disease and with a history of disease, indicating more accurately the potential public health burden of the disease. Total life expectancy (LE) and residual life expectancy free of disease from specified ages, based on a population free of cardiovascular disease at age 40 is presented in Table 3.3. The number in parentheses represents the proportion of time spent without the relevant

cardiovascular disease subtype. Total life expectancy at the age of 40 was 38.5 years, which is consistent with a relatively healthy population (Table 3.3) (Leaverton, 1987). At age 50, a participant of FHS cohort can expect to survive 29.32 additional years, of which 23.11 (79 percent) free of cardiovascular disease and the residual 6.21 (21 percent) years with cardiovascular disease. Of the residual life expectancy at age 50, 4.27 (15 percent) years are spent with coronary heart disease. Less time is spent with MI (7 percent), congestive heart failure (3 percent) and stroke (4 percent). Although it is possible for individuals to be in more than one disease state at any point in time, we have not specifically modelled this co-morbidity.

Table 3.3 Life expectancy and residual life expectancy free of disease at specified ages, based on a population free of cardiovascular disease at age 40, FHS

Age	Total LE	Life expectancy (proportion in %) free of a history of:				
		Cardiovascular disease	Coronary heart disease	Acute myocardial infraction	Congestive heart failure	Stroke
40	38.48	32.27(84)	34.20(89)	36.43(95)	37.61(98)	37.40(97)
50	29.32	23.11(79)	25.05(85)	27.43(93)	28.44(97)	28.22(96)
60	21.40	15.45(72)	17.34(81)	19.49(91)	20.50(96)	20.29(95)
70	14.30	9.35(65)	11.02(77)	12.75(89)	13.43(94)	13.25(93)
80	8.57	5.03(59)	6.34(74)	7.46(87)	7.84(91)	7.69(90)

3.4.3 Male-female differences

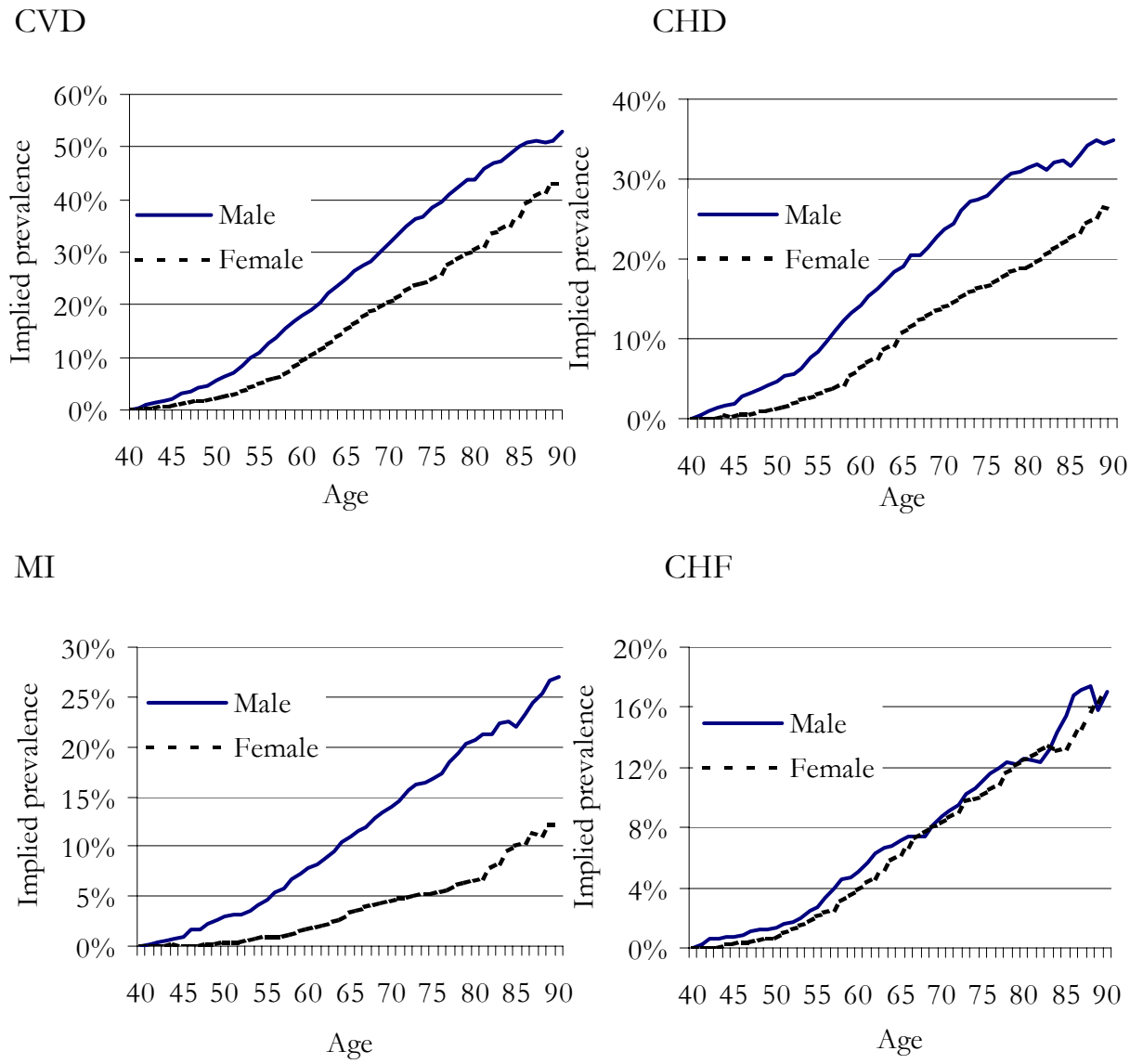
The number of transitions for all the examined cardiovascular events is consistently higher in males than in females (Table 3.2) but the greater longevity of females means that the burden of disease can be higher for females. In this section, therefore, the emphasis is on comparing the burden of cardiovascular disease between males and females in respect of the implied prevalence, life expectancy (in proportion of time), lifetime probability and number of years lived with a history of cardiovascular disease and its subtypes.

Implied prevalence

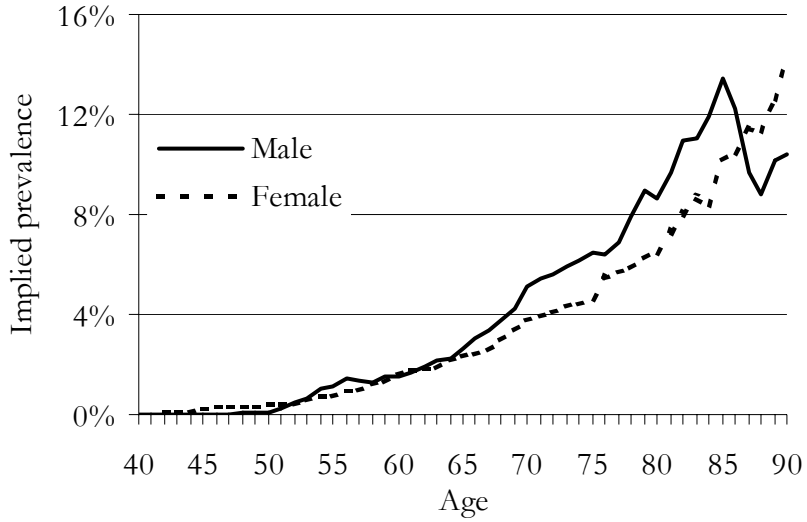
The life table prevalence of cardiovascular disease and its subtypes by sex are presented in Figure 3.5. Males have a higher prevalence of cardiovascular disease than females at all ages. This difference is even higher for coronary heart disease. At age 75, the prevalence of CVD is around 10 percentage points higher for males compared to females (30% vs. 20%). It is nearly 20 percent higher for coronary heart disease. The main reason for this very considerable difference is that males

experience more myocardial infarctions than females. For the other subtypes of cardiovascular disease, the difference in implied prevalence is smaller.

Figure 3.5 Implied prevalence of a history of cardiovascular disease by sex



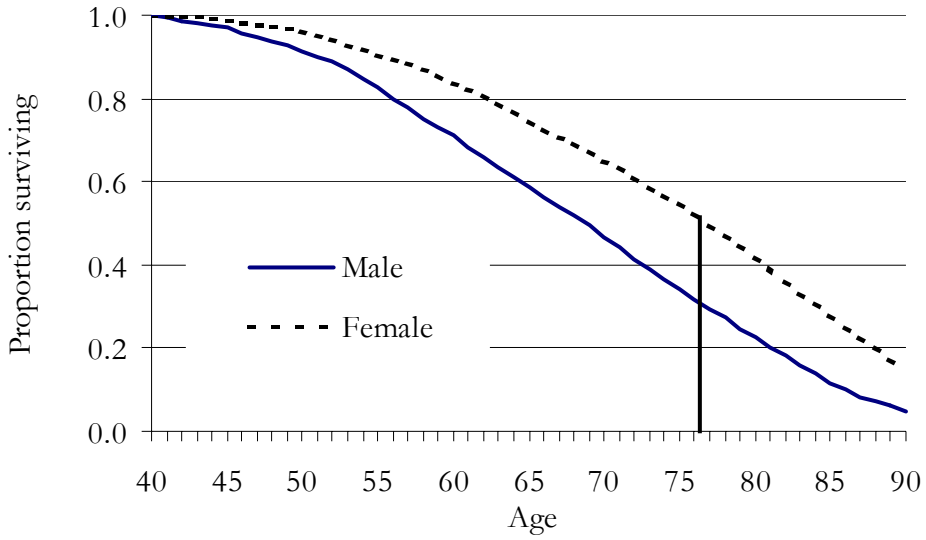
Stroke



Cohort survival

Male and female survival (in percentages) of the life table cohort free of cardiovascular disease is presented in Figure 3.6. Over time, females not only survive longer but also survive longer free of cardiovascular disease compared to males (Figure 3.6). The differences in male-female survival start immediately after age 40 (nearly at age 42) and reach 21 percent (maximum) at age 78. At age 90, the difference is still around 11 percent.

Figure 3.6 Survival probabilities free of cardiovascular disease by sex

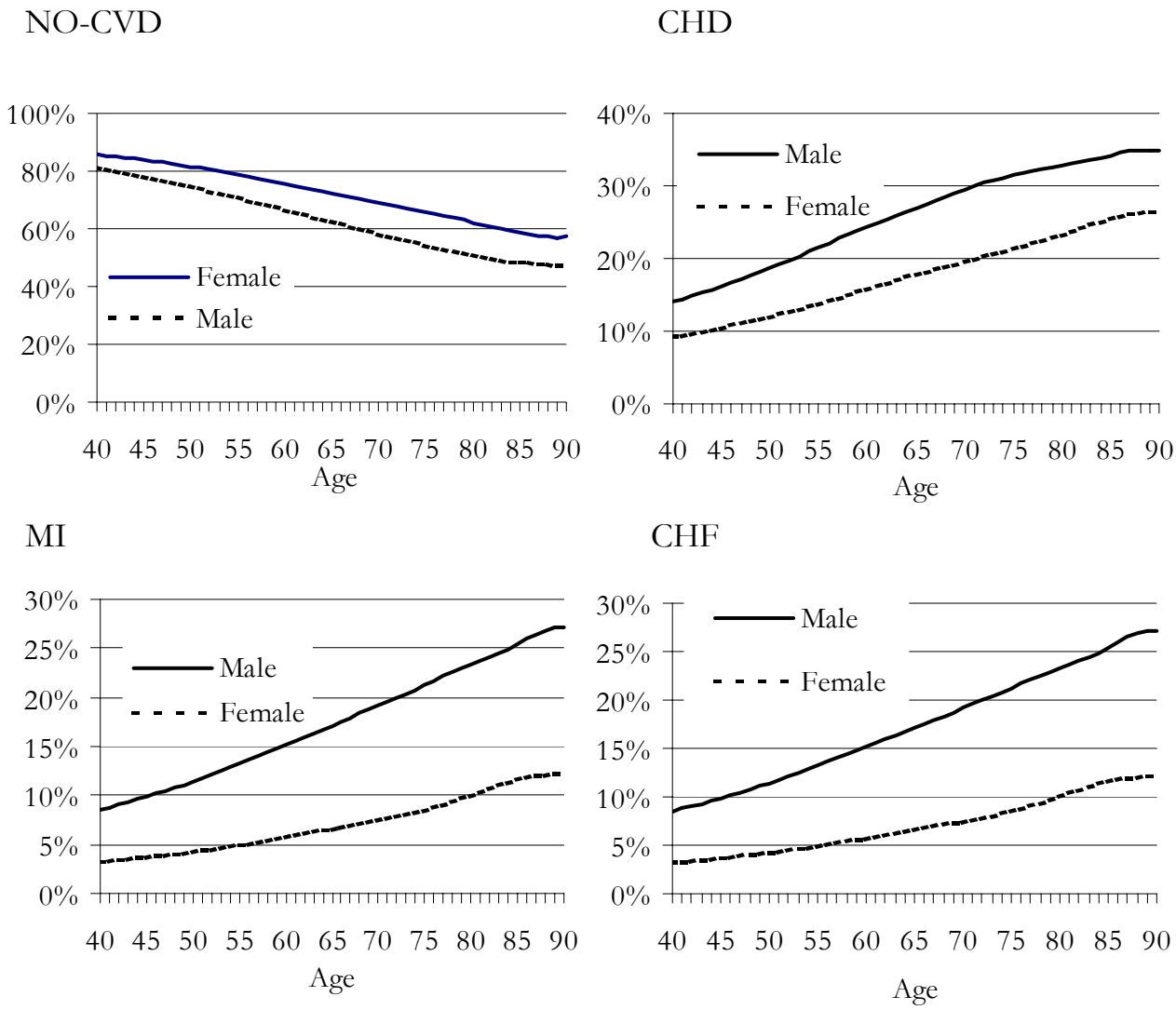


Life expectancy

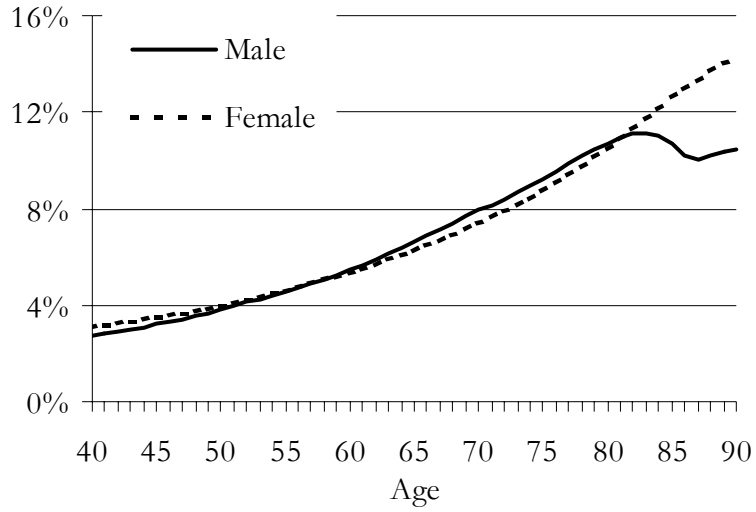
The multistate life table estimates the expected number of years lived in a different state. We have presented the life expectancy in a state by sex (Figure 3.7). The results are presented in terms of the life table percent of lifetime spent in a

particular state. At age 40, a male can expect to survive 81 percent of his remaining life free of cardiovascular disease and a female of that age can expect 86 percent. At age 70, a man can expect 13 percent less years free of cardiovascular disease life expectancy than a female. Throughout life, females can expect to remain free of cardiovascular disease longer than males. Male-female differences are also substantially higher for coronary heart disease and myocardial infarction. Males and females can expect nearly an equal percentage of lifetime in the disease states of congestive heart failure or stroke.

Figure 3.7 Life table percentage of lifetime spent in a state by sex



Stroke



Lifetime probability of disease

The life table offers a simple method for the calculation of lifetime risks, automatically accounting for competing causes of morbidity and mortality. The lifetime risk of developing cardiovascular-disease is presented in Table 3.4. For the synthetic cohort derived from transition rates within the Framingham Cohort, the lifetime probability, at age 40, of developing any cardiovascular disease, including sudden cardiovascular death, is 67 percent for males and 55 percent for females (60 percent for the total population). For a 40 year old male and female without cardiovascular disease, the lifetime probability of developing coronary heart disease is 50 percent and 33 percent respectively, while the probability of an acute myocardial infarction is 33 percent and 17 percent, respectively. The lifetime probability of developing congestive heart failure for NO-CVD men and women at age 40 is 20 percent vs. 18 percent. One in five NO-CVD 40 year-old women and one in six NO-CVD 40 year-old men will suffer a stroke at some point in time. The higher lifetime probabilities of stroke in females are largely caused by the greater female life expectancy. The probabilities at age 40 of developing coronary heart disease, stroke or congestive heart failure before the age of 70 are all greater in males than females (32% vs. 16%, 6% vs. 5%, or 8% vs. 5%, respectively).

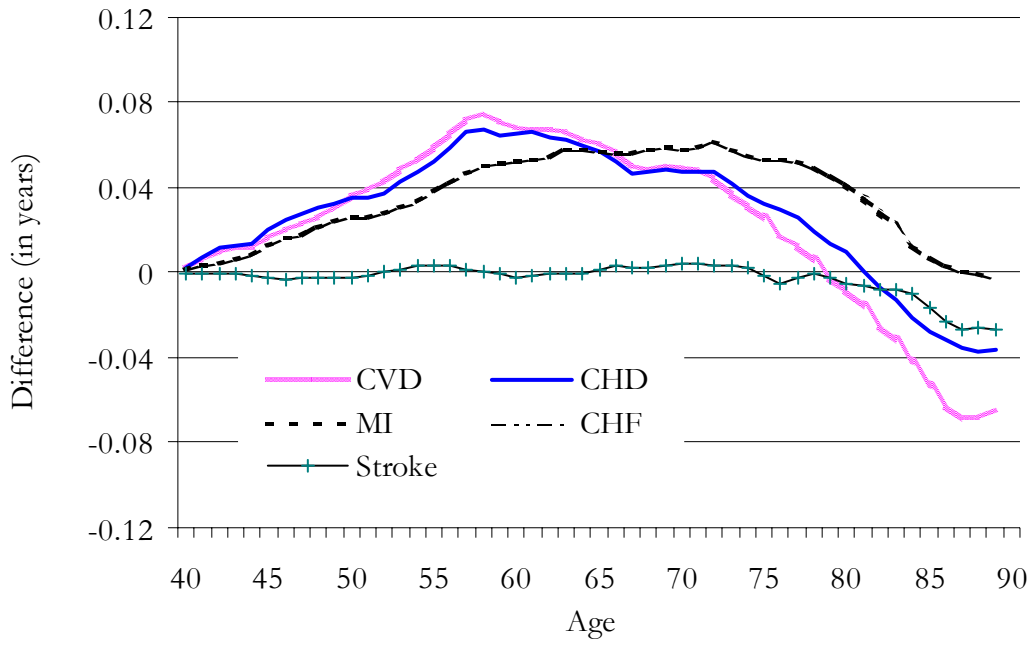
Table 3.4 Lifetime risk of developing cardiovascular disease (%) for cardiovascular disease-free individuals at age 40

		Probability of developing disease before age			
		Within lifetime	60	70	80
CVD	Male	67	23	42	58
	Female	55	11	25	40
	Total	*60*	*17*	*33*	*48*
CHD	Male	50	18	32	44
	Female	33	7	16	25
	Total	*40*	*12*	*23*	*33*
MI	Male	33	10	20	29
	Female	17	2	6	11
	Total	*24*	*6*	*12*	*19*
CHF	Male	20	3	8	14
	Female	18	2	5	10
	Total	*19*	*2*	*6*	*12*
Stroke	Male	16	2	6	12
	Female	19	2	5	11
	Total	*17*	*2*	*6*	*11*

Differences of the years spent with disease

Not only do women survive longer, they can expect to spend more time free of cardiovascular disease. They moreover have less lifetime risk of developing cardiovascular disease. However, the burden of the disease could be higher as they survive longer, with or without disease. The male-female differences in number of person years lived in a disease state are presented in Figure 3.8. Before age 80, male exposure time to cardiovascular disease is higher compared to that of the female, which is substantially higher in the age interval between 50 and 75. At older ages (usually after age 80) females spend more time with cardiovascular disease compared to males. Throughout most of life, the differences in the number of person years lived with myocardial infraction is higher for males compared to females. Although male-female differences for the other cardiovascular subtypes (stroke and congestive heart failure) are negligible before age 80, they are higher for females thereafter.

Figure 3.8 Male-female differences in the person years lived in each disease state in the age interval x to x+1



3.5 Discussion and conclusion

In this chapter, we presented an analysis of the life history of cardiovascular disease of a white American population: the Framingham Heart Study Original Cohort. The published literature rarely discusses how to obtain the input data from micro data needed to produce a multistate life table. This study has demonstrated how the basic input data, i.e. occurrence-exposure rates, can be obtained. The enormous impact of cardiovascular disease on the human life course is translated into life years lost to disease and life years lived with a history of disease. We distinguish the life expectancy with and without cardiovascular disease, lifetime risk of developing the disease and the difference between males and females in number of years lived in a disease state.

From the age of 40, nearly two-thirds of the men (67 percent) and more than half (55 percent) of the women were shown to develop cardiovascular disease within their lifetime. Lloyd-Jones (1999) reported that one in two men and one in three women would develop coronary heart disease from the age of 40, which is consistent with our study (males 50 percent and females 33 percent). In addition, one out of six men and one out of five women will at some point suffer a stroke. One in three men and one in six women will suffer an acute myocardial infarction at some time. We have shown that the greater longevity of women is the primary

cause of both their greater lifetime probability of stroke and the greater number of years of life lost for an equivalent disease, as compared to men.

Cardiovascular disease not only reduces life expectancy but is also a major cause of morbidity. Its potential contribution to population morbidity is highlighted, with 21 percent of this synthetic cohort's residual life expectancy from the age of 50 spent with the cardiovascular disease. These results exhibit the utility of transforming epidemiological data into time-based health policy measures. While epidemiological data enables of the number of coronary heart disease events and deaths to be predicted, the multistate life table technique enables estimation of the overall potential burden of specific diseases in terms of years of life lost to and lived with disease. This collective effect of differences in disease incidence and mortality probabilities cannot be intuitively estimated but is important for health care development.

Previous analyses have reported the burden of cardiovascular disease to be a loss of approximately 15,300 years of life and approximately 3,000 years lived with disability in countries such as the USA and Western Europe (Murray and Lopez, 1996). However, more detailed analyses have hitherto not been available. The advantages of the present analysis are the range of cardiovascular disease sub-types; long time follow-up and age groups examined the accuracy of disease definitions and the internal consistency of the various transition rates within the Framingham Heart Study.

One of the model's strengths is that it symbolizes the relationships within a single, homogeneous historical cohort. However, one of its major limitations is also derived from this property. Because of the long follow-up and the broad age range at inception of the cohort, the forces of mortality and disease incidence by age are a mixture of cohort and period effects. At younger ages, the cohorts are exposed to the higher mortality of the older periods; at older ages, the cohorts are exposed to the lower mortality of more recent periods. As a result, transition rates for the intermediate ages are derived from a number of different periods. In addition, coronary heart disease case-fatality and incidence rates changed significantly during this period in the USA (Rosamond et al., 1998; McGovern et al., 1996; Sytowski, 1990). Because of the advancement of medical technology and diet intake, the population is surviving longer with cardiovascular disease; as a result, we expect the life expectancies with cardiovascular disease presented here to be less than those for current low mortality populations. An analysis of life tables constructed solely using the period between approximately 1970-1990 indicated that total life expectancy and life expectancy with cardiovascular disease at the age of 50 were 1.0 and 0.07 years higher than those presented here (Peeters et al, 2002). Therefore, our results suggest that the total and sex specific life expectancies by total cardiovascular disease and its subtypes presented here are an approximation of those experienced by a similar population today.

Another limitation is that the current model structure is primarily of use for descriptive rather than interventional analyses. Here, a unidirectional transition is used as the simplest way to confine all time spent with a history of cardiovascular disease without the creation of further mixed disease states. Addition of back-flow to the model would require age and sex specific transitions from all disease states. Our data does not permit any back flow from a disease state to NO-CVD state (i.e. CVD to NO-CVD). But some repeated transitions from one disease-state to another are possible. For instance, in model 3(c) the OCVD and CHD could be communicable states. However, when the required disease state is the end state, the results from that model would not be influenced by the reverse transitions. For instance, in model 3(c), we were interested in estimating life table parameters for CVD or CHD or CHF or MI or Stroke but not for the OCVD state. Some of the models are structured in Technical Appendix 3.2, which includes many transitions that are possible theoretically. We could not apply them since the life table method requires more power (sample size) than was available from the original Framingham cohort. While this structure is appropriate for the descriptive analyses presented here, a more biological pathway would be preferred (for example allowing transitions from coronary heart disease to congestive heart failure transitions or remission from angina pectoris) for any interventional analyses. While we have demonstrated different model structures of cardiovascular disease process in Technical Appendix 3.2, we applied a more consistent model 3(b) in the rest of the study (Chapter 6, Chapter 7 and Chapter 9).

Entering the 21st century, one of the most important dilemmas both developed and developing societies will face is how to maximize the health of the elderly. In this regard, cardiovascular disease intervention is one of the major targets for improving population health. Chronic diseases are long-term illnesses that are rarely cured. These diseases can become a significant health and financial burden to not only those persons who have them, but also their families and the nation's health care system. Chronic conditions such as heart disease, diabetes and arthritis negatively affect the quality of life, contributing to declines in functioning and an inability to remain in the community. The method and resultse presented here is a simple and transparent one to enable meaningful conclusions about the potential burden of cardiovascular disease life history on both the total population and on the male-female population separately.

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Technical Appendix 3.1

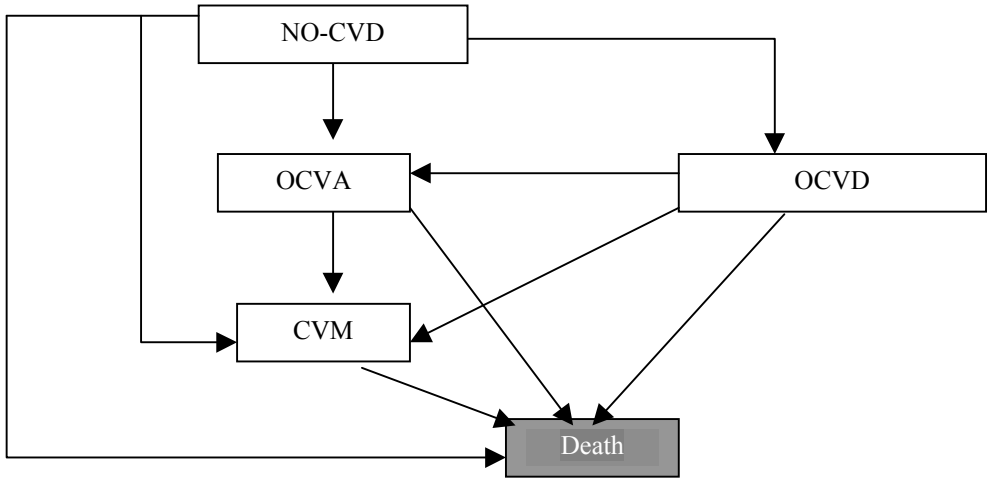
Glossary

AP: Angina Pectoris.
MI: Acute Myocardial Infarction. Acute manifestation of CHD: acute blocking of heart vessel, leading to death of the muscle dependent from that vessel. May be silent, and pass unnoticed, but will then cause typical ECG changes. Called **MI** in the FHS data-files.
CHD: Coronary Heart Disease. Identical to **IHD** (Ischaemic Heart Disease). Atherosclerotic disease of the vessel walls of the heart, which leads to chronic manifestations of ischaemia: Angina Pectoris (AP) or ECG manifestations, and acute manifestations: Acute Myocardial Infarction, (MI) or unstable angina pectoris (called Coronary Insufficiency, CI, in FHS).
CHF: Congestive Heart Failure. Failure of the heart muscle to deliver sufficient power to pump blood, and deliver all the needed oxygen. May or may not be a consequence of CHD. Is not yet estimated as part of the FHS-CHD model.
CI: Coronary Insufficiency. Outside Framingham a forgotten diagnosis. Seems equivalent to unstable angina pectoris and epimural infarctions. Is classified as an acute event by FHS.
CVA: Cerebrovascular accidents. The equivalent of CHD in the brain (although there are several types of stroke: thrombotic blocking due to a thrombus or an embolism (see further), or acute bleeding through rupture. Leads to acute brain infarctions (ABI, atherothrombotic BI), paralysis or death. To avoid misunderstanding with cardiovascular disease, I consistently use 'stroke'. It is one of the main causes of disability in human populations. One or more strokes may also cause dementia.
CVD: All cardiovascular diseases. Include in this dataset CHD, Congestive Heart Failure (CHF), Stroke (in the dataset called CVA, cerebrovascular accidents), PAD (Peripheral Arterial Disease, in the dataset called Intermittent Claudication, IC).
HA: Heart Attacks. Includes MI, CI, death from CHD. Unclear what happens to sudden cardiac death which is not CHD.
Ischaemia: Lack of sufficient oxygen in the (muscle) tissues. Causes pain and/or ECG changes.
PAD: Peripheral arterial disease. The equivalent of CHD and Stroke in the legs (or potentially all body-parts). Called **IC** in FHS: intermittent claudication, which is the equivalent of angina pectoris: ischaemic pains by use of the muscles. This is a relatively rarer cause of death. If it causes death, it is through rupture of the aorta (the main body artery). Blood clots, formed on the damaged vessel walls, may travel through the arteries and cause acute blockings in the brain (causing a stroke)
Stroke: See CVA. Acute blocking of brain vessels, with often irreversible disabling consequences.
TIA: Transient Ischaemic Attack. Equivalent of unstable angina pectoris in the brain. 'Small' stroke, leading to temporary (< 24 hours) but not definitive disability.

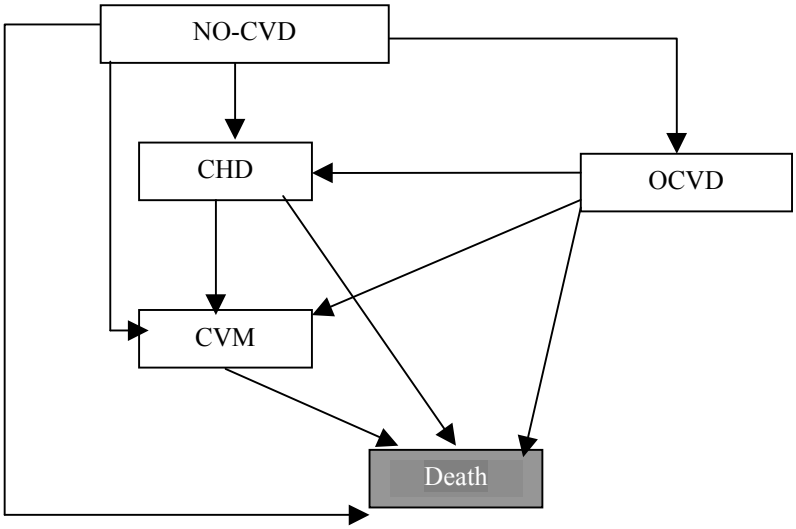
Technical Appendix 3.2

Multistate model of cardiovascular disease

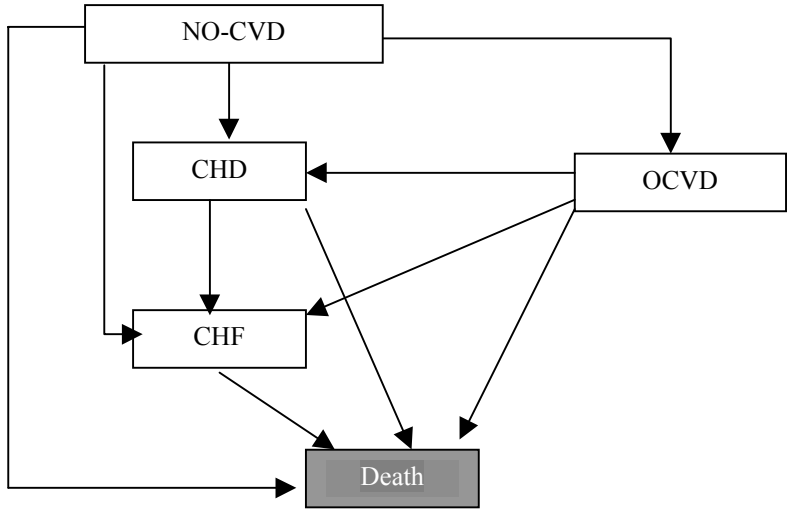
A. NO-CVD (i.e. without other states in model) to OCVD (to) OCVA (to) CVM (hard stroke; ABI, embolism, haemorrhage and other CVA) to death. OCVD is first CVD events other than CVA. OCVA is first CVA events other than CVM (i.e. TIA)



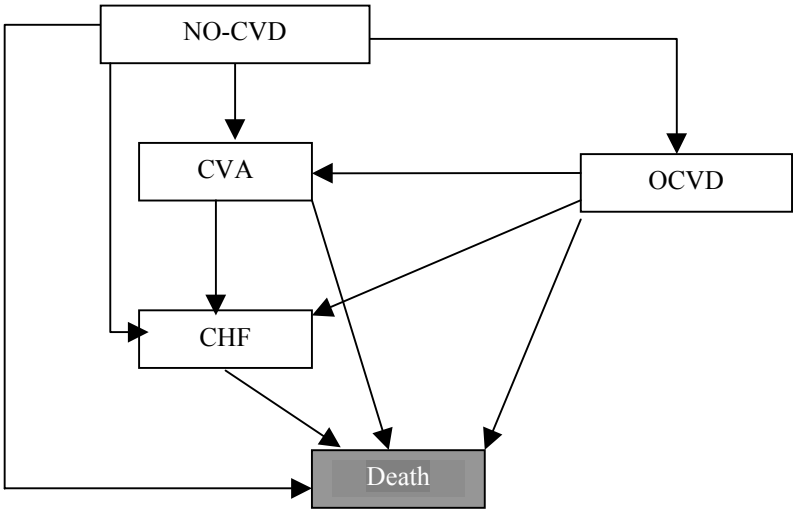
B. NO-CVD (i.e. without other states in model) to OCVD (to) CHD (to) CVM to death
(could replace CHD with MI for direct effects of changes in MI)



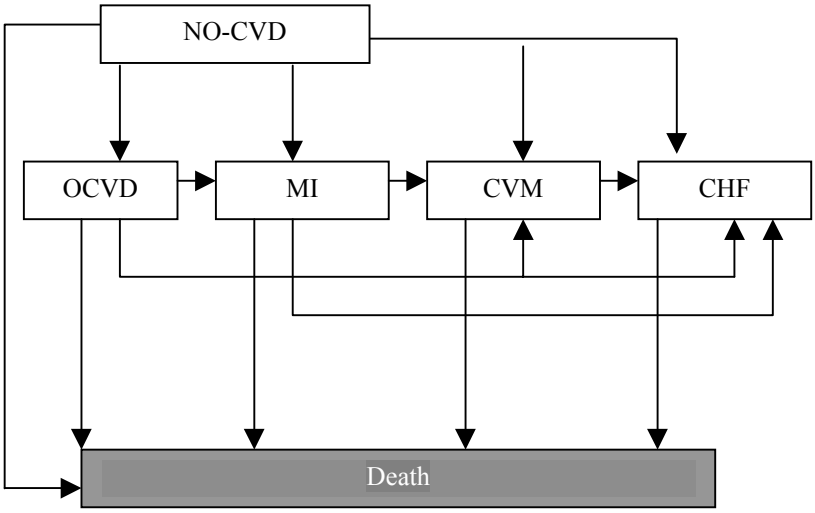
C. NO-CVD (i.e. without other states in model) to OCVD (to) CHD (to) CHF to death
(could replace CHD with MI for direct effects of changes in MI)



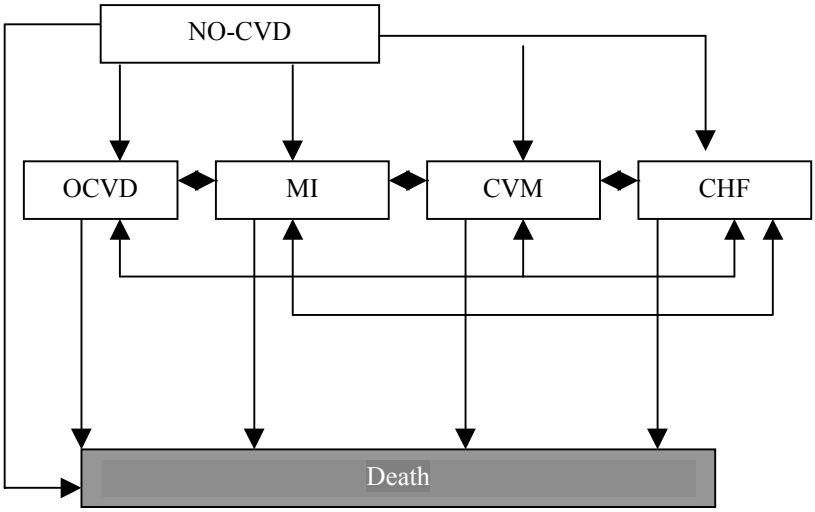
D. NO-CVD (i.e. without other states in model) to OCVD (to) CVA (to) CHF to death
(could replace CVA with CVM for direct effects of changes in stroke)



E. NO-CVD (i.e. without other states in model) to OCVD (to) MI (to) CVM (to) CHF to death



F. NO-CVD (i.e. without other states in model) to OCVD (to) MI (to) CVM (to) CHF to death, incorporating back-flow



Technical Appendix 3.3

SPSS-syntax: estimation of occurrence-exposure

```
Get file ='C:\a\b.sav'. /* open the individual level data file with list of following variables

Variable labels      Pid            'Cohort general exam data random ID'
                     /Ybirth    'Exact year of birth relative to 1900'
                     /Ycvd        'Exact year of CVD relative to 1900'
                     /Ydth        'Exact year of death relative to 1900'
                     /Sex         '1=Male & 2=Female'
                     /Lost        'Lost of follow-up'
                   /Age1      'Completed age in years at exam1'
                     /Eage      'Exact age in years at exam1'
                     /Endstudy 'Exact year of ending study time relative to 1900' .
```

***Event counts: occurrences**

```
Compute Hcvd=trunc(ycvd-ybirth). /* Age at transition from no-cvd to cvd
If (missing(Ycvd)) Hd=trunc(ydth-ybirth)./* age at transition forn no-cvd to death
If (Ycvd>0) Cvdd=trunc(ydth-ybirth). /* age at transition from cvd to death

*Age-specific   occurrences  in tabular form

Tables
  /Format zeros missing('.')  /Tables(labels)
   BY sex>( Hcvd + Hd + Cvdd)
  /Statistics count ((f5.0) 'Count' ) . /* Number of occurrences is counted separately for males and females
```

***Exposure time: no-cvd to cvd or death**

```
If (ycvd>0) Agecvdfr=(ycvd-ybirth).  /* Exact age of transition from h to cvd
If (missing(ycvd)) Agecvdfr=min((ydth-ybirth),(endstudy-ybirth)). /* Exact time to death or censored  (without
experiencing CVD)
Compute Agecvd=trunc(agecvdfr). /* Transition from h to cvd at completed age

If (age1=agecvd) Tcvdage1=agecvdfr-eage. /* Fraction of time contributed to exam1
If (not(age1=agecvd)) Tcvdage1=age1+1-eage./* Fraction of time contributed to exam1
If(age1=agecvd) Tcvdagef=agecvdfr-eage. /*Fraction of time contributed to last age
If (not(age1=agecvd)) Tcvdagef=agecvdfr-agecvd. /* Fraction of time contributed to last age

If (age1=28) Tcvd0=tcvdage1.

Vector Tcvd(74). /* Total number of age groups by one-year age band

Loop Cvdring=1 to 74.
        If  (age1=(cvdring+28)) Tcvd(cvdring)=tcvdage1.
        If  (age1<(cvdring+28) and agecvd>(cvdring+28)) Tcvd (cvdring)=1.
        If  (agecvd=(cvdring+28)) Tcvd (cvdring)=tcvdagef.
End loop.
```

*** Aggregate outfile for h-cvd or h-d transition**

```
Aggregate outlife='C:\FHS_2002_24exam\chap3_h_cvd_d.sav' /break=sex /sumt28 to sumt102=sum(tcvd0 to
tcvd74).
```

*Aggregate outfile command combines groups of cases into single summary cases and creates a new aggregated data file. Cases are aggregated based on the value of one or more grouping variables. Cases are grouped together based on the values of the break variables.

***Exposure time cvd to death**

```
If (ycvd>0) Cvddfr=min((ydth-ybirth), (endstudy-ybirth)).  /* Exact age of transition from Cvd to death or censored
Compute Cvdd=trunc(cvddfr). /*Cvd to death or censored at completed age

If  (agecvd=cvdd) Tcvdd1=cvddfr-agecvdfr. /* Fraction of time contributed to agecvd
If  (not(agecvd=cvdd)) Tcvdd1=agecvd+1-agecvdfr. /* Fraction of time contributed to agecvd
If (agecvd=cvdd) Tcvddf=cvddfr-agecvdfr. /*Fraction of time contributed to last age
If (not(agecvd=cvdd)) Tcvddf=cvddfr-cvdd. /*Fraction of time contributed to last age

If (agecvd=28) Ttcvdd0=tcvdd1.

Vector Ttcvdd(74). /* total number of age groups by one year age band

Loop cddring=1 to 74.
      If (agecvd=(cddring+28)) Ttcvdd(cddring)=tcvdd1.
      If (agecvd<(cddring+28) and cvdd>(cddring+28)) Ttcvdd(cddring)=1.
      If (cvdd=(cddring+28)) Ttcvdd(cddring)=tcvddf.
End Loop.

Aggregate outlife='C:\FHS_2002_24exam\chap3_cvd_d.sav'/break=sex /sumt28 to sumt102 =sum(ttcvdd0 to
ttcvdd74).
```

Get file ='C:\FHS_2002_24exam\chap3_cvd_d.sav'.

Transfer the occurrences (from SPSS output) and exposures (getting file 'C:\a\chap3_h_cvd_d.sav' and 'C:\a\chap3_cvd_d.sav') tables
into (say) Excel work sheet. The occurrence and exposure rates are estimated for different age intervals with the number of people who experienced an event in a given age interval as the numerator and the total person-years (i.e. risk period) of observations of at-risk participants in that interval as the denominator.

Technical Appendix 3.4

Occurrences, exposures and occurrence-exposure rates matrices: 3-state cardiovascular disease model (males and females combined)

	Occurences			Exposure			Occurrence/exposure rates		
Age	No-CVD to CVD	No-CVD to D	CVD toD	No-CVD to CVD	No-CVD to D	CVD toD	No-CVD to CVD	No-CVD to D	CVD toD
40	5	2	1	1904.34	1904.34	11.81	0.003	0.001	0.085
41	6	5	0	2062.18	2062.18	16.60	0.003	0.002	0.000
42	5	2	2	2240.53	2240.53	20.59	0.002	0.001	0.097
43	11	2	3	2414.95	2414.95	26.09	0.005	0.001	0.115
44	9	3	3	2585.30	2585.30	35.15	0.003	0.001	0.085
45	18	3	2	2752.77	2752.77	44.10	0.007	0.001	0.045
46	11	6	2	2896.17	2896.17	57.34	0.004	0.002	0.035
47	21	5	7	3023.57	3023.57	70.39	0.007	0.002	0.099
48	15	4	5	3148.42	3148.42	81.15	0.005	0.001	0.062
49	24	16	5	3269.89	3269.89	94.00	0.007	0.005	0.053
50	29	10	6	3384.12	3384.12	115.27	0.009	0.003	0.052
51	27	10	7	3507.58	3507.58	137.88	0.008	0.003	0.051
52	41	24	9	3607.63	3607.63	167.00	0.011	0.007	0.054
53	60	16	16	3678.32	3678.32	202.39	0.016	0.004	0.079
54	45	16	14	3756.65	3756.65	237.69	0.012	0.004	0.059
55	61	20	20	3823.10	3823.10	275.36	0.016	0.005	0.073
56	56	15	24	3876.44	3876.44	313.90	0.014	0.004	0.076
57	67	19	17	3933.52	3933.52	352.96	0.017	0.005	0.048
58	78	16	24	3961.21	3961.21	401.97	0.020	0.004	0.060
59	76	19	24	3975.94	3975.94	456.13	0.019	0.005	0.053
60	73	24	29	3967.70	3967.70	505.61	0.018	0.006	0.057
61	83	23	29	3924.70	3924.70	549.61	0.021	0.006	0.053
62	94	30	40	3827.63	3827.63	609.89	0.025	0.008	0.066
63	89	19	37	3714.39	3714.39	660.29	0.024	0.005	0.056
64	95	21	40	3600.49	3600.49	722.31	0.026	0.006	0.055
65	84	32	44	3490.61	3490.61	758.35	0.024	0.009	0.058
66	87	25	49	3377.89	3377.89	796.96	0.026	0.007	0.061
67	74	21	46	3271.30	3271.30	834.78	0.023	0.006	0.055
68	82	33	56	3159.93	3159.93	863.11	0.026	0.010	0.065
69	90	29	54	3044.13	3044.13	897.30	0.030	0.010	0.060
70	71	39	55	2923.82	2923.82	922.57	0.024	0.013	0.060
71	97	36	66	2810.99	2810.99	945.57	0.035	0.013	0.070
72	87	37	73	2686.39	2686.39	961.63	0.032	0.014	0.076
73	76	34	96	2564.41	2564.41	960.79	0.030	0.013	0.100
74	84	38	82	2445.91	2445.91	952.18	0.034	0.016	0.086
75	75	44	70	2327.36	2327.36	952.09	0.032	0.019	0.074
76	85	52	80	2185.21	2185.21	956.33	0.039	0.024	0.084
77	82	49	92	2018.25	2018.25	938.46	0.041	0.024	0.098
78	78	54	100	1836.93	1836.93	891.92	0.042	0.029	0.112
79	66	41	106	1642.15	1642.15	822.16	0.040	0.025	0.129
80	68	53	83	1461.65	1461.65	753.08	0.047	0.036	0.110
81	59	47	71	1282.27	1282.27	704.43	0.046	0.037	0.101
82	59	52	104	1128.03	1128.03	622.38	0.052	0.046	0.167
83	54	43	85	972.59	972.59	562.80	0.056	0.044	0.151
84	51	46	73	830.53	830.53	498.11	0.061	0.055	0.147
85	40	42	67	695.43	695.43	445.52	0.058	0.060	0.150
86	42	29	72	583.73	583.73	403.22	0.072	0.050	0.179
87	22	40	57	482.47	482.47	343.36	0.046	0.083	0.166
88	22	36	53	392.95	392.95	289.60	0.056	0.092	0.183
89	24	26	58	319.50	319.50	234.49	0.075	0.081	0.247
90	18	23	42	249.29	249.29	187.72	0.072	0.092	0.224

Technical Appendix 3.5

Multistate life table of 3-state cardiovascular disease: males and females combined

	Transition probability			Survival probability		Person years lived or		Total person years lived		Life expectancy		
Age	NO-CVD to CVD	CVD to death	CVD to Death	NO-CVD	CVD	NO-CVD	CVD	NO-CVD	CVD	NO-CVD	CVD	Total
	1	2	3	4	5	6	7	8	9	10	11	12
40	0.003	0.001	0.081	1.000	0.000	0.998	0.001	32.27	6.21	32.27	6.21	38.48
41	0.003	0.002	0.000	0.996	0.003	0.994	0.004	31.27	6.21	31.30	6.22	37.52
42	0.002	0.001	0.093	0.991	0.006	0.989	0.006	30.27	6.21	30.38	6.23	36.61
43	0.005	0.001	0.109	0.988	0.007	0.985	0.009	29.29	6.20	29.43	6.23	35.66
44	0.003	0.001	0.082	0.983	0.011	0.980	0.012	28.30	6.19	28.48	6.23	34.72
45	0.007	0.001	0.044	0.978	0.013	0.974	0.016	27.32	6.18	27.55	6.23	33.79
46	0.004	0.002	0.034	0.971	0.019	0.968	0.021	26.35	6.17	26.62	6.23	32.84
47	0.007	0.002	0.095	0.965	0.022	0.961	0.024	25.38	6.14	25.71	6.22	31.93
48	0.005	0.001	0.060	0.957	0.027	0.954	0.028	24.42	6.12	24.83	6.22	31.05
49	0.007	0.005	0.052	0.951	0.030	0.945	0.032	23.46	6.09	23.92	6.21	30.14
50	0.009	0.003	0.051	0.939	0.035	0.934	0.038	22.52	6.06	23.11	6.22	29.32
51	0.008	0.003	0.050	0.929	0.041	0.924	0.044	21.58	6.02	22.25	6.21	28.46
52	0.011	0.007	0.052	0.919	0.046	0.911	0.050	20.66	5.98	21.40	6.19	27.60
53	0.016	0.004	0.076	0.902	0.054	0.893	0.059	19.75	5.93	20.64	6.20	26.84
54	0.012	0.004	0.057	0.884	0.065	0.877	0.068	18.86	5.87	19.87	6.18	26.06
55	0.016	0.005	0.070	0.870	0.072	0.861	0.076	17.98	5.80	19.10	6.16	25.26
56	0.014	0.004	0.074	0.852	0.080	0.844	0.083	17.12	5.72	18.37	6.14	24.51
57	0.017	0.005	0.047	0.836	0.087	0.827	0.091	16.27	5.64	17.64	6.11	23.75
58	0.019	0.004	0.058	0.818	0.097	0.808	0.102	15.45	5.55	16.89	6.07	22.96
59	0.019	0.005	0.051	0.799	0.107	0.789	0.112	14.64	5.45	16.16	6.01	22.18
60	0.018	0.006	0.056	0.780	0.117	0.771	0.120	13.85	5.34	15.45	5.95	21.40
61	0.021	0.006	0.051	0.761	0.124	0.751	0.129	13.08	5.22	14.77	5.89	20.66
62	0.024	0.008	0.063	0.741	0.134	0.729	0.138	12.33	5.09	14.10	5.82	19.91
63	0.024	0.005	0.054	0.717	0.143	0.707	0.148	11.60	4.95	13.48	5.75	19.23
64	0.026	0.006	0.054	0.697	0.152	0.686	0.157	10.89	4.80	12.83	5.66	18.49
65	0.024	0.009	0.056	0.675	0.162	0.664	0.166	10.21	4.64	12.20	5.55	17.75
66	0.025	0.007	0.060	0.653	0.169	0.642	0.172	9.54	4.48	11.62	5.45	17.07
67	0.022	0.006	0.054	0.631	0.175	0.622	0.178	8.90	4.31	11.03	5.34	16.37
68	0.025	0.010	0.063	0.613	0.180	0.602	0.182	8.28	4.13	10.44	5.20	15.64
69	0.029	0.009	0.058	0.591	0.184	0.580	0.188	7.68	3.95	9.90	5.09	14.98
70	0.024	0.013	0.058	0.569	0.191	0.558	0.192	7.10	3.76	9.35	4.95	14.30
71	0.034	0.013	0.067	0.548	0.193	0.535	0.196	6.54	3.57	8.83	4.81	13.64
72	0.032	0.013	0.073	0.522	0.199	0.510	0.200	6.00	3.37	8.33	4.67	13.00
73	0.029	0.013	0.095	0.499	0.201	0.488	0.198	5.49	3.17	7.85	4.53	12.39
74	0.034	0.015	0.083	0.478	0.196	0.466	0.196	5.01	2.97	7.43	4.41	11.84
75	0.031	0.018	0.071	0.455	0.196	0.443	0.196	4.54	2.78	6.98	4.27	11.25
76	0.038	0.023	0.080	0.432	0.196	0.419	0.197	4.10	2.58	6.52	4.11	10.63
77	0.039	0.024	0.093	0.406	0.197	0.393	0.196	3.68	2.38	6.10	3.96	10.06
78	0.041	0.028	0.106	0.380	0.194	0.367	0.192	3.29	2.19	5.72	3.81	9.53
79	0.039	0.024	0.121	0.354	0.189	0.343	0.185	2.92	2.00	5.37	3.67	9.05
80	0.045	0.035	0.104	0.331	0.180	0.318	0.178	2.58	1.81	5.03	3.54	8.57
81	0.044	0.035	0.096	0.305	0.176	0.293	0.175	2.26	1.63	4.69	3.39	8.08
82	0.050	0.044	0.154	0.281	0.173	0.268	0.166	1.96	1.46	4.33	3.21	7.55
83	0.053	0.042	0.140	0.255	0.160	0.242	0.156	1.70	1.29	4.09	3.12	7.21
84	0.058	0.052	0.136	0.230	0.151	0.217	0.148	1.46	1.14	3.81	2.98	6.79
85	0.054	0.057	0.140	0.205	0.144	0.193	0.139	1.24	0.99	3.55	2.83	6.38
86	0.068	0.047	0.164	0.182	0.135	0.172	0.130	1.04	0.85	3.29	2.68	5.97
87	0.043	0.078	0.153	0.161	0.125	0.151	0.119	0.87	0.72	3.04	2.51	5.55
88	0.052	0.085	0.167	0.142	0.113	0.132	0.107	0.72	0.60	2.83	2.36	5.18
89	0.070	0.075	0.219	0.122	0.101	0.113	0.094	0.59	0.49	2.63	2.20	4.83
90	0.067	0.085	0.200	0.105	0.088	0.476	0.399	0.48	0.40	2.28	2.28	4.55