# 6

# Life history of cardiovascular disease
## A comparison of smokers and non-smokers

## Abstract

Smokers combine an increased risk of a number of diseases with an increased risk of death. The duration of morbidity depends on that balance. This study compares the burden of cardiovascular disease in terms of lifetime risk and life years lived with disease between smokers and non-smokers. We constructed multistate life tables describing transitions through various cardiovascular diseases for 4723 smokers and non-smokers observed during 20 biannual observations in the Framingham Heart Study. The risk of developing any cardiovascular disease before age 70 is higher among smokers. Associated with their longer life expectancy, male non-smokers have higher lifetime risks of coronary heart disease, myocardial infarction, stroke and congestive heart failure, while female non-smokers have higher lifetime risks of coronary heart disease and congestive heart failure. Non-smokers live 8.66 years (95% CI 7.61- 9.63) (men) and 7.59 (95% CI 6.33- 8.92) (women) years longer than smokers but also spend more years with cardiovascular disease: 2.43 (95% CI 1.72-3.16) years for males and 2.66 (95% CI 1.87-3.38) years for females. Non-smokers live more years free of cardiovascular disease: 6.22 (95% CI 5.09-7.30) years for males and 4.93 (95% CI 3.54-6.29) for females. Not smoking will not eliminate cardiovascular disease, but it will postpone it to older ages. Smoking, by shortening life, decreases the years lived with cardiovascular disease throughout the life course. Paradoxically, in a non-smoking society, more people will live with cardiovascular disease but this will be concentrated at the end of life.

# 6.1   Introduction

In this chapter, we investigated cardiovascular disease in the life course of smokers and non-smokers and addressed the compression of morbidity hypotheses. The thesis of compression of morbidity, as put forward by Fries (Fries, 1980), suggested that lifestyle modification might decrease morbidity. The main propositions of Fries were based on the observations that the length of life is limited and that chronic disease can be postponed. He pointed to the decline of tobacco consumption as an example. If incidence (inflow) decreases and mortality (outflow) remains constant, the prevalence (stock) will decrease. However, smoking has been identified as the major cause of death among smokers. The age adjusted disease incidence of non-smokers is lower, but because of a lower mortality they live a longer period at risk. Recent papers have suggested that smokers experience both more (Nusselder et al., 2000; Bronnum-Hansen and Juel, 2001) and fewer (Ferrucci et al., 1999; Martel et al., 2000) years lived with disability than non-smokers, and that they cost more to health care (Barendregt et al, 1997) over the life course. While the reason(s) for these differences is not yet clear, probable significant factors include differences in smoking status definitions, start ages, assumptions regarding the relationship between smoking relative risks and age, model types and disability definitions. The potential age dependence of the relative risks associated with smoking are probably the most crucial.

Cardiovascular diseases are common both among smokers and non-smokers, and increase sharply with age. The interplay between different incidence rates, mortality rates and age structures between smokers and non-smokers cannot be gauged intuitively (Lloyd-Jones, et al., 1999). The question addressed in this chapter is whether non-smoking will shorten the time lived with cardiovascular disease, given the competing forces of an increased risk of cardiovascular disease and increased mortality in smokers.

Section 6.2 discusses data source, smoking status definition, estimation of hazard ratios and the construction of multistate life table. Results are described in Section 6.3. First, we described the hazard ratios of disease occurrences or deaths in sub-section 6.3.1. Second, the life table outcomes are illustrated in sub-section 6.3.2. The chapter is concluded with a discussion in Section 6.4.

# 6.2   Data and Methods

We took advantage of the data available from the Framingham Heart Study, which gave us the unique historical documentation of fifty years of cardiovascular health damage due to smoking. We compared the cardiovascular life histories of smokers and non-smokers by constructing multistate life tables from the first 40 years of follow-up from the original Framingham Heart Study cohort. This enabled a

comparison to be made of the life years lived with and without cardiovascular disease and lifetime risk of cardiovascular disease for smokers and non-smokers.

### Data source

The original Framingham Heart Study cohort consisted of 5209 respondents (45% male) from a random sample of adults aged 28 through 62 years residing in Framingham, Massachusetts between 1948 and 1951. The participants were tracked by standardised biennial cardiovascular examinations, daily surveillance of hospital admissions, death information and information from physicians and other sources outside the clinic, ensuring highly accurate follow-up of death and clinically presenting cardiovascular disease. In the Framingham Heart Study current smoking status (yes or no) was recorded at all but 4 of the 20 biennial exams. Missing values for this variable were recorded at each exam.

For this chapter, we used the data on age at the onset of cardiovascular disease or death over forty years of follow-up (exam rounds 1 to 21) for the 4723 participants without cardiovascular disease at study entry. Some 139 respondents had cardiovascular disease at study entry. The smoking status of 13 respondents was unknown during the follow-up; for another 334 respondents, only one observation of smoking status was available. These (139+13+334=486) were excluded. Smoking status information was missing on 13% of the 4723 respondents for more than half of the rounds (excluding the four rounds with no information at all).

### Definition of smoking status

Smoking status for each participant was allocated based on the current smoking status recorded at each available exam between study entry and death or study exit. We classified *never smokers* as those with all available smoking records coded as a non-smoker and *always smokers* as those with all available smoking records coded as a smoker. *Ever smokers* were the rest of the participants, characterized by a mixture of smoking and non-smoking throughout the study.

Of the 4723 participants included, 381 (18%) men were classified as never smokers and 674 (33%) as always smokers. 1384 (52%) women were found to be never smokers and 448 (17%) were classified as always smokers. The remaining 1018 (49%) men and 818 (31%) women were classified in the residual group of ever smokers.

### Estimation of hazard ratios

The risk of cardiovascular disease or death for smokers or ever smokers relative to never smokers was calculated using Cox proportional hazards analysis. The events considered were death, and onset of: all cardiovascular disease (CVD); all coronary heart disease; acute myocardial infarction; stroke, and congestive heart failure

(Shurtleff, 1971). Coronary heart disease included angina pectoris, coronary insufficiency, myocardial infarction and sudden death. Cardiovascular disease included all coronary heart diseases, all cerebrovascular diseases (including stroke), intermittent claudication and congestive heart failure.

Analyses were performed separately for each sex with an adjustment for the mean values of educational levels. Educational status has an influence on smoking status and on cardiovascular disease and mortality. Educational status is the main socioeconomic indicator of the FHS cohorts. We treated it as a confounder. The information on educational status was collected at the first exam. The educational level was grouped into six categories: 1 8th grade or less; 2 high school but not a graduate; 3 high school graduate; 4 college but not a graduate; 5 college graduate; and 6 post graduate or business college or nursing school. Age at transition was the time variable in this model. We have presented mean hazard ratios.

### Multistate life tables
Separate multistate life tables were created to analyze annual transitions through each of the cardiovascular disease types described above. The basic multistate life table structure had the state space {NO-CVD, history of CVD, dead} (Section 3.3.2, Figure 3.1(b)), CVD represents one of the specific CVD states (cardiovascular disease, coronary heart disease, acute myocardial infarction, stroke, or congestive heart failure). For example, in the life table for all CVD, the possible transitions were, "NO-CVD" to "death", "NO-CVD" to "history of CVD", and "history of CVD" to "death".

The empirical transition rate was calculated for each single year of age by dividing the number of events between exact ages by the corresponding risk period of exposure in each state. Each set of rates was calculated separately for male never smokers, male always smokers, female never smokers and female always smokers. The method used to estimate the observed occurrence-exposure was the same as those described in Section 3.3.3 in Chapter 3. For smoothing empirical age-specific transition rates, we applied Gompertz regression models (Gompertz, 1825). In this model the transition rates depend on age alone. For life table construction, the rates were converted to probabilities, by assuming that within each single year age interval the hazard remained constant and taking into account the competition between risks (Schoen, 1988). All life tables were constructed from age 50 and 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, 1988-91). The procedure used to construct the life tables was the same as the procedure described and applied in Chapter 3 (Section 3.3.4).

The measures directly available from the multistate life tables are life expectancy with and without disease and the lifetime risk of an event over a certain period (inclusive of lifetime). Confidence intervals were derived using a non-

parametric bootstrap procedure, based on 2,000 replicates, in S-plus 2000 (MathSoft Inc., Washington, USA). We have reported the bootstrap bias-correct, adjusted 95% confidence intervals (Efron and Tibshirani, 1993). The basic steps to calculate the confidence intervals of the outcomes of multistate life table were discussed in Section 2.4.5 of Chapter 2 of this study.  An example of an S-plus script is presented in Technical Appendix 6.1

## 6.3     Results

The results are presented in two parts. *First*, we have described the risk of cardiovascular disease or death for smokers or ever smokers relative to never smokers calculated using Cox proportional hazards analysis. *Second*, we have described the life table outcomes: survival probability, lifetime probability of disease, differences in the number of years spent with disease and life expectancy by smoking status.

### 6.3.1   Disease incidence and death

 The risk of death or cardiovascular disease incidence was analysed for ever and always smokers relative to never smokers using proportional hazards regression. As expected, always smokers were found to have an increased risk of all cardiovascular disease sub-types examined, ranging from a hazard ratio of 1.29 [95% CI 1.04-1.60] for coronary heart disease (females) to 2.00 [95% CI 1.38-2.91 for stroke (males) (Table 6.1). Always smokers also had a significantly higher risk of dying once they had cardiovascular disease compared to never smokers (Table 6.2), with relative risks ranging from 1.28 [95% CI 0.99-1.66] from myocardial infarction (males) to 2.23 [95% CI 1.85-2.68] from cardiovascular disease (females). The risk of death among smokers without cardiovascular disease was significantly higher compared to never smokers (Table 6.2). Note that people without cardiovascular disease constitute a mixed group, including healthy people and people with cancer, and other diseases.

Table 6.1    Risk of cardiovascular disease (including sudden death) by smoking status, relative to never smokers (95% confidence intervals in parentheses)

|  | CVD | CHD | MI | CHF | Stroke | Total number |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Ever smoker | 1.15 (0.98-1.34) | 1.04 (0.87-1.24) | 0.98 (0.79-1.22) | 1.05 (0.77-1.43) | 1.45 (1.03-2.08) | 381 |
| Always smoker | 1.65 (1.39-1.94) | 1.41 (1.17-1.71) | 1.38 (1.09-1.74) | 1.64 (1.17-2.28) | 2.00 (1.37-2.91) | 674 |
| **Female** | | | | | | |
| Ever smoker | 1.04 (0.91-1.19) | 0.97 (0.81-1.15) | 1.24 (0.97-1.59) | 1.32 (1.03-1.72) | 1.05 (0.83-1.35) | 1384 |
| Always smoker | 1.42 (1.21-1.67) | 1.29 (1.05-1.59) | 2.06 (1.55-2.74) | 1.62 (1.62-2.24) | 1.75 (1.31-2.34) | 448 |

Table 6.2    Risk of death (from given states) by smoking status, relative to never smokers (95% confidence intervals in parentheses)

|  | Non-CVD | CVD | CHD | MI | CHF | Stroke |
|---|---|---|---|---|---|---|
| **Male** | | | | | | |
| Ever smoker | 0.92 (0.71-1.21) | 0.81 (0.68-0.98) | 0.78 (0.63-0.96) | 0.71 (0.55-0.91) | 1.14 (0.81-1.60) | 1.07 (0.72-1.58) |
| Always smoker | 2.51 (1.93-3.27) | 1.62 (1.34-1.95) | 1.55 (1.26-1.91) | 1.28 (0.99-1.66) | 1.64 (1.15-2.34) | 2.00 (1.32-3.02) |
| **Female** | | | | | | |
| Ever smoker | 1.05 (0.86-1.29) | 0.94 (0.79-1.12) | 1.05 (0.84-1.31) | 1.20 (0.88-1.65) | 1.01 (0.76-1.34) | 0.92 (068-1.25) |
| Always smoker | 2.31 (1.86-2.87) | 2.23 (1.85-2.68) | 2.13 (1.67-2.72) | 1.96 (1.40-2.75) | 1.48 (1.05-2.10) | 2.08 (1.49-2.90) |

Ever smoking was not significantly associated with an increased risk of mortality or of any of the cardiovascular disease sub-types examined. This is most likely due to the heterogeneity in smoking intensities (duration and time since quitting) in this group. To make comparisons between smokers and non-smokers we used the more homogeneous groups of never and always smokers for all further analyses.

## 6.3.2    Life table outcomes

**Survival probability**
The dynamics of differential incidence of cardiovascular disease and death over increasing age cannot be determined intuitively. Therefore, the age-specific rates of

transition were combined using multistate life tables.  Figure 6.1 shows the survival free of cardiovascular disease, coronary heart disease, acute myocardial infarction, stroke or death of fifty-year-old smokers and never-smokers. While never smokers have a much larger gap between total survival and disease-free survival, overall they lead a longer life and survive longer free of cardiovascular disease than always smokers. The mortality incidence differences between the different smoking groups lead to large differences in early mortality and morbidity. Among males, 46% of always smokers and 15% of never smokers die before the age of 70. Among females, these figures are 30% of always smokers but only 10% of never smokers. While an average six in ten male never smokers who were free of cardiovascular disease at age 50 will still be alive and free of cardiovascular disease twenty years later, only four in ten always smokers will remain in this state (Figure 6.1). Of females free of cardiovascular disease at age 50, only 6 in 10 always smokers compared to 7 in 10 never smokers will be alive and free of cardiovascular disease at age 70.

Figure 6.1    Survival curves illustrating the probability of surviving and surviving free of cardiovascular disease (CVD), coronary heart disease (CHD), myocardial infarction (MI), or stroke
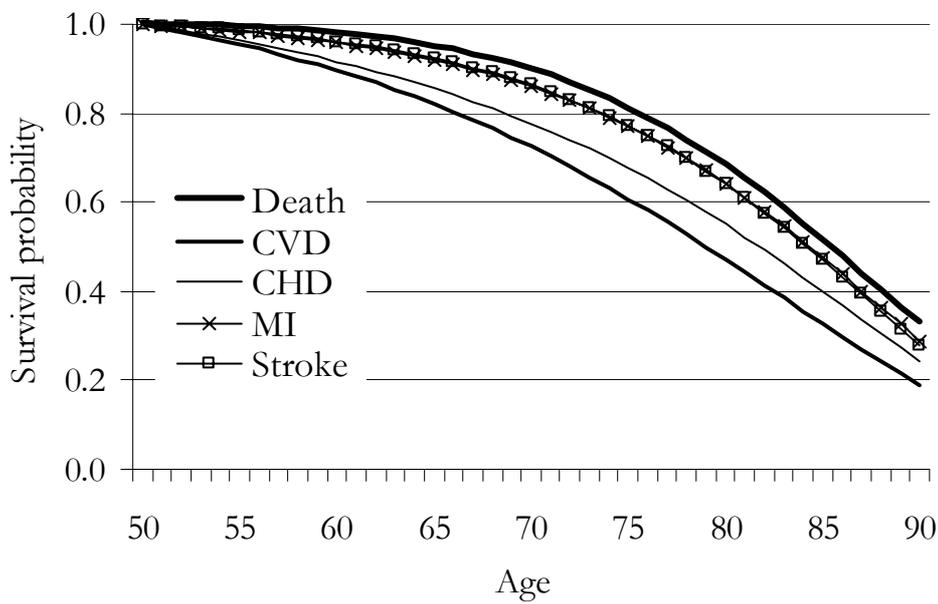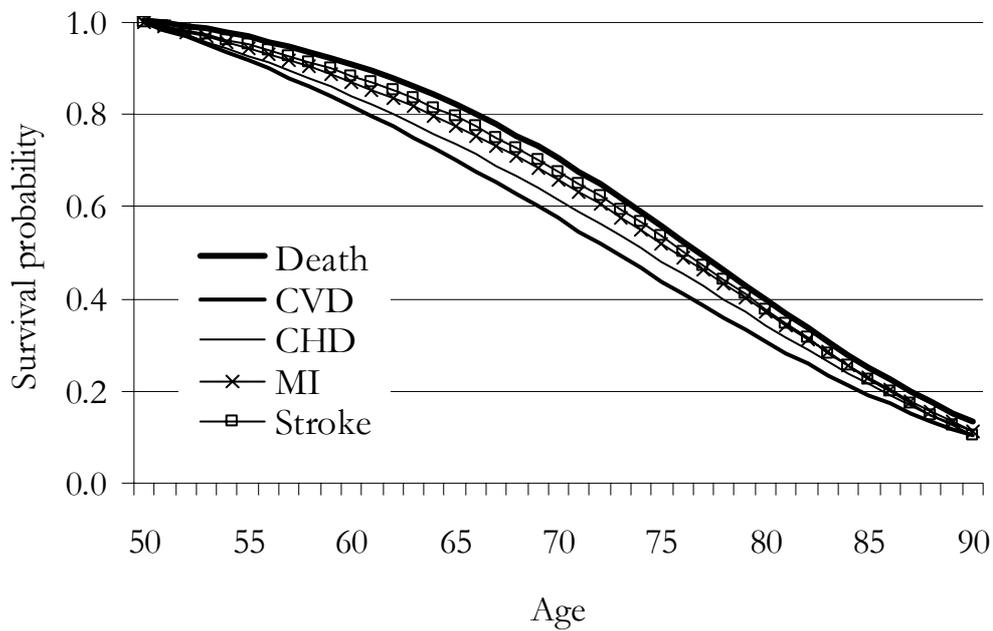
Male never smokers
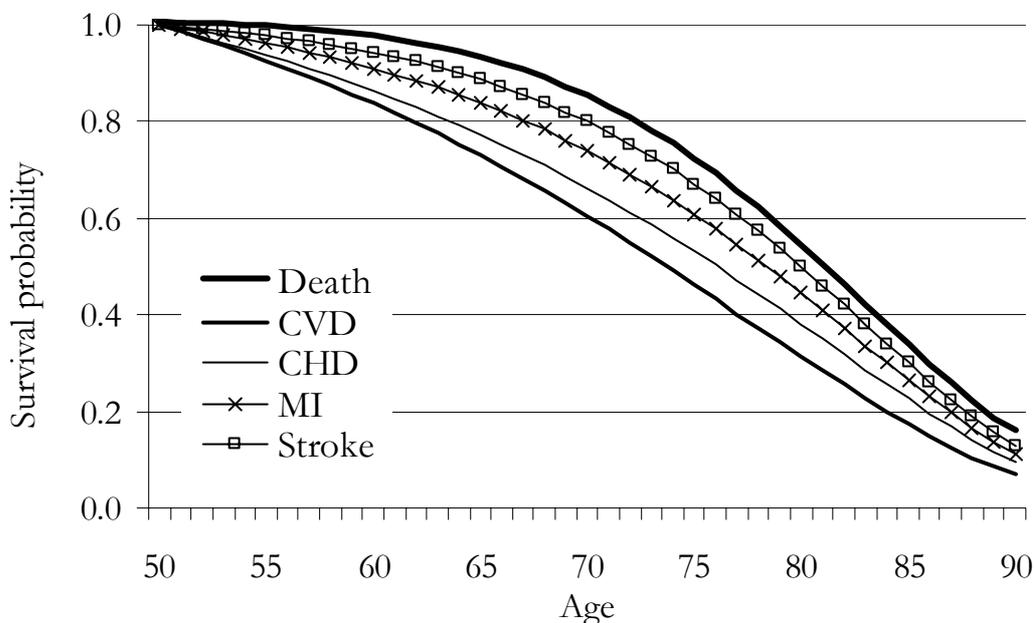
Male smokers
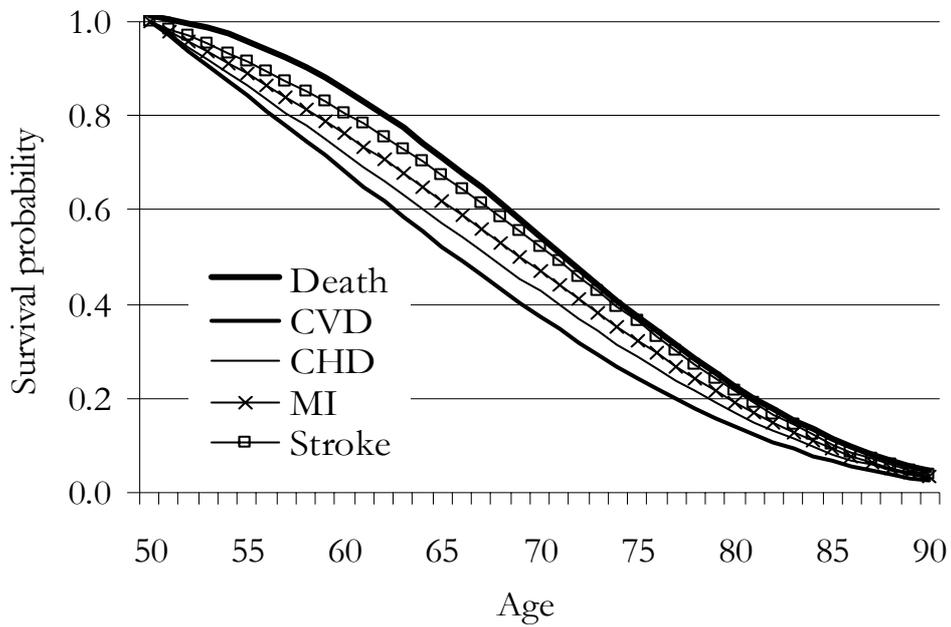


Female never smokers

Female smokers



## Lifetime probability of disease

The probability of developing cardiovascular disease before age 70 or deaths among person free of CVD at age 50 is presented in Table 6.3. As can be seen in this table, always smokers experience a significantly greater risk than never smokers for developing every cardiovascular sub-type examined before the age of 70. However, over a lifetime never-smokers have approximately the same risk of cardiovascular disease as always smokers, simply because they live longer (Table 6.3). For males, while never smokers tend to have a higher lifetime risk of any coronary heart disease, myocardial infarction, stroke and congestive heart failure than always smokers, this is only statistically significant at the 5% level for myocardial infarction.

Table 6.3    Risk of developing cardiovascular disease before age 70 or death for any person free of CVD at age 50. 95% confidence intervals are presented in parentheses

|  |  | CVD | CHD | MI | CHF | Stroke |
|---|---|---|---|---|---|---|
| **Before age 70** |  |  |  |  |  |  |
| **Males** | Never smoker | 34.12% (31.93-36.67) | 26.17% (24.16-28.18) | 15.37% (13.77-17.26) | 5.78% (4.68-6.86) | 5.70% (4.68-6.88) |
|  | Always smoker | 46.27% (42.64-49.97) | 33.32% (29.72-36.22) | 19.83% (16.95-23.00) | 9.61% (7.72-11.89) | 7.89% (6.15-10.13) |
| *Difference (never-always)* |  | -12.15% (-16.76--7.92) | -7.16% (-10.54 - -2.90) | -4.46% (-8.04 - -0.90) | -3.83% (-6.48- -1.63) | -2.19% (-4.67- -0.11) |
| **Females** | Never smoker | 21.99% (20.33-23.70) | 14.62% (13.23-15.87) | 4.76% (3.95-5.59) | 3.92% (3.22-4.69) | 4.19% (3.51-5.03) |
|  | Always smoker | 25.90% (22.52-29.93) | 16.81% (13.93-19.88) | 8.62% (6.50-11.25) | 5.49% (3.79-7.67) | 6.06% (4.39-8.44) |
| *Difference (never-always)* |  | -3.91% (-8.15- -0.03) | -2.18% (-5.43-1.11) | -3.86% (-6.62- -1.59) | -1.57% (-3.89- 0.31) | -1.87% (-4.25-0.04) |
| **Before death** |  |  |  |  |  |  |
| **Males** | Never smoker | 67.53% (64.46-70.41) | 50.78% (47.56-53.33) | 35.27% (32.33-38.26) | 20.32% (17.74-23.09) | 18.88% (16.33-21.37) |
|  | Always smoker | 65.97% (62.04-69.47) | 46.48% (42.36-49.54) | 28.55% (24.99-32.45) | 16.71% (14.05-19.94) | 14.90% (12.22-18.28) |
| *Difference (never-always)* |  | 1.56% (-2.98-6.58) | 4.30% (0.02-9.26) | 6.72% (1.83-11.16) | 3.62% (-0.30-7.82) | 3.98% (-0.59-7.45) |
| **Females** | Never smoker | 56.37% (53.87-58.85) | 33.88% (31.5-35.8) | 17.06% (15.28-19.16) | 17.75% (15.65-19.88) | 19.08% (16.98-21.21) |
|  | Always smoker | 54.80% (48.42-60.1) | 31.04% (25.98-35.55) | 19.55% (14.98-24.02) | 15.82% (11.71-20.59) | 19.03% (14.25-23.87) |
| *Difference (never-always)* |  | 1.57% (-4.43-8.27) | 2.84% (-2.08-8.49) | -2.49% (-7.37-2.37) | 1.93% (-2.98-6.56) | 0.01% (-5.27-5.28) |

## **Life expectancy**

Concordant with the often-higher lifetime risk of disease and the lower mortality rates post disease, the duration of disease is generally longer among never smokers (Table 6.4). Male never smokers live 2.43 [95% CI 1.72-3.16] years longer with a history of cardiovascular disease, 2.01 [95% CI 1.43-2.66] years longer with a history of coronary heart disease, 1.13 [95% CI 0.60-1.68] years longer with a history of myocardial infarction, 0.68 [95% CI 0.33-0.96] years longer with a history of stroke and 0.39 [95% CI 0.13-0.65] years longer with heart failure. Female never-smokers live 2.66 [95% CI 1.87-3.38] years longer with a history of cardiovascular disease, 1.82 [95% CI 1.26-2.47] years longer with a history of coronary heart disease, and 0.49 [95% CI 0.11-0.83] years longer with a history of stroke, but show no significant difference in time spent with a history of myocardial infarction or heart failure.

Of course, most impressive is the change in life expectancy free of any cardiovascular disease: 50 year-old always smokers live five to six years less free of cardiovascular disease than never smokers (men 6.22 [95% CI 5.09-7.30] years and women 4.93 [95% CI 3.54-6.29] years). Both male and female always smokers live significantly fewer years free of myocardial infarction, stroke and congestive heart failure than never smokers. The combination of the extra years lived with and without cardiovascular disease leads to a difference in total life expectancy at age 50 between never smokers and always smokers of around 8 years (men 8.66 [95% CI 7.61-9.63], women 7.59 [95% CI 6.32-8.92], Table 6.4).

Table 6.4    The burden of cardiovascular disease in always smokers versus never smokers free of any cardiovascular disease at age 50. Life years lived with a history of cardiovascular disease. 95% confidence intervals are presented in parentheses

|  | CVD | CHD | MI | Stroke | CHF | Total LE |
|---|---|---|---|---|---|---|
| **Males** | | | | | | |
| Never smokers | 7.25 (6.77-7.81) | 5.36 (4.92-5.75) | 3.20 (2.85-3.58) | 1.33 (1.10-1.57) | 1.00 (0.82-1.19) | 30.42 (29.79-30.92) |
| Always smokers | 4.81 (4.34-5.35) | 3.34 (2.87-3.75) | 2.07 (1.73-2.51) | 0.64 (0.49-0.90) | 0.61 (0.46-0.78) | 21.77 (20.96-22.66) |
| *Difference (never-always)* | 2.43 (1.72-3.16) | 2.01 (1.43-2.66) | 1.13 (0.60-1.68) | 0.68 (0.33-0.96) | 0.39 (0.13-0.65) | 8.66 (7.61- 9.63) |
| **Females** | | | | | | |
| Never smokers | 6.23 (5.83-6.68) | 4.05 (3.71-4.41) | 1.30 (1.12-1.51) | 1.36 (1.18-1.60) | 1.06 (0.90-1.23) | 34.14 (33.68-34.63) |
| Always smokers | 3.57 (3.04-4.34) | 2.23 (1.74-2.76) | 1.07 (0.78-1.49) | 0.87 (0.59-1.20) | 0.71 (0.48-1.27) | 26.55 (25.35-27.69) |
| *Difference (never-always* | 2.66 (1.87-3.38) | 1.82 (1.26-2.47) | 0.23 (0.17-0.61) | 0.49 (0.11-0.83) | 0.35 (0.19-0.63) | 7.59 (6.33- 8.92) |

**Difference of the years spent with disease**

The difference in life years lived with cardiovascular disease and its various subtypes by age is shown in Figure 6.2. The estimation procedure is described in Section 2.4.7 of Chapter 2. Importantly, the life years lost to cardiovascular disease for never smokers fall predominantly late in life, with always smokers living more years with cardiovascular disease throughout middle age (Figure 6.2). Non-smokers live longer with cardiovascular disease, but predominantly at older ages.

Figure 6.2    Difference in life years lived with cardiovascular disease, coronary heart disease, myocardial infarction, stroke, or congestive heart failure, by age (smokers – never smokers)

Males
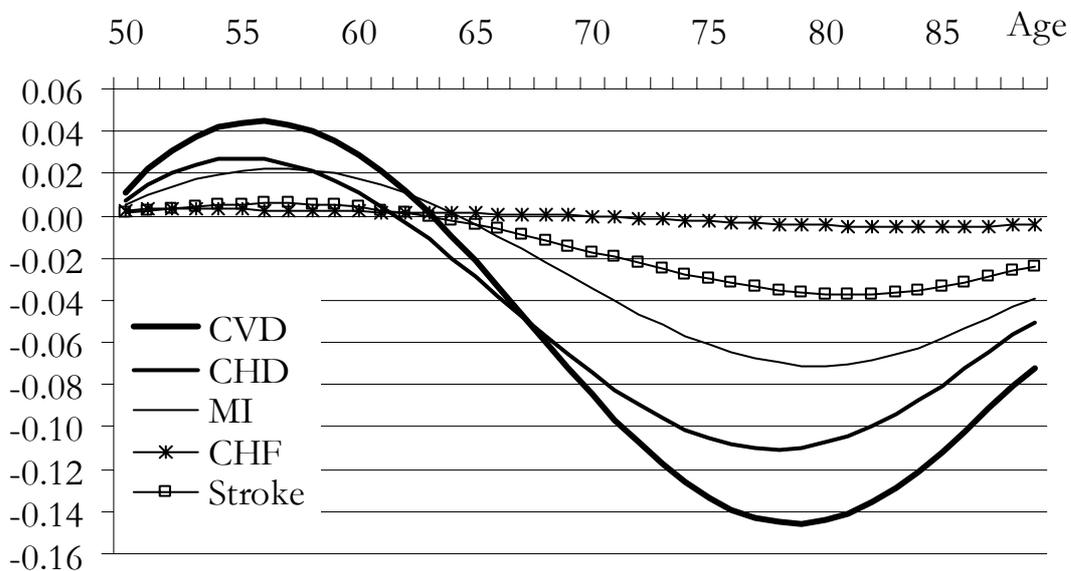


Females
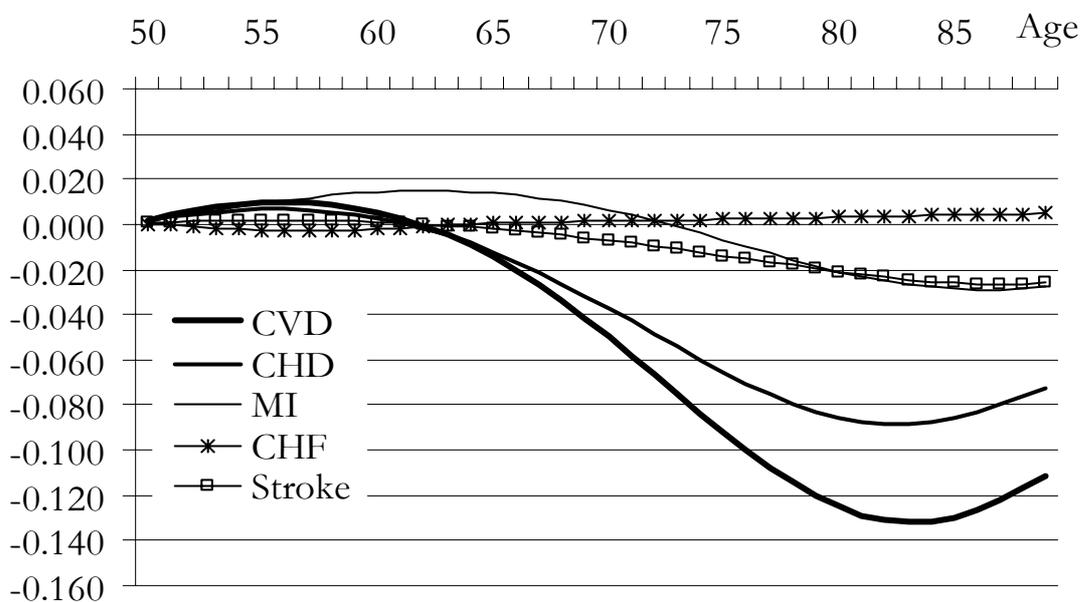
# 6.4    Discussion

This chapter shows the cardiovascular life course of the Framingham Heart Study cohort by smoking status. It was seen that non-smoking expanded both the duration of life free of cardiovascular disease and the duration of cardiovascular disease. Over a life course, non-smokers lived longer with cardiovascular disease and its manifestations such as cerebrovascular and coronary disease. We found that male and female never smokers lived 2.43 and 2.66 years, respectively, more with a history of cardiovascular disease than always smokers. Importantly, never smokers also lived more years free of cardiovascular disease: 6.22 years for males and 4.93 years for females. We demonstrated that this was the result of a complex combination of (i) the increased rate of cardiovascular disease, (ii) the increased rate of mortality from the cardiovascular disease state and (iii) the higher rate of mortality from the non-cardiovascular disease state to death associated with smoking.

While the increased incidence and mortality rates together led to fewer years lived with each form of cardiovascular disease for always smokers throughout the life course, this was seen to result from a combination of more years lived with disease at younger ages and less at older ages. Similarly, the risk of cardiovascular disease before age 70 was consistently greater for always smokers, in both males and females. Six out of ten never smoking males and seven out of ten never smoking females could expect to reach age 70 alive and free of any cardiovascular disease. This was strikingly less for smokers: four out of ten males and six out of ten females.

Previous analysis suggested that smokers lived longer with coronary heart disease than non-smokers (Barendregt, 1998). However, our empirical study took into account the increased risk of mortality after disease incidence due to smoking and the age dependence of the relative risks associated with smoking.

The main power of this study is in the Framingham Heart Study, which gave us 40 years of follow-up of a single cohort. All transition rates were estimated from this study, and treated with the time-honored multistate life-table method (Schoen, 1988; Rogers, 1995). Such life-tables are intuitively simple and appealing because they transparently describe the disease epidemiology as a life course. The transition rates at every age are the result of a mixture of both the broad age range at entry and the long follow-up, and they may come from very different periods. However, as long as the dynamics between "always smokers" and "never smokers" are not very different in these periods, this should not bias the results presented here.

Correct estimation of the transition rates is crucial. Testing the modifying effect of potential confounders, such as obesity, blood pressure and cholesterol level, increased the numbers of missing values, and selected a healthier subgroup

with more complete observations. As this may introduce selection bias, we have presented the life table outcomes without further adjustment.

Here, we have chosen our case definitions to maximize transparency, power and homogeneity. If, instead, smoking is used as a time varying covariate, the same individual is able to participate in both cohorts, non-smoking and smoking. However, the timing of incidence and mortality after starting and quitting smoking is different, which makes interpretation of the synthetic cohorts so constructed difficult. Smoking status at baseline yields cohorts that are too heterogeneous, including future quitters as smokers and future starters as non-smokers. We therefore described the life course for "always smokers" and "never smokers", defined as smoking or non-smoking for 100% of the recorded exams in the Framingham cohort.

Life course analysis translates transition rates into dwelling times, and gives more transparent information about the consequences of risk. The risks of smoking translated into the loss of 8.66 (men) and 7.59 (women) life years. This is in the same order of magnitude as found in many other studies (Bronnum-Hansen et al., 2001; Martel et al., 2000; Rogers and Powell-Griner, 1991), but this study adds the consequences of smoking for cardiovascular disease in terms of incidence and duration throughout the life course. Male never smokers appear to have a greater lifetime risk of all forms of cardiovascular disease, including those considered most severe such as congestive heart failure and stroke. However, female never smokers show no difference in the lifetime risk of myocardial infarction, congestive heart failure or stroke compared to always smokers.

It appears that in smokers the higher outflow through mortality more than compensates the higher inflow through cardiovascular disease incidence: smoking leads to a shorter life expectancy with cardiovascular disease by increasing mortality from all causes. However, it would be possible to estimate health-adjusted life expectancy (combining life years free of CVD and life years with CVD) using "weigh" years lived with CVD against years lived without CVD. From this calculation it may be possible to conclude that smoking results in less health-adjusted life expectancy than non-smoking, as one might expect. In public health terms, the effects of smoking on cardiovascular disease are an expression of the folk wisdom "those who don't want to die old and disabled, are advised to die young".

The increased mortality among smokers will remain one of the primary challenges to public health as long as smoking is not abolished. But this study shows that public policy should not conclude simplistically that morbidity would decrease if people stop smoking. Incidence of cardiovascular morbidity will be postponed, years lived free of cardiovascular disease will be gained, but incidence as well as the life years lived with cardiovascular disease will be increased in the older population of never smokers. The central paradox of health and health care is

caused by ageing: the more successful we are in postponing the onset of, and the mortality associated with, age-related diseases with high case fatality, such as cardiovascular disease, the longer we live, the more we suffer from the disease at older age, and the more we need care. If, through that care, we successfully palliate morbidity, it is money well spent.

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# Technical Appendix 6.1[*]

S-Plus code to construct multistate life table along with confidence intervals of the life table outcomes using non-parametric bootstrapping.

```
lowage<-25 # lowest age (LA)
hiage<-105 # highest age (HA)
hiind<-hiage-lowage+1 # difference between 105-25 and plus 1
Ages<-lowage:hiage #25, 26,27,……..,105

ltlowage<-50 # life table (LT) lowest age
lthiage<-90  # LT highest age
lthiind<-lthiage-ltlowage+1 # difference between LT lowage & LT hiage
ltAges<-ltlowage:lthiage # LT ages: 50, 51,52,53, ….90

lowoffset<-ltlowage-lowage+1 #lowest offset, needed to estimate smoothed rates
hioffset<-lthiage-lowage+1   #highest offset

uitvoer<-matrix(data=0,nrow=lthiind,ncol=6)        # define a matrix of lthiind by 6
lx<-vector(mode="numeric",length=lthiind)          # define lx as a vector & length=lthiind
Lx<-vector(mode="numeric",length=lthiind)          # define Lx as a vector & lenght=lthiind
dx<-vector(mode="numeric",length=lthiind)          # define dx as a vector & lenght=lthiind
pH<-vector(mode="numeric",length=lthiind)          # define pH  as a vector & lenght=lthiind
lxCVD<-vector(mode="numeric",length=lthiind)       # define lxCVD as a vector & lenght=lthiind
LxCVD<-vector(mode="numeric",length=lthiind)       # define LxCVD as a vector & lenght=lthiind
dxCVD<-vector(mode="numeric",length=lthiind)       # define dxCVD as a vector & lenght=lthiind
H2Drate<-vector(mode="numeric",length=lthiind)     # define H2Drate as a vector & lenght=lthiind
                                                   # H2Drate is transition rate from healthy to death
H2Crate<-vector(mode="numeric",length=lthiind)     # define H2Drate as a vector & lenght=lthiind
                                                   # H2Crate is transition rate from healthy to cvd
C2Drate<-vector(mode="numeric",length=lthiind)     # define C2Drate as a vector & lenght=lthiind
                                                   # C2Drate is transition rate from cvd to death
MaleBool<-logical(length=1)     # define length 1 for last age group
Maleex90<-3.93                  # life expectancy for last age group (male)
Femaleex90<-4.76                # life expectancy for last age group (female)

PY<-function(x)                 # a function to calculate  person years
{
  for(i in 1:(lthiind-1))
   if ((x[i] > 0) & (x[i+1]>0) & (x[i]!=x[i+1]))  # if non-negative and not equal to the previous value
        x[i] <- ((x[i]-x[i + 1])/(-log(x[i+1]/x[i]))) # exponential  estimate
   else x[i]<-0.5*(x[i]+x[i+1])+0.0000001              # linear estimate (an approximation)
  x
}

DoPY<-function(tmat,tmp)         # a function to estimate exact age specific exposure
{
    lowb<-trunc(as.double(tmat[1]))
    hihb<-trunc(as.double(tmat[2]))
    lowb<-min(lowb,hiage)
    hihb<-min(hihb,hiage)
  tmp[lowb-lowage+1]<-tmp[lowb-lowage+1]+
```

---

[*] This S-plus code was written by Jan Barendregt, Public Health  Department, Erasmus University, Rotterdam.  The short description was noted by Abdullah Al Mamun, Population Research Centre, University of  Groningen.

```
         max((1.0-(as.double(tmat[1])-lowb))*min(1,hihb-lowb),
            min(as.double(tmat[2])-as.double(tmat[1]),lowb+1-as.double(tmat[1]))))
      tmp[(lowb-lowage+2):(hihb-lowage)]<-
            tmp[(lowb-lowage+2):(hihb-lowage)]+min(1,max(0,hihb-lowb))
      tmp[hihb-lowage+1]<-tmp[hihb-lowage+1]+
        (as.double(tmat[2])-hihb)*min(1,hihb-lowb)
tmp
}


PYExAges<-function(tmat)
{
      tmp<-vector(mode="numeric",length=hiind)
      tmp<-apply(tmat,1,DoPY,tmp)
      tmp<-apply(tmp,1,sum)
      for (i in 1:hiind) if (tmp[i]==0) tmp[i]<-0.0001
tmp
}


 LifeTabsub<-function(Deaths,EntryCVD,H2Drate,H2Crate,C2Drate,MaleBool)
                              # a function to construct LT
{
 lx[1]<-100000                 # initial value of lx (e.g. at age 50 everybody is healthy)
 lxCVD[1]<-0                   # initial value of lxCVD (e.g. nobody with CVD at age 50)
 pH<-1-exp(-H2Drate-H2Crate) # transition probability to leave healthy state
 pCVD<-1-exp(-C2Drate)         # transition probability to leave CVD state
 for(i in 2:lthiind)
 {
     dx[i-1]<-lx[i-1]*pH[i-1]        #  # of transitions from healthy states
     lx[i]<-lx[i-1]-dx[i-1]
     pH2CVD<-pH[i-1]*(H2Crate[i-1])/(H2Crate[i-1]+H2Drate[i-1])
                              # transition probability healthy to CVD
     dxCVD[i-1]<-lxCVD[i-1]*pCVD[i-1]  # of transitions from CVD to death
     lxCVD[i]<-lxCVD[i-1]-dxCVD[i-1]+pH2CVD*lx[i-1]
 }
Lx<-PY(lx)
LxCVD<-PY(lxCVD)
if (MaleBool)
{tmp2<-(lx[lthiind]-dx[lthiind])*(Maleex90-1)
    tmp3<-(lxCVD[lthiind]-dxCVD[lthiind])*(Maleex90-1)}
  else
    {tmp2<-(lx[lthiind]-dx[lthiind])*(Femaleex90-1)
    tmp3<-(lxCVD[lthiind]-dxCVD[lthiind])*(Femaleex90-1)}

i<-lthiind
while(i>0)
{tmp2<-tmp2+Lx[i]                   # calculate  Tx for no-CVD state
 uitvoer[i,1]<-tmp2/(lx[i]+lxCVD[i]) # calculate ex for no-CVD state
 tmp3<-tmp3+LxCVD[i]                # calculate  TxCVD
 uitvoer[i,2]<-tmp3/(lx[i]+lxCVD[i]) # calculate exCVD
 uitvoer[i,3]<-uitvoer[i,1]+uitvoer[i,2] # Total life expectancy
 i<-i-1
 }
uitvoer[,4]<-(Lx*H2Crate)/lx[1]
uitvoer[,5]<-lx
```

```
uitvoer[,6]<-LxCVD
# uitvoer                        # if the survival curves are needed
LTrisk<-sum(uitvoer[1:lthiind,4])     # lifetime risk
risk70<-sum(uitvoer[1:20,4])          # lifetime risk until age 70


ttt<-c(HE=uitvoer[1,1],DE=uitvoer[1,2],LE=uitvoer[1,3],LTrisk=LTrisk,Riskb70=risk70)
}


LifeTab<-function(lrauw)      # LT function by sex and smoking status
{
 MaleBool<-(lrauw[1,2]==1)
 Deaths<-table(factor(trunc(lrauw$YDTHE-lrauw$YBIRTH),levels=Ages),
        na.include(factor(cut(lrauw$YCVDI-lrauw$YBIRTH,breaks=c(45,100)))))
#Numbers of deaths by age, Deaths[,1] are the CVD deaths, Deaths[,2] are the NonCVD deaths
# YDTHE is year of death; YBIRH is year of birth; YCVDI is year of CVD


 EntryCVD<-table(factor(trunc(lrauw$YCVDI-lrauw$YBIRTH),levels=Ages))
#Numbers of incident cases by age

tmat<-matrix(nrow=nrow(lrauw),ncol=2)  #A dataframe with entries by age in col 1 and exits by age in col 2

tmat[,1]<-lrauw$YENTRY-lrauw$YBIRTH  # YENTRY is year of 1st entry into the follow-up
tmat[,2]<-ifelse(is.na(lrauw$YCVDI-lrauw$YBIRTH),
        ifelse(is.na(lrauw$YDTHE-lrauw$YBIRTH),lrauw$YENTRY-lrauw$YBIRTH+40,
         lrauw$YDTHE-lrauw$YBIRTH),lrauw$YCVDI-lrauw$YBIRTH)
PYfuNonCVD<-PYExAges(tmat)


tmat[,1]<-lrauw$YCVDI-lrauw$YBIRTH
tmat[,2]<-ifelse(is.na(lrauw$YDTHE-lrauw$YBIRTH),lrauw$YENTRY-lrauw$YBIRTH+40,
        lrauw$YDTHE-lrauw$YBIRTH)
tmat<-na.exclude(tmat)       #Remove the NonCVD cases
PYfuCVD<-PYExAges(tmat)

nlsmat<-data.frame(Ag=ltAges,Occ=Deaths[lowoffset:hioffset,2],PY=PYfuNonCVD[lowoffset:hioffset])

  #A dataframe with age in col 1, occurrences by age in col 2, and PY in col 3

glmpars<-glm(Occ~offset(log(PY))+Ag,family=poisson(link=log),data=nlsmat) # smoothing death rates
H2Drate<-exp(coef(glmpars)[1]+coef(glmpars)[2]*ltAges)

nlsmat[,2]<-EntryCVD[lowoffset:hioffset]
glmpars<-glm(Occ~offset(log(PY))+Ag,family=poisson(link=log),data=nlsmat)
H2Crate<-exp(coef(glmpars)[1]+coef(glmpars)[2]*ltAges)

nlsmat[,2]<-Deaths[lowoffset:hioffset,1]
nlsmat[,3]<-PYfuCVD[lowoffset:hioffset]
glmpars<-glm(Occ~offset(log(PY))+Ag,family=poisson(link=log),data=nlsmat)
C2Drate<-exp(coef(glmpars)[1]+coef(glmpars)[2]*ltAges)

tt<-LifeTabsub(Deaths,EntryCVD,H2Drate,H2Crate,C2Drate,MaleBool)
tt
}
```

```
ByLifeTab<-function(lrauw)
{
    tttt<-by(lrauw,list(Male=(lrauw$SEX==1),Smoker=(lrauw$SMSTATUS==' Always')), LifeTab)
    uitpars<-matrix(nrow=4,ncol=5) # Is a by-object, bootstrapping requires matrix output
    uitpars[1,]<-tttt[1][[1]]
    uitpars[2,]<-tttt[2][[1]]
    uitpars[3,]<-tttt[3][[1]]
    uitpars[4,]<-tttt[4][[1]]
 uitpars
 #tttt
}
options(contrasts = c(factor = "contr.treatment",ordered = "contr.poly")) # Factor contrast has to be
    treatment, not helmert (the default)

#temp <-ByLifeTab(SMNeverCVD)

temp <- bootstrap(SMNeverCVD,ByLifeTab,B=1000) # hist(temp$replicates[,1],nclass=40) gives a
    histogram, for 1-40 outputs
```