8

A multivariate analysis of the risk factors of cardiovascular disease and its subtypes

Abstract

The objective of this chapter was to investigate the effect of risk factor status at middle age (age 30 to 50) on the incidence of cardiovascular disease and its subtypes and post-disease mortality. The analysis is based on a 48-year follow-up of the original Framingham Heart Study cohort. The following risk factors were considered: smoking, body mass index, serum cholesterol level and blood pressure. Three risk levels- optimal, elevated and high - were distinguished for each risk factor The effects of the major cardiovascular risk factors are expressed in terms of relative risk (RR) of disease incidence and death. We performed both univariate and multivariate regression analysis using the Cox proportional hazard model. The univariate analysis indicates the effect of the level of a single risk factor irrespective of the levels of the other risk factors. Since the effect of a risk factor may differ by level from another risk factor, multivariate analysis was used to control for the confounding effects of the presence of other risk factors. Interaction effects were not included in the multivariate analysis. Although there were interactions between the risk factors, the sample size did not permit the study of the interaction effects.

Univariate analysis indicated that each risk factor had a substantial effect on the risk of CVD and mortality. For instance, males with a life history of smoking (always smoker) were found to have a 34% excess risk (ER) of CVD and a 63% excess mortality compared to never smokers. Obese males (BMI $\geq$ 30) were shown to have an 81% excess risk of CVD and a 47% excess mortality compared to males of normal weight. The effect of smoking was aggravated by the presence of other risk factors. For instance, a male always smoker of normal weight, with an optimal blood pressure and an optimal cholesterol level had a 44% excess risk of CVD and a 72% excess mortality as weighed against a comparable male who never smoked. The effect of obesity, hypertension, or high cholesterol level on CVD was reduced by the presence of other risk factors. For instance, a downward change in excess

risk of 41% for CVD and 42% for mortality was found for a never-smoking obese male with an optimal blood pressure, and an optimal cholesterol level. The effect of obesity, hypertension or high cholesterol was less strong when the confounding effect of other risk factors was removed (in the absence of interaction effects). A significant reduction in long-term risk may be brought about by appropriate prevention or intervention of major cardiovascular risk factors, ultimately leading to a reduction of the incidence of cardiovascular disease

8.1 Introduction

To obtain precise estimates of the net or partial effect of a specific cardiovascular risk factor on cardiovascular disease incidence and mortality, we needed to control for other risk factors. The best strategy for the prevention of cardiovascular disease is to take into consideration various risk factors simultaneously (Anderson et al., 1991; Lowe et al., 1998). The multifactoral risk factor impact on the incidence of cardiovascular disease and mortality has been measured (Stamler et al., 1999; Anderson et al., 1991). Most of the studies measured multifactoral risk factor impact relying on one measurement and a short follow-up. Any major risk factor left untreated for many years has the potential to produce cardiovascular disease. Even though the use of risk-reducing drugs can significantly lower the risk when begun in later years, there is no evidence that it can return a person to the optimal risk status of a younger person (Grundy et al., 1999). In public health research, an important aim of primary prevention is to reduce cardiovascular disease over the long term and not just over the short term. Therefore, the primary objective of this chapter was to investigate the effect of the risk factor status at middle age (age 30 to 50) on the incidence of cardiovascular disease, its subtypes and post-disease mortality considering a long follow-up. Moreover, in this chapter the groundwork is laid for the next chapter, in which an MSLT is created for a single risk factor and for a combination of several risk factors.

Risk factors in early life, like tobacco use and obesity, not only affect an individual's own later health but also the health of the next generation (WHO, 2002). People with low risk profiles in middle age survive longer (Stamler et al., 1999, Lowe et al., 1998) and consume lower average annual costs for medical care in older age (Daviglus et al., 1998). In this chapter, we have focused on an association of the multifactoral risk factor status at middle age and the disease incidence and mortality at older ages. Although there are many established risk factors for CVD, we focused on the following major CVD risk factors: *smoking*, *systolic blood pressure* (SBP), *diastolic blood pressure* (DBP), *blood pressure* (BP), *serum cholesterol level* (SCL), and *body mass index* (BMI). These are the standard cardiovascular risk factors (Pooling Project Research Group, 1978; Berenson et al.,

1998; Stamler et al., 1999; Lowe et al., 1998). They are likely to have a beneficial impact on all-cause mortality and incidence of cardiovascular disease (Norrish et al., 1995).

The major cardiovascular risk factors are additive in predictive power (Wilson et al., 1998). Thus, the total risk of a person can be estimated by summing the risk conveyed by each of the major risk factors (Grundy et al., 1999). We performed both univariate and multivariate analysis of the major cardiovascular risk factors in middle age to assess their effects on CVD and mortality in the later ages of life. We estimated the effect of each risk factor status separately in a univariate analysis. The multivariate analysis was carried out to study the relative risk of cardiovascular disease or death associated with a risk factor, adjusted for the presence of other risk factors. These associations between risk factor status in middle age and disease incidence and mortality in later ages were investigated using the first 48 years of follow-up data in the Framingham Heart Study. We measured the effects in terms of relative risk of disease incidence and mortality.

In Section 8.2, we have illustrated the data and methods. In this section, the data source, risk factor definition, state space, transitions, relative risk estimation and model specification are described. Results are discussed in Section 8.3. In subsection 8.3.1, we have briefly described the disease transitions. Deaths are discussed in subsection 8.3.2. The chapter is concluded with a discussion in Section 8.4.

8.2 Data and methods

8.2.1 Data source

We used the original Framingham Heart Study cohort, which consisted of 5209 respondents (45% male) from a sample of adults aged 28 through 62 years residing in Framingham, Massachusetts between 1948 and 1951. The selection criteria and study design have been described elsewhere (Dawber et al., 1951). In the Framingham Heart Study, current smoking status (yes or no, number of cigarettes smoked in a day), serum cholesterol level, systolic blood pressure, diastolic blood pressure, height and weight were measured and recorded at most biennial examinations.

For this chapter, we have used the data regarding the age at onset of cardiovascular disease and its subtypes, and age at death over 48 years of follow-up (exam rounds 1 to 24) of the participants who were free of cardiovascular disease at age 50. We excluded the participants whose risk factor status was below optimal levels (Table 8.1). People with risk levels that are below the optimal are often at a high risk of experiencing disease and mortality. For instance, low blood cholesterol

increases mortality (Jacobs et al., 1992). We found a total of 3045 participants for whom all risk factors had been recorded at least two exams during the age interval from 30 to 50[1]. The same number of participants was included in both the univariate and the multivariate regression analysis.

8.2.2 Risk factor definition

An individual was included in our analysis if he or she had appeared between the ages of 30 and 50 at minimally two exams at which data on all risk factors were recorded. Smoking status was allocated for each participant based on the current smoking status recorded at each available exam from age 30 to 50. 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* constituted the remaining group of participants, a group that is characterized by a mixture of smoking and non-smoking throughout the period from entry at the survey to age 50. Systolic blood pressure or diastolic blood pressure is defined at each exam based on the mean value of recorded SBP or DBP from two different examiners. We took the average of the recorded mean SBP or DBP between age 30 and 50 years. Using World Health Organization (WHO, 1999) guidelines, we categorized blood pressure combining SBP and DBP as follows: optimal BP- SBP<120 and DBP<80, high BP- SBP>140 or DBP>90, otherwise high normal or elevated BP. Likewise, we took the average of recorded serum cholesterol and body mass index (BM)[2] between age 30 and 50 as predictors. Body mass index was calculated as weight in kg/height in m^2 (m is meter). We defined three BMI categories based on the World Health Organization guidelines (1998): normal weight- BMI of 18.5 to 24.9 kg/m^2; overweight- BMI of 25 to 29.9 kg/m^2 and obese- BMI greater than or equal to 30 kg/m^2. Similarly, we defined three categories of total cholesterol levels: optimal SCL- SCL<200 and SCL>160, high normal SCL- SCL>200 and SCL<240, high SCL- SCL>240.

[1] Note that at onset of the FHS follow-up, respondents were at least 28.

[2] **BMI:** BMI is derived by dividing weight (in kg) by height square (m^2). Respondent's weights are measured at all exams but heights are missing for several exams (9 exams out of 24 exams). Since adults' height usually does not change during a short time interval, we assume that the height for the missing exams is same as of the nearest recorded exam (before age 50).

The risk factor exposures are defined in Table 8.1 as follows:

Table 8.1 Categorization of the risk factor exposures

Risk factor	Exclude	Optimal	Moderately elevated/high normal	High
Smoking (yes/no)		Never smoker	Ever smoker	Always smoker
Systolic blood pressure (mm Hg)	<100	100-119.9	120-139	140+
Diastolic blood pressure (mm Hg)	<60	60-79.9	80-89.9	90+
Serum cholesterol (mg per deciliter)	<160	160-199.9	200-239.9	240+
BMI (wg/m^2)	<18.5	18.5-24.9	25-29.9	30+

For males, the mean values in the optimal risk category were a BMI of 23 w/h^2, SBP 114 mm Hg, DBP 74 mm Hg and SCL 184 mg per deciliter, and in the high risk category, a BMI of 32 kg/m^2, SBP 152mm Hg, DBP 97mm Hg and SCL 270 mg per deciliter (Technical Appendix 8.1). Overall, the differences in mean values of the optimal risk profiles and high-risk profiles by sex were comparable. Respectively 67 percent and 18 percent of the men were defined as smokers and non-smokers, compared to 39 percent and 48 percent of the women. Nearly 56 percent of women (36 percent men) had a normal BMI. Thirty-six percent of women (26 percent men) were classified into the low SBP group. More than 21 percent of the sampled population had high SBP. Twenty-four percent of males had high DBP (16 percent females). Thirty percent of males and 24 percent of females had hypertension. Thirty-nine percent of men and 36 percent of women had high cholesterol levels.

The basic multi-state model has the state space {NO-CVD, history of CVD, dead} where each ((Figure 3.1(b), Chapter 3)) of the model has CVD represented by one of the specific CVD states: all *cardiovascular disease*, *all coronary heart disease,* a*cute myocardial infarction, stroke and congestive heart failure*. For example, for the CVD model, the possible transitions are *NO-CVD to death*, *NO-CVD to CVD*, and *CVD to death*. Following the risk factor categories as defined in Table 8.1, the number of possible transitions throughout 48 years of follow-up of the Framingham original cohort are presented in Technical Appendix 8.1. Since we have analyzed the data on men and women separately, the number of transitions by each category of risk

factor is given in Technical Appendix 8.1 by sex. There were always fewer people in the ever-smoking categories both for men and women.

8.2.3 Estimation of relative risk and model specification

Relative risk

To measure the effect of risk factors on disease incidence and mortality, we estimated the relative risk. The relative risk (RR) is the ratio of the absolute risk of a given group to that of a reference group, i.e. it is the ratio of two absolute risks. Literally, relative risk represents the ratio of the incidence in the exposed population divided by the incidence in the unexposed population. The denominator of the ratio can be either the average risk of the entire population or the risk of a group free of the risk factors. For instance, the relative risk of smokers developing cardiovascular disease can be defined as the ratio of the risk of a smoker developing CVD to the risk of non-smoker developing CVD. We have estimated the relative risks of each transition (e.g. from NO-CVD to CVD) separately for males and females. Relative risks were estimated to determine the likely effect of risk factors. To estimate the relative risk for an event occurrence throughout 48 years of follow-up of the FHS for each risk factor, the optimal risk category (e.g. never smoker in Table 8.1) of each risk factor was taken as the reference category. The events considered were death and the onset of all CVD, CHD, MI, CHF and stroke. The relative risk of each risk factor was calculated using Cox regression analysis, taking age at transition as the time scale.

Model specification

Univariate analysis was performed to estimate the effect of each single risk factor separately on disease incidence and post-disease mortality. Multivariate analysis was carried out to estimate the impact of several risk factors, as well as to investigate the potential confounding effects. If the relative risks were statistically significant, the upward or downward change in excess risk (CIER) in the multivariate model is given in the parenthesis with bold phase. This risk in the multivariate model is estimated using the following formula:

$$CIER = (RR_{multivariate} - RR_{univariate})/(RR_{univariate}-1)*100.$$

Take, for example, smoking for which the RR changes from 1.34 in univariate analysis to 1.44 in multivariate analysis, which is a change of 29%. An upward CIER is indicated by a "+", a downward CIER by a "-". The excess risk was estimated using the simple formula: RR-1.

We used Cox proportional hazard models to estimate the relative risk. A basic feature of the Cox proportional hazard model is that hazard curves or transition rates for different explanatory variables must be proportional to $\mu_0(x)$, the baseline hazard which is left unspecified. For each transition *i* to *j* we fit the Cox regression model with covariates and tested the assumption of proportionality. Although there are many procedures to test the proportionality, we applied two simple ones: (1) a *graphical method,* where we plotted the *log-log* of survival function, and (2) the *time-dependence of covariates*. We opted for the graphical method because we had categorical covariates with few categories. Sometimes the mere visual inspection of the plotted curves is inadequate for determining whether the differences in the log-log plot by different categories are sufficiently large as to violate the proportionality assumption. For instance, we tested the proportionality of listed risk factors on the process time of the occurrences of cardiovascular disease. If visual inspection was inadequate to inspect the proportionality, we tested the *time-dependence* of covariates. This test is based on the idea that if the proportionality assumption is correct, there should be no interaction effect between the covariates and process time. Details of this procedure are described elsewhere (Blossfeld and Rohwer, 2002).

We found a few cases where post-disease mortality rates were non-proportional for some of the risk factor status. For males, we found the CVD to death rates to be non-proportional by BMI categories; MI to death was non-proportional for BMI categories; stroke to death was non-proportional for smoking status. For females, we found CHD to death by BMI category to be non-proportional in the univariate analysis; MI to death was non-proportional in both the univariate and multivariate analysis for BMI category. Post-disease mortality was influenced by other factors status and disease treatment at that time. The association with risk factor status at midlife was complex as well. We estimated the relative risk of post-disease death, assuming that the proportionally assumption remains valid for all risk factor statuses

8.3 Results

8.3.1 Disease incidence

Univariate analysis

The effect of each risk factor on disease incidence and mortality was estimated separately for men and women (Table 8.2). For men, smoking was a highly significant predictor which increased the occurrences of CVD (RR= 1.34, CI: 1.11-1.61) and stroke (RR=1.82, CI: 1.17-2.82) compared to non-smoking. The higher the BMI in midlife, the higher the relative risk of CVD and its subtypes at older ages. This ranged from 1.23 (CI: 1.03-1.47) for CHD in the moderate BMI group to 2.37 (CI: 1.50-3.75) for stroke in the obese group. The relative risk of experiencing CHF was 2.20 (1.50-3.22) for obesity, which was consistent with the estimate by Kenchaiah et al. (2002). Both systolic and diastolic blood pressure had significantly positive effects on the occurrences of CVD and it subtypes. For moderately elevated SBP, the RR varied from 1.36 (CI: 1.14-1.62) for CVD to 1.68 (CI: 1.18-2.41) for stroke compared to optimal SBP. For high SBP, the RR ranged from 1.98 (CI: 1.47-2.66) for MI to 3.76 (CI: 2.56-5.52) for CHF. For high DBP, it fluctuated from 1.85 (CI: 1.51-2.26) for MI to 3.41 (2.33-5.01) for stroke. A similar effect was observed for the blood pressure categories. A high or moderately high cholesterol level had a significant effect on the occurrence of CVD, CHD, MI and CHF.

For women smokers, the risk of experiencing MI (RR=1.49, CI: 1.15-1.94), CHF (RR= 1.34, CI: 1.03-1.75) and stroke (RR=1.39, CI: 1.07-1.81) was higher and statistically significant compared to never smoking women. Females with moderate or high BMI in midlife had a significantly higher relative risk of experiencing CVD and its subtypes compared to the optimal BMI group. The higher the SBP or DBP or BP, the higher the relative risks for all cardiovascular disease subtypes. For high SBP, this ranged from 2.12 (CI: 1.52-2.96) for stroke to 3.19 (CI: 2.30-4.40) for CHF. For DBP it ranged from 2.25 for CVD (CI: 1.88-2.70) or MI (CI: 1.65-3.06) to 2.75 (CI: 2.03-3.72) for CHF. Like in men, high cholesterol levels in women had a significantly higher effect on the occurrence of CVD (RR= 1.51, CI: 1.23-1.85), CHD (RR=2.12, CI: 1.58-2.83) and MI (RR=1.79, CI: 1.23-2.60).

Table 8.2 Relative risk of cardiovascular disease and its subtypes (including sudden death) by single risk factor (95% confidence intervals in parentheses) during age 30-50

Male

Risk factors	CVD	CHD	MI	Stroke	CHF
Smoking status					
Never smoker	1.00	1.00	1.00	1.00	1.00
Ever smoker	1.03	0.85	0.79	1.86	0.92
	(0.80-1.31)	(0.64-1.13)	(0.55-1.13)	(1.10-1.176)	(0.57-1.48)
Always smoker	1.34	1.14	1.16	1.82	1. 30
	(1.11-1.61)	(0.93-1.40)	(0.90-1.50)	(1.17-2.82)	(0.93-1.81)
Log likelihood	-5292.65**	-3992.*	-2598.64*	-1212.12*	-1489.67
BMI					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.24	1.23	1.04	1.71	1.18
High normal	(1.07-1.45)	(1.03-1.47)	(0.84-1.30)	(1.21-2.40)	(0.88-1.57)
High	1.81	1.84	1.83	2.37	2.20
	(1.46-2.25)	(1.44-2.36)	(1.37-2.46	(1.50-3.75)	(1.50-3.22)
Log likelihood	-5285.96***	-3984.34***	-2490.93**	-1208.40**	-1484.51**
SBP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.36	1.47	1.46	1.41	1.68
High normal	(1.14-1.62)	(1.20-1.80)	(1.13-188)	(0.95-2.09)	(1.18-2.41)
High	2.30	1.98	1.97	3.27	3.76
	(1.88-2.81)	(1.56-2.52)	(1.47-2.66)	(2.15-4.97)	(2.56-5.52)
Log-likelihood	-5266.31***	-3979.26***	-2591.92***	-1199.14***	-1467.19***
DBP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.18	1.07	1.15	1.75	1.37
High normal	(1.00-1.39)	(0.88-1.30)	(0.91-1.45)	(1.20-2.55)	(1.00-1.89)
High	2.01	1.85	1.69	3.41	2.69
	(1.68-2.39)	(1.51-2.26)	(1.31-2.18)	(2.33-5.01)	(1.94-3.74)
Log likelihood	-5261.44***	-3975.32**	-2593.80**	-1196.04***	-1467.16***
BP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.34	1.42	1.42	1.46	1.48
High normal	(1.11-1.62)	(1.14-1.78)	(1.08-1.87)	(0.94-2.27)	(1.01-2.17)
High	2.19	2.09	1.96	3.17	3.22
	(1.80-2.68)	(1.65-2.65)	(1.47-2.63)	(2.04-4.91)	(2.19-4.74)
Log-likelihood	-5265.46***	-3974.87***	-2591.32***	-1198.46***	-1468.76***
SCL					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.53	1.56	1.43	1.34	0.84
High normal	(1.22-1.93)	(1.18-2.07)	(1.02-2.01)	(0.84-2.12)	(0.56-1.25)
High	2.22	2.48	2.08	1.45	1.50
	(1.76-2.79)	(1.88-3.27)	(1.49-2.91)	(0.91-2.31)	(1.02-2.19)
Log-likelihood	-5270.71***	-3966.47**	-2589.77***	-1215.17	-1483.43**

*p-value: *<0.05; **<0.01; ***<0.001*

Continuation of Table 8.2…

Female

Risk factors	CVD	CHD	MI	Stroke	CHF
Smoking status					
Never smoker	1.00	1.00	1.00	1.00	1.00
Ever smoker	1.00	0.84	1.14	1.29	1.10
	(0.80-1.25)	(0.62-1.13)	(0.76-1.72)	(0.86-1.94)	(0.73-1.66)
Always smoker	1.14	1.04	1.49	1.34	1.39
	(0.98-1.32)	(0.85-1.26)	(1.15-1.94)	(1.01-1.77)	(1.07-1.81)
Log likelihood	-5422.49	-3290.08	-1741.75*	-1570.40	-1753.59*
BMI					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.30	1.38	1.15	1.34	1.61
High normal	(1.12-1.52)	(1.13-1.69)	(0.87-1.53)	(1.02-1.77)	(1.23-2.11)
High	1.91	2.12	2.37	1.42	2.72
	(1.56-2.34)	(1.64-2.731)	(1.71-3.29)	(0.94-2.13)	(1.95-3.79)
Log likelihood	-5405.10***	-3274.87**	-1734.46***	-1569.86	-1739.66***
SBP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.59	1.64	1.87	1.27	1.57
High normal	(1.34-1.88)	(1.31-2.06)	(1.35-2.57)	(0.93-1.74)	(1.14-2.16)
High	2.57	2.57	3.01	2.12	3.19
	(2.14-3.10)	(2.02-3.28)	(2.14-4.22)	(1.52-2.96)	(2.30-4.40)
Log-likelihood	-5374.76***	-3261.48**	-1724.91***	-1562.90**	-1730.60***
DBP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.57	1.65	1.47	1.42	1.55
High normal	(1.34-1.48)	(1.34-2.04)	(1.10-1.95)	(1.05-1.92)	(1.16-2.07)
High	2.25	2.43	2.25	2.17	2.75
	(1.88-2.70)	(1.93-3.06)	(1.65-3.06)	(1.57-3.01)	(2.03-3.72)
Log likelihood	-5369.59***	-3247.56**	-1733.11***	-1555.34***	-1735.79***
BP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.60	1.62	1.85	1.30	1.55
High normal	(1.33-1.92)	(1.28-2.04)	(1.33-1.58)	(0.94-1.80)	(1.11-2.16)
High	2.60	2.57	2.72	2.10	3.13
	(2.15-3.13)	(2.02-3.29)	(1.93-3.84)	(1.50-2.94)	(2.25-4.35)
Log –likelihood	-5373.37***	-3261.41***	-1728.73***	-1563.08**	-1730.82***
SCL					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.12	1.49	1.16	0.79	0.89
High normal	(0.91-1.38)	(1.11-2.01)	(0.78-1.71)	(0.55-1.14)	(0.62-1.27)
High	1.51	2.12	1.79	1.11	1.25
	(1.23-1.85)	(1.58-2.83)	(1.23-2.60)	(0.78-1.58)	(0.88-1.75)
Log-likelihood	-5412.77***	-3275.07***	-1738.73**	-1569.92	-1672.47*

*p-value: *<0.05; **<0.01; ***<0.001*

Multivariate analysis

We studied the relative risk of cardiovascular disease or death associated with a risk factor adjusted for the presence of other risk factors in the multivariate analysis. We assumed that risk factors act independently, which meant that the level of a risk factor had no influence on the levels of the other risk factors that were present. The absence of interaction between risk factors is an assumption that was made because of inadequate sample size. The number of observations was not sufficient to study interaction effects between risk factors. Table 8.3 shows the relative risk of CVD and its subtypes associated with each risk factor when the effect of the risk factor is controlled or adjusted for the level of other risk factors. Results are presented separately for males and females.

Consider males. Always smoking increased the risk of CVD by 34% when the level of other risk factors (RR is 1.34 in univariate analysis) was not controlled for. When we controlled for the level of other risk factors, it increased to 44%, which is an upward CIER of 29%. The upward CIER is 28% for CHF and 33% for stroke. The RR of CVD and its subtypes for obese males was lower when the levels of other risk factors were controlled for than when they were not. The univariate analysis yielded an RR of 1.81; the multivariate analysis produced an RR of 1.48, which is a 41% downward CIER, indicating that part of the effect of obesity could be attributed to other risk factors. Obese males were likely to have unfavorable levels of other risk factors. Otherwise than might be expected, being obese did not increase the RR of CVD, as long as the other risk factors were at their optimal level. The downward CIER was 36% for MI and 58% for CHF. Similarly, for hypertension the downward CIER was 16% for CHF and 31% for CHD. For high cholesterol level, the downward CIER was about 20% for CVD, CHD or MI.

Similarly, when we controlled for the level of other risk factors for female smokers, the upward CIER was 53% for stroke and 136% for CVD. The RR of CVD and its subtypes for obese females was lower when the levels of other risk factors were controlled for than when they were not, indicating that part of the effect of obesity could be attributed to other risk factors. The downward CIER ranged from 32% for MI to 53% for CVD. Similarly, the downward CIER for hypertension was about 2% for stroke and 31% for CHD. For high cholesterol level, the downward CIER was about 28% for MI and 37% for CVD.

Table 8.3 Relative risk of cardiovascular disease and its subtypes (including sudden death) by multiple risk factor (95% confidence intervals in parentheses) status during age 30-50

Male

Risk factors	CVD	CHD	MI	Stroke	CHF
Smoking status					
Never smoker	1.00	1.00	1.00	1.00	1.00
Ever smoker	1.09 (0.85-1.40)	0.89 (0.67-1.19)	0.83 (0.58-1.20)	2.05 (+**22%**) (1.21-3.47)	0.96 (0.60-1.55)
Always smoker	1.44(**+29%**) (1.20-1.74)	1.21 (0.98-1.49)	1.24 (0.96-1.60)	2.06 (**+28%**) (1.32-3.19)	1.40 (+**33%**) (1.00-1.95)
BMI					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/ High normal	1.15 (0.99-1.35)	1.13 (0.94-1.36)	0.98 (0.77-1.21)	1.52 (-**27**%) (1.07-2.15)	1.02 (0.76-1.38)
High	1.48 (-**41%**) (1.18-1.85)	1.49 (-**42%**) (1.15-1.93)	1.53 (-**36%**) (1.19-2.08)	1.82 (-**40%**) (1.12-2.95)	1.51 (-**58%**) (1.08-2.26)
BP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/ High normal	1.25 (**-26%**) (1.03-1.52)	1.31 (-**26%**) (1.04-1.64)	1.35 (-**17%**) (1.02-1.79)	1.34 (0.85-1.09)	1.42 (0.96-2.10)
High	1.89 (-**25%**) (1.54-2.33)	1.75 (-**31%**) (1.37-2.24)	1.69 (-**28%**) (1.25-2.30)	2.76 (-**19%**) (1.74-4.36)	2.86 (-**16%**) (1.90-4.30)
SCL					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/ high normal	1.48 (-**9%**) (1.18-1.87)	1.49 (-**13%**) (1.13-2.98)	1.36 (0.97-1.91)	1.31 (0.82-2.08)	0.77 (0.52-1.14)
High	1.97 (-**20%**) (1.56-2.49)	2.20 (-**19%**) (1.67-2.92)	1.85 (-**21%**) (1.32-2.60)	1.21 (0.76-1.94)	1.23 (0.83-1.81)
Log likelihood	-5230.19***	-3944.18***	-2573.45***	-1188.39***	-1457.43***

*p-value: *<0.05; **<0.01; ***<0.001*

Continuation of Table 8.3…

Female

Risk factors	CVD	CHD	MI	Stroke	CHF
Smoking status					
Never smoker	1.00	1.00	1.00	1.00	1.00
Ever smoker	1.18	1.00	1.40	1.49)	1.41
	(0.94-1.49)	(0.74-1.37)	(0.92-2.12)	(0.99-2.25)	(0.93-2.13)
Always smoker	1.33(**+136%**)	1.21	1.82(+**67%**)	1.52(+**53%**)	1.78 (+**100%**)
	(1.14-1.56)	(0.99-1.48)	(1.38-2.39)	(1.14-2.02)	(1.36-2.33)
BMI					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.13	1.19	1.04	1.22	1.43 (-**30%**)
high normal	(0.96-1.32)	(0.97-1.46)	(0.78-1.39)	(0.92-1.64)	(1.08-1.90)
High	1.43 (**-53%**)	1.60 (-**46%**)	1.93 (-**32%**)	1.11	2.04 (-**40%**)
	(1.15-1.79)	(1.21-2.11)	(1.34-2.77)	(0.72-1.73)	(1.42-2.94)
BP					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.52 (-**13%**)	1.47 (-**24%**)	1.76 (-**11%**)	1.29	1.45 (-**18%**)
high normal	(1.27-1.82)	(1.15-1.86)	(1.26-2.47)	(0.92-1.79)	(1.03-2.04)
High	2.34 (-**16%**)	2.08 (-**31%**)	2.35 (-**13%**)	2.08 (-**2%**)	2.64 (-**23%**)
	(1.91-2.88)	(1.59-2.72)	(1.61-3.44)	(1.44-3.02)	(1.84-3.80)
SCL					
Optimal	1.00	1.00	1.00	1.00	1.00
Elevated/	1.09	1.44 (-**10%**)	1.12	0.79	0.85
high normal	(0.89-1.35)	(1.07-1.94)	(0.76-1.66)	(0.54-1.13)	(0.60-1.22)
High	1.32 (-**37%**)	1.83 (-**26%**)	1.57 (-**28%**)	1.01	1.06
	(1.07-1.62)	(1.37-2.46)	(1.07-2.28)	(0.71-1.44)	(0.75-1.50)
Log likelihood	-5358.38***	-3245.01***	-1710.11***	-1556.23**	-1715.32***

*p-value: *<0.05; **<0.01; ***<0.001*

8.3.2 Death

The risk of death after having experienced cardiovascular disease is heavily dependent on the severity of the disease. The transition to death is classified into three categories: *alive to death* (irrespective of disease status), *free of disease to death* and *post-disease death*. Here, alive to death transitions are considered, irrespective of any cardiovascular diseases. Using a two-state model (model 3.1(a)), the risk factor status at middle age and the burden on overall mortality is estimated in terms of the relative risk of dying. The transition from free of disease to death refers to the death that occurs without experiencing any cardiovascular disease. Post-disease death is the death that occurs after having experienced any cardiovascular disease[3]. Both the univariate and multivariate analysis was performed for all three types of transitions. The effect of risk factors on three different types of transitions to death might not be same.

[3] Cause of death is not necessarily cardiovascular disease

Univariate analysis

The relative risk of dying for each single risk factor category is presented in Table 8.4. For males, the rates of death (any type, except from MI or stroke) for smokers were considerably higher. The relative risk was 1.63 (CI: 1.39-1.99) for the transition from alive to death, 1.84 (CI: 1.34-2.52) for free of CVD to death and 1.24 (CI: 1.01-1.54) for post-disease death. The effect of obesity on overall mortality was significantly higher (RR=1.47, CI: 1.20-1.80) compared to normal BMI. The relative risk of death, whether from alive or from CVD, from CHD or from MI was significantly higher for the males with high SBP, DBP or BP at middle age. For males with high BP, this ranged from 1.33 (CI: 1.00-1.85) for MI to death to 1.85 for alive to death. Cholesterol levels at middle age and mortality at older ages were only significant for post-CHF death (RR=1.57, CI: 1.03-2.41).

For female always smokers, the risk of any type of death except from MI was significantly higher than for non-smokers. RR ranged from 1.34 (CI: 0.99-1.83) for CHF to 1.85 (CI: 1.45-2.34) for CHD. Like males, the overall mortality (irrespective of disease status) in the obese females was significantly higher (RR=1.54, CI: 1.29-1.85) than the normal BMI group. The effect of high SBP was significantly larger for the transition alive to death, CVD to death or CHD to death. The effect of elevated or high DBP and BP was significantly higher only for overall deaths (irrespective of disease status). For females, high cholesterol levels at middle age had significant impact on overall mortality and post-disease deaths. The RR ranged from 1.32 (CI: 1.10-1.58) for alive to death to 1.95 (CI: 1.28-2.96) for death from CHF. High normal cholesterol levels also had a significant impact on post-stroke deaths (RR=1.75, CI: 1.12-2.74) or CHF (RR=1.57, CI: 1.01-2.43).

Table 8.4 Relative risk of deaths (total death and post-disease death) by single risk factor (95% confidence intervals in parentheses) status during age 30-50

Male

Risk factors	Alive	NO-CVD	CVD	CHD	MI	Stroke	CHF
Smoking status							
Never smoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ever smoker	1.12	1.34	1.00	0.92	0.74	1.20	0.80
	(0.88-1.43)	(0.88-2.03)	(0.74-1.34)	(0.65-1.29)	(0.48-1.13)	(0.67-2.18)	(0.47-1.37)
Always smoker	1.63	1.84	1.24	1.20	0.91	1.03	1.40
	(1.39-1.99)	(1.34-2.52)	(1.01-1.54)	(0.95-1.52)	(0.69-1.21)	(0.65-1.66)	(0.96-2.05)
Log likelihood	-6202.52***	-2078.23**	-3345.88*	-2390.01	-1409.08	-540.22	-640.20*
BMI							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.08	0.84	1.00	1.02	0.97	0.81	0.82
high normal	(0.94-1.24)	(0.67-1.07)	(0.84-1.19)	(0.83-1.25)	(0.76-1.24)	(0.56-1.18)	(0.60-1.13)
High	1.47	1.07	1.03	1.11	1.05	0.74	0.72
	(1.20-1.80)	(0.75-1.54)	(0.81-1.32)	(0.84-1.47)	(0.76-1.46)	(0.44-1.22)	(0.46-1.11)
Log likelihood	-6216.73**	-2085.62	-3349.09	-2392.27	-1409.97	-539.60	-643.19
SBP							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.17*	0.91	1.08	1.23	1.13	0.79	0.58
High normal	(1.00-1.37)	(0.71-1.17)	(0.88-1.32)	(0.97-1.56)	(0.84-1.51)	(0.51-1.22)	(0.39-0.86
High	2.05	1.12	1.59	1.87	1.69	1.13	0.87
	(1.71-2.45)	(0.81-1.55)	(1.27-1.99)	(1.43-2.44)	(1.21-2.36)	(0.71-1.80)	(0.57-1.33)
Log likelihood	-6190.84***	-2086.07	-3338.51**	-2381.19**	-1404.44**	-538.46	-639.47
DBP							
Optimal	1.00	1.00	1.00	1.00	1.000	1.000	1.000
Elevated/	1.11	1.04	1.08	1.16	1.28	0.92	0.77
high normal	(0.95-1.28)	(0.81-1.32)	(0.89-1.30)	(0.94-1.44)	(0.98-1.66)	(0.61-1.42)	(0.53-1.09)
High	1.80	1.08	1.40	1.42	1.43	1.31	0.85
	(1.53-2.12)	(0.80-1.46)	(1.15-1.70)	(1.13-1.77)	(1.08-1.90)	(0.86-1.99)	(0.59-1.23)
Log likelihood	-6181.88***	-2079.95	-3339.56**	-2387.85*	-1406.76*	-538.71	-642.72
BP							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.15	0.94	1.09	1.20	1.03	0.97	0.63
High normal	(0.97-1.37)	(0.72-1.23)	(0.87-1.36)	(0.93-1.56)	(0.75-1.42)	(0.59-1.60)	(0.42-0.97)
High	1.85	1.01	1.46	1.52	1.33	1.33	0.72
	(1.55-2.21)	(0.74-1.37)	(1.16-1.83)	(1.16-1.98)	(1.00-1.85)	(0.81-2.17)	(0.47-1.10)
Log-likelihood	-6194.29***	-2086.89	-3341.45**	-2387.15**	-1407.65	-538.78	-642.42
SCL							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.03	0.70	0.90	1.09	1.00	1.28	2.12
High normal	(0.85-1.24)	(0.53-0.92)	(0.70-1.17)	(0.79-1.50)	(0.68-1.48)	(0.76-0.21)	(1.36-3.30)
High	1.18	0.58	0.82	1.01	1.01	1.25	1.57
	(0.97-1.42)	(0.43-0.79)	(0.64-1.07)	(0.73-1.39)	(0.69-1.50)	(0.74-2.12)	(1.03-2.41)
Log likelihood	-6220.93*	-2081.00*	-3347.86	2392.24	-1410.10	-540.01	-638.49*

*p-value: *<0.05; **<0.01; ***<0.001*

Continuation of Table 8.4…

Female

Risk factors	Alive	NO-CVD	CVD	CHD	MI	Stroke	CHF
Smoking status							
Never smoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ever smoker	1.09	1.24	0.98	1.13	1.03	0.69	1.60
	(0.87-1.36)	(0.90-1.71)	(0.72-1.34)	(0.76-1.69)	(0.63-1.69)	(0.40-1.22)	(0.98-2.62)
Always smoker	1.73	1.93	1.68	1.85	1.25	1.64	1.34
	(1.51-1.98)	(1.59-2.36)	(1.40-2.02)	(1.45-2.34)	(0.91-1.72)	(1.19-2.26)	(0.99-1.83)
Log likelihood	-6643.01***	-3034.25***	-2824.33**	-1545.66**	-725.18	-632.80**	-691.98
BMI							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.06	0.92	0.93	0.78	0.88	1.23	1.17
High normal	(0.93-1.22)	(0.75-1.13)	(0.77-1.12)	(0.61-1.00)	(0.63-1.23)	(0.89-1.71)	(0.85-1.61)
High	1.54	1.11	1.15	1.06	1.26	1.00	1.34
	(1.29-1.85)	(0.83-1.49)	(0.91-1.45)	(0.79-1.43)	(0.87-1.82)	(0.63-1.59)	(0.92-1.96)
Log likelihood	-6666.37***	-3054.86	-2840.06	-1555.54	-724.70	-639.37	-693.35
SBP							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.27	1.04	0.97	0.94	1.86	1.11	1.07
High normal	(1.09-1.47)	(0.84-1.28)	(0.78-1.20)	(0.70-1.25)	(0.58-1.28)	(0.75-1.64)	(0.73-1.58)
High	1.90	1.10	1.35	1.46	1.41	1.24	1.35
	(1.61-2.23)	(0.86-1.42)	(1.08-1.69)	(1.09-1.95)	(0.95-2.09)	(0.83-1.84)	(0.92-1.98)
Log likelihood	-6646.84***	-3055.30	-2835.12**	-1551.62**	-721.68*	-639.69	-692.99
DBP							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.23	0.97	1.01	0.95	0.91	1.05	1.07
High normal	(1.07-1.42)	(0.80-1.23)	(0.83-1.23)	(0.73-1.24)	(0.64-1.28)	(0.74-1.50)	(0.76-1.51)
High	1.69	1.14	1.16	1.20	1.39	1.02	1.02
	(1.44-1.99)	(0.89-1.47)	(0.94-1.43)	0.91-1.57)	(0.98-1.98)	(0.68-1.48)	(0.72-1.43)
Log likelihood	-6648.40***	-3054.35	-2834.52	-1551.57	723.32*	636.30	694.50
BP							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.28	1.04	1.05	1.05	0.90	1.32	1.09
High normal	(1.10-1.50)	(0.84-1.29)	(0.84-1.32)	(0.77-1.41)	(0.60-1.35)	(0.87-1.98)	(0.73-1.63)
High	1.83	1.10	1.23	1.28	1.41	1.07	1.24
	(1.55-2.15)	(0.86-1.41)	(0.98-1.55)	(0.94-1.72)	(0.94-2.10)	(0.71-1.62)	(0.84-1.84)
Log likelihood	-6649.92***	-3055.27	-2839.34	-1556.50	-722.34*	-639.12	-693.88
SCL							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.07	0.98	1.25	1.16	1.41	1.75	1.57
high normal	(0.89-1.29)	(0.75-1.26)	(0.95-1.64)	(0.79-1.70)	(0.87-2.28)	(1.12-2.74)	(1.01-2.43)
High	1.32	0.98	1.43	1.47	1.33	1.62	1.95
	(1.10-1.58)	(0.75-1.27)	(1.10-1.85)	(1.02-2.12)	(0.83-2.11)	(1.07-2.48)	(1.28-2.96)
Log likelihood	-6670.01**	-3055.57	-2837.36*	-1555.00	-725.17	-636.59*	-689.11**

*p-value: *<0.05; **<0.01; ***<0.001*

Multivariate analysis

The multivariate analysis of mortality describes the change in excess risks of death that are associated with a risk factor, after controlling for the levels of the other risk factors. Male always smokers had an excess risk of death (irrespective of disease status) of 63% without controlling for the levels of other risk factors and 72% if the levels of the other risk factors were controlled for. When other risk factors were controlled for, the CIER of death for always smoking was 14% upward. The upward CIER of death for always-smoking males with CVD was 25% after controlling for the levels of other risk factors (RR increased from 1.24 to 1.30). For obesity, the effect of controlling for the levels of risk factors was different. The RR of death, irrespective of whether the person had CVD or not, declined from 1.47 in the absence of any control to 1.27 if the levels of other risk factors were controlled for. The downward CIER of mortality was 43%.

Table 8.5 Relative risk of deaths (total death and post-disease death) by multiple risk factor (95% confidence intervals in parentheses) status during age 30-50

Male

Risk factors	Alive	NO-CVD	CVD	CHD	MI	Stroke	CHF
Smoking status							
Never smoker	1.00	1.00	1.00	1.00	1.000	1.000	1.000
Ever smoker	1.17	1.31	1.04	0.98	0.73	1.55	0.83
	(0.92- 1.49)	(0.86- 1.99)	(0.77-1.40)	(0.70-1.38)	(0.47-1.13)	(0.83-2.90)	(0.48-1.44)
Always	1.72(+**14%**)	1.86 (+2%)	1.30(+**33%**)	1.26(**+30%**)	0.94	1.12	1.20
Smoker	(1.44-2.05)	(1.35-2.55)	(1.05-1.62)	(1.00-1.60)	(0.71-1.25)	(0.68-1.84)	(0.80-1.80)
BMI							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.03	0.89	0.94	0.92	0.89	0.71	0.86
High normal	(0.89- 1.19)	(0.70- 1.13)	(0.78-1.12)	(0.75-1.14)	(0.69-1.16)	(0.47-1.07)	(0.62-1.19)
High	1.27 (-**42%**)	1.18	0.91	0.92	0.85	0.57	0.75
	(1.03-1.58)	(0.81-1.56)	(0.70-1.18)	(0.68-1.25)	(0.59-1.23)	(0.33-1.00)	(0.47-1.21)
BP							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.16	1.02	1.16	1.27	1.07	1.13	0.69
high normal	(0.97-1.38)	(0.77- 1.34)	(0.92-1.46)	(0.97-1.66)	(0.77-1.48)	(0.66-1.95)	(0.44-1.07)
High	1.81 (-**5%**)	1.13	1.59(+**28%**)	1.64(+**23%**)	1.4(+**30%**)	1.57	0.79
	(1.50-2.19)	(0.81-1.56)	(1.25-2.03)	(1.22-2.20)	(1.00-2.06)	(0.92-2.68)	(0.49-1.27)
SCL							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	0.97	0.69 (-**3%**)	0.84	1.00	0.95	1.41	1.93(-**17%**)
high normal	(0.80- 1.17)	(0.52- 0.91)	(0.65-1.10)	(0.72-1.39)	(0.64-1.41)	(0.82-2.43)	(1.23-3.07)
High	1.04	0.56 (-**3%**)	0.77 (-**6%**)	0.93	0.97	1.29	1.55
	(0.86-1.26)	(0.41-0.76)	(0.59-1.00)	(0.68-1.29)	(0.65-1.44)	(0.74-2.24)	(0.98-2.44)
Log likelihood	-6167.58***	-2070.14***	-3335.11**	-2383.44*	-1406.18	-535.82	-633.84**

*p-value: *<0.05; **<0.01; ***<0.001*

Continuation of Table 8.5…

Female

Risk factors	Alive	NO-CVD	CVD	CHD	MI	Stroke	CHF
Smoking status							
Never smoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ever smoker	1.23	1.29	1.05	1.21	1.02	0.76	2.0(+**65%**)
	(0.99-1.55)	(0.93- 1.78)	(0.77-1.44)	(0.80-1.82)	(0.61-1.69	(0.43-1.35)	(1.19-3.33)
Always	1.94(+**29%**)	2.01(+**9%**)	1.75(+**10%**)	1.90(+**6%**)	1.16	1.81(+**27%**)	1.4(+**15%**)
smoker	(1.69-2.22)	(1.64-2.46)	(1.45-2.11)	(1.49-2.43)	(0.84-1.60)	(1.28-2.57)	(1.00-1.92)
BMI							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.02	0.99	0.96	0.80	0.79	1.37	1.15
high normal	(0.88- 1.18)	(0.79- 1.22)	(0.79-1.17)	(0.62-1.03)	(0.55-1.12)	(0.97-1.96)	(0.81-1.62)
High	1.33 (-**39%**)	1.19	1.09	0.95	0.93	1.05	1.13
	(1.09-1.63)	(0.86-1.64)	(0.84-1.42)	(0.68-1.33)	(0.59-1.45)	(0.63-1.77)	(0.71-1.81)
BP							
Normal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	1.30(+**7%**)	1.09	1.07	1.15	0.91	1.17	1.11
Elevated/high	(1.11- 1.52)	(0.87- 1.35)	(0.85-1.35)	(0.85-1.57)	(0.60-1.37)	(0.77-1.78)	(0.73-1.67)
Normal							
High	1.85(+**2%**)	1.21	1.27(+**17%**)	1.4(+**57%**)	1.40	0.95	1.25
	(1.55-2.22)	(0.92-1.59)	(1.00-1.63)	(1.03-2.00	(0.90-2.17)	(0.62-1.48)	(0.80-2.53)
SCL							
Optimal	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Elevated/	1.07	0.99	1.23	1.14	1.31	1.87(+**16%**)	1.62(+**9%**)
high normal	(0.89- 1.29)	(0.76-1.28)	(0.94-1.61)	(0.78-1.68)	(0.79-2.14)	(1.18-2.96)	(1.04-2.53)
High	1.22 (-**31%**)	0.96	1.39(-**9%**)	1.49 (-**4%**)	1.27	1.46	1.97(+**2%**)
	(1.01-1.46)	(0.74-1.25)	(1.07-1.61)	(1.03-2.16)	(0.78-2.06)	(0.94-2.26)	(1.27-3.05)
Log likelihood	-6599.02***	-3031.93***	-2816.75***	-1537.27**	-720.29	-626.27***	-684.45**

*p-value: *<0.05; **<0.01; ***<0.001*

Similarly, female always smokers had an excess risk of death of 73% if the levels of other risk factors were not considered and 94% if the levels of the other risk factors were controlled for. The upward CIER of death for females who always smoke and have suffered a stroke was 27% after controlling for the levels of other risk factors. The downward CIER of death, irrespective of disease status for females who are obese, was 39%after controlling for the levels of other risk factors.

8.4 Discussion

In this chapter, we performed both univariate and multivariate analyses of the major cardiovascular risk factors in middle age and their effects on cardiovascular disease, its subtypes and mortality over a long follow-up. Both for men and women, the effect of being in a high risk category between the ages of 30 and 50 and the disease incidence in older ages of life was highly significant. It was also observed that the impact of moderately normal risk profiles at middle age also had a significant effect on the occurrence of CVD and its subtypes. This reinforces Grundy et al., (1999), who stated that while the ' short-term risk may not be high in

adult population who have multiple risk factors of only moderate severity, long-term risk can be unacceptably high'. The relative risk of experiencing cardiovascular disease and its subtypes was the highest for men or women who had high SBP or hypertension at middle age compared to being in high-risk of other risk factors. The relative risk of experiencing CVD or CHD or MI was also higher for males who had high cholesterol levels at middle life. For females, the second highest important risk factor to experience CVD or CHD was the DBP.

In this chapter, we investigated the long-term nature of relationships, not only of primary relationships as shown in univariate analyses, but also of confounding relationships as shown in the changes of relative risk after adjusting for the levels of other risk factors. Both for men and women, the adjusted relative risk and the risk of experiencing congestive heart failure were consistent with the previous study by Kenchaiah et al., (2002), who examined the relation of BMI to the risk of heart failure. In the multivariate model, the estimated risk of coronary heart disease by blood pressure and total cholesterol categories was consistent with the previous study (Wilson et al., 1998).

The association between the risk factors at middle age and post-disease death at older age is complex. However, in the multivariate model, the CIER of dying associated with smoking was upward; for obesity, downward. A male with high a cholesterol level was shown to have a significantly lower risk of post-disease death than a male with an optimal cholesterol level. By contrast, a female with high cholesterol had significantly higher post-disease (CHD, MI or CHF) mortality. While there have been reports that optimal cholesterol may be associated with increased mortality (Schatz et al., 2001), it is unclear as to what extent the results presented here support this or are merely due to chance.

The effect of a risk factor in a multiple risk factor context was controlled for the confounding effects of other risk factors. Therefore, the RR in multiple risk factor contexts could go up or down compared to the RR estimated in univariate analysis. For example, when we controlled for the level of other risk factors in male smokers the upward change in excess risk was 29% for CVD. The relative risk of CVD and its subtypes for obese males was lower when the levels of other risk factors were controlled for than when they were not. The direction in which the relative risk moves (e.g. upward for smoking and downward for obesity) is likely to be the result of the pattern of co-occurrence of risk factors in the population. In the FHS population, smokers were probably less exposed to other risk factors than non-smokers, which would explain why the RR goes up; obese people more than non-obese people, which is why the RR goes down. The substantive interpretation could be that smoking prevents obesity, and obesity leads to high serum cholesterol and high blood pressure.

We tested several interaction effects among the risk factors states. We found no risk factor interaction that significantly affected the occurrence of cardiovascular

disease and post-disease death rates. The main reason could be the small sample size. Although interactions between risk factors did exist, the sample size did not permit the study of the interaction effects. We analyzed the data separately for males and females since cardiovascular risk factors and gender differentials in all-cause and cardiovascular disease mortality are not same (Janghorbani et al., 1993; Castelli 1984; Thom et al., 1992; WHO MONICA Project, 1994).

The major strength of this chapter is that the Framingham Heart Study has accurate long follow-up of the cardiovascular disease incidence and mortality and the record of risk factor by biannual interview. Using this long-time follow-up information, it was possible to measure the impact of risk factor status in middle age and the disease incidence and mortality at older ages.

Upward or downward changes in excess risk of CVD and mortality affect the outcomes of life table analysis, which is the subject of chapter 9. For example, always smoking was shown to lead to a greater excess risk of CVD and mortality for males of normal weight, with an optimal blood pressure and an optimal cholesterol level than for average males. Therefore, a larger effect on life expectancy of smokers and non-smokers might be expected after adjusting for potential confounders than in the absence of adjustments. Similarly, the difference in expected lifetime between obese persons and persons with normal weight might be smaller when other risk factors are controlled for (multivariate analysis) than when they are not (univariate analysis).

The findings of this chapter highlight the need for early prevention of high levels of major cardiovascular risk factors. Appropriate prevention has the potential to bring about a significant reduction in long-term risk.

References

Anderson KM, Odell P, Wilson PWF, Kannel WB, (1991). Cardiovascular disease risk profiles. *American Heart Journal,* 121(1):293-298.

Anderson KM, Wilson PWF, Odell P, Kannel WB, (1991). An updated coronary risk profile. A statement for health professionals. *Circulation,* 83:356-362.

Berenson GS, Srinivasan SR, Bao W, et al., (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *New England Journal of Medicine,* 338:1650-1656.

Blossfeld, HP, Rohwer G, (2002). *Techniques of Event History Modeling. New Approaches to Causal Analysis*. Second edition, Lawrence Erlbaum Associates, Mahwah, New Jersey.

Castelli WP, (1984). Epidemiology of coronary heart disease: the Framingham Study. *American Journal of Medicine*, 76:4–12.

Daviglus ML, Liu K, Greenland P, et al., (1998). Benefits of a favorable cardiovascular risk-factor profile in middle age with respect to medicare costs. *New England Journal of Medicine*, 339:1122-9.

Dawber TR, Meadors GF, Moore FE, (1951). Epidemiological approaches to heart disease: the Framingham Heart Study. *American Journal of Public Health*, 41:279-86.

Grundy SM, Pasternak R, Greenland P, et al., (1999). Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation,* 100:1481-1492.

Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, et al., (1992). Report of the Conference on Low Blood Cholesterol: Mortality Associations. *Circulation,* 86(3):1046-60.

Janghorbani M, Heldey AJ, Jones RB et al., (1993). Gender differential in all-cause and cardiovascular disease mortality, *International Journal of Epidemiology*, 22:1065-1063.

Kenchaiah S, Evans JC, Levy D, et al., (2002). Obesity and the risk of heart failure. *New England Journal of Medicine*, 347(5):305-313.

Lowe LP, Greenland P, Ruth KJ, et al., (1998). Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Archive of Internal Medicine*, 158:2007-2014.

Norrish A, North D, Lee RL, Jackson R, (1995). Do cardiovascular disease risk factors predict all-cause mortality? *International Journal of Epidemiology,* 24(5):908-914.

Pooling Project Research Group, (1978). Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *Journal of Chronic Diseases*, 31:201-306.

Stamler J, Stamler R, Neaton JD, et al., (1999). Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy. *Journal of American Medical Association*, 282(21):2012-2018.

Schatz IJ, Masaki K, Yano K., et al., (2001). Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *The Lancet*, 358:351-355.

Thom TJ, Epstein FH, Feldman JJ et al., (1992). Total mortality and mortality from heart disease, cancer and stroke from 1950 to 1987 in 27 countries. National Institutes of Health (NIH), USA, NIH publication 92–3088.

Wilson PWF, Ralph B, Agostino D, et al., (1998). Prediction of coronary heart disease using risk factor categories. *Circulation*, 97:1837-1847.

WHO MONICA Project, (prepared by Tunstall-Pedoe H, Kuulasmaa K, Amouyel P et al.), (1994). Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation*, 90:583–612.

World Health Organization (1998). Obesity. Preventing and Managing the Global Epidemic. Report of a WHO Consultation on Obesity, 3-5 June 1997. World health Organization, Geneva, Switzerland.

World Health Organization (1999). Guidelines Subcommittee: 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. Journal of Hypertension, 17:151-183.

World Health Organization (2002). Life course perspectives on coronary heart disease, stroke and diabetes. Key issues and implications for policy and research. Summary report of a meeting of experts 2-4 Mat 2001. Department of Noncommunicable Disease Prevention and Health Promotion. Noncommunicable Disease and Mental Health Cluster, World Health Organization, Geneva.

Technical Appendix 8.1

Risk factor characteristics, observed state occupancies, and number of possible transitions in FHS

Male

	Smoking status			BMI			SBP			DBP			BP			SCL		
	N	E	A[+]	I	II	III[++]	I	II	III	I	II	III	I	II	III	I	II	III
Number	235	207	887	480	683	166	342	697	290	480	522	325	292	638	399	211	597	521
Mean	-	--	-	23	27	32	114	129	152	74	84	97	-	-	-	184	220	270
Alive to death	157	119	695	344	495	132	229	490	252	328	362	279	193	440	338	147	434	390
CVD model																		
NoCVD to death	47	42	235	135	151	38	98	165	61	126	131	66	84	158	82	75	150	99
NoCVD to CVD	144	115	556	269	427	119	180	423	212	266	309	239	149	377	289	91	357	367
CVD to death	110	77	460	209	344	94	131	325	191	202	231	213	109	282	256	72	284	291
CHD model																		
NoCHD to death	63	64	353	191	235	54	137	226	117	170	191	117	116	214	150	102	226	152
NoCHD to CHD	115	80	408	196	313	94	126	331	146	201	220	182	104	288	211	60	250	293
CHD to death	94	55	342	153	260	78	92	264	135	158	171	162	77	226	188	45	208	238
MI model																		
NoMI to death	92	87	473	236	338	78	169	317	166	227	242	181	141	292	219	116	294	242
NoMI to MI	77	48	267	136	190	66	82	216	94	130	152	110	69	190	133	42	164	186
MI to death	65	32	222	108	157	54	60	173	86	101	120	98	52	148	119	31	140	148
Stroke model																		
NoCVM to death	136	95	585	302	406	108	201	418	197	293	307	214	172	380	264	129	359	328
NoCVM to CVM	24	34	126	48	106	30	35	89	60	43	73	68	27	77	80	23	86	75
CVM to death	21	24	110	42	89	24	28	72	55	35	55	65	21	60	74	18	75	62
CHF model																		
NoCHF to death	117	96	551	275	390	99	194	389	181	271	284	208	163	354	247	119	358	287
NoCHF to CHF	46	28	161	76	118	41	40	119	76	66	89	79	35	100	100	34	86	115
CHF to death	40	23	144	69	105	33	35	101	71	57	78	71	30	86	91	28	76	103

[+]N- never smoker; E- ever smoker; A- always smoker

[++] I- optimal, II- high normal or elevated, III- high

Female

	Smoking status			BMI			SBP			DBP			BP			SCL		
	N	E	A[+]	I	II	III[++]	I	II	III	I	II	III	I	II	III	I	II	III
Number	829	220	667	973	543	200	617	731	368	879	543	291	572	732	412	329	726	661
Mean	-	--	-	22	27	34	113	128	156	74	84	98	-	-	-	185	220	273
Alive to death	457	96	446	518	330	151	283	415	301	435	326	237	257	411	331	157	391	451
CVD model																		
NoCVD to death	189	47	215	257	140	54	160	192	99	229	138	84	147	190	114	84	189	178
NoCVD to CVD	397	93	306	396	279	121	212	346	238	330	281	183	190	343	263	123	311	362
CVD to death	268	49	231	261	190	97	123	223	202	206	188	153	110	221	217	73	202	273
CHD model																		
NoCHD to death	289	67	313	368	215	86	212	283	174	320	213	136	194	280	195	123	274	272
NoCHD to CHD	246	50	178	225	169	80	118	208	148	183	169	120	107	204	163	57	185	232
CHD to death	168	29	133	150	115	65	71	132	127	115	113	101	63	131	136	34	117	179
MI model																		
NoMI to death	370	75	362	430	269	108	245	338	224	367	262	177	222	334	251	135	323	349
NoMI to MI	55	114	86	101	87	67	35	92	128	87	21	84	51	114	90	88	61	43
MI to death	87	21	84	88	61	43	38	77	77	68	64	60	35	77	80	22	68	102
Stroke model																		
NoCVM to death	374	81	366	432	262	127	243	342	236	372	263	186	222	336	263	128	329	364
NoCVM to CVM	113	30	90	114	90	29	66	95	72	94	79	59	59	95	79	44	83	106
CVM to death	83	15	80	86	68	24	40	73	65	63	63	51	35	75	68	29	62	87
CHF model																		
NoCHF to death	360	75	363	440	253	105	243	339	216	366	259	172	220	339	239	128	319	351
NoCHF to CHF	129	29	104	108	102	52	59	105	98	96	89	77	53	101	108	45	94	123
CHF to death	97	21	83	78	77	46	40	76	85	67	69	65	37	72	92	29	72	100

[+]N- never smoker; E- ever smoker; A- always smoker

[++] I- optimal, II- high normal or elevated, III- high