9

Risk factors and compression of cardiovascular morbidity

Abstract

The objective of this chapter is to investigate whether being at optimal risk for the major cardiovascular risk factors at middle age (age 30-50) compresses cardiovascular morbidity. We used the first 48 years of follow-up of the Framingham Heart Study original cohort. We considered several risk factors separately (univariate analysis) and in combination (multivariate analysis). We distinguished two risk status levels: optimal (also referred to as favorable) and high-risk. In the univariate analysis, we constructed multistate life tables for optimal and high-risk categories of each single risk factor. In the case of the multivariate analysis, the optimal risk profile was defined as a never smoker, with, on average, an optimal blood pressure (SBP<120 and DBP<80), optimal cholesterol level (SCL<200) and optimal BMI (BMI<25) between age 30 and 50. The high-risk profile was defined as a smoker, with high blood pressure (SBP>140 or DBP>90), high serum cholesterol (SCL>240) and obesity (BMI>30). The effects of an optimal (high) risk factor profile combined the effects of optimal (high) single risk factors. These were not based on observations of individuals with such combinations, as they did not exist in the data set. Age-specific transition rates were estimated using a Gompertz regression model both for the univariate and multivariate analysis. The univariate analysis indicated that the difference in life expectancy free of CVD for males is the highest between optimal and high SBP (7.29 years). For females, this difference was the highest between optimal blood pressure and hypertension (7.84 years). While the differences in life expectancy with CVD between low cholesterol and high cholesterol levels are the highest for males (3.71 years more for high cholesterol), it is the highest between optimal BP and hypertension categories for females (3.00 years more for hypertension). Univariate analysis indicated that the major cardiovascular risk factors (except smoking) at middle age compressed cardiovascular morbidity. Multivariate analysis shows that a fifty year-old male with an optimal risk profile can expect to survive 6 additional

years compared to the total male population in the FHS. Similarly, fifty year-old females in the optimal risk group, can expect to survive 5 additional years compared to the total females in the FHS. At age 50, a male with an optimal risk profile can expect to survive 17 years more free of cardiovascular disease compared to a subject with a high-risk profile; a similarly aged female can expect to survive an extra 16 years compared to females with a high-risk profile. A high-risk profile at middle age shortens the duration of life, increases the lifetime probability of experiencing CVD and extends the period of life spent with cardiovascular disease. As the optimal risk profile increases the number of years lived free of cardiovascular disease and decreases the years lived with cardiovascular disease, we can conclude that an optimal risk profile for major cardiovascular disease risk factors in middle age compresses cardiovascular morbidity.

9.1 Introduction

The impact of risk factors on the cardiovascular disease incidence and mortality has been estimated in the past (Stamler et al., 1999; Anderson et al., 1991). However, what is not known is whether optimal risk status for the most common cardiovascular risk factors compresses cardiovascular morbidity. The primary objective of this chapter is to investigate whether being at optimal risk (both in single risk factor and combined risk factor status) for the major cardiovascular risk factors (both single risk factor status and multiple risk factor profiles) at middle age compresses cardiovascular morbidity. Henceforth, the term risk factor "profiles" will refer solely to a status defined by combination of risk factors. Here, we estimate the population burden of cardiovascular risk factors, expressed as life years lost to disease, life with disease, and life years lost through death i.e. life expectancy.

Experience has shown that a multifactoral approach, one that takes into consideration most of the risk factors, is probably the best strategy for the prevention of cardiovascular disease (Anderson et al., 1991; Lowe et al., 1998) and premature death. The multifactoral risk factor impact on the incidence of cardiovascular disease and mortality has been measured in earlier studies (Stamler et al., 1999; Anderson et al., 1991). Using the Framingham Heart Study, several prediction equations (both parametric and non-parametric) for CVD have been developed to date to predict CVD and its different manifestations. Anderson et al. (1991) used an accelerated failure time model for the prediction of CVD (including its different manifestation) within a short period of time. Wilson (1998) developed a simple coronary heart disease prediction algorithm using risk factors as categorical variables, which allows physicians to predict coronary heart disease (CHD) risk in patients without overt CHD. All these estimates refer to the risk of experiencing CVD within a short period of time (usually less than 12 years) under certain

specified risk factor profiles. They say nothing about the time spent in a specific disease state associated with those risk factors. For instance, life expectancy with cardiovascular disease and without cardiovascular disease by risk profile at middle age is unknown. That is, although the impact of cardiovascular disease risk factors on the risk of cardiovascular disease has been measured, the impact of a single risk factor and of multifactoral risk factor profiles on the life expectancy with and without cardiovascular disease has not been investigated.

A recent review study by Ben-Shlomo and Diana Kuh (2002) concluded that life course epidemiology has challenged the contentment with the adult lifestyle model of chronic disease risk. Risk factors in early life like tobacco use and obesity, for example, not only affect an individual's own later health but also the health of the next generation (WHO, 2002). Recent studies have concluded that overweight or obesity in adulthood decreases life expectancy by a similar magnitude to smoking (Peeters et al, 2003; Fontaine et al, 2003). The impact of a single risk factor status and risk profiles at middle age (e.g. 30-50 years) on later ages of life is important and preventable compared to the single risk factor status and risk profiles at older ages. The relationship of the risk profiles at older ages with morbidity and mortality are also more complex (Kaplan et al., 1999). People with favorable risk profiles of CVD at middle age survive several years longer compared to those with unfavorable risk factor profiles (Lowe et al., 1998; Daviglus et al., 1998; Stamler et al., 1999). Low risk at middle age is also associated with lower average annual costs for medical care at older age (Daviglus et al., 1998). It is unknown whether such risk factors also decrease the lifetime probability of CVD and the duration of life with and without CVD. Therefore, in this chapter, we have focused on the important CVD risk factors during middle age and their impact on CVD and mortality at later ages.

Although there are many established risk factors for CVD, our focus will be 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; Manson et al., 1990; Berenson et al., 1998; Stamler et al., 1998; Lowe et al., 1998). Improvements in these risk factors are likely to have a beneficial impact on all-cause mortality and incidences of cardiovascular disease (Norrish et al, 1995).

To measure the compression of cardiovascular morbidity for each risk factor, we constructed multistate life tables separately for each risk factor category (i.e. univariate analysis) by sex. To obtain precise estimates of the net or partial effect of a specific covariate on CVD, we needed to control for other covariates. Therefore, to estimate the combined effect of several risk factors, we constructed multistate life tables in multiple-covariates context (i.e. multivariate analysis) by bridging the multivariate regression model and the multistate life table. We estimated the age-

specific transition rates by means of both univariate and multivariate analysis using the Gompertz (1825; 1827) regression models described in Chapter 7 of this study. We used the estimated parameters to construct the life table. We took the opportunity afforded by the FHS data of using risk factor status between the ages of 30 and 50, and the first 48 years of follow-up of cardiovascular disease history and mortality in the Framingham Heart Study original cohort. Our analysis of the effects of risk factor profiles combines the effects of single risk factors. For instance, the analysis of the effects of an optimal risk factor profile combines the effects of optimal single risk factors. It is not based on observations of individuals with such combinations, as these did not exist in the data set.

We estimated the lifetime risk of CVD (any cardiovascular disease) and its subtypes (any coronary heart disease and any myocardial infarction) given the specific CVD risk factor status and risk profiles at middle age. These were thought to yield an indication of the potential to control the risk factors in adulthood and the consequences at later ages. We calculated the expected number of years lived free of CVD and with CVD given the risk factor status at middle age, in order to arrive at an indication of cardiovascular risk free life expectancy, i.e. such as health expectancy related to the cardiovascular disease risk factor at middle ages of life.

Section 9.2 describes the data and methods: the data source and risk factor exposures, state space and model selection procedure, the estimation of transaction rates using Gompertz model, and construction of life tables. Results are illustrated in Section 9.3. In subsection 9.3.1, we have described the results obtained from the univariate analysis. Results from the multistate life tables in multiple covariate contexts are described in subsection 9.3.2. We have concluded the chapter with a discussion in Section 9.4.

9.2 Data and methods

9.2.1 Data and risk factor exposure

We used the Framingham Heart Study, which began in 1948 and has followed 5209 participants (28 to 62 years of age at entry to the study) as part of a prospective epidemiologic study of cardiovascular disease. Enrollment criteria and study design have been previously published (Dawber et al., 1951). For the purpose of this chapter, we used the data regarding age at onset of cardiovascular disease or death over forty--eight years of follow-up (exam rounds 1 to 24) for the 3045 participants free of cardiovascular disease before age 50 and the risk factor status recorded at minimally two exams undergone by the subject between the ages of 30 and 50. Eligibility criteria for inclusion in our study are described in Chapter 8. Among many established cardiovascular risk factors, we considered four major risk factors: *smoking status*, *systolic blood pressure* (SBP), *diastolic blood pressure* (DBP), *serum cholesterol*

level (SCL) and *body mass index* (BMI). Methods for assessing risk factors have been published previously (Dawber et., 1951; Cupples et al., 1988). All these risk factors cause premature death, increased cardiovascular disease, pulmonary disease, cancer and other diseases (Yusuf et al., 2001). The sample population and risk factor exposure used in this chapter are the same as the population and risk exposure defined in Chapter 8.

In the multivariate analysis, an *optimal risk* profile was defined as a non-smoker with, on average, optimal blood pressure (SBP<120 and DBP<80), optimal serum cholesterol level (SCL<200) and optimal BMI (BMI<25) throughout the period from age 30 to 50. If an individual was a smoker, had high blood pressure (SBP>140 and DBP>90), high serum cholesterol (SCL>240) and was obese (BMI>30), he or she was considered to have a *high-risk* profile.

9.2.2 State space and model

State space

The basic multistate life table has the state space {NO-CVD, history of CVD, dead} (model 3.1(b), Section 3.3.2, Chapter 3) where CVD is represented by one of the specific CVD states: *all cardiovascular disease*, *all coronary heart disease* and *acute myocardial infarction*. In the life table for all CVD, the possible transitions are, "NO-CVD" to "death", "NO-CVD" to "history of CVD", and "history of CVD" to "death". In the life table for all CHD, the possible transitions are, "NO-CHD" to "death", "NO-CHD" to "history of CHD", and "history of CHD" to "death". Similarly, in the life table for MI, the possible transitions are, "NO-MI" to "death", "NO-MI" to "history of MI", and "history of MI" to "death".

Risk factor status throughout the age interval from 30 to 50 years, disease incidence and mortality throughout the 48 years of follow-up of the Framingham original cohort, from different states, were the same as in Table 8.2 of Chapter 8.

The model selection

We used the Gompertz regression model to specify the shape of the age dependence of the occurrences of an event. We described this model in Chapter 7 of this study. The model was based on risk factor levels and age until events or censored. Several models are distinguished for each transition. We considered the following three levels:

a. The *null-model*, which is the transition rate model without any covariate.
b. *Model with covariates*: this model is broken down into two types:
    - *Covariates with the b parameters*: Fit the model incorporating covariates with the *b* parameters and compare the change in likelihood ratio. If the change in likelihood ratio is significant, select the model.

- *Covariates with b and c parameters*: include covariates with *b* and *c* parameters and compare the changes in likelihood ratio with the model where covariates are included with *b* parameters. If the reduction is significant consider this third model, otherwise select the second model.

From the overall analysis, we found that incorporation of the time constant covariates with *b* parameters was significant compared to the null model. In most of the cases, we found that with the inclusion of the covariates with *c* parameters, reduction of the likelihood ratio was not significant. We therefore selected only the Gompertz model with covariates with the *b* parameters (Blossfeld and Rohwer, 2002). We assumed that the *c* parameter was not influenced by the covariates.

9.2.3 Estimation of transition rates

The basic parameter for constructing the multistate life table was the transition rate. In both univariate and multivariate analysis, the transition rates were estimated applying Gompertz regression models.

Univariate analysis

In the univariate analysis, we performed Gompertz regression analysis incorporating only one risk factor as an independent variable in the model for each transition defined in the previous section. We estimated the age-specific transition rate for each transition separately for males and females. Using these age-specific transition rates we constructed separate multistate life tables for the optimal and high-risk category of that risk factor, in order to establish whether each risk factor could independently compresses cardiovascular morbidity.

Multivariate analysis

Recent applications of the multistate life table technique with a few covariates have included applications in the area of work and retirement (Hayward and Grady, 1990), active life expectancy (Land et al., 1994) and life cycle model of labor force inequality (Hayward and Lichter, 1998). The authors used a *piecewise-constant transition rates* model for the panel data where transitions occurred at the middle of the interval or at a discrete time point, in the absence of exact timing of event or censoring. If the exact dates of transitions into and out of the states in continuous event histories are known, the estimation of hazard regression models at individual level with the computation multistate life tables would be directly applicable (Land et al., 1994). Here, we have described the multivariate rate models that we used to estimate the transition rates. We chose the Gompertz regression model, as it has fewer parameters (only two) and yields smoothed transition rates. Other features are described in Chapter 7.We assumed that any disease incidence or mortality rates

(following the basic model of cardiovascular disease, Figure 3.1(b), Chapter 3) follow Gompertz's law.

We conducted multivariate analysis to construct multistate life tables in multiple covariate contexts. These we called multistate life tables in a multiple covariate contexts since each age-specific transition rate, which was the key component of the multistate life table, was adjusted with the described risk factors. The effect of the covariates on the transition rates can be given an interpretation similar to the conventional hazard rate regression models. For a better understanding, we have provided an example. Say we would like to estimate the age-specific transition rates for the transition- NO-CVD to CVD of male participants in FHS. We estimated the regression coefficients and standard errors, incorporating all mentioned covariates in the Gompertz regression models (Table 9.1). If we wanted to predict the transition rate-NO-CVD to CVD for the high-risk profile male at age 60, we could do so by using the estimated parameters in Table 9.1 as follows:

$$\begin{aligned} &\mu_{nocvd,cvd}(x, x+1) \\ &= \text{EXP}(-5.3958+0.3686+0.396+0.6421+0.6756)*\text{EXP}(0.0504*(60-50)) \\ &= 0.060 \end{aligned} \qquad (9.1)$$

We used a TDA (*Transitional Data Analysis*) program to estimate the age-specific transition rates for the transitions from NO-CVD to CVD or NO-CVD to death. Since TDA starts counting age or time from '0', we needed to subtract 50 from 60 to estimate the transition rates at age 60. We used STATA-7 for the post-disease transitions. TDA cannot control the left-truncation, left entry or left censoring.

In this way, we can estimate the transition rates for any other specific age. We assume that each transition rate depends only on age and risk factor status before age 50, providing a common prediction model across types of events.

Table 9.1 Regression coefficients and standard error of Gompertz regression models for the transition NO-CVD to CVD for males

Risk factors		Coefficients	Standard error
Smoking status	Never smoker	-	-
	Ever smoker	0.0907	0.1256
	Always smoker	0.3686	0.0943
Blood pressure	Optimal	-	-
	Elevated/high normal	0.2203	0.0983
	High	0.6421	0.1057
Body mass index	Optimal	-	-
	Elevated/high normal	0.1453	0.0796
	High	0.3960	0.1155
Cholesterol	Optimal	-	-
	Elevated/high normal	0.3867	0.1179
	High	0.6756	0.1184
Constant	*a*	-5.3958	0.1726
Constant	*b*	0.0504	0.0036
-Log likelihood		-3530.29	

'-' reference category

9.2.4 Life table construction

Separate multistate life tables were constructed for each of the cardiovascular disease types described above, for optimal and for high-risk groups. For the purpose of the univariate and multivariate analysis, the transition rates for each single year of age were calculated applying the Gompertz regression models described in the previous section. In the univariate analysis, age-specific transition rates were unadjusted and in the multivariate analysis, age-specific transition rates were the combined effects of all risk factors.

To construct the life table, the transition rates were converted to probabilities by assuming that within each single year age interval, the hazard remained constant, taking into account the competing risk. Once we derived the age-specific transition probability, construction of the life tables was straightforward, as described in Section 3.3.4 of Chapter 3. The life tables constructed for each single risk factor category were the same as the life table constructed for always smokers and never smokers in Chapter 6. The main difference is that in Chapter 6, the empirical occurrence-exposure rates were smoothed using the Gompertz regression, while in

this chapter, we use Gompertz regression as a transition rate model to the individual level data to predict the age-specific transition rates. In chapter 6, the relative risk of disease incidence and mortality by smoking status for each one-year age band was age dependent. The relative risks did not differ by age. In the multivariate analysis, the age-specific rates are estimated for the combined effects of all risk factors. The procedures to construct other life table statistics in both the univariate and multivariate analysis are the same.

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 and total population 4.55 years). We assumed that mortality rates beyond age 90 were similar irrespective of risk factor profiles at middle age.

We constructed a total of 8 life tables (2 for alive to death model; 2 for CVD model; 2 for CHD model and 2 for MI model) for one category of each risk factor, where each disease model was constructed separately for males and females. To compare high and optimal risk for each univariate case, we therefore constructed a total of 96 life tables (16 for smoking status; 16 for SBP; 16 for DBP; 16 for BP; 16 for BMI and 16 for cholesterol). For the multivariate case, we constructed a total of 16 life tables (8 for optimal risk and 8 for high-risk profiles).

9.3 Results

The results are presented into two parts. The first part describes the life table outcomes obtained from the univariate analysis. Here, we investigate whether optimal risk status for each single risk factor compresses cardiovascular morbidity, ignoring potential confounding. We mainly present the life expectancies free of cardiovascular disease and with cardiovascular disease, the lifetime probability of cardiovascular disease and the differences in the number of years spent with disease between optimal and high-risk exposure of each risk factor.

In the second part, we investigated whether optimal risk profiles compress cardiovascular morbidity. We constructed multivariate multistate life tables that translate age-specific transition rates for the combined risk factors into life table estimates: survival probabilities, life expectancies free of cardiovascular disease and with cardiovascular disease, lifetime probability of cardiovascular disease and the differences in number of years spent with disease between optimal and high-risk profiles. We then compared the results between the optimal and high-risk profiles.

9.3.1 Univariate analysis

Life expectancy

Total life expectancy, life expectancy free of CVD and with CVD at age 50 and 70 are presented by the optimal and high-risk category of each risk factor separately

for males and females (Table 9.2). A 50-year male smoker can expect to survive 19.86 additional years free of CVD and 6.54 years (25%) with CVD. At the same age, a non-smoking male can expect 4.16 more years of life free of CVD, as compared to a male smoker. However, life expectancy with CVD for a male never smoker is also longer (0.26 years) compared to a male smoker. Similarly, total life expectancy of a 50-year female never smoker is 34.50 years, of which 28.16 years free of CVD and 6.35 years (18%) with CVD. At the same age, a female never smoker can expect to survive 1.44 years more with CVD compared to a female smoker. For males, similar trends are exhibited for coronary heart disease and myocardial infarction. At age 70, the trends seen in the results are similar to those at age 50. For females, life expectancy with MI at age 50 and 70 is slightly higher among female smokers.

A 50-year old male with optimal SBP can expect to survive 23.87 years free of CVD and 5.95 years (21%) with CVD. A male of that age with high SBP can expect to survive 16.58 years without CVD and 6.60 years (28%) with CVD. A male at age 50 with optimal SBP can expect to survive 6.64 more years compared to a male of that age with high SBP. At the same age, a male with high SBP can expect to survive 0.65 years more with CVD. Life expectancy with CHD at age 50 or 70 is marginally higher for males with optimal SBP compared to males with higher SBP, and it remains nearly same with MI. A fifty-year-old female can expect to survive 7.75 years more free of CVD if she had optimal SBP instead of high SBP before age 50. A female with high SBP can expect to survive 2.71 years more with CVD compared to a female with optimal SBP at the same age. Overall, females with high SBP at mid-life can expect to survive longer with disease at age 50 or 70 compared to the females with optimal SBP: from –0.75 years with MI at age 70 to –2.71 years with CVD at age 50.

The life expectancy with CVD or CHD or MI is higher for males or females with high DBP compared to males or females with optimal DBP. For males, this ranges from –0.13 years with MI at age 50 to –0.59 years with CVD at age 50. The difference is higher for females in whom this varies from –0.50 with MI or CHD at age 70 to 1.95 years with CVD at age 50.

A male with optimal blood pressure at middle age can expect to survive 6.75 years more free of cardiovascular disease at age 50 compared to a hypertensive male of that age. The life expectancy with CVD of a hypertensive male at age 50 is 1.05 years higher compared to a male with optimal blood pressure of that age. Likewise, a female with optimal blood pressure at middle age can expect to survive 7.84 (more than one year higher compared to a male) years more free of cardiovascular disease at age 50 compared to a hypertensive female of that age. The life expectancy with CVD of a hypertensive male at age 50 is 3.00 years (nearly 2 years higher compared to a male) higher compared to a female with optimal blood pressure., Similar trends are observed in the differences between life expectancy free of

disease (CVD or CHD or MI) and with disease at age 50 or 70(Table 9.2) for both males and females.

Table 9.2 Total life expectancy (LE) and residual life expectancy free from cardiovascular disease based on a population free of cardiovascular disease at age 50, by single risk factor status

Male

Risk factors	Age	Total	Free of CVD	With CVD	Free of CHD	With CHD	Free of MI	With MI
Never smoker	50	30.82	24.02	6.80	25.43	5.36	27.68	2.91
	70	14.80	9.31	5.49	10.71	4.15	12.43	2.25
Always smoker	50	26.40	19.86	6.54	21.60	4.65	23.13	2.50
	70	11.87	6.59	5.28	8.14	3.62	9.40	1.94
Difference	50	4.42	4.16	0.26	3.83	0.72	4.55	0.41
	70	2.93	2.72	0.20	2.57	0.53	3.03	0.31
SBP<120	50	29.82	23.87	5.95	25.29	4.43	26.93	2.62
	70	14.07	9.15	4.92	10.40	3.58	11.76	2.18
SBP 140+	50	23.19	16.58	6.60	18.88	4.20	20.32	2.64
	70	9.74	4.64	5.10	6.56	3.11	7.48	2.06
Difference	50	6.64	7.29	-0.65	6.41	0.23	6.62	-0.01
	70	4.33	4.51	-0.18	3.84	0.47	4.29	0.13
DBP<70	50	29.11	22.65	6.46	24.05	4.75	25.65	2.97
	70	13.63	8.29	5.34	9.59	3.83	10.85	2.50
DBP 90+	50	24.27	17.22	7.05	18.88	5.30	21.00	3.11
	70	10.46	4.95	5.51	6.40	4.06	7.81	2.50
Difference	50	4.84	5.43	-0.59	5.18	-0.55	4.65	-0.13
	70	3.17	3.34	-0.17	3.19	-0.23	3.03	0.00
BP<120	50	30.07	24.16	5.91	25.66	4.27	27.68	2.91
	70	14.26	9.34	4.91	10.67	3.47	12.43	2.25
BP 140+	50	24.37	17.41	6.96	19.23	4.97	21.12	2.99
	70	10.52	5.05	5.47	6.59	3.84	7.89	2.41
Difference	50	5.70	6.75	-1.05	6.43	-0.69	6.56	-0.08
	70	3.74	4.30	-0.56	4.09	-0.37	4.54	-0.16
SCL <200	50	28.09	23.70	4.39	25.02	3.10	25.96	2.04
	70	13.00	9.40	3.61	10.45	2.52	11.32	1.70
SCL 240+	50	26.98	18.89	8.09	20.67	6.14	23.07	3.60
	70	12.38	5.80	6.58	7.45	4.84	9.15	2.94
Difference	50	2.13	4.82	-3.71	4.35	-3.04	2.90	-1.56
	70	1.25	3.59	-2.97	3.00	-2.33	2.17	-1.24
BMI<25	50	28.46	22.50	5.95	24.00	4.30	25.47	2.79
	70	13.25	8.37	4.87	9.74	3.41	10.87	2.27
BMI 30+	50	24.66	17.10	7.57	19.03	5.82	20.73	4.04
	70	10.74	4.70	6.04	6.43	4.57	7.49	3.34
Difference	50	3.79	5.41	-1.61	4.97	-1.52	4.74	-1.25
	70	2.51	3.67	-1.16	3.32	-1.16	3.37	-1.07

Continuation of Table 9.2…

Female

Risk factors	Age	Total	Free of CVD	With CVD	Free of CHD	With CHD	Free of MI	With MI
Never smoker	50	34.50	28.16	6.35	30.17	4.24	32.88	1.31
	70	17.15	11.79	5.36	13.64	3.50	15.84	1.15
Always smoker	50	30.07	25.16	4.91	26.96	2.96	28.45	1.46
	70	14.00	9.94	4.06	11.55	2.35	12.60	1.30
Difference	50	4.43	3.00	1.44	3.20	1.27	4.43	-0.15
	70	3.15	1.86	1.30	2.09	1.15	3.24	-0.14
SBP<120	50	34.59	30.17	4.42	31.98	2.62	33.66	0.87
	70	17.35	13.58	3.78	15.23	2.16	16.63	0.76
SBP 140+	50	29.55	22.42	7.13	24.83	4.53	27.48	1.75
	70	13.66	7.75	5.91	9.97	3.68	11.98	1.51
Difference	50	5.04	7.75	-2.71	7.15	-1.91	6.18	-0.88
	70	3.70	5.82	-2.13	5.26	-1.52	4.65	-0.75
DBP<70	50	33.87	28.87	5.01	32.52	1.13	32.52	1.13
	70	16.82	12.56	4.26	15.76	1.00	15.76	1.00
DBP 90+	50	29.54	22.58	6.95	27.86	1.73	27.86	1.73
	70	13.65	7.85	5.81	12.27	1.49	12.27	1.49
Difference	50	4.34	6.28	-1.95	4.67	-0.60	4.67	-0.60
	70	3.17	4.72	-1.55	3.49	-0.50	3.49	-0.50
BP<120	50	34.72	30.37	4.35	32.11	2.60	33.75	0.89
	70	17.46	13.74	3.73	15.33	2.16	16.71	0.78
BP 140+	50	29.88	22.53	7.35	24.99	4.77	27.99	1.65
	70	13.93	7.79	6.15	10.02	3.95	12.39	1.43
Difference	50	4.85	7.84	-3.00	7.12	-2.17	5.76	-0.76
	70	3.53	5.95	-2.42	5.30	-1.79	4.32	-0.65
SCL <200	50	34.06	28.39	5.67	31.13	2.74	32.46	1.26
	70	17.06	12.13	4.93	14.57	2.34	15.67	1.13
SCL 240+	50	31.63	25.38	6.25	27.33	4.22	29.73	1.69
	70	15.17	9.95	5.23	11.77	3.43	13.60	1.49
Difference	50	2.25	3.02	-0.58	3.80	-1.47	2.73	-0.44
	70	1.65	2.18	-0.30	2.80	-1.09	2.08	-0.36
BMI<25	50	33.29	28.18	5.11	30.25	2.94	31.93	1.19
	70	16.39	12.07	4.33	13.95	2.40	15.29	1.05
BMI 30+	50	29.52	22.61	6.92	24.66	4.83	27.39	2.05
	70	13.66	7.93	5.73	9.79	3.93	11.81	1.77
Difference	50	3.77	5.58	-1.81	5.59	-1.89	4.54	-0.85
	70	2.74	4.14	-1.40	4.16	-1.53	3.47	-0.72

At age 50, the total life expectancy differences between optimal BMI and obese males or females are nearly 4 years. Using a similar data set, Peeters et al. (2003) found a life expectancy difference between normal and obese males or females of about 6 years at age 40. Peeters et al., (2003) stratified the population by smoking status, used the first 40 years of follow-up and considered only the baseline BMI

status. In our analysis, we excluded CVD and death before age 50. All these assumptions may have contributed to our arriving at the different estimate. At age 50, males can expect 5.41 years more free of CVD; this is 5.58 years for females. Life expectancy with CVD is higher (1.61 years for males and 1.81 years for females) in obese males and females compared to males and females with normal BMI at middle age. Similar patterns were found for CHD or MI at age 50 or 70.

The total life expectancy difference between a fifty year-old male with an optimal or with a high cholesterol level is 2.13 years. However, at the same age, a male with low cholesterol can expect to survive 4.82 years more free of CVD and 3.71 years less with CVD. A female of the same age and category can expect to survive 3.02 years more without CVD and 0.58 year less with CVD. Males with high cholesterol levels consistently survive longer with CVD or CHD or MI at age 50 or 70. However, females at that age survive longer with CHD.

Lifetime risk

The lifetime probability (before death) and the probability of developing CVD before the age of 70 of the male and female cohorts free of CVD at age 50 are presented in Table 9.3 by risk factor status for the age interval extending from 30 to 50 years of age. Both men and women smokers have a higher chance of developing CVD before age 70, as compared to non-smokers (men 42% vs. 35%; women 25% vs. 23%); non-smokers have a higher or similar chance (1% for men and 4 % for women) of developing CVD during their lifetime.

The lifetime probability of a male with optimal SBP developing CVD is 58% and 78% for males with high BP; for CHD, these percentages are 41% vs. 53% for CHD and for MI 27% vs. 34% for MI. Before age 70, the difference in the probability of developing CVD between the high and optimal SBP categories is –24% percent (31% vs. 55%). This difference is also huge for CHD (-15%) and MI (-9%). Similarly, females with high SBP have a 67% chance of developing CVD before death and a 35% chance of developing this before age 70. For developing CVD, the differences between optimal and high SBP are –19% (16% vs. 35%) before age 70 and –24% (42% vs. 67%) before death. Like SBP, DBP also has a huge impact on the chance of developing CVD or CHD or MI before age 70 or during lifetime. For males, the impact is higher before age 70. For females, the impact is higher in lifetime.

The probability of developing CVD, CHD or MI before age 70 or before death is, as expected, significantly higher for hypertensive males as compared to the males who had optimal blood pressure at middle age. Before age 70, the probability is –22% (30% vs. 52%) for CVD, -16% (22% vs. 38%) for CHD, and -9% (13% vs. 22%) for MI. Over lifetime, the difference is slightly lower than before age 70. Like males, hypertensive females have a significantly higher chance of developing CVD or CHD or MI before age 70 or in lifetime as compared to the females who have

optimal blood pressure at middle age. Before death, this is –24% (41% vs. 64%) for CVD, -18% (23% vs. 41%) for CHD, and -11% (12% vs. 23%) for MI. The difference is significantly higher in lifetime compared to before age 70.

Men and women with normal cholesterol levels before age 50 have a significantly lower risk of developing CVD or CHD or MI before age 70 or before death compared to individuals with high cholesterol levels at that age. For men, this ranges from –11% (12% vs. 22%) for MI before age 70 to –29% (32% vs. 60%) for CHD before death; For females, from –3% (4% vs. 7%) for MI before age 70 to –16% (21% vs. 37%) for CHD before death.

The probability of developing CVD or one of its subtypes either before age 70 or before death is significantly higher among obese males or females compared to males or females who have optimal levels of BMI between the ages of 30 and 50. For males, this ranges from –10% for MI before age 70 to –17% for CVD before age 70. For females, this probability runs from -6% for MI before age 70 to –16% for CHD before death. For females the difference is higher before death, while for males the difference is only higher for CVD before age 70, otherwise it is the same.

Table 9.3 Lifetime probability (%) of subjects without cardiovascular disease developing cardiovascular disease at age 50, by single risk factor

Male

Risk factor	Before age 70			Before death		
	CVD	CHD	MI	CVD	CHD	MI
Never smoker	35	29	17	67	54	37
Always smoker	42	31	19	67	49	33
Difference	-7	-2	-1	1	5	4
SBP<120	31	22	13	58	41	27
SBP 140+	55	37	22	76	53	34
Difference	-24	-15	-9	-18	-13	-7
DBP<70	34	26	15	63	45	30
DBP 90+	54	41	23	77	59	37
Difference	-19	-15	-8	-14	-14	-7
BP<120	30	22	13	57	40	27
BP 140+	52	38	22	76	55	35
Difference	-22	-16	-9	-19	-15	-8
SCL <200	27	18	12	51	32	23
SCL 240+	49	39	22	75	60	39
Difference	-21	-21	-11	-25	-29	-16
BMI<25	35	26	16	62	45	32
BMI 30+	52	41	27	74	59	43
Difference	-17	-15	-10	-12	-15	-11

Continuation of Table 9.3…

Female

Risk factor	Before age 70			Before death		
	CVD	CHD	MI	CVD	CHD	MI
Never smoker	23	15	5	55	34	17
Always smoker	25	15	7	51	29	19
Difference	-2	0	-2	4	4	-2
SBP<120	16	10	3	42	23	12
SBP 140+	35	23	9	67	41	25
Difference	-19	-13	-6	-24	-18	-13
DBP<70	19	12	4	48	27	15
DBP 90+	33	22	9	63	40	24
Difference	-14	-10	-5	-16	-13	-10
BP<120	16	10	3	41	23	12
BP 140+	35	22	9	66	41	23
Difference	-19	-13	-5	-24	-18	-11
SCL <200	19	10	4	47	21	14
SCL 240+	27	19	7	59	37	22
Difference	-8	-9	-3	-12	-16	-7
BMI<25	20	12	5	49	27	16
BMI 30+	34	23	11	65	43	28
Difference	-14	-11	-6	-16	-15	-12

Differences in years spent with disease

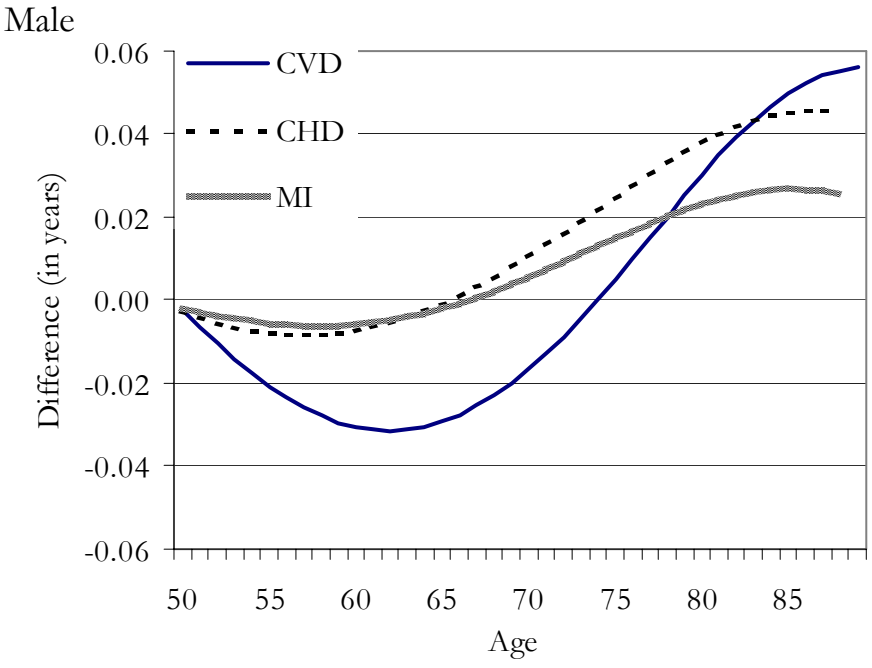
Here, the burden of CVD, CHD or MI is measured in terms of the differences in the life-table person years lived in the age interval [x, x+1) with disease between the optimal group and the high-risk group. We used the simple equation described in Chapter 2 (subsection 2.4.7) to estimate the life years lost to disease or number of years lived with disease of the life table population between optimal and high-risk groups. The number of age-specific person years lived with disease for the high-risk group is subtracted from the number of age-specific person years lived with disease for the optimal risk group (Figure 9.1). This approach enables us to establish the length of time spent with cardiovascular morbidity at the relevant age by risk factor status. For instance, in Figure 9.1 (male: *never smoker-always smoker*), a male who smoked at middle age, spent 0.1991 years with cardiovascular disease in the age interval 60 to 61. In the same age interval, a male who was non-smoker at middle age spent 0.1078 years with cardiovascular disease. The difference is –0.0913 years, i.e. a smoker spends 0.0913 years more with CVD in the age interval 60 to 61. A difference resulting in negative values indicates that a high-risk individual spends a

longer time with disease, i.e. elimination of that risk from the population at middle age will reduce the life years lost to disease at that age.

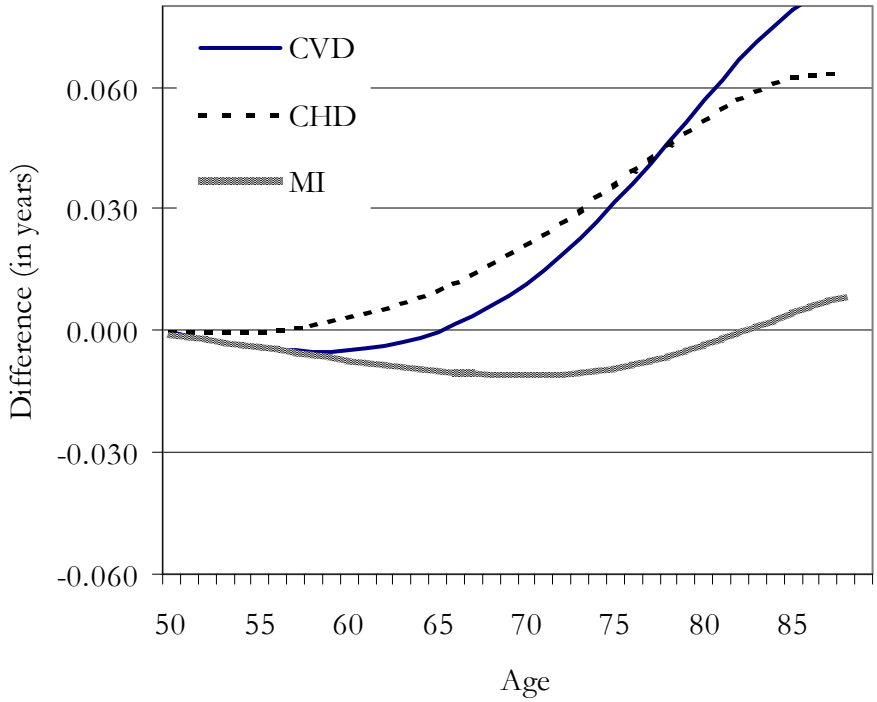
Male smokers spend more years with CVD before age 75 as compared to never smokers (Figure 9.1). Male never smokers spend more years with CHD or MI from age 65 onwards. Similarly, women smokers spend more time with CVD before age 65. Female never smokers spend more time with CHD. However, they spend less time with MI until age 83. While males with high SBP spend more time with CVD before age 74, females spend more time with CVD throughout life (at least until age 88). Similar trends are seen in males and females for DBP. Hypertensive males spend more years with CVD or CHD until age 78 (MI until 76). Hypertensive females spend more years with CVD and its subtypes over lifetime. Males with obesity at middle life spend more time with CVD before age 83. They spend more years with CHD or MI until age 75. Obese women spend a longer time with CHD or MI until the endpoint of life. While males with high cholesterol levels spend more time with CVD, CHD or MI throughout life, females spend slightly more time with CVD until age 82, compared to optimal cholesterol levels. However, females spend more years with CHD or MI throughout life.

Figure 9.1 The differences in the number of years lived with cardiovascular disease between optimal risk and high-risk category (difference: optimal–high)

a. Never smoker- always smoker

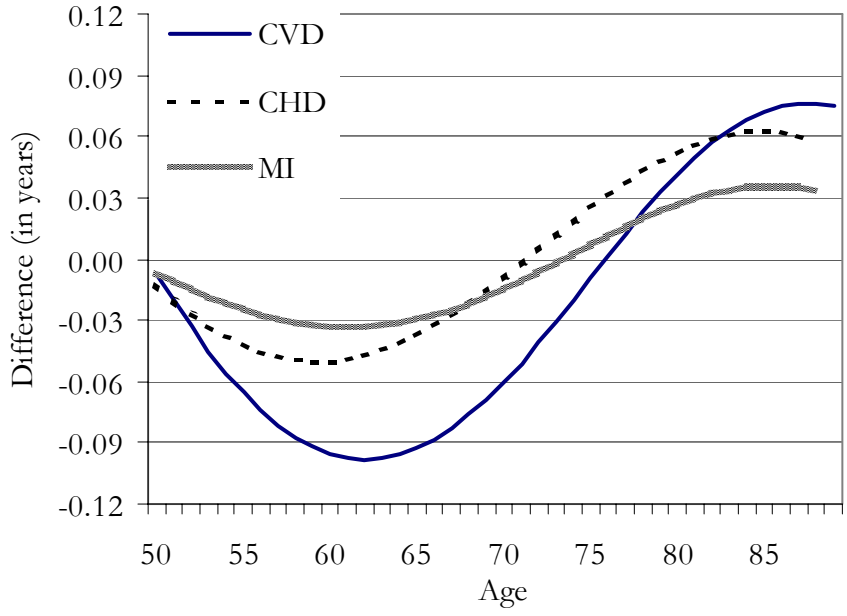


Female

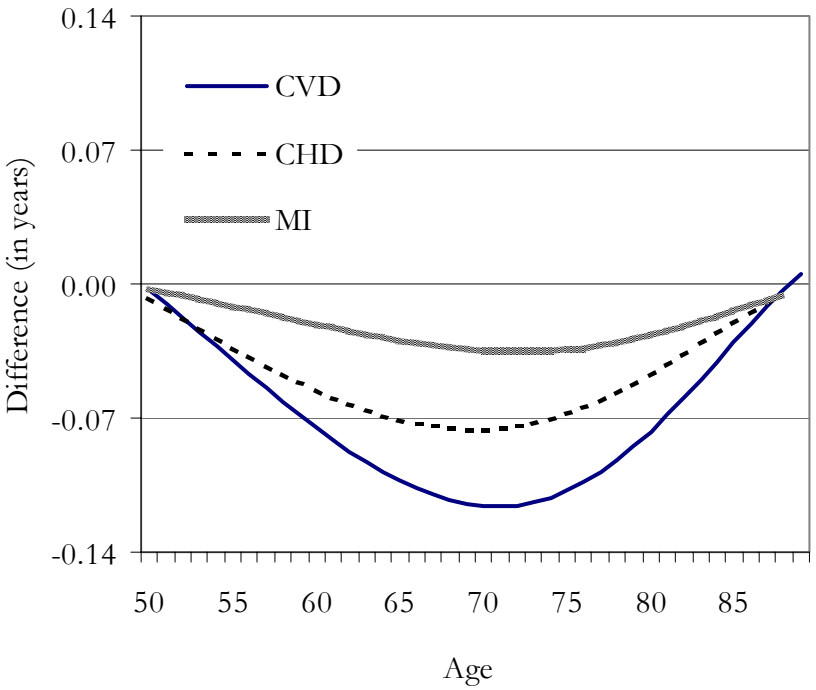


b. Optimal SBP-high SBP

Male

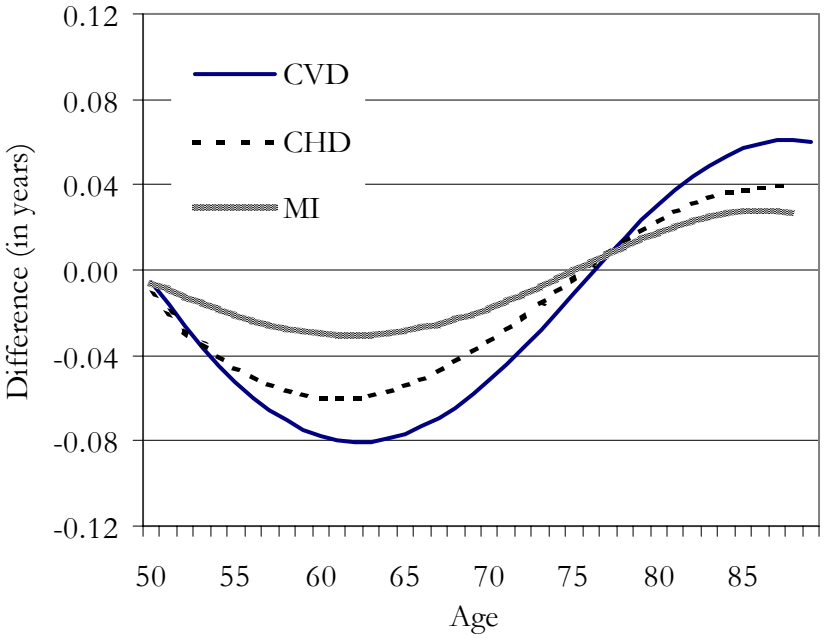


Female

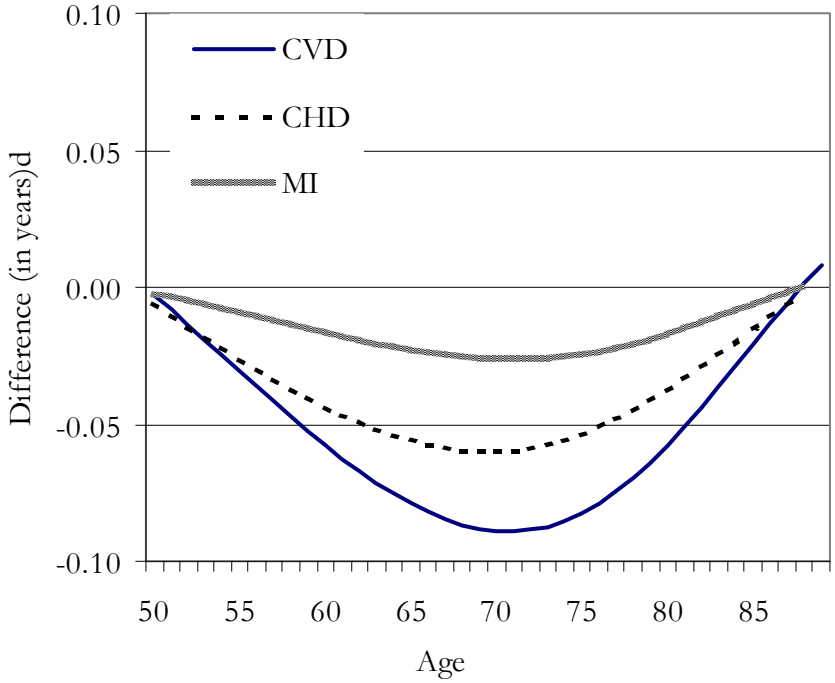


c. Optimal DBP-high DBP

Male

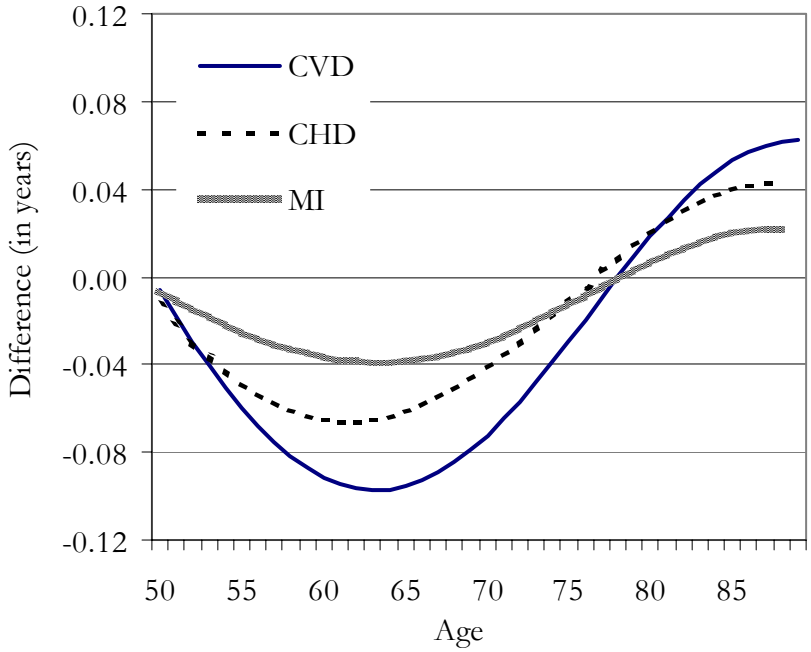


Female

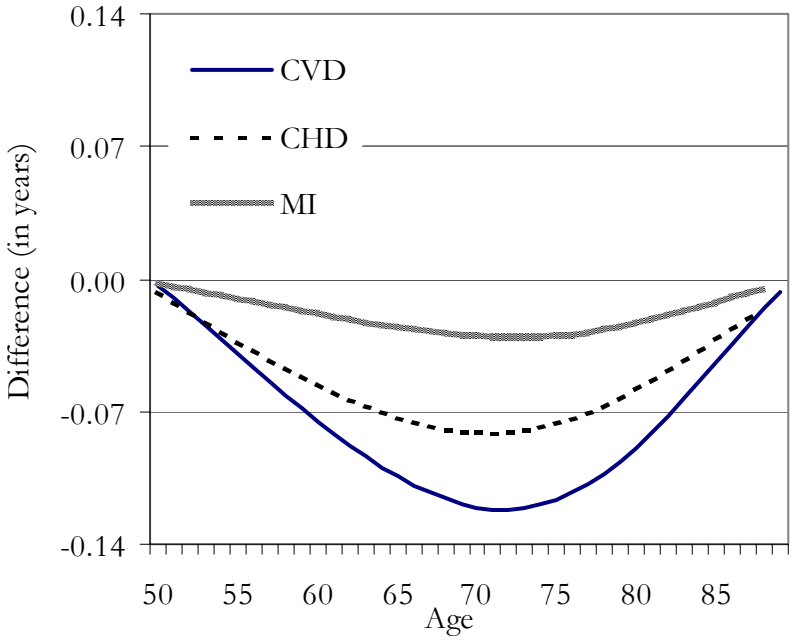


d. Optimal BP-high BP

Male

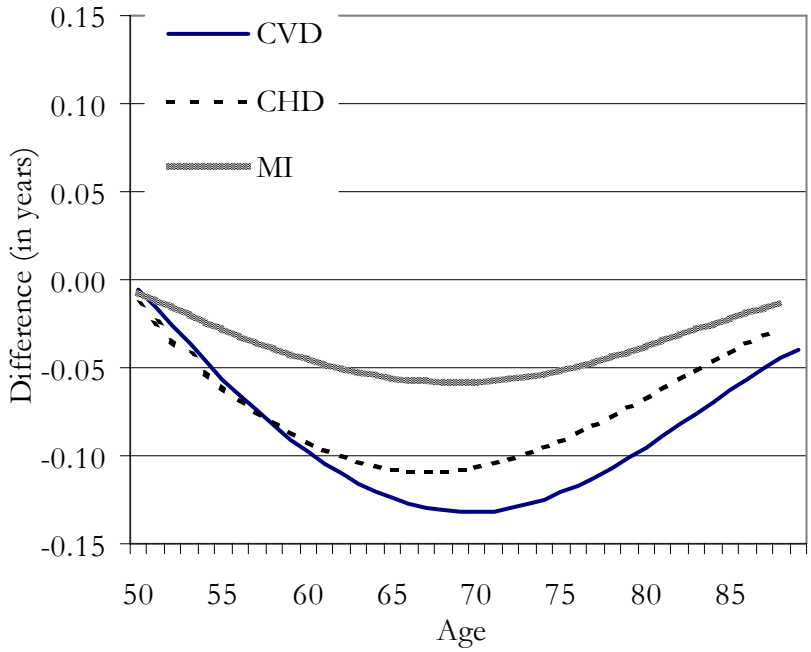


Female

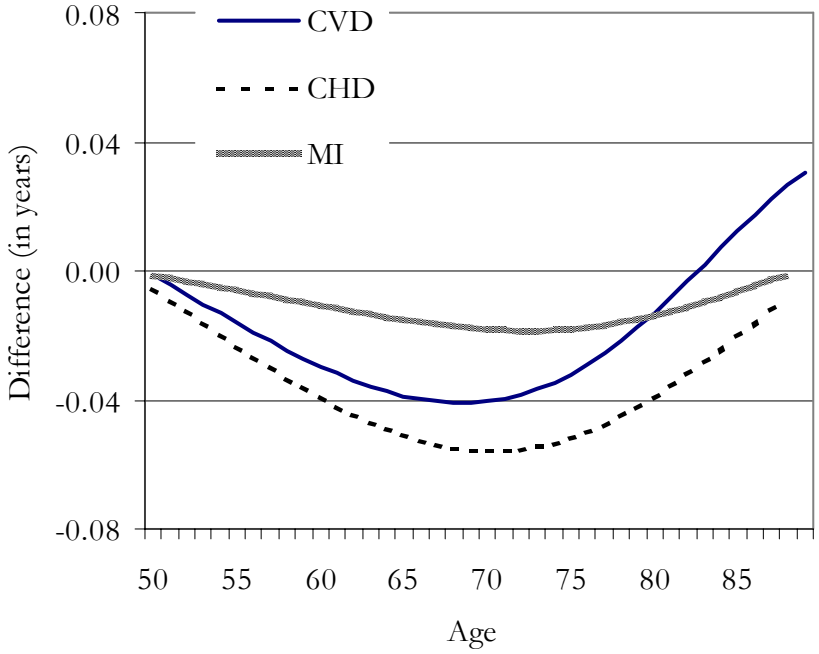


e. Optimal cholesterol-high cholesterol

Male

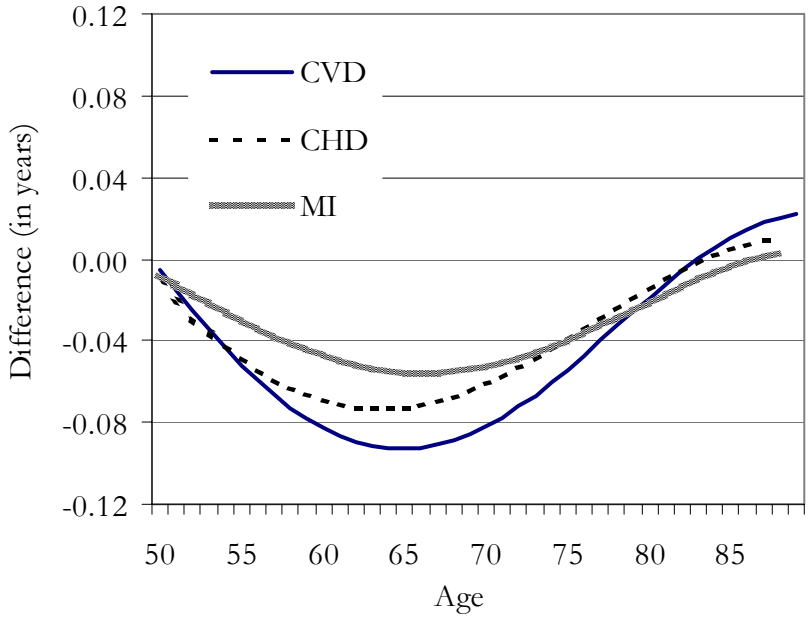


Female

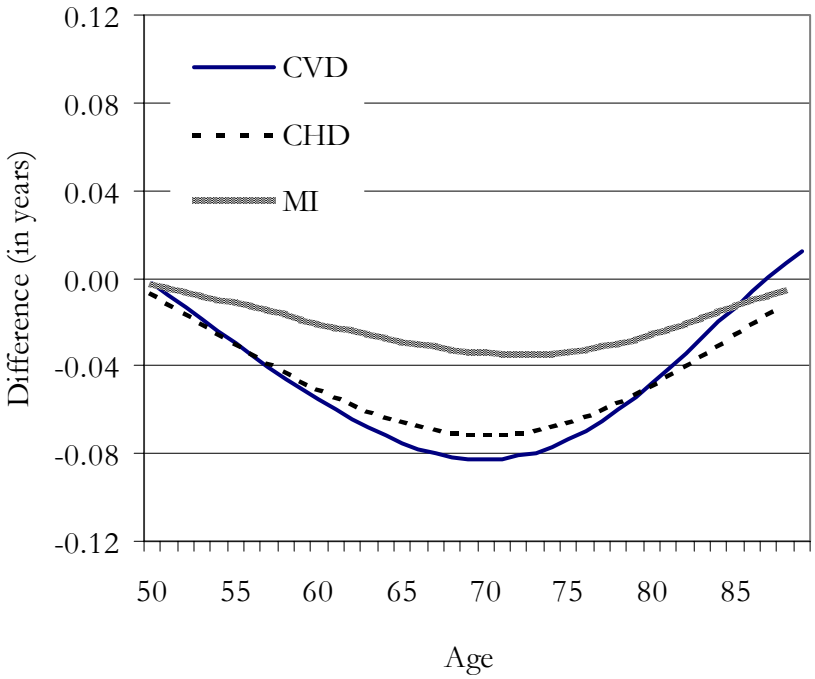


f. Optimal BMI-obesity

Male



Female



9.3.2 Multivariate analysis

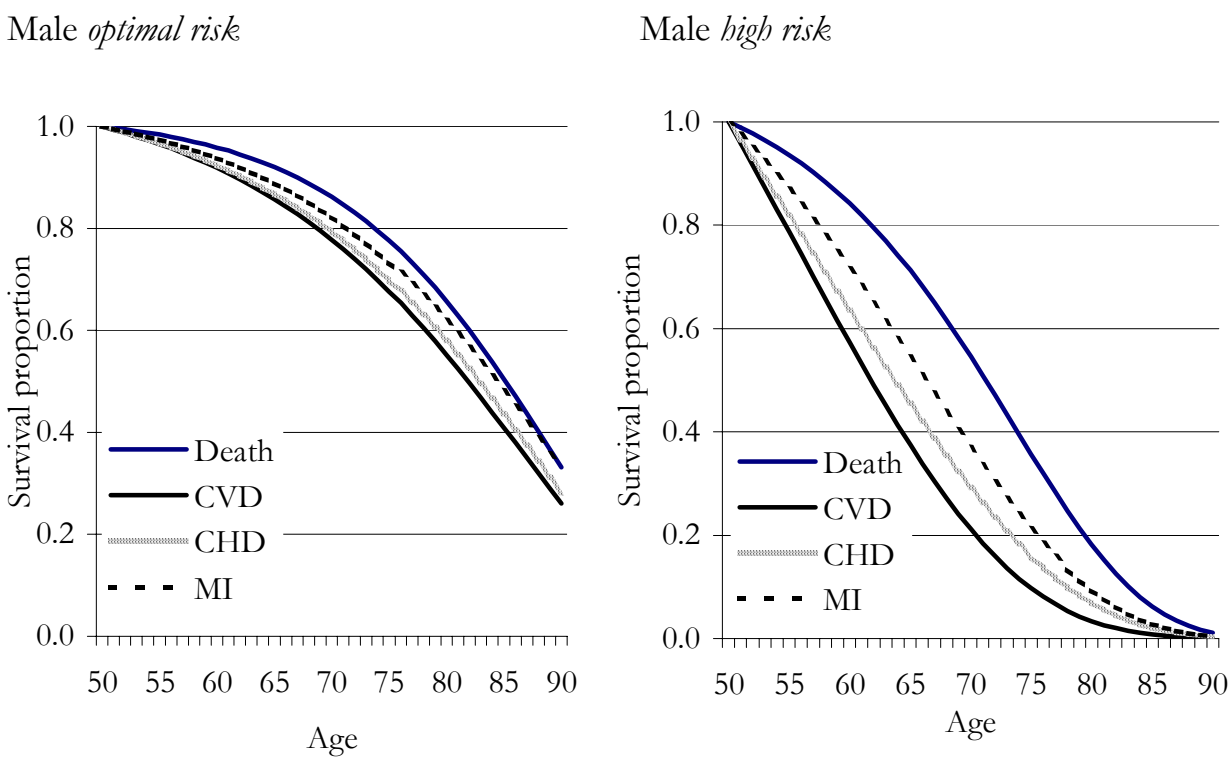
In the univariate analysis, we measured whether each cardiovascular disease risk factor compressed cardiovascular morbidity. In the multivariate analysis, we aim to investigate whether optimal risk profiles compress cardiovascular morbidity. We constructed multistate life tables in a multiple covariate context that translated age-specific transition rates for the combined effects of several risk factors into life table estimates: survival probabilities, life expectancies, lifetime risk and the differences in number of years spent with disease between optimal and high-risk profiles.

Survival curves

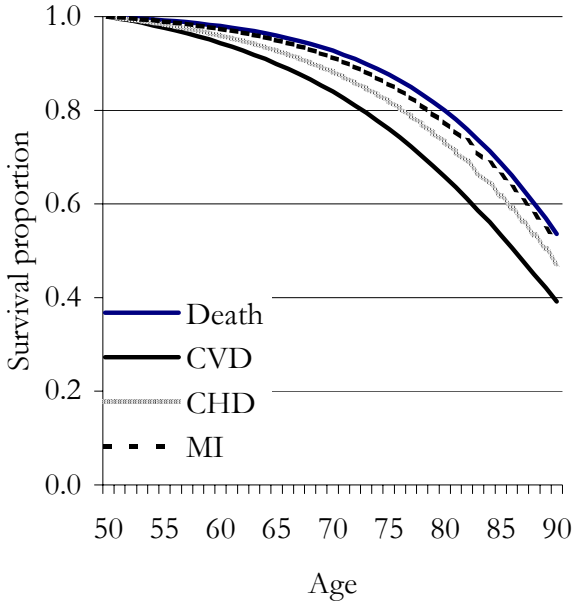
The age profiles of survival from death and survival free of cardiovascular disease for the lowest and highest risk groups in our life table population are shown in Figure 9.2. This figure shows the survival free of cardiovascular disease, coronary heart disease, acute myocardial infarction, or death of fifty-year-old men and women with optimal and higher risk profiles. As expected, men and women with an optimal risk profile lead a longer life and survive longer free of any cardiovascular disease.

Both mortality and cardiovascular disease incidence led to large differences throughout life between optimal and high-risk profiles. Among fifty year-old males, 47% of those in the high-risk and 14% of those in the low risk groups die before the age of 70. In females, these figures are 36% for the high-risk, but only 7% for optimal risk profiles. While an average of 4 in 5 males with an optimal risk profile who are free of cardiovascular disease at age 50 will be alive and free of cardiovascular disease twenty years later, only 1 in 5 males with a high-risk profile will remain in this state (Figure 1). Among the females free of cardiovascular disease at age 50, 1 in 5 with an optimal risk profile compared to 2 in 5 in the high-risk group will be alive and free of cardiovascular disease at age 70.

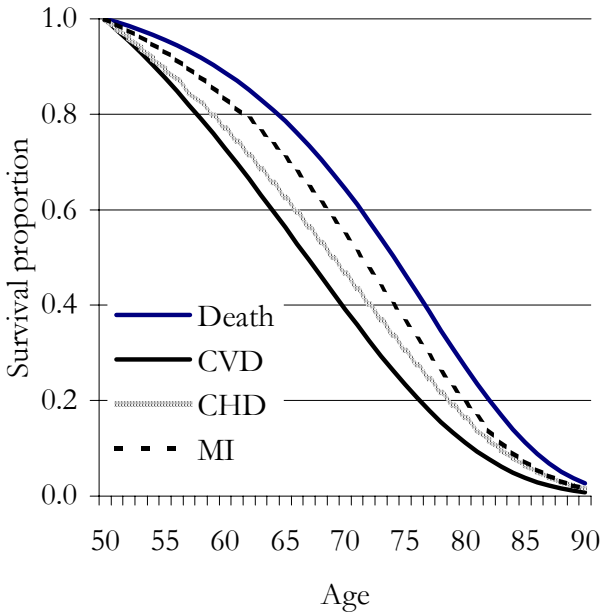
Figure 9.2 Survival curves illustrating the probability of surviving and surviving free of cardiovascular disease (CVD), coronary heart disease (CHD), and myocardial infarction (MI), by sex and risk profile



Female *optimal risk*



Female *high risk*



Life expectancy

While survival probabilities are important indicators of the potential burden of a disease by risk factor status, they give no indication of the impact of that disease on life expectancy. To synthesize the consequences of age-specific disease incidence and mortality, the multivariate multistate life table estimates the life expectancies in specific disease states by risk profile (Table 9.4).

At age 50, the life expectancy of a male is 27.25 years, for a female, 32.41 years, in the selected sample population from the Framingham heart study. At age 50, a man with an optimal risk profile can expect to live another 33.04 years, compared to 20.74 years for a man who is in the high-risk group. A female of that age, with an optimal risk profile, can expect to live 37.57 additional years, while a female in the high-risk group can look forward to 23.30 years. The difference in number of additional survival years between an optimal risk and a high-risk profile is for males 12.29 years, and for females, 14.27 years. Even at age 70, this difference is 8.29 years for males and 10.20 years for females. The males in the optimal risk profiles can expect to survive 6 additional years compared to the total male population in the FHS. Similarly, females in the low risk group can expect to survive 5 additional years compared to the total female respondents of the FHS. This huge difference in life expectancy between optimal and high-risk profiles offers an the indication that risk factor status at an earlier stage of life has a significant impact at older ages.

The most impressive is the number of years lived free of disease for the optimal risk profiles. A 50-year-old man with an optimal risk profile can expect to live 17.19 years more free of cardiovascular disease than a member of the high-risk

group. A woman of that age with optimal risk can expect to survive 16.22 additional years free of cardiovascular disease. Importantly, at age 70, this difference is 11.37 years for males and 11.36 years for females. Both for males and females, similar patterns of life expectancy free of CHD or MI are also observed at age 50 and 70 (Table 9.4).

Concordant with the often-higher incidence of cardiovascular disease, the duration of disease is longer among members of the high-risk group than among those in the optimal risk group (Table 9.4). At age 50, males in the high-risk group can expect to live 38 percent (7.90 years) of remaining life in the CVD state; for the low risk group, this is 9 percent (3.0 years). Similarly, fifty year-old females with an optimal risk profile spend 11 percent (4.12 years) of the rest of their life with CVD; for the high-risk group, this is26 percent (6.07 years). Seventy year-old males and females with optimal risk profiles can expect to spend nearly 83 percent and 81 percent of their remaining life free of cardiovascular disease. By contrast, only 27 percent of males and 48 percent of females in the high-risk group can at that same age expect to remain free of CVD. Similar patterns are exhibited for coronary heart disease and myocardial infractions.

Table 9.4 Total life expectancy and life expectancy free from diseases based on a population free of cardiovascular disease at age 50 by risk profiles at middle age

Male

		Age 50	Age 60	Age 70
Total LE				
	Low risk	33.03	24.21	16.29
	High risk	20.74	13.56	8.00
	Difference	*12.29*	*10.64*	*8.29*
Without CVD				
	Low risk	30.03	21.06	13.56
	High risk	12.84	5.77	2.19
	Difference	*17.19*	*15.29*	*11.37*
Without CHD				
	Low risk	30.71	21.77	14.19
	High risk	14.69	7.59	3.61
	Difference	16.02	14.18	10.57
Without MI				
	Low risk	31.96	23.05	15.35
	High risk	16.64	9.37	4.67
	Difference	15.32	13.68	10.69

Continuation of Table 9.4…

Female

		Age 50	Age 60	Age 70
Total LE				
	Low risk	37.57	28.23	19.50
	High risk	23.30	15.53	9.30
	Difference	*14.27*	*12.70*	*10.20*
Without CVD				
	Low risk	33.45	24.14	15.84
	High risk	17.23	9.41	4.48
	Difference	*16.22*	*14.73*	*11.36*
Without CHD				
	Low risk	35.59	26.26	17.77
	High risk	19.04	11.27	6.06
	Difference	*16.56*	*14.99*	*11.71*
Without MI				
	Low risk	36.89	27.56	18.92
	High risk	20.86	12.93	6.99
	Difference	*16.03*	*14.64*	*11.93*

Lifetime probability of disease

The lifetime probability of a fifty year-old without cardiovascular disease, developing cardiovascular disease is presented by risk factor status in Table 9.5. This probability is a life table probability, as it applies to a synthetic cohort of people aged 50 and free of CVD at that age.

The lifetime probability of developing cardiovascular disease, including sudden cardiovascular death is 82 percent for males with high-risk profile vs. 38 percent for males with optimal risk profiles. Females with optimal risk profiles have a lifetime chance of experiencing CVD of 35 percent; for high-risk women this is 69 percent. It is estimated that within 10 years (i.e. from age 50 to 60) 37 percent of the high-risk males and 24 percent of females will experience CVD. Within 20 years, 67 percent of the males and 45 percent of the females with high-risk profiles will experience CVD. Fifty year-old males and females with optimal risk profiles have a chance of respectively 14 and 11 percent of experiencing CVD before age 70. For males and females, similar patterns are also observed in relation to coronary heart disease and myocardial infarction.

Table 9.5 Lifetime probability (%) of developing cardiovascular disease, for the cardiovascular disease free person of age 50 by optimal and high-risk profiles

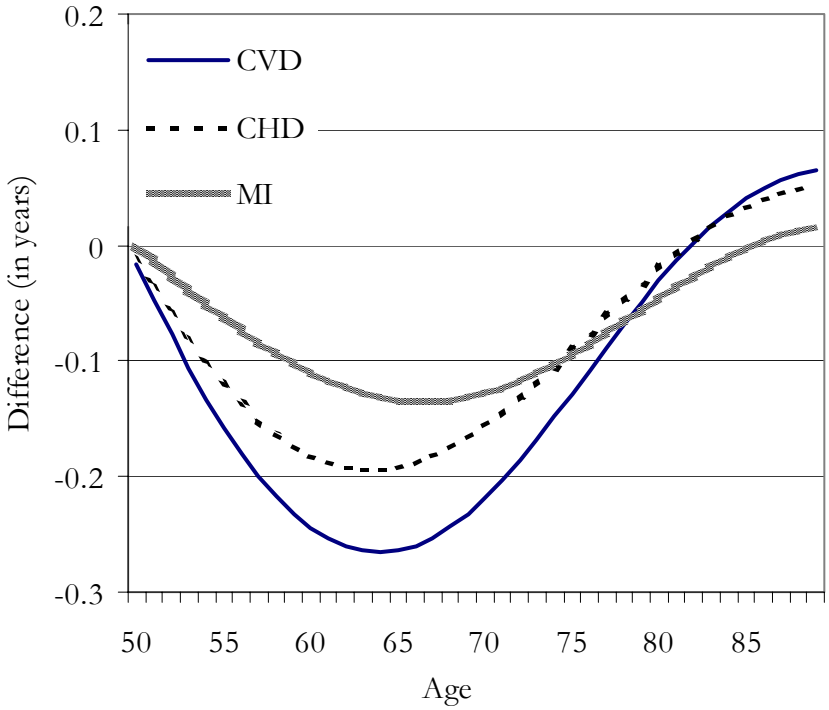
	Before age 60		Before age 70		Before death	
	Optimal risk	High risk	Optimal risk	High risk	Optimal risk	High risk
Male						
CVD	6	37	14	67	38	82
CHD	5	34	11	53	27	68
MI	3	17	8	34	21	47
Female						
CVD	5	24	11	45	35	69
CHD	2	15	6	31	16	48
MI	1	8	2	18	8	35

Differences in years spent with disease

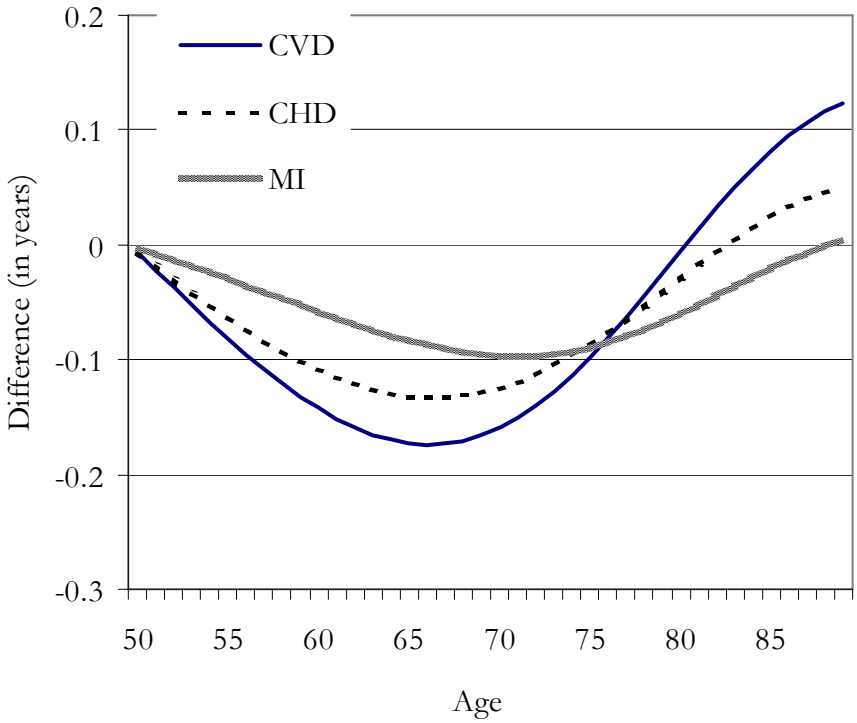
The difference between optimal and high-risk profiles (optimal-high-risk profiles) in the number of years spent with disease is presented in Figure 9.3. The enormous impact of cardiovascular disease on the human life course is translated into life years lost to disease. Importantly, the life years lost by those in the higher risk profiles to cardiovascular disease fall predominantly before age 80. The optimal risk group survives longer with cardiovascular disease after age 80 (Figure 9.3). Only at older ages (after age 80) do both males and females in the optimal risk group spend more years with cardiovascular disease. After age 80, males and females with an optimal risk profile spend more years with CVD than the high-risk group. Only the subjects in the low risk group survive longer, which indicates that, as people age, the tendency to experience CVD increases. That is, aging itself causes cardiovascular disease.

Figure 9.3 Differences of the number of years lived with diseases: optimal risk profiles–high-risk profiles

Male



Female



9.4 Discussion

The aim of this chapter was to investigate whether optimal levels of cardiovascular risk factors (single and multiple risk factors) at middle age compressed cardiovascular morbidity. To measure this, we constructed multistate life tables of cardiovascular disease history by risk factor status for the 30-50 age interval. In the following sub-sections, the major findings are discussed by comparing our methods and findings with existing studies, in addition to examining the strengths and limitation of our proposed method. In the last section, we briefly discuss the public health implications of this study.

Principal findings

Across all single risk factor categories, males who did not smoke and females who had optimal blood pressure at middle age were shown to have the highest life expectancy at age 50, namely 30.82 years for males and 34.72 years for females. The difference in life expectancy free of CVD for males was highest between optimal SBP and high SBP (7.29 years). For females, this difference was highest between optimal blood pressure and hypertension (7.84 years). While the differences in life expectancy with CVD were highest for males with low and males with high cholesterol levels (3.71 years more for high cholesterol), for females this was highest between the optimal BP and hypertension categories (3.00 years more for hypertension). The probability of developing CVD, CHD, or MI before age 70 was higher for the higher risk categories than for the optimal risk groups. The lifetime probability of a male smoker developing cardiovascular disease was equal to a male non-smoker. The lifetime probability of developing CVD or CHD was higher for female non-smokers, although the reverse holds for MI. These results are consistent with Chapter 6. For males and females, the major cardiovascular risk factors at middle age compress cardiovascular morbidity.

We demonstrated the possibility of using multivariate Gompertz regression models for long time continuous event histories to estimate the state transition rates, after which these estimated transition rates could be used to construct a multistate life table in multiple covariate contexts. Using this multistate life table, we found that, on average, 4 in 5 males with a low risk profile who were free of cardiovascular disease at age 50 would still be alive and free of cardiovascular disease twenty years later. By contrast, only 1 in 5 of high-risk profile males would still be in that state at age 70. Of the females free of cardiovascular disease at age 50, 1 in 5 in the optimal risk profile, as compared to 2 in 5 of low risk profile would be alive and remain free of cardiovascular disease.

A female of age 50 with an optimal risk profile could expect to survive another 37.57 years, as compared to another 23.30 years for a female in the high-risk group. These findings are consistent with Peeters et al., (2003) who estimated these figures

for non-smoking, non-obese females (13 years at age 40) using the Framingham Heart Study original cohort. The differences in total life expectancies at age 50 for males and females with optimal risk and high-risk profiles were 12.29 and 14.27 years. The males in the low risk groups could expect to survive 6.0 additional years compared to the total male respondents in the FHS. Similarly, females with optimal risk profiles could expect to survive 5 additional years compared to the total female respondents in the FHS. Overall, females with high-risk profiles were more vulnerable compared to high-risk profile males, which is consistent with a previous study (Jousilahti et al., 1999).

The most impressive findings concerned the number of years lived free of cardiovascular disease for subjects with optimal risk profiles. A man who had optimal risk profile at middle age, and was free of disease before age 50, could expect to survive 17.19 more years free of cardiovascular disease than a member of the high-risk group. A woman of that age with an optimal risk profile could expect to survive 16.22 years more free of cardiovascular disease. A similar pattern in life expectancy free of CHD or MI for males and females was also observed at age 50 and 70.

The duration of disease was generally longer among members of the high-risk profile than among those in the optimal risk profile. At age 50, a male in the high-risk profile could expect to live 7.90 years of remaining life with CVD; a male with an optimal risk profile, only 3.0 years. Similarly, a female of that age with a high-risk profile could expect to survive 6.07 years with CVD, a female with an optimal risk profile, 4.12 years. This indicates that high risk at adulthood not only shortens the duration of life but also extends life with cardiovascular disease. The optimal risk profile in middle age compresses the cardiovascular morbidity.

For individuals with favorable levels of cholesterol, blood pressure, BMI and for those who do not smoke, the long term incidence of cardiovascular disease and mortality is much lower and longevity is much greater, which is consistent with the previous study by Lowe et al (1998) and Stamler et al (1999). Stamler et al.(1999) estimated greater life expectancy (6 years) of low risk sub-cohorts vs. others based on multiple risk factor intervention trial for a cohort aged 35-39 years or 40-49 years from the Chicago Heart Association detection project population. This was underestimated, because of the greater risk of misclassifying individuals by using a single measurement of the major risk factors. These findings also directly confirm earlier statistical estimates of the benefits of low-risk status (Daviglus, et al., 1998).

Another important finding of this study was the lifetime probability of CVD-free fifty year-olds developing cardiovascular disease. The lifetime probability of developing cardiovascular disease, including sudden cardiovascular death, was, for the synthetic CVD-free cohort at age 50, 82 percent for males, and 69 percent for females in the high-risk profile. For the optimal risk profile, this was 38 percent for males and 35 percent for females. Remarkably, we also found that within 20 years,

67 percent of the males and 45 percent of the females in the high-risk group would experience CVD. It further became evident that the number of life years lost to cardiovascular disease for the higher risk profile fall dramatically before age 80, with the optimal risk group living more years with cardiovascular disease after age 80. After age 80, males and females with an optimal risk profile spent more years with CVD than did those with a high-risk profile. The low risk group survived longer, indicating that as the people age, the tendency to experience CVD also increases. That is, aging itself causes cardiovascular disease.

Strengths and limitations

The main strength of this chapter is that it is based on the prospective surveillance of a community-based cohort over a period of 48 years. Over this period, risk factors were measured and accurate data on the incidence and mortality of CVD and its sub-types y were gathered consistently, routinely and accurately. Without such an extended follow-up period, it is not possible to empirically analyze the burden of cardiovascular disease risk factors throughout life.

To estimate the transition rates, we chose the Gompertz model since it could capture the biological effect of morbidity and mortality well and give us smoothed transition rates. However, the Gompertz law is not applicable to the oldest-old (usually age 85+) mortality (Olshansky and Carnes, 2001; Yue, 2002). Olshansky and Carnes (2001) suggested that this might be the result of population heterogeneity at advanced ages. We did not extend our life table that was based on the Gompertz model beyond age 90, since Gompertz may overestimate the rates after that age. The life tables were closed at age 90 using the Massachusetts life expectancy for 1989-91 population, assuming that life expectancy remained same after age 90 irrespective of disease incidence and risk factor status. This assumption would not influence our major findings. Life expectancy of the optimal risk group would to some extent be under estimated and overestimated for the higher risk group, but other measures would remain the same, e.g. life time probability, number of years lived with disease and so on. However, by closing the life table at age 80, we dealt with this assumption of the Gompertz model. The observed life expectancy of Massachusetts males, females and total population at age 80 was 7.17, 9.25 and 8.56 years, respectively (Centers for Disease Control, 1989-91). Closing the life table at age 80 based on this observed life expectancy of males, we found that the total life expectancy for the low risk profiles decreased about one-and-a-half years and increased about one-and–a-half years for the high-risk profiles. This slight difference was largely due to our assumption that both the optimal and the high-risk group had the same observed life expectancy at age 80. Similar patterns were also exhibited for females.

We derived total life expectancy and life expectancy with cardiovascular disease by risk factor profiles based on the multivariate regression models. To validate the results, an empirical investigation was made, in which the optimal and high-risk profiles were defined slightly differently from the present approach. We selected the sample population from the same population analyzed in this chapter. We assumed, in those who had never smoked or who smoked less that 20 percent of the recorded time, a mean blood pressure of less than 140 (mm Hg), mean cholesterol level of less than 240 (mg per deciliter) and mean BMI (w/h^2) under 30 before age 50. We found 471 (100 males and 371 females) participants who complied with these conditions. A basic multistate life table (Figure 3.1(b), Chapter 3) was constructed using this sample population. It was found that total life expectancy (male-female combined) at age 50 would be is 35.3 years, while life expectancy with cardiovascular disease would be 4 years. These estimates are slightly lower for total life expectancy (1.5 years) but higher (around 0.5 years) for life expectancy with cardiovascular disease compared to the estimated values obtained in this chapter. This difference is mainly due to the different definition of optimal risk profiles and population selection. The sample population (15% of the 3045 sample population) consisted of a mixture of optimal and high normal risk profiles, indicating that the total life expectancy of this selected sample would be less, and longer with cardiovascular disease as compared to the sample population of 3045.

Another major strength of this study is the multistate life tables in multiple covariate contexts. The transition rate transfers into dwelling times give more transparent information about the consequences of risk factors. This study adds the consequences of risk factor status for cardiovascular disease in terms of incidence and years free of CVD and years with CVD throughout the life course.

Instead of only the baseline risk factor (Stamler et al., 1999; Lowe et al., 1998) status, we also considered at least two risk factor measurements, recorded between the ages of 30 and 50. We defined the risk factor statuses before age 50 and measured their impact on later ages of life. We were able to do so only because of the long period of follow-up of the FHS. Usually, single measures have a large variance, and relating a single (as opposed to multiple) measure of a risk factor to an outcome leads to substantial underestimation of the strength of association (Yusuf et al., 2001). Since the effect of several risk factors for vascular disease may take several years to fully manifest (Yusuf et al., 2001), cohort studies of relatively short duration may therefore only identify a part of this effect, while the extended period covered by the FHS might uncover a larger effect.

The relationships of major cardiovascular disease risk factors (e.g. smoking, blood pressure, cholesterol level) have been assumed to be "… strong, continuous, graded, consistent, independent, predictive, and etiologically significant for those with and without coronary heart disease" (Stamler et al., 1999). We defined the risk factors as categorical variables, since our intention was to construct multistate life

tables by risk factor profiles. We constructed a life table for a specific group (single or combined). Wilson et al., (1998) used the Framingham Heart Study to predict coronary heart disease using risk factors as categorical variables.

We addressed only the major cardiovascular risk factors between age 30 and 50 and not the risks of other diseases of the elderly. Therefore, we can only make conclusions regarding cardiovascular disease, not disability. The optimal risk profile in the MSLT in multiple covariate contexts is the (unobserved) combination of optimal levels of four risk factors, ignoring possible interactions between them. However, we found no evidence in Chapter 8 of non-independence.

The most important outstanding question is to what extent the observed association between the major risk factors and the indicators derived using multistate life tables are causal and applicable to today's populations. The risks associated with risk factor status that were defined 50 years ago may not be same as those defined today because of differences in the risk factor status in population and treatment. However, the hazard ratios estimated in chapter 8 are consistent with those derived from the more recent studies (Kenchaiah et al., (2002); Wilson et al., 1998).

There have been great improvements in mortality over the past 50 years. However, the Framingham Heart Study cohort is relatively healthy, and its life expectancy is similar to that of the 1990 Massachusetts population (Peeters et al., 2002; Centers for Disease Control and Prevention, 1989-91). Although the results presented here will not represent the absolute figures of today's populations, they are a robust estimation of the relative magnitude of the life table outcomes (e.g. number of years lived with CVD) by risk profiles.

The major limitations of this chapter are that we could not identify what proportion of the increased life expectancy with cardiovascular diseases or decreased life expectancy free of cardiovascular disease has directly resulted from a high risk at middle age, and would therefore be preventable through high-risk prevention. In the multivariate analysis, we did account for major risk factors of cardiovascular disease.

Public health implications

For individuals with favorable levels of blood pressure, total cholesterol levels, BMI and those who do not smoke, the long-term incidence of cardiovascular disease and mortality is much lower and longevity is much greater. On average, 4 in 5 males or females with favorable levels of cholesterol, blood pressure, BMI who do not smoke throughout the age interval of 30-50,and who remain free of cardiovascular disease until age 50 would still be alive and free of cardiovascular disease twenty years later. The same holds for a mere 2 or 3 in 10 members of the high-risk group. This reemphasizes the fact that the presence of major risk factors such as high BP, a high SCL and BMI poses a major public health burden.

These remarkable differences in life expectancy with and without cardiovascular disease between low and high-risk profiles indicate that risk factor status at middle age of life has a significant impact at later ages. Low risk in adulthood compresses cardiovascular morbidity and high risk expands cardiovascular morbidity. The findings reinforce the guidelines of American Public Health Association (Pearson et al., 2002) and the recent life course epidemiology approach (WHO, 2002). We have provided some empirical evidence on the impact of major risk factors in middle age on the cardiovascular life course. It is widely accepted that these risk factors are preventable through lifestyle modification (Pearson et al., 2002, WHO, 2002). Therefore, the high-risk group of adults needs to be motivated to change their lifestyle, keeping in mind that "prevention is better than cure", in order to stay healthy, save lives and increase healthy life.

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.

Ben-Shlomo Y, Kuh D, (2002). A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International Journal of Epidemiology*, 31:285-293.

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, Mahwah, New Jersey: Lawrence Erlbaum Associates.

Centers for Disease Control and Prevention. U.S. Decennial Life Tables 1989-91. Volume II, State life tables number 22, Massachusetts, National center for health statistics, USA.

Cupples LA, D'Agostino RB, Kannel WB et al., (1988). The Framingham Study: An epidemiological investigation of cardiovascular disease. Section 34: Some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements. Framingham Heart Study, 30 year follow-up. Publication PB87-177499. Bethesda: National Institutes of Health; 1988.

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 Medicine*, 339:1122-9.

Dawber TR, Meadors GF, Moore FE, (1951). Epidemiological approaches to heart disease: The Framingham Study. Am J Public Health. 1951;41:279-86.

Fontaine KR, Redden DT, Wang C et al., (2003). Years of life lost due to obesity. *Journal of American Medical Association*, 289: 187-193.

Gompertz B, (1825). On the nature of the function expressive of the law of human mortality, and on a new method of determining the value of life contingencies. *Philosophical Transactions of the Royal Society* 115:513-585.

Gompertz B, (1827). On one union law of mortality from birth to extreme old age, and on the law of sickness. *Journal of the Institute of Actuaries,* 16:329-344

Hayward MD, Grady WR, (1990). Work and retirement among a cohort of older men in the United States, 1963-1983. *Demography,* 27:337-56.

Hayward MD, Lichter DT, (1998). A life cycle model of labor force inequality- extending Clogg's life table approach. *Sociological Methods and Research*, 26(4):487-510.

Jousilahti P, Vartianinen E, Toumilehto J et al. (1999). Sex, age, cardiovascular risk factors, and coronary heart disease- a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation*, 99:1165-1172.

Kaplan GA, Haan MN, Wallance RB (1999). Understanding changing risk factor associations with increasing age in adults. *Annual Review of Public Health*, 20:89-108.

Land KC, Guralnik JM, Blazer DG, (1994). Estimating increment-decrement life tables with multiple covariates from panel data: the case of active life expectancy. *Demography,* 31(2):297-319.

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.

Manson JE, Colditz GA, Stampfer MJ et al., (1990). A prospective study of obesity and risk of coronary heart disease in women. *New England Journal of Medicine*, 322:882–889.

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.

Olshansky SJ, Carnes BA, (2001). Prospects for human longevity. *Science*, 291:5508: 1491.

Pearson TA, Blair SN, Daniels SR et al., (2002). AHA Guidelines for primary prevention of cardiovascular disease and stroke:2002 Update. Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation*, 106:388-391.

Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Mamun AA, Bonneux L, (2003). Obesity in adulthood and its consequences for life expectancy: a life-table analysis*, Annals of Internal Medicine*, 138:24-32.

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.

Stamler J, Greenland P, Neaton JD, (1998). The established major risk factors underlying epidemic coronary and cardiovascular disease. *CVD Prevention*, 1:82-97.

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

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.

Yue JC, (2002). Oldest-old mortality rates and the Gompertz law: a theoretical and empirical study based on four countries. Manuscript. Department of Statistics, National Chengchi University, Taipei, Taiwan. http://www.soa.org/research/Yue_Final.PDF, accessed October 2002.

Yusuf S, Reddy S, Ounpuu S, Anand S, (2001). Global burden of cardiovascular diseases. Part I: gender considerations, the epidemiologic transitions, risk factors, and impact of urbanization, *Circulation*, 104:2746-2753.