A Prospective Study of Chronic Disease and Risk Factors in an Urban Chinese Population

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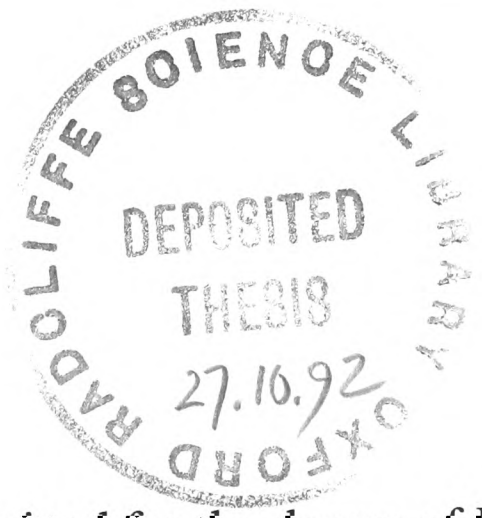

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To my wife Yi Ping

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A prospective study of chronic disease and risk factors in an urban Chinese population

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Abstract

The relationships of serum cholesterol, blood pressure and cigarette smoking with certain chronic diseases were investigated in a prospective study among more than 9,000 middle-aged adults in urban Shanghai. At baseline, the mean serum cholesterol was 4.2 mmol/l, 14 per cent of the participants had definite hypertension, and 61 per cent of males and 7 per cent of females were regular smokers. During 8-13 years of follow-up, 620 deaths were recorded. 231 (37%) of the deaths were ascribed to cardiovascular disease, including 44 (7%) from CHD and 152 (25%) from stroke. Cancer caused 274 deaths (44%), of which 66 deaths (11%) were from lung cancer, 63 (10%) from stomach cancer and 54 deaths (9%) from liver cancer. Other causes accounted for 115 deaths (19%), 29 (5%) of which were from chronic liver disease, and 31 (5%) from chronic obstructive pulmonary disease.

In this study, there was a strong positive and apparently independent relationship of serum cholesterol level to CHD death ($z=3.47$, $2P<0.001$). Within the range of usual serum cholesterol studied (about 3.8-4.7 mmol/l), there was no evidence of any apparent "threshold". After appropriate adjustment for the "regression dilution" bias, a 4% difference in **usual** cholesterol was associated with a 21% (95% confidence interval 9-35%) difference in the risk of CHD death. There was no significant relationship of serum cholesterol with total stroke mortality, or with total cancer mortality. The 79 deaths due to liver cancer or other chronic liver diseases were inversely related to cholesterol concentration at baseline. This inverse association appears to be secondary to prolonged hepatitis B virus infection, which accounts for most of the deaths from liver disease in China and which chronically lowers blood cholesterol.

There was a strong positive relationship between blood pressure and risk of death from stroke and CHD. Within the range of usual blood pressure studied (SBP: 117-161 mmHg; DBP:75-101 mmHg), there was no evidence of any apparent threshold. After appropriate adjustment for the "regression dilution" bias, a 10 mmHg difference in **usual** SBP was associated with a 67% (95% CI 52-83%) difference in the risk of stroke deaths, and with a 44% (95% confidence interval 21-73%) difference in the risk of CHD death; a 7 mmHg difference in **usual** DBP was associated with a 124% (95% CI 96-155%) difference in the risk of stroke deaths, and with a 58% (95% CI 22-105%) difference in the risk of CHD deaths.

Cigarette smoking was significantly associated with deaths from any disease. There was a strong positive relationship between cigarette smoking and risk of all cancer deaths, and specifically cancer of the lung and cancer of the upper aero-digestive tract. The relative risk of lung cancer for a current smoker was 3.5 (95% CI 1.8-7.0; $2P<0.001$), and among the male population 63% of lung cancers were directly attributed to the smoking. The relative risk of upper aero-digestive cancer death for regular smokers was 3.4 (95% CI 1.1-10.5; $2P<0.05$). The risk of chronic obstructive lung disease was also significantly related to smoking, with a relative risk in a smoker of 2.2 (95% CI 1.1-4.4; $2P<0.05$). In the present population, smokers had a 60% excess risk of deaths from total stroke compared with non-smokers ($z=2.40$, $2P<0.05$).

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Chapter 1

Chronic disease, risk factors and major issues in the present study

1.1 The changing patterns of disease in China

In China prior to the 1950s, the life expectancy at birth was less than 40 years of age, and more than half of the children born in China could expect to die before ever reaching middle age because of the high death rates from acute infective and parasitic diseases or malnutrition. Even during middle age, infective and parasitic diseases accounted for more deaths than any of the chronic diseases. Therefore, in previous decades, the most important medical priorities in China were the provision of adequate nutrition and the control of infective and parasitic diseases. In contrast, control of chronic degenerative and non-communicable diseases has not previously been a major priority, partly because little was known of their pattern and causes and partly because they were overshadowed by endemic and infectious diseases.

China has, over the last few decades, experienced a remarkable improvement in the general health of its population, greater than in any other country of similar economic development. This improvement in health is due to the progressive control of infectious and parasitic diseases, the provision of family planning, childhood immunization, accessible primary health care, improved nutrition, better education, sanitation and housing. The infant mortality rate, for most of China has declined from 250 per 1,000 live births in 1950 to about 20 per 1,000 live births in 1987 as a national average, although certain regions of China still have higher infant mortality rates *(World Health Organization 1989).* The death rates from all causes both in younger (ages 1-4) and older children (ages 5-14) have also shown a consistent and dramatic decline in the past few decades. For adults, the probability of premature death in China is lower than in many other

countries of similar economic development, and is moving close to that found in most developed countries. The international comparisons of the probabilities of death for both children and adults in some selected countries according to the level of economic development are shown in Table 1.1. In 1987 the probability of

Table 1.1. The probability of death in children and in adult in 1987 in some selected countries.

Countries	Probabilities of death between age (%)			
	0-5 years		**15-60 years**	
	Males	Females	Males	Females
High income countries				
Britain	1.1	0.8	14.5	7.7
Canada	1.1	0.9	14.2	7.6
United States	1.4	1.1	17.5	9.3
Middle income countries				
Poland	2.1	1.6	24.8	10.3
Malaysia	3.3	2.4	20.4	14.5
Brazil	6.9	5.6	23.5	14.5
Low income countries				
China	**4.4**	**3.3**	**15.0**	**11.1**
Kenya	12.1	10.5	32.4	18.2
India	13.8	11.8	24.6	27.0
Nigeria	18.3	16.3	36.1	30.3

dying for males aged between 15 and 60 years in China was about 15%, while for females of the same age groups, the probability of death was lower, at 11%. The death rates in both children and adults in China compare favourably with most other developing countries, and are close to that found in developed countries *(World Bank 1990)*. Life expectancy in China is currently 70 years (about as great as in the United States), and about 95% of Chinese can now expect to live well into middle age and 70% to old age. This would represent an increase in life expectancy at birth of about 30 years within just three decades. This achievement has significantly surpassed that which could be expected for China's stage of economic development.

Conditions such as cancer, vascular disease or chronic obstructive lung diseases do not usually cause much death or disability until at least middle age

(35-65 years). The progressive control of infective, parasitic and nutritional disorders has been, and continues to be, so remarkably successful that a rapidly increasing proportion of those born in China survive into middle age. Infective and parasitic diseases now account for only a small minority of all deaths. As a result an epidemiological transition has taken place in China, with a shift in disease predominance from mainly Infectious diseases to mainly chronic and non-communicable diseases. The overall pattern of disease and death in China has become very much like that of the developed countries, with cancer, stroke and heart disease predominating as the major causes of premature death and disability.

Analysis of the causes of death in adult life (Table 1.2) show that the probability of dying from infective and parasitic diseases in China has fallen to about 1% in

Table 1.2. Probabilities of death due to various causes in Chinese adults in 1987.

Causes of death	Probabilities of death between 15-60 years (%)	
	Males	Females
Infective & parasitic diseases	1.05	1.24
Non-communicable diseases	10.28	7.71
Cancer	4.28	2.45
Vascular disease	3.17	2.98
COPD & cor pulmonale	1.56	1.32
Other diseases	1.27	0.96
Injury & Poisoning	3.71	2.12
Total deaths	**15.04**	**11.08**

both males and females, while non-communicable diseases such as cancer, stroke, heart disease and chronic obstructive lung diseases are about 10 times more likely to cause death than infectious diseases. The probability of dying from external causes of injury and poisoning is also very high, and accounts for double the mortality of infectious disease. *(World Bank 1990).*

1.2 Comparison of the patterns of chronic disease in China with those in Western countries

Although chronic diseases (such as cancer, stroke and heart disease) have emerged as the most important cause of morbidity and mortality in both urban and rural Chinese populations, the patterns of individual diseases and the levels of major risk factors thought to be related to these diseases are still substantially different from those in Western populations. This part provides a general comparison of the patterns of major chronic diseases in China with those in Western populations. In addition, the future trends of chronic diseases in China will be discussed briefly, in view of the evidence on the trends of chronic diseases observed in the Western countries, and the future possible changes in exposure to various risk factors in the population.

1). Vascular disease

Vascular diseases, such as coronary heart disease (CHD) and stroke are the leading causes of premature death and illness throughout the world. The overall

Table 1.3. Mortality rates for causes of vascular and respiratory diseases in China and in Britain for people aged 35-74 years in 1987.

Cause of death	China		Britain	
	Mortality (1/100,000)	% of total deaths	Mortality (1/100,000)	% of total deaths
All vascular diseases	353.5	35.5	385.3	43.5
Coronary heart disease	53.1	5.3	267.2	30.2
Stroke	196.7	19.8	67.5	7.6
Hypertensive heart disease	12.9	1.3	5.7	0.6
Rheumatic heart disease	17.8	1.8	5.2	0.6
Cor pulmonale	53.5	5.4	3.5	0.4
COPD	136.7	13.7	17.8	2.0
All causes	**995.1**	**100.0**	**885.7**	**100.0**

patterns of vascular diseases in China are at present characterised by a low incidence of CHD and a high incidence of stroke. The ratio of stroke to CHD

incidence is estimated to be between 4 and 5 in Chinese in contrast to between 0.3 and 0.4 in many Western populations. Moreover, the overall mortality rates from hypertensive heart disease and from rheumatic heart disease are significantly higher in China, especially in rural China, than in Western populations. Comparison of the mortality rates, based on national vital statistical data in 1987, for different categories of vascular and respiratory diseases between Chinese adults and British adults aged 35-74 years, are shown in Table 1.3. While the overall mortality rate for all vascular disease in Chinese is similar to that of the British, the mortality due to individual categories of vascular disease is significantly different between the two countries.

Coronary heart disease

At present coronary heart disease causes only about 240,000 deaths annually in China (with a total population of 1100 million), compared with about 175,000 CHD deaths in Britain with a population of 57 million. In 1987, the national mortality rate from CHD in China for people aged 35-74 years, standardised to the age distribution of the "world" population, was 53/100,000, which accounts for only 5% of all deaths. In contrast about a third of all deaths in Western populations such as Britain are attributed to CHD. The mortality rate from CHD in Britain is more than 5 times higher than in China, with an age-standardised mortality rate of 267/100,000. The age-standardised mortality rate from CHD in rural China is even lower at 34/100,000 for people aged 35-74 years, which is approximately one-tenth of the levels for many Western populations *(World Health Organization 1989)*. The exceptionally low rate of CHD in China in comparison with Western populations has also been confirmed in a number of well-designed international comparative studies using standardised methodology *(Tao, et al 1989; WHO MONICA Project 1989)*. In the MONICA Project *(1989)*, the mortality rate for CHD in Beijing, was shown to be one of the lowest among all the study populations, with a standardised mortality rate for

people aged 35-64 years of 27/100,000, compared with 133 in a UK population. The ratio of CHD in males compared to females is also significantly lower in China, at about 1.4 than the ratio of between 3 and 4 which is typically found in many Western populations *(Tao, et al 1989).*

Different patterns emerge when the secular trend data are examined for CHD mortality among the different countries *(Thom, et al 1985; Dodu 1988).* The trend in CHD was generally upward in the industrialized countries until the 1960s, then a peak was reached, which was followed by a downward trend in many countries *(Thom, et al 1985).* At present, Western countries such as the United States, Canada, and Australia have experienced a substantial decline in mortality from CHD, which started 20 years ago. Others countries have had little or no change in secular trends for CHD or have shown just a modest recent decline, as in Britain. In a few countries (mainly in Eastern Europe), there has been a substantial increase in CHD mortality *(Dodu 1988; Thom, 1989).* Although the death rate for CHD is exceptionally low in Japan, there has been a continuous decline throughout the last 35-years in both males and females *(Thom, 1989).* Although differences in classification or diagnostic practices may influence temporal trends in mortality or even produce spurious CHD trends, the magnitude of these changes and their consistency over long periods of time, together with associated changes in total mortality in many countries, indicate that these trends are both real and important *(Harlan 1989).*

The reasons for the underlying decline in CHD mortality in many Western countries have evoked considerable speculation and inquiry *(Pyorala, et al 1985).* Claims have been made for primary prevention as expressed by decreased incidence of first events due to the decline in exposure to risk factors, and for improved care leading to better case-fatality rates. There is evidence from a longitudinal study of a large population sample in USA that the pattern of decline in the incidence of CHD is quite similar to that for CHD mortality, and this

has shown an estimated average annual decline of 2.7% over the past two decades *(Reed & Maclean 1989).* Other studies have also observed that, while the incidence rate of CHD has decreased gradually over time, there was also a substantial decline in the CHD case-fatality over the same period *(Burke, et al 1989).* Hence it is difficult to quantify the individual contributions of primary prevention and of better medical care to the decline in CHD mortality. The exact contribution of each may differ depending on socio-demographic status and on the different time periods during the decline, and the relative effects of prevention and medical care might also differ by regions within the USA *(Harlan 1989).*

In China, the overall and age-and sex-specific secular trends for CHD are unclear because mortality statistics in the country are still incomplete. Surveillance of major cardiovascular disease did not begin until the late 1980s and even then only in some selected populations. However, there is evidence from a limited number of epidemiological studies, that the mortality rate from CHD is increasing in some areas, especially in urban China *(Tao,et al 1982; Tung, et al 1984).* Such a tendency is consistent with the observation of an increased consumption of dietary fat and cholesterol in some Chinese populations in recent years *(Tung, et al 1984; Tao,et al 1989).*

Cerebrovascular disease

Stroke rates: Cerebrovascular diseases, mainly completed stroke, are the most common cause of death and disability in China, and account for 4 to 5 times the percentage of deaths due to CHD. The occurrence of stroke in Chinese people has been shown in a number of epidemiological studies to be higher than the international average. According to mortality statistics in 1987 *(World Health Organization 1989)*, about 20% of all deaths in China were attributed to stroke, and the age-standardized mortality rate from stroke for people aged 35-74 years was about 200 per 100,000 compared with a rate of 67 per 100,000 in Britain. The absolute risk of stroke death in China is also substantial given the size of its

population. It is estimated that stroke now causes about a million deaths each year in China, and may cause disability in about two or three times that number. With an increasing proportion of older people in China, even if the age-specific stroke rate remains constant, the absolute number of deaths from stroke would be expected to increase further in the future.

Stroke mortality rates average about 100 per 100,000 population worldwide, with rates ranging from 36 in the Philipines to 197 per 100,000 in Japanese populations *(Schoenberg 1980; Malmgren, et al 1987)*. The overall age-adjusted mortality rate of completed stroke in China is slightly higher than the international average, but there are also large regional variations within the country. In a cross-sectional survey carried out in six cities of China in 1983, the mortality rate from stroke for all ages, averaged 116 per 100,000 population *(Li, et al 1985)*. In each of the six cities, however, the age-adjusted mortality rates varied markedly, ranging from 59 per 100,000 population to 272 per 100,000 population. There was a south-to-north gradient, with the highest stroke mortality rate in the northeast region of the country.

Annual incidence rates of stroke, as reported by many studies worldwide, are about 150 to 250 per 100,000 population. In the survey of six Chinese cities, the average incidence rate of stroke among the whole study population was 219 per 100,000 population, which was higher than the rate reported from Rochester, MN (170/100,000), but lower than that from Hisayama, Japan (290/100,000). However, the incidence rate of stroke for those aged 20 years or over in the Chinese population was significantly higher than that for Japanese, with the rate being 360 per 100,000 population in Chinese compared with 270 per 100,000 population in Shibata, Japan *(Tanaka, et al 1981)*. The reported annual incidence rate of stroke in one of the cities, Harbin, is among the highest in the world at 441 per 100,000 population. The WHO MONICA Project, using standardized diagnostic criteria and a comprehensive case finding system, has

also confirmed the relative high incidence rate of stroke in China, especially in the north. In a MONICA study population of 700,000 residents in Beijing, the age standardized incidence rate of first completed strokes was shown to be 239 per 100,000 population, which is similar to that in Japan, but higher than that in most Western populations *(Chen, et al 1987)*.

Stroke types: There are four main pathological categories of stroke. These are cerebral infarction due to thrombosis, cerebral infarction due to embolus, cerebral hemorrhage and subarachnoid hemorrhage. The relative frequencies of the four different types of stroke vary with age and, to some extent, with different populations. Cerebral infarction, which accounts for approximately 80% of strokes in Western populations, may result from atherothrombotic disease of the extracranial and intracranial arteries or as a result of an embolism from a cardiac or other extracerebral source. Intracerebral haemorrhage and subarachnoid haemorrhage account for approximately 20% of strokes and occur as a result of a rupture of an intracranial aneurysm, an arterioverous malformation or hypertensive vascular disease *(Ostfeld 1980)*. In China, 30-48% of strokes have been reported to be due to haemorrhagic stroke *(Li, et al 1985; Chen, et al 1987)*. This is approximately three times the proportion in North America but is similar to that observed in other Chinese populations (such as, Chinese in Taiwan and Hong Kong) *(Hu, et al 1986; Huang, et al 1990)*. The distribution of subarachnoid hemorrhage is similar in different Western populations, and usually accounts for about 4-8% of all stroke *(Ostfeld 1980)*. While cerebral embolus with a documented cardiac source is the underlying cause of stroke in 5-15% of stroke cases in the Western populations, it is much less common in China or in Japan, perhaps due to the low rate of CHD in these populations.

In the six Chinese Cities survey, it was found that 51% of the incident cases of stroke were diagnosed as cerebral infarction, 44% as intracerebral hemorrhage and 2% as subarachnoid hemorrhage *(Li, et al 1985)*. The percentage of

intracerebral hemorrhage (44%) among the incident cases is much higher than that reported in Western populations, where it was about 12% *(Gross, et al 1984),* and also somewhat higher than figures reported for Japan (22%) *(Tanaka, et al 1981).* Because of the higher case-fatality ratio and relatively short survival of intracerebral hemorrhage, it accounts for a greater proportion of mortality due to stroke. The WHO MONICA Project in China, using standard diagnostic criteria, also found a high percentage of intracerebral hemorrhagic stroke in Chinese *(Chen, et al 1987).* The incidence rate of intracerebral hemorrhagic stroke for a study population of 700,000 people in Beijing, aged 25-74 years was 78 per 100,000 of population,which accounted for 42% of all stroke cases. A collaborative stroke registry carried out in a Chinese population living in Taiwan, also reported similar findings to those in the People's Republic of China *(Hu, et al 1986).* In that study the percentage of the major types of stroke in a stroke registry of 1,120 patients, which were all verified by computed tomography (CT), was 47%, 48% and 5% for cerebral hemorrhage, cerebral infarction and subarachnoid hemorrhage respectively. Although direct comparison of stroke incidence rates among countries may be confounded by possible differences in admission policy, completeness of case ascertainment, diagnostic accuracy as well as the age distribution of the populations, the age-adjusted stroke incidence rate in some urban Chinese populations (approximately 219 per 100,000 population) is approximately 1.5 times that of many Western populations. Assuming that about 10% of strokes in Western countries and approximately one third of strokes in China are due to intracerebral hemorrhage, it can be estimated that the stroke incidence in China excluding intracerebral hemorrhage approximates that of Western populations. It appears that the excess stroke rate in the Chinese is largely due to intracerebral hemorrhage, which is about three to five times that in most Western populations.

Why Chinese and many other Asian people are predisposed to intracerebral hemorrhage remains unexplained. The prevalence of definite hypertension in

adults (WHO criteria, blood pressure of ≥160/95 mmHg) is 5-8% in China *(Wu, et al 1982)*, is lower than the 10-15% prevalence observed in most Western populations *(Shaper, et al 1985)*. The incidence of intracerebral hemorrhage (defined by clinical criteria) in Western populations before the availability of effective antihypertensive therapy was still only a fraction of its current incidence in the Chinese *(Furlan, et al 1979)*. Thus, uncontrolled chronic hypertension alone does not seem to fully account for the high rate of cerebral hemorrhage in China. While the pathogenesis of intracerebral hemorrhage may be quite complex, it appears that chronic levels of blood pressure below those usually defined as hypertensive may not be tolerated by Chinese, either because of the interaction from other environmental and dietary factors, or because of differences in genetic composition. Racial differences in the pattern of stroke have previously been reported to show similar increases in the incidence of hemorrhagic stroke among the Japanese *(Komachi, et al 1984)* and black *(Gross, et al 1984)*. A number of studies have suggested that stroke in Chinese and Japanese is characterized by predominantly small-vessel pathology that results in lacunar infarction and hemorrhage *(Gorelick, et al 1984; Huang, et al 1990; Feldmann, et al 1990)*.

Stroke trends: During the past few decades, a number of epidemiological studies have indicated that there has been a remarkable downward trend in mortality rates from stroke (both in cerebral haemorrhage and cerebral infarction) in most Western countries (such as US, Australia, UK), as well as in Japan, where there is a very high stroke rate *(Fratiglioni, et al 1983)*. However, not all countries have experienced a similar magnitude of decline during the same period, and some have experienced a slight increase in mortality rate *(Editorial 1983; Whelton & Klag 1987)*. In many Western countries in which there has been an apparent downward trend in both incidence and mortality rates from stroke, the decline in stroke mortality started in the 1930s and 1940s or even earlier, and accelerated in the 1970s *(Baum & Goldstein 1982; Whisnant 1984)*. This

contrasted to the general upward trend for CHD mortality over the same period of time. In Japan, however, the decline started only in the mid-1960s and accelerated downwards in the 1970s *(Tanaka, et al 1982; Komachi, et al 1984; Omae & Ueda 1988)*. There is, however, no systematic epidemiological data available on secular trends of stroke incidence or mortality rates in China.

In the US, the decline of stroke rate after 1975 was estimated to be 4-7% per annum compared with 1.5% annum between 1951 and 1974, and 1% per annum between 1920 and 1950 *(Ostfeld 1980; Klag, et al 1989)*. The results from Rochester are the most frequently quoted regarding the secular decrease of stroke incidence *(Garraway, et al 1983)*. Over 35 years, 2,133 first-ever strokes occurred in 1.5 million person-years of observation. Starting in 1945, and continuing through 1979, the incidence rates were calculated for 5-year periods. When the incidence in the first five-year period was compared with that in the most recent 5-year period, the incidence of all first-ever strokes had decreased by 54%. This decrease was observed for all age groups, but was largest in those aged 85 and older. In Hisayama, Japan *(Ueda, et al 1981)* the incidence of both cerebral haemorrhage and infarction has decreased with time. The annual age-adjusted rate for cerebral haemorrhage decreased by 29% between 1961-66 and 1972-76, while the rate of cerebral infarction also fell significantly by 34% over the same period of time. There is some speculation that the decline in mortality from stroke in the first half of this century could be, to some extent, attributed to changes in death certification practice and improvement in the diagnosis of clinical stroke cases. But, the consistency and magnitude of the decline in stroke mortality prior to 1950 almost certainly reflects a true decrease in stroke incidence. The mechanism underlying this decline in the first half of this century is uncertain, and antihypertensive therapy certainly cannot account for the decline during this early period. It has been suggested that the pre-1970 fall in stroke mortality was largely attributed to the reduction of blood pressure in the population, much of which may in turn be due to a decline in salt intake

(Joossens 1980). This decline has been ascribed to the increasing use of refrigerators and consequent lesser need for salt as a preservative, as documented in some data from Japan and a few Western countries *(Joossens 1980)*.

The more recent decline in mortality from stroke since the 1970s suggests that there has been some change in some widely distributed environmental agents. It seems quite likely that small changes in the mean blood pressure of the population, due to interventions other than the treatment of hypertension, may have had a more pronounced effect on mortality from stroke. In a recent report on dynamic trends in risk factor levels and cardiovascular disease rates in rural Japan *(Shimamoto, et al 1989)*, there was a significant reduction in the mean blood pressure for both men and women aged 40-69 years, averaging 13 mmHg for systolic blood pressure and 4 mmHg for diastolic blood pressure. During that 20 year period, the incidence of all stroke declined by approximately 60% in both men and women. The significant and consistent decline in blood pressure occurred across all age and sex groups without any significant increase in the use of antihypertensive medication. A considerable part of the blood pressure decline may, therefore, be attributed to changes in related behaviour and environmental factors, such as decreased salt intake, improvement of working conditions, replacement of manual work with mechanized farming, and improvement of domestic heating in cold weather. In many Western countries, there has been an acceleration in the decline of tobacco consumption since the mid 1970s, and trends in cigarette smoking may have contributed more to the decline in mortality from stroke than has previously been recognised. Variation of stroke mortality in Britain has been shown to be related to the ingestion of fresh fruit and vegetables, and particularly to the intake of vitamin C *(Acheson & Willams 1983)*. Further research is necessary to clarify the factors underlying the decline of mortality from stroke.

Other vascular diseases

Rheumatic heart disease is a result of poorly managed treatment of streptococal infections of the throat among children and young adults. Rheumatic fever and rheumatic heart disease have virtually disappeared in Western countries, and new cases of rheumatic heart disease are becoming rare in China. Among those over 35 years of age, however, rheumatic heart disease morbidity and mortality still represents a significant problem, with the age-adjusted mortality rates in Chinese (18/100,000) being more than three times as high as that in the British population (Table 1.3). It is estimated that about 200,000 deaths in China are attributed to rheumatic heart disease each year.

Although hypertensive heart disease is a relative infrequent cause of death and illness compared with stroke and CHD, it also presents a health problem in the Chinese population. The mortality rate from hypertensive heart disease is twice that of Western populations (Table 1.3). Most of the hypertensive heart disease, especially in middle age, is avoidable or postponable with proper control of hypertension. While the prevalence of hypertension is generally more common in urban Chinese than in rural Chinese *(Wu, et al 1982)*, the rates of hypertensive heart disease show an opposite pattern, with mortality rate in rural China (17 per 100,000) being almost twice that in urban China (10 per 100,000). This may reflect chiefly the less effective control and poor management of hypertension in rural China.

2). Cor pulmonale and chronic obstructive pulmonary disease

Another important cause of heart disease in China is cor pulmonale, which is most frequently a consequence of chronic obstructive pulmonary disease (COPD). The overall mortality rate from COPD and cor pulmonale rank highly in the population, with an age adjusted mortality rate for people aged 35-74 years of 190 per 100,000 population. This figure is almost equal to the stroke death rate, and about 10 times as high as that found in Western populations. Each year

COPD and cor pulmonale account for a million deaths in China, and disability in perhaps five to ten times as many.

Smoking is the most significant risk factor for COPD in Western populations, where both COPD prevalence and COPD deaths are limited largely to smokers *(Surgeons General's report 1984)*. About 80-90% of COPD in Western populations are estimated to be attributed directly to smoking. In China, smoking is uncommon among women so it cannot account for the high female death rates from the disease, nor can smoking explain the great variation between different geographic regions in China. The national average mortality rate from COPD for Chinese women aged 35-74 years is 170 per 100,000 population which is very close to the male rate of 210 per 100,000 population, even though the prevalence of smoking is less than 10% in Chinese women. Moreover, the mortality rate from COPD and cor pulmonale in rural China is more than double that found in urban China, with an average rate of 274/100,000 and 131/100,000 respectively for rural and urban Chinese aged 35-74 years. This implies that the current high rates of COPD and cor pulmonale in China may be linked, in ways not yet fully understood, to conditions other than smoking. These might include poverty, poor nutritional status, frequency of early childhood respiratory infections, and substandard living conditions (including severe indoor air pollution, exposures to heating or cooking smoke). However so far, no well-designed epidemiological studies have demonstrated a significant role for any of these factors. Atmospheric pollutants (such as smog, industrial pollutants, exposure to dust in mines, textile mills and factories) together with respiratory infections are also believed to exacerbate the disease and can compound the severity and outcome of COPD. However there is no strong evidence that general environmental pollution is a major risk factor for COPD.

3). Cancer

Cancer is among the most common cause of chronic disease in China, and at present accounts for more than a million Chinese deaths annually. The leading cancer mortality rates and their relative frequencies in China as compared with those in a Britain are shown in Table 1.4. The average cancer mortality rate in China, adjusted to the world population, was 263 per 100,000 population for people aged 35-74 years, and the relative frequency of cancer as a cause of death was 26%. The overall cancer rate in China compares favourably with those of developed countries, for instance 312 per 100,000 population in Britain. However, cancers of some sites, especially in some regions of China, occur at a much higher frequency than anywhere else in the world.

Table 1.4. Mortality rates for various causes of cancer in China and in Britain for people aged 35-74 years in 1987.

Cancer sites	China		Britain	
	Mortality (1/100,000)	% of total deaths	Mortality (1/100,000)	% of total deaths
All cancer	262.9	26.4	312.1	35.2
Lung	56.3	5.7	86.5	9.8
Stomach	50.8	5.1	17.6	2.0
liver	49.5	5.0	1.8	0.2
Oesophageal	32.3	3.2	10.7	1.2
Colorectal	14.9	1.5	33.6	3.8
Breast (Female)	11.4	1.4	59.5	9.0
All causes	**995.1**	**100.0**	**885.7**	**100.0**

Lung cancer

In the 1973-75 mortality survey in China (*Li, et al 1981)*, lung cancer ranked fourth in males and fifth in females among cancers as the leading cause of death. By 1987, lung cancer had exceeded stomach cancer (which was the commonest type of cancer during the previous few decades), and is now ranked as the leading cause of death from cancer in both males and females. Although the national average mortality rate of lung cancer still compares favourably with

those of developed countries (about 50% of that in USA) where cigarettes have been widely smoked for several decades, the rate is already more than 25 times that in the lowest incidence country (Nigeria). Moreover, the available evidence indicates that the lung cancer rate has increased steadily in the last 15 years at a rate of about 9% a year. This substantial growth in lung cancer in China is consistent with the current high prevalence (over 60% in males) and duration of cigarette smoking among Chinese, especially among males, and parallels the earlier experience in Europe and US of an increase in lung cancer associated with **prolonged** use of cigarettes. In some areas, particularly in Shanghai where people started to smoke much earlier than in most other parts of China, lung cancer rates significantly exceed the Chinese national average *(Shanghai Cancer Institute 1982).*

An interesting feature of lung cancer occurrence in China is the relatively high incidence rate among Chinese females, which can not be explained entirely by smoking. The incidence rate of lung cancer in nonsmoking Chinese women is nearly three times that in any other nonsmoking female populations, irrespective of where they live *(Shimizu, et al 1985).* The annual incidence rate for lung cancer is about 20 per 100,000 population for nonsmoking Chinese women, compared with only 7 per 100,000 for female nonsmokers in the West and in Japan *(Fraumeni & Mason 1974; Koo, et al 1985; Gao, et al 1987).* The difference is unlikely to be genetic in origin, since the incidence of lung cancer in nonsmoking Chinese men is similar to that in other male nonsmokers throughout the world. A recent case-control study in Shanghai suggested that the excess of lung cancer found in Chinese women is due to methods of cooking *(Gao, et al 1987).* This study found, in addition to the usual relationship with smoking, that lung cancer was also associated with the fumes of oil produced by cooking in a wok. The risk was greatest when rapeseed oil was used in preference to soybean oil and where the frequency of eye irritation was greatest. The conclusion that pollution associated with cooking in this way constitutes a risk is further

supported by the laboratory finding that extracts of the condensate of both types of oil are mutagenic and that hazards of rapeseed oil are even greater than that of soybean oil *(Qu, et al 1986)*.

With the exception of Britain and Finland, where lung cancer rates have declined since the early 1960s, virtually all countries have experienced a steady increase in mortality from lung cancer in men, irrespective of their baseline rates. This rise of lung cancer mortality parallels the substantial increase of cigarette consumption in the 1950s. It has been estimated that the number of lung cancer has been increasing by nearly 3% a year, while the number of stomach cancer has been decreasing by about 0.2% annually, despite the increase in the population at risk *(Parkin, et al 1988; Stanley, et al 1988)*. Meanwhile, it is evident that the incidence of lung cancer is low and remarkably consistent among life-long non-smokers, with similar low rates recorded in different countries at different periods of the time *(Doll & Peto, 1981; Shopland, et al 1991)*. This suggests that there are no major differences in the environmental, behavioural, and genetic factors that determine the incidence of lung cancer in the absence of smoking in these countries.

There has been a definite reduction in mortality from lung cancer since the early 1960s in Britain, where the death rate has fallen by two-thirds in men aged 30-39 years and is declining in men of all ages up to 75 years *(Doll 1989)*. The fatality of lung cancer has been affected only very little by improved treatment, the five-year survival rate being only 5-10% for all types of lung cancer. This substantial fall preceded any material reduction in the amount of tobacco smoked in the corresponding sex and age groups (which started only from mid-1970s) and seems most likely to have been due largely to the reduction in the tar yield of the cigarettes smoked. A few studies have shown that the relative risk of lung cancer for lifelong non-filter cigarette smokers was approximately twice that for smokers of filter cigarette alone, although no dose-response relationship could

be found between risk of lung cancer and a cigarette tar index *(Lubin, et al 1984).* That the effect should have been so much more marked in Britain and Finland (where the trends have been similar) than in many other countries can be explained by the fact that smoking habits had stabilized in these countries earlier than elsewhere, so that the mortality rate in men up to 50 years of age had already reached a plateau before tar yields began to be reduced. Whereas in many other countries, including the US, the effects of tar reduction have been largely cancelled by the delayed effect of the increase in consumption that continued throughout the 1950s. The decline of lung cancer mortality may also have been contributed to by the reduction in atmospheric pollution from the combustion of coal that began as a result of government intervention in 1952. Data from epidemiological studies suggests that atmospheric pollution may have been responsible, in conjunction with cigarette smoking, for some 5-10% of all lung cancers in men *(Cederlof, et al 1978; Doll 1989).*

While there has been a steady decrease in tobacco consumption in many Western countries, particularly in the UK and US, China has seen a rapid increase in the amount of tobacco consumption in the population. Total consumption of cigarettes in China has grown at a rate of 4.2% annually between 1952 and 1965; at 7.5% annually from 1965 to 1978, and at 9.6% annually from 1978 to 1987 *(World Bank 1990).* In 1987, the total consumption of cigarettes in China was estimated to be 1,400 billion cigarettes (or 28% of the world's total), and overall consumption of manufactured cigarettes continues to rise rapidly. Moreover, the tar delivery remains high in Chinese cigarettes, ranging from 21 to 33 mg per cigarettes compared with an average of 14 mg per cigarette in Britain *(IARC 1986).* Because the effects of smoking on lung cancer only emerge after prolonged smoking, in the next several decades a rapid increase in lung cancer incidence appears to be inevitable in China. This should occur first among males in the urban cities then throughout the rural areas and among women who have taken up smoking.

Stomach cancer

Stomach cancer is the second most important type of cancer leading to death in China, both among males and females. The national age adjusted mortality rate from stomach cancer is 51 per 100,000 in people aged 35-74 years, and is nearly three times that of Western populations, such as 18 per 100,000 in Britain (Table 1.4). The average 1987 stomach cancer rates in Chinese males and females were 67 and 34 per 100,000 respectively, which was similar to those in Japan (male: 73/100,000, female: 32/100,000) where the stomach cancer rates are the highest in the world. Stomach cancer rates are very heterogeneous in China, with the mortality rates varying by more than 50-fold from one county to another, with eastern areas having the highest rates *(Chen, et al 1990).* The regions in China in which gastric cancer is common are characterised by dietary habits such as low consumption of fresh fruit, vegetables, meat and eggs and a high consumption of salted and pickled vegetables and sweet potatoes.

During the past few decades, the mortality from stomach cancer has consistently and significantly decreased by more than 50% in nearly all countries, although the size of the decrease both in absolute and in relative terms, is variable *(Stanley, et al 1988; Vecchia, et al 1992).* This reduction in the incidence of stomach cancer is nearly identical between the sexes and between countries irrespective of the original rates. This suggests that a common factor may underlie this universal decline. This common factor appears to act uniformly over the entire time period in diverse countries, but also appears to affect both sexes to a similar extent. The most remarkable decline in the mortality of stomach cancer was seen in the US, where stomach cancer used to be the most common cancer earlier in this century. The rate has dropped by two-thirds over the past few decades, and now US stomach cancer rates are among the lowest recorded in any country in the world. No new and effective form of treatment has been introduced and the survival rate of stomach cancer has remained virtually

unchanged over the last 20 years (with a five year survival rate of approximately 15%), so the reduction must be almost entirely due to a reduction in the incidence of the disease.

The cause of the substantial and consistent decline in the stomach cancer remains unexplained. There are a number of hypotheses concerning the precise mechanisms, but none have been proven at this time *(Joossens & Geboers 1981)*. Factors associated with the changes in the methods of food preservation (in particular the use of refrigeration and perhaps the addition of antioxidants in place of preservation by salt) and increased consumption of fruit and vegetables appear to be the most likely reason to account for this secular decline in stomach cancer *(Mirvish, 1983)*. The increase in fruit and vegetable consumption is inversely associated with risk of the disease in almost all case-control studies; but the size of the increase is insufficient to explain the decreased incidence of the disease. The decrease in the salt intake seems also likely to have contributed to this secular decline in stomach cancer, although there is no direct evidence to support this *(Joossens 1980; Whelton & Goldblatt 1982)*.

Recent studies have suggested that infection of the human gastric mucosa by the bacterium *H. pylori* may play an important role in the etiology of gastric cancer. In two recent case-control studies in which serum was obtained on average more than a decade prior to the diagnosis of gastric cancer, the presence of *H. Pylori* antibodies was significantly associated with the risk of development of stomach cancer (odd ratios of 3.6 in one study and of 6.0 in the other) *(Nomura, et al 1991; Parsonnet, et al 1991)*. In an ecological study of rural Chinese counties, there was a significant geographical correlation between gastric cancer mortality and *H. pylori* prevalence in adult men *(Forman, et al 1990)*. Gastric cancer is associated with poor socioeconomic conditions, as is the case with *H. pylori* infection. It is plausible that the worldwide decline in gastric cancer mortality could, at least partly, be due to secular changes in bacterial

infection rates *(Forman, et al 1990; Taylor & Blaser 1991).* If *H. pylori* is involved in the etiology of the disease, then the attributable risk is likely to be high, perhaps as many as 60% of all gastric cancers would disappear if *H. pylori* did not exist *(Parsonnet, et al 1991).* No other single agent has yet been identified that could play as important a role in the aetiology of gastric cancer. The data on secular trends of stomach cancer in China are not yet available, but given the consistent decline of stomach cancer elsewhere in the world, it is likely that with improvements in living standards, the stomach cancer rate in China may be expected to decline in the long-term.

Liver cancer

Liver cancer is the third most important cancer as a cause of death in China, and accounts for 15-20% of all cancer deaths. The rate of liver cancer in China is among the highest in the world, and about 45% of all liver cancer cases in the world occur in China *(Parkin, et al 1988).* In 1987, the overall mortality rate from liver cancer was about 50 per 100,000 for people aged 35-74 years, which was more than 20 times the rate in Britain (Table 1.4). The social significance of liver cancer in China is greater than other cancers because, in high-incidence areas, the incidence is highest is in the fifth or sixth decades of life as compared with the eighth decade for other cancers. Therefore, liver cancer accounts for a significant number of years of potential life lost.

The major factors which contribute to the high incidence rates of liver cancer in China are believed to be chronic lifelong infection with the hepatitis B virus (HBV), and perhaps also consumption of aflatoxins (naturally occurring substances produced by fungi which grow on grains and nuts). About 15% of adult Chinese are chronic life-long carriers of HBV, compared with less than 0.5% in most Western populations *(Jiang 1982).* Comparing those people who are chronically infected with HBV with those who are not, the difference in the incidence of liver cancer (and some other chronic liver diseases) is so extreme

that HBV is likely to be the cause of the large majority of all Chinese liver cancer *(Beasley, et al 1981)*. The geographic distribution of high liver cancer incidence areas differ from that of gastric cancer. These are mainly concentrated in the south-east, in warm humid areas along the coast. The highest rates are seen in the Yangtse river delta, with rates in Qidong county, for example, of 76 and 22 per 100,000 in males and females respectively *(Armstrong 1982)*. The incidence rates are not believed to have changed greatly in recent years. Populations migrating from high-mortality areas to low-mortality areas have shown a fall in incidence, and vice versa. On present evidence, it appears most likely that the high incidence of liver cancer in the south-east of China is due to an interaction between HBV and an environmental carcinogen, most probably aflatoxin B_1, although the influence of other factors such as the nature of the water supply, parasitic infection, environmental contamination with pesticides, and the presence of nitrosamines in food can not be excluded.

Most transmission of HBV which results in development of chronic carrier status in China occurs at birth. The primary prevention of immunization with HBV vaccine in early childhood should lead to a lower incidence of hepatitis B-related illness throughout life and – in the long term – by a very sharp reduction in mortality from both liver cancer and other chronic liver diseases in middle and old age. Public health measures such as regulations controlling the sale of food and changes in food processing and storage procedures could reduce exposure to aflatoxins in the population. These too may contribute to a reduction in liver cancer occurrence among the hundreds of millions of children and adults who are already infected by HBV.

Oesophageal cancer

Cancer of the oesophagus has a long history in China having been referred to as "Ye Ge" (difficulty with swallowing) for more than 2,000 years. A number of historical documents attributed the disease to excessive consumption of alcohol

or very hot food. Among countries reporting mortality by site of cancer, China has the highest mortality in the world from oesophageal cancer in both males and females *(Parkin, et al 1988)*. In 1987, the national mortality rate in China for people aged 35-74 years, standardized to the age distribution of the world population, was 32 per 100,000 compared with about 11 per 100,000 in the comparable population in Britain. It is estimated that China accounts for about 54% of all new oesophageal cancer in the world *(Parkin, et al 1988)*.

Oesophageal cancer demonstrates striking geographical variation, perhaps more than any other tumour, although the aetiological factors concerned are not thought to be the same in different parts of the world. Within China, oesophageal cancer mortality rates vary more than 600-fold (in both sexes), with high rates concentrated mainly on the Tai-hang mountains at the border of Henan, Hebei and Shangxi provinces in North China, and in northern Sichuan and the Da-bie mountains on the border of Anhui and Hubei provinces *(Li, et al 1981)*. The high rate areas tend to be dry, infertile and poor, providing a limited food supply, particularly in respect to vegetables and fruits. Lin Xian county in Henan province, has the highest rates in both sexes (161 per 100,000 in males and 103 per 100,000 in females) which, at least for males, are equal to or higher than those in the Gonbad region of Iran and the adjacent parts of the USSR – and may, therefore, be the highest rates in the world *(Lu, et al 1985)*.

Tobacco and alcohol consumption are the major causes of oesophageal cancer to have been identified so far in the West. The carcinogenic effect of alcohol appears to be largely dependent on the synergistic effect of smoking, although it does have some effect independent of tobacco. This was demonstrated in a case-control study of oesophageal cancer in non-smokers *(Tuyns 1983)*. Theories about the etiology of oesophageal cancer in China relate mainly to dietary factors – either nutrient insufficiency or ingestion of carcinogens or carcinogen precursors. With respect to nutrient insufficiency, poor diet is a

common feature of high-risk groups in China. Concern about dietary carcinogens has centred around the consumption of pickled vegetables which are heavily contaminated with various moulds. Extracts of these vegetables have been found to be mutagenic and have produced oesophageal dysplasia and liver tumours in rats. Mouldy foods are also commonly eaten by other high-risk groups. In a recent ecological survey of diet and cancer in 65 Chinese counties *(Chen, et al 1990)*, oesophageal cancer mortality was shown to be significantly higher in areas of low plasma vitamin C concentration and low fruit consumption. Age-adjusted mortality rates were more than 3 times higher in these counties in the lowest quartiles of plasma vitamin C levels and intake compared with those in the highest quartiles. In addition, positive correlations were observed between oesophageal cancer and intake of mouldy vegetables. Neither tobacco nor alcohol consumption have been shown to be the major determinants of the large regional variations of oesophageal cancer in China. Further improvements in diet and nutrient intake in the population might be expected to produce a gradual decline in the oesophageal cancer rates in China, as has already been seen in some of high-risk areas *(Lu, et al 1985).* But, in the long term, the reduction in the risk of oesophageal cancer due to the improvement of nutrition may well be offset, at least to some extent, by a substantial increase due to cigarette smoking.

Other sites of cancer

Cancer of colon and rectum is the fifth most common cause of cancer death in China, with an age-adjusted mortality rate of about 15 per 100,000 population for people aged 35-74 years (Table 1.4). This rate compares favourably with those in most Western populations, for example 34 per 100,000 in the comparable population in Britain. There are, however, areas with very high mortality rates in China, mainly around the lower reaches of the Yangtse river, where schistosomiasis is endemic. The highest rate in China was recorded in a county with a high prevalence of schistosomiasis in Zhejiang province, with the rates

being 33 and 32 per 100,000 population in males and females respectively *(Liu, et al 1983)*. These rates are at least equivalent to the rates in New Zealand, which has the highest rate of colorectal cancer in the world. Elsewhere in Zhejiang province, the rates are comparatively low at 4-5 per 100,000 population, and this variation appears to correlate with the prevalence of infection with *schistosoma japonicum.* In an ecological study of colorectal cancer in 24 provinces in China *(Liu, et al 1983)*, the mortality rates from colorectal cancer were strongly correlated with schistosomiasis, with about 50% of the regional variation explained by schistosomiasis infection. The highest mortality due to colorectal cancer was in the four provinces which also had the highest prevalence of schistosomiasis and the highest mortality due to schistosomiasis. In the high-incidence areas, where schistosomiasis is endemic, the peak incidence with age is some 5-10 years earlier than it is in Western populations.

Except for some high incidence rates in the schistosomiasis endemic areas, colorectal cancer tends to be more common in urban than in rural China. Internationally, there is a strong correlation between colon cancer incidence and meat consumption in different countries, with New Zealand, United States and Canada having high rates for colon cancer, and China and Japan having low rates *(Doll & Peto 1981).* A recent comparative study of colon cancer and of rectal cancer in Chinese and Americans found that, on average, Americans had fourfold higher rates of colon cancer, and two fold higher rates of rectal cancer than Chinese. This is consistent with the elevated per capita intake of fat and the lower intake of cereals and vegetables in the US *(Yu, et al 1991)*. The incidence rates of colon and rectal cancer in Chinese-Americans have almost reached American levels, indicating that the risk for tumour development in the lower intestinal tract increases rapidly with transition to the US diet. It is suggested that the key difference among these two populations is the intake of dietary fat which is currently hypothesized to be a ubiquitous tumour promoter.

Breast cancer ranks at present as the sixth most common cancer as a cause of death in Chinese women, with the average age adjusted mortality rate being 11 per 100,000 population for women aged 35-74 years (Table 1.4). This rate is considerable lower than the rate in most Western populations, for example 60 per 100,000 in Britain. In China, breast cancer rates are generally higher in urban areas than in rural areas, with rates being 17 and 8 per 100,000 for urban and rural Chinese women aged 35-74 years respectively. A number of factors have been identified to data which increase the risk of breast cancer in women *(Kelsey 1979)*. The majority of these factors relate to a woman's reproductive history and it seems highly probable that hormones, particularly oestrogen, play an important role in the development of breast cancer *(Kelsey 1979)*. However, because these factors are not readily modified, attention has been focused on factors that may be more amenable to change, with consequent reduction in risk of breast cancer. In this context, there is considerable interest in the possible associations between the risk of breast cancer and dietary factors, particularly fat intake *(Kelsey 1979)*. Internationally, there is a strong correlation between total dietary fat intake and incidence rates of breast cancer in the population *(Doll & Peto 1981)*. In a comparative study of breast cancer between Chinese and Americans, it was found that the breast cancer incidence was about 5 times higher in Americans than in Chinese. The divergence in the age-specific incidence of breast cancer is most dramatic in the postmenopausal years when the Americans have tenfold higher rates than Chinese. Comparisons of dietary intake reveal marked differences, with the average total dietary fat intake in the US about 3 times higher than in China. In contrast, consumption of fish and cereals is roughly three times higher in China than in the US, and per capita vegetable consumption is about 30% higher in China. Results from a number of epidemiological studies also demonstrate a strong association between fat intake, fruit and vegetable intake and risk of breast cancer in individuals *(Kelsey 1979; Howe, et al 1990)*.

4). Future chronic disease in China

China has experienced an "epidemiological transition" during the past few decades, with the mortality pattern changing from one dominated by communicable diseases to a pattern in which deaths are predominantly due to chronic diseases. The main chronic diseases causing premature death and disability in China are, at present, various cancers, stroke, various heart diseases, and COPD. As a result of further demographic changes and trends in risk factor exposures in the population, the relative and absolute importance of various chronic diseases in Chinese are expected to change greatly in the future.

In the next four decades, the total population of young adults and children in China will not increase much, as a result of successful fertility control. However, many more will survive to middle-age and beyond, and will therefore constitute a larger population at risk for chronic disease. It is estimated that in the next 40 years the middle age population (ages 35-69 years) will more than double. Based on the current mortality levels and assuming no changes in the present risk factor distribution, the total number of deaths in China will rise sharply from about 5 million annually now to about 17 million by 2030 *(World Bank 1990)*. The impact of epidemiological changes on the future chronic disease rates in China is more difficult to summarise, for lifestyle, dietary, environmental, occupational and other risk factor exposures are changing dramatically with economic developments. Some increase and some decrease, both in duration and in degree of exposure. Moreover, the future large effects of current smoking patterns will materialise. Nevertheless as a general proposition it can be expected that, with what is known of China's current disease pattern and risk factors, the diseases which will show the largest increases will be smoking-related diseases, mainly lung cancer and various vascular and respiratory diseases. Mortality rate from CHD is likely to increase rapidly with the change of dietary pattern, in particular the increase in the animal fat consumption in the population. The current mortality rates from lung cancer and COPD in China are unlikely to reflect

the full effects of cigarette smoking during previous decades, and future death rates seem likely to be substantially higher than current levels. Prospects for COPD in China represent a case for particular concern given the very high mortality rate at present in the Chinese population.

Economic development is not necessarily associated with an increase in chronic disease, provided that tobacco and certain dietary (particularly animal) products can largely be avoided. Indeed development may facilitate the control of various chronic diseases which are common in China, such as stroke, COPD, cor pulmonale, hypertensive heart disease, rheumatic heart disease, cirrhosis and cancer of stomach, esophagus, and liver. Together, these particular chronic diseases now account for more than half of all Chinese deaths in middle age. Some are likely to decrease with economic development (or due to control by vaccination or antibiotic therapy of an antecedent infective cause), but, if, the use of tobacco is not properly controlled, the decrease in some diseases may well be, at least to some extent, offset by increases in the incidence of smoking-related diseases.

1.3 Major risk factors for chronic diseases in Western and Chinese populations

Chronic disease is the result of exposures to risk factors which are often multifactorial, synergistic and socially complex. They can play many roles in different settings, can modify each other, and can operate simultaneously in several disease processes. Evidence accumulated over the last several decades has indicated that elevated blood cholesterol, cigarette smoking and high blood pressure are the three most important risk factors identified for chronic diseases. The principal impact of them is on the incidence of coronary heart disease, stroke, various cancers and COPD, which at present account for the majority of the deaths in middle-aged adults in many societies. Evidence about the distribution and determination of these three risk factors in Chinese and Western

populations, and their impact on various chronic diseases will be reviewed briefly here. In addition the background and relevance of these issues to he objectives of the present study in a Chinese population will be discussed.

1). Blood cholesterol

Metabolism and Determination of blood cholesterol

Cholesterol is a fat-like substance (lipid) that is a key component of cell membranes and a precursor of bile acids and steroid hormones. Cholesterol circulates in the blood in spherical particles containing both lipids and proteins, known as lipoproteins. The lipoproteins can be classified in terms of their density on ultracentrifugation into three major classes: very low density lipoprotein (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). LDL is the major cholesterol-carrying lipoprotein in serum, and typically contains 60-70% of the total serum cholesterol. HDL usually contains 20-30% of the total serum cholesterol. VLDL, which is largely composed of triglycerides, contains 10-15% of the total serum cholesterol. The liver plays a central role in the metabolism of lipids and is involved in the synthesis, catabolism, conversion and excretion of both cholesterol and apolipoprotein particles.

Humans derive cholesterol both exogenously, from the consumption of animal products, and endogenously, from synthesis in the liver and other tissues. Dietary fat, particularly triglycerides are absorbed through the gut and incorporated into lipoprotein particles called chylomicrons. These chylomicrons enter the bloodstream and deliver their content of triglyceride to adipose tissue (where it is used for storage) and to muscle (where it is used for oxidation to supply energy). Once the bulk of triglycerides have been removed from the chylomicrons, the remnant of the chylomicron, containing cholesterol esters, is removed from the circulation by a specific receptor found only in the liver cells.

This chylomicron-remnant receptor does not bind LDL or take part in its removal from the circulation *(Kesaniemi & Miettinen, 1988)*.

Synthesis of LDL occurs consequent on the catabolism of the triglyceride-rich VLDL, which is involved mainly in the endogenous pathway. The core of VLDL particle consists mostly of triglycerides which are synthesized in the liver, and also contains a small amount of cholesterol esters. The liver secretes the VLDL into the bloodstream. When a VLDL particle reaches the capillaries of adipose tissue or of muscle, its triglyceride content is hydrolysed by lipoprotein lipase (LPL), an enzyme located on the surface of capillary endothelial cells. Hydolysis of most triglycerides transform VLDL into VLDL remnants, but a portion of VLDL is taken up directly by the liver before transformation to remnants. Up to 50% or even more of newly secreted VLDL is cleared by the liver before reaching the remnant stage *(Grundy 1986)*. VLDL remnants, like VLDL, have one of two fates: removal directly by the liver or degradation into LDL by lipolytic removal of the remaining triglycerides. The major pathway for the removal of cholesterol-rich LDL is largely via LDL receptors on liver cells (about 75%), and the remainder is cleared by a variety of extrahepatic tissues *(Goldstein & Brown 1977)*. HDL is believed to participate in cholesterol removal from peripheral tissues by initiating the process of reverse cholesterol transport. HDL is synthesised by the liver and intestine. The mechanisms for delivery of cholesterol to the liver are incompletely understood, but may involve specific membrane-bound receptors or transfer to lipoproteins that contain apoprotein B, or both *(Gordon & Rifkind, 1989)*.

LDL receptor activity plays a key role in the regulation and determination of plasma LDL levels *(Brown & Goldstein, 1983, 1984; Lewis, et al 1986)*. The most severe elevation in LDL cholesterol occurs in a disorder called familial hypercholesterolemia (FH), which results from a defect in the gene encoding for the LDL-receptor protein. In the heterozygous state, the patient has one nonfunctioning gene and one normal gene for LDL receptors *(Brown & Goldstein,*

1983; 1984). Heterozygotes for FH, thus synthesize half the normal number of LDL receptors and their level of LDL-cholesterol is approximately twice normal. The estimated prevalence of heterozygous FH is 1 in 500 of the population in most ethnic groups. The prevalence of homozygous FH is approximately one in a million people. In such people, who lack any functioning gene for LDL receptors, blood cholesterol levels are approximately four times that of normal subjects, typically ranging from 13 to 25 mmol/l. These homozygous FH patients present with complications of advanced atherosclerosis at a very early age.

In the normal situation, synthesis or activity of LDL receptors is under feedback regulation controlled by the amount of cholesterol in cells *(Brown & Goldstein 1975)*. Thus, any factor that increases the hepatic cholesterol concentration should suppress LDL receptor activity. It has been suggested that a lifelong diet rich in cholesterol and saturated fat may lead to chronic suppression of LDL receptors, resulting in increased levels of LDL-cholesterol and consequently mass atherosclerosis in the population *(Grundy 1986)*. Delivery of excessive dietary saturated fat and cholesterol to the liver via the chylomicron remnant receptor may stimulate the liver to produce increased amounts of VLDL and perhaps LDL. In the face of a fixed removal capacity that is limited by the number of receptors, the increased production causes the plasma LDL to rise. As the activity of the LDL receptor is under a feedback mechanism, the elevated level of hepatic cholesterol suppresses the activity of LDL receptor, resulting in further rise in plasma LDL levels.

Animal experiments have shown that when rabbits and dogs are fed diets high in cholesterol and saturated fat, synthesis of LDL receptors by the liver is suppressed by as much as 90 percent, and this results in an accumulation of LDL in the bloodstream *(Brown & Goldstein, 1984)*. Data from metabolic ward studies suggest that an increase in cholesterol intake from 250 to 500 mg will raise the plasma cholesterol level by an average of about 0.26 mmol/l (or 10 mg/dl) *(Keys,*

et al 1965; Mattson 1972), although the response differs substantially between individuals. The role of saturated fatty acids in raising plasma cholesterol levels has also been demonstrated in many studies. According to *Keys et al (1965)*, a 1% increase in the total energy intake contributed by saturated fatty acids causes an increase in plasma cholesterol level of 0.07 mmol/l (or 2.7 mg/dl). Most of this increment occurs in the LDL cholesterol level, and the HDL cholesterol level is largely unchanged. Monounsaturated fatty acids have been found to have a neutral effect on the plasma cholesterol, while, on the other hand, polyunsaturated fats (with fatty acids having two or more double bonds in the carbon chain, found in fish and vegetable oil) appear, at least to some extent, to reduce plasma cholesterol *(Keys, et al 1965)*.

There is substantial evidence that high plasma levels of LDL cholesterol are atherogenic, but the specific events induced by high levels of LDL are less well understood. Recent studies, both in vitro and in vivo, suggest that LDL undergoes oxidative modification which then allows it to be taken up via the macrophage scavenger receptor in the subendothelial space *(Steinberg, et al 1989)*. Subentholial macrophages loaded with cholesteryl esters ("foam cells") are then supposed to lead to the development of "fatty steak" lesions in the vessel wall, which are precursors of the atherosclerotic plaque. Oxidised LDL is a potent chemoattractant to macrophages and can be cytotoxic, and thus may explain, in part, the progression of the relatively benign fatty steak lesion into the atherosclerotic plaque. In animal studies, the progression of fatty steaks to atherosclerotic plaques can be slowed by antioxidants *(Daugherty, et al 1989)*.

Contrast of the cholesterol distributions in China and in Western countries

Striking variations in plasma cholesterol concentrations have been observed both between and within various populations *(Blackburn, et al 1979)*. In different populations, irrespective of whether the mean population cholesterol is high or

low, the individual blood cholesterol varies (proportionately) by about the same extent, suggesting that between population differences are unlikely to be due to genetic variation, but rather result from a shift of the whole population distribution – a mass influence acting on the population as a whole *(Blackburn, et al 1979; Rose & Day 1990)*.

The mean cholesterol concentrations are known to be uniformly high in most Western populations, in the range of 5.5 to 6.3 mmol/l, although there is evidence that in some populations the mean cholesterol values have decreased gradually over the last 20 years *(Collaborative Lipid Group 1987)*. In the British Regional Heart Study conducted between 1978 and 1980 *(Shaper, et al 1981)*, the mean cholesterol concentration of men aged 40-59 years was 6.3 mmol/l. There was very little regional variation with the mean cholesterol ranging from 6.0 to 6.6 mmol/l among the 24 towns selected for the study. In another more recent study, which was carried out in four British cities involving more than 12,000 men and women aged 25-59 years, the mean cholesterol concentrations were 5.9 and 5.8 mmol/l for men and women respectively *(Mann, et al 1988)*. Approximately 5% of the population studied had cholesterol values greater than 7.8 mmol/l, a concentration that is regarded as needing active treatment according to the guidelines of the European Atherosclerosis Society *(Study Group of the European Atherosclerosis Society 1987)*. The data from the US National Health and Nutrition Examination Surveys (NHANES) reported mean cholesterol levels of 5.5 mmol/l for men and 5.6 mmol/l for women aged 25 to 74 years *(Collaborative Lipid Group 1987)*.

In contrast, the mean cholesterol concentration in China is considerably lower when compared with that in Western populations. The mean cholesterol values are in the range of 4.0 to 4.7 mmol/l for urban China and less than 4.0 mmol/l for rural China. In an international comparative study of blood cholesterol between urban China and Belgium, using standardised methodology *(Yang, et al 1986)*,

the mean cholesterol concentrations for adults aged 35 and over, were 4.3 mmol/l in China and 6.0 mmol/l in Belgium. Comparing the distribution of serum cholesterol in the two populations, the maximum Chinese values were close to the lowest Belgian values. No apparent differences were demonstrated in HDL-cholesterol levels between the Chinese and their Belgian counterparts. The WHO MONICA Project *(1989)*, which used a carefully standardized method of measurement of serum cholesterol measurements, also showed low blood cholesterol levels in the general Chinese population. The mean cholesterol in urban China was found to be the lowest of the 27 countries participating in this study, with mean values of 4.2 mmol/l for men and 4.3 mmol/l for women. In a survey of middle-aged men and women in Beijing and Guangzhou in 1983-84, in which serum lipids were measured in laboratories using the quality control procedures which had been standardized by the US Centres for Disease Control, further evidence for low mean blood cholesterol in Chinese compared with Western population was obtained *(Tao, et al 1989)*. This survey reported mean concentrations of cholesterol ranging from 4.0 mmol/l in Guangzhou to 4.8 mmol/l in Beijing urban adults. In rural China, the mean concentration of blood cholesterol are even lower than that found in Chinese cities. According to a recent international cooperative study of 65 rural Chinese counties, the mean concentration of plasma cholesterol in samples of the adult population ranged from 2.3 mmol/l to 4.4 mmol/l among the 65 counties, with an average level of only 3.3 mmol/l *(Chen, et al 1990)*.

The quality and quantity of dietary intake, particularly the fat and cholesterol content but also total caloric intake, are the most important determinants of cholesterol levels in the population. In many Western populations, more than 40% of total calories are derived from fat, most of this being from animal and dairy fat. In general, the Chinese diet is characterised by low dietary fat and low cholesterol intake. In a dietary survey of adults in Shanghai, fat was shown to account for only 24% of total calories, a third of which was from saturated fat

(Zhuang, et al 1986). The figure for rural China is even lower. In the 65 rural Chinese counties survey *(Chen, et al 1990)*, an average of only 15% of total calories was derived from fat, and virtually all of that came from plant fat rather than fat from animal or dairy products. Comparisons of daily food consumption reveals a markedly disparity between China and Western food consumption patterns *(Chen, et al 1990; Yu, et al 1991)*. For instance, Americans in the USA consume six times more meat and eggs and 55 times more milk than Chinese. In contrast, the consumption of fish and cereals is about three times higher in China than in the US, and per capita vegetable consumption is about 30% higher in China. Most notably, the total fat intake in the Americans is three times higher than in Chinese *(Yu, et al 1991)*.

Relationship between blood cholesterol and diseases

(i). Blood cholesterol and coronary heart disease

There is overwhelming evidence linking elevated blood cholesterol to CHD. Epidemiologic, clinical, genetic and laboratory animal studies all indicate that high levels of blood cholesterol are strongly related to coronary atherosclerosis and increased risk of CHD. In patients who have the rare homozygous familial hypercholesterolemia, LDL-cholesterol levels can be as high as 25 mmol/l, and severe atherosclerosis and heart attacks can occur as early as two years of age, and are almost inevitable by the age of 20. In patients with heterozygous FH,CHD is almost universal in middle age *(Jensen, et al 1976)*. However, these genetic abnormalities account for only a small proportion of the total cases of CHD in the population, and among people under 60 who have heart attacks, only one in 20 has FH.

In populations where the mean blood cholesterol level is relatively high (such as those in Europe and North America), prospective observational studies indicate a strong, direct association between blood cholesterol level and risk of

CHD *(Kannel, et al 1971, 1974; Stamler, et al 1986; Rose & Shipley 1986; Marmot, et al 1975; The Pooling Project Group 1978).* The significance of blood cholesterol as a risk factor for CHD at levels that are currently considered as "normal" or "low" in Western populations is unclear. Indeed, some investigators have suggested that there may even be a "threshold" – sometimes hypothesized to be at, or about, 5.2 mmol/l (or 200 mg/dl) – below which lower serum cholesterol concentrations are no longer associated with lower risks of CHD *(The Pooling Project Group 1978; Goldbourt, et al 1985; Bottiger & Carlson 1980).* In view of the possibility in Western populations of lowering the cholesterol concentrations of some individuals into this range by dietary changes (or, in individuals at particularly high risk of CHD, by drugs), there is a need for more reliable information about the shape of this relationship at lower levels of cholesterol. But direct investigation of the relationship at cholesterol levels below 5.2 mmol/l is difficult in Western populations, because the number of people who really have such cholesterol concentrations after repeated measurements is relatively small. It can, however, be studied directly in populations where most people have low cholesterol levels. The present study in a population with low cholesterol levels provides such an opportunity to examine whether throughout the lower end of the "Western" cholesterol distribution there continues to be a strong dose-response relationship between serum cholesterol and the risk of CHD death. Moreover, since cholesterol levels were remeasured a few years after baseline in a sample of the study population, it is possible to determine the extent to which differences in "baseline" cholesterol correlate with long-term **usual** differences in cholesterol, and so to estimate the relationship between **usual** cholesterol and CHD mortality.

(ii). Blood cholesterol and stroke

While there is strong evidence relating elevated plasma cholesterol with increased risk of CHD, the data incriminating cholesterol in the development of

cerebrovascular disease is more fragmentary and inconclusive *(Dyken, et al 1984)*. Many epidemiologic studies have failed to demonstrate a consistent relationship between the level of plasma cholesterol and the risk of cerebral infarction *(Kannel, et al 1965; Heyman, et al 1971; Neaton, et al 1984; Salonen, et al 1982; Welin, et al 1987)*, while some prospective studies, mostly in Japan, indicated an inverse association between the risk of intracerebral hemorrhage and serum cholesterol levels *(Tanaka, et al 1982; Ueshima, et al 1980; Kagan, et al 1980)*. A recent report from the MRFIT study has suggested that low cholesterol may cause haemorrhagic stroke, and that this might be of particular importance in countries such China and Japan, where mortality from haemorrhagic stroke is high and cholesterol levels are low *(Iso, et al 1989)*. The present study, which included as many strokes as the largest Western studies that have examined the association between cholesterol and stroke may be particularly informative about any possible inverse relationship between serum cholesterol and risk of stroke.

(iii). Blood cholesterol and non-vascular disease

In most Western populations where the blood cholesterol levels are high, CHD accounts for one third of total deaths in middle aged adults. In some studies, however, serum cholesterol was not directly correlated with total mortality over the whole range of the cholesterol distribution, and a U-shaped association has been observed with increased risk of death from non-vascular diseases, especially cancer, at lower levels of the cholesterol distribution *(Sherwin, et al, 1987; Yaari, et al 1981; Cambien, et al 1980; Kozarevic, et al 1981; Isles, et al 1989; Stemmermann, et al 1991; Smith, et al 1992)*. Furthermore, although most of the previous randomised controlled clinical trials of lowering cholesterol (either by drug therapy or by dietary change) for just a few years have shown that the risk of CHD is significantly reduced *(Peto, et al 1985)*, it has been suggested that this might be offset by an increase in non-CHD mortality *(Dayton, et al 1969; Muldoon, et al 1990)*. This apparent excess of non-CHD mortality in the

cholesterol lowered group could well be largely or wholly due to the play of chance, for it is only marginally significant (2P=0.02), is unrelated to the degree or duration of cholesterol lowering, and is the sum of a number of smaller non-significant differences spread over several different diseases. Nevertheless it has attracted much comment over the years *(Oliver, 1981, 1988; 1991)*, and lead to great concern about the public health implications of cholesterol lowering.

If a low level of blood cholesterol is a cause of increased risk of cancer, then efforts to lower serum cholesterol levels for the purpose of reducing CHD might be questioned. If, however, the association is casual rather than causal then it is important to establish this, so as not to inhibit efforts toward deliberate reduction of serum cholesterol levels in Western populations. The results from previous prospective studies have been inconsistent. Several studies indicate that the inverse association between cholesterol and cancer is largely or wholly secondary to the metabolic consequences of cancer present at the time of entry to the study (a phenomenon referred to as the "preclinical cancer" effect) *(Rose & Shipley, 1980; International Collaborative Group 1982; Tornberg, et al 1989; Smith, et al 1992)*. However, evidence from other studies is not consistent with the hypothesis of a preclinical cancer effect as an explanation for the inverse association between serum cholesterol levels and cancer *(Kark, et al 1980; Beaglehole, et al 1980; Williams, et al 1981; Schatzkin, et al 1987; Isles, et al 1989)*. There have also been some reports that the inverse association between cholesterol and cancer may be secondary to the relationship between serum cholesterol and some other factors which may be causally related to cancer such as low levels of serum retinol *(Wald, et al 1980; Kark, et al 1982)*, or serum alpha-tocopherol *(Knekt, et al 1988)*. It is noteworthy that most of the previous studies were conducted mainly in Western populations where the mean serum cholesterol levels are high. The present study, in which the mean cholesterol concentration is unusually low and in which chronic liver disease (which might be expected to influence cholesterol levels since the liver is so importantly involved

in cholesterol metabolism) is common might be particularly informative about the mechanisms of any possible inverse relationship between serum cholesterol and cancer or chronic liver disease.

2). Blood pressure

Determinants of blood pressure level in the population

Although significant progress has been made in understanding the mechanisms of secondary forms of hypertension, the etiology of essential hypertension remains much less clearly understood. More than 90% of all cases of hypertension, have no underlying renal, endocrine or vascular abnormality to account for hypertension and are labelled as "essential" hypertension *(Pickering 1972).* A number of environmental factors have been implicated in the genesis of essential hypertension, of which growing interest has centred around the relationship of dietary sodium chloride to both the mean level of blood pressure in the population and to clinical and experimental hypertension. Under ordinary circumstances (i.e., without excess sweating), the daily salt requirement is probably well below 1 g *(Dahl 1977).* In most populations, especially in urban economically developed communities, the daily salt intake ranges from 5 to 35 g/day between different populations, and substantially exceeds the amount required by body.

Cross-sectional studies of isolated populations around the world have found that populations with a very high salt intake generally have a high prevalence of hypertension, while areas with a low intake (i.e., less than 4 g of sodium chloride per day) have a low mean blood pressure and among these adults, the blood pressure does not tend to increase with age. It is noteworthy that farmers in Akita, a northern province of Japan where a large amount of salt is used to preserve food, consume up to 35 g of salt daily. About 84% of these farmers have a systolic blood pressure greater than 140 mmHg, and stroke is the most common cause of

death in this population *(Sasaki 1962)*. In contrast, Yanomamo Indians in South America, who live on a diet containing less than 30 mg of salt, have virtually no hypertension. Adults have mean systolic and diastolic blood pressure of about 100 mmHg and 60 mmHg respectively, and blood pressure in this population does not rise with age *(Oliver, et al 1975)*. When these natives migrate to modern coastal cities, where they acquire the dietary habits of new places, they develop the usual amount of hypertension *(Creiz-Cohe, et al 1964)*. Although other elements of their lifestyle (such as body weight, physical activity, alcohol consumption, dietary potassium and calcium intake) may be responsible, increased salt consumption appears to be the most important factor contributing to such rise in blood pressure.

In a recent overview of all published between population studies of sodium intake and blood pressure involving 47,000 people from 24 different communities throughout the world *(Law, et al 1991)*, blood pressure was generally higher on average in developed communities than in the undeveloped communities, but the association with sodium intake was similar in both types of communities. This association is substantially stronger than is generally appreciated, and increases with age and initial blood pressure levels. A difference in sodium intake of 100 mmol/24 h (about 5.8 g salt) was shown to be associated with an average difference in SBP that ranged from 5 mmHg at age 15-19 years (2 mmHg at the fifth and 8 mmHg at the 95th blood pressure centiles) to 10 mmHg at age 60-69 years (6 mmHg at the fifth and 15 mmHg at the 95th centiles). The differences in DBP were about half as great as for SBP. Several studies of individual subjects within populations have also shown significant positive associations between sodium intake (or excretion) and levels of blood pressure *(Smith, et al 1988; Kesteloot, et al 1987).* These within population studies are subject to substantial systematic underestimation (referred to as the "regression dilution" bias), due partly to the random errors in measurement process and partly to any real but temporary intraindividual biological variation at the baseline visit. In a recent

overview of 14 published within population studies, only 6 of them showed significant associations between individual's SBP and sodium intake, but collectively they were highly significant *(Frost, et al 1991)*. When allowance was made for the underestimation due to the "regression dilution" bias, the results of the within population studies were entirely consistent with the results of the between population estimation on blood pressure and sodium intake. Further evidence from randomised clinical trials of dietary salt reduction support the estimates from these observational studies *(Law, et al 1991)*. In people aged 50-59 years a reduction in daily sodium intake of 50 mmol (about 3 g of salt), attainable by moderate dietary salt reduction would, after a few weeks, lower systolic blood pressure by an average of 5 mm Hg, and by 7 mm Hg in those with high blood pressure (170 mm Hg).

It is hypothesized that an increased salt intake leads to an increased extracellular fluid volume which by circulatory and hormonal mechanisms leads to increased excretion of salt by the kidneys. In some individuals the kidney's ability to excrete salt and water at a given pressure is limited to a greater extent, and so a higher pressure is required to augment filtration and maintain adequate excretion of salt and water *(Tobian 1978)*. There is some evidence to suggest that calcium intake may modify the sodium effect, and high dietary intake of potassium may suppress the sodium-induced rise in blood pressure *(Kromhout, et al 1985)*. In the INTERSALT study, potassium excretion was negatively and independently associated with blood pressure of individuals within centres after adjustment for sodium excretion, body mass index and alcohol intake *(Intersalt Cooperative Research Group 1988)*.

A number of investigators have reported that there is a positive correlation between obesity and hypertension in children, adolescents, and adults *(Chiang, et al 1969; Kannel, et al 1967; Morton & Knudsen, 1975)*. The INTERSALT study has found that there was a strong positive independent association between

body mass index and blood pressure in individuals across diverse populations included in the study *(Intersalt Cooperative Research Group 1988).* The mechanism whereby obesity might cause hypertension remains unclear. Some have suggested that increased consumption of sucrose may account for excess weight gain and hypertension *(Ahrens 1974)*, while others believe that excess salt consumption and the associated body fluid expansion can explain the hypertension occurring with obesity. In this case, it is suggested that it is not weight reduction that lowers blood pressure in some obese patients, but rather the salt restriction that accompanies caloric restriction *(Dahl 1977).* It seems likely that the appearance of hypertension accompanying the development of obesity may be related to weight gain or an increased salt consumption or a combination of both.

It is well known that acute stress can significantly increase blood pressure, but, this rise is only transitory. To what extent repeated and prolonged stress may result in the establishment of permanent hypertension in human beings is unknown. Some studies have indicated that air traffic controllers, whose occupation causes severe psychologic stress, develop hypertension at a rate of 5.6 times greater than nonprofessional pilots *(Cobb & Rose, 1973).* Some have also linked the greater prevalence of hypertension in blacks than whites to a greater degree of stress and discontent *(Harburg, et al 1973).* It is hypothesized that increased nervous stimulation might induce hypertrophic smooth-muscle change with medial thickening. Such change not only increases blood pressure responsiveness to adrenergic stimulation but may possibly diminish the sensitivity of the baroreceptors and further interfere with blood pressure regulation and the maintenance of vascular homeostasis.

Other environmental factors such as cigarette smoking, heavy alcohol drinking, and oral contraceptive use, as well as certain metals have also been implicated in the genesis of hypertension. There is, however, no solid evidence that they

play any significant role in causing essential hypertension *(Criqui, et al 1981).* Some studies have indicated that vegetarians have a lower blood pressure than omnivorous people *(Rouse & Beilin, 1984).* The nature of the beneficial effect of a vegetarian diet remains unclear, although the most popular explanation, for which there is some clinical as well as experimental evidence, is that the increased proportion of polyunsaturated vegetable fats have a hypotensive effect *(Puska, et al 1983).* Clearly further research is required in order to get a better understanding of the dietary and other determinants of population blood pressure levels.

The prevalence of high blood pressure in China

In a national hypertension screening survey in 1979-80 involving about 5 million people from 90 cities and 208 rural regions in China, the prevalence of definite hypertension (SBP≥160 or/& DBP≥95 mm Hg) for adults aged 15 years and above was 4.8% on average, while for borderline hypertension it was 2.9% *(Wu, et al 1982).* Given the size of the population, this would mean that about 50 million Chinese were already affected, to some extent, by hypertension in 1980. This figure is likely to increase substantially in the future with the increasing proportion of old people in the population, even if the age-specific hypertension rates remain constant. There is also a large geographical variation in the prevalence of hypertension, being generally more common in the north than in the south, and in urban than in rural populations. In all the provinces surveyed, urban populations had a prevalence of hypertension which was twice that of rural populations. The overall prevalence of hypertension (including borderline hypertension) was 10.8% in urban populations compared with 6.2% in the rural areas. Among all the areas studied throughout the country, Guangdong had the lowest prevalence, with age-adjusted definite hypertension rates of 2.4%, whereas the Lahsa in Tibet had the highest prevalence of 17.8%. Beijing had the second highest prevalence of hypertension of 9.5% which was almost twice that

found in Shanghai. In the WHO MONICA Project *(1989)* using a standard protocol for blood pressure measurement, the overall prevalence of definite hypertension ranged from 8.4% in a Spanish population to 45.3% in a Finish population for men aged 35-64 years, with the prevalence rate in a Chinese population from Beijing being 25%.

The factors contributing to the north-to-south gradient and the large urban-rural difference in the prevalence of hypertension may lie in geographic and climatic differences, local food habits and other socioeconomic factors. The salt intake in China is high when compared with that found in other populations. In the INTERSALT Study *(1988)*, the highest sodium excretion among all 52 centres around the world was seen in a population from northern China, with mean values of 246 mmol/24 h (or about 15 g/day salt intake). The sodium excretion in two other Chinese populations studied was also very high at 169 (10 g/day salt) and 204 mmol/24 h (12 g/day salt) respectively. In an ecological survey of 65 rural Chinese counties *(Chen, et al 1990)*, the mean salt intake estimated from the diet survey ranged from 2 g/day to 39 g/day, with a mean of 15 g/day (which was twice the mean intake found in Britain, and three times the maximum recommended intake for Britain). There was a significant geographical correlation between salt intake and mortality from stroke and hypertensive heart disease among the 65 counties surveyed.

Issues in the present study on blood pressure and disease

Most previous studies have shown that high blood pressure is a major risk factor for the development of stroke and CHD. But these studies were mainly in Western populations, and there is much less evidence about the relationships in populations with much lower CHD risk and with a large proportion of strokes attributed to cerebral haemorrhage. Moreover, previous studies have examined only the relationship of disease with **baseline** blood pressure measured at a single occasion at entry to the study. Baseline measurements are subject to

random errors due partly to the measurement process and partly to any real but temporary deviations from an individual's long-term **usual** level. Such random errors result in systematic underestimation of the slope of any real association between the risk factor and risk of disease. This is referred to as the "regression dilution" bias, and represents the degree of underestimation that is directly related to the extent to which the measurements are subject to the phenomenon of regression to the mean. Remeasurement of blood pressure some years after screening in a sample of the study population was available in the present study, and this allows estimation of the relationship between usual blood pressure and disease rate after appropriate adjustment for this important bias.

3). Cigarette smoking

Historical background and health effects of tobacco smoking

Tobacco has been smoked for centuries and possibly used for millenia. At first it was smoked only by the native populations of America. Subsequently, after tobacco was brought to Europe by Columbus in 1492, its use spread to many countries throughout the world during the sixteenth century. Originally, tobacco was smoked in pipes, but gradually cigarettes and cigars became more popular. During the eighteenth century, the cigarette became widely accepted, and the first cigarette-machine factories were set up in Havana, Cuba, in 1853, in London in 1856 and in the American colonies in 1860. Tobacco is now produced and consumed in every parts of the world.

When tobacco was first introduced into Europe, smoking was recommended for medicinal purposes. The major health effects of smoking had not been recognised until the late 1940s, during which period medical textbooks either ignored the subject altogether or referred briefly to tobacco amblyopia, a form of blindness associated with heavy pipe smoking and poor nutritional status, to tobacco angina (that is attacks of angina brought on by smoking, which are also

rare), and to cancer of lip and tongue, which had for long been suspected to be associated with the smoking of pipes. Then, in 1950, five case-control studies were reported, which were mostly concerned with cancer of lung, but they also provided evidence on several other cancers of the upper respiratory and digestive tracts *(Doll & Hill 1950; Levin, et al 1950; Mills & Porter 1950; Schrek, et al 1950; Wynder & Graham 1950)*. This marked the beginning of the modern era for the study of the health effects of smoking.

During the past four decades, a substantial number of prospective epidemiological studies have been carried out to assess the health consequences of smoking in human beings *(Doll & Hill 1956; Hammond & Horn 1958; Hirayama 1967; Carstensen, et al 1987)*. Clearly tobacco smoking, particularly cigarette smoking, is one of the most important causes of disability and death from a wide range of neoplastic, vascular and respiratory diseases. The total mortality rates of regular cigarette smokers is 60-70% higher than that of non-smokers *(Surgeon General's Report 1989)*. Tobacco is probably the most important known carcinogen for human society today. It is estimated that more than 30% of all human cancers are caused by smoking *(Doll & Peto 1981, Surgeon General's Report 1982)*. The neoplastic diseases which are related to smoking include cancer of the lung, oral cavity, pharynx, larynx, oesophagus, urinary bladder, renal pelvis and pancreas. The most important of these neoplastic disease is lung cancer, of which 80-90% are attributed directly to smoking in men and women. In addition, in Western populations, smoking causes even more deaths from non-neoplastic diseases, such as coronary heart disease *(Surgeon General's Report 1983)* and stroke *(Abbott, et al 1986; Wolf, et al 1988)*. Strong epidemiological evidence has also indicated that more than 80% of all COPD in Western populations is directly attributed to cigarette smoking, and this proportion is similar to that which causes lung cancer *(Doll & Peto 1976; Surgeon General's Report 1984)*.

Tobacco smoke is a complex mixture, containing some 4,000 different chemical compounds which have been identified so far and including many that are pharmacologically active, toxic, mutagenic, and carcinogenic. Many of these constituents of tobacco smoke can be absorbed into the bloodstream. Further study of the diverse biological effects of tobacco smoke constituents have helped explain the multiple adverse consequences of smoking. So far, 43 different carcinogenic substances in tobacco smoke have been identified, and this helps explain why cigarette smoking can cause diverse types of cancer at different sites.

The adverse effects of smoking are much greater when tobacco is smoked in the form of cigarettes than when it is smoked in other ways, such as in cigars or pipes *(Surgeon General's Report 1982)*. Chemical analysis of the constituents of smoke from various tobacco products such as pipes, cigars and cigarettes have found a similar level of carcinogens in the smoke condensates produced from these tobacco products. Experimental studies in a variety of animal models have shown that, smoke condensates from pipes and cigars are equally, if not more, carcinogenic than condensates from cigarettes *(Surgeon General's Report 1979; IARC 1986)*. The lower risk of lung cancer among pipe and cigar smokers, when compared with cigarette smokers may be explained by the lesser amount of tobacco smoked, and by the lesser extent to which it is inhaled *(Wald, et al 1981)*. The effects of different types of cigarette may likewise differ from each other. The low-tar (and low-nicotine) yield cigarettes that are more frequently used today in Western countries are associated with a lower risk of lung cancer than the old fashioned high-tar cigarettes *(Doll & Peto 1981; Doll 1989; Peto 1986)*. Between the 1930s and the 1970s there have been substantial reductions in the mean tar delivery per cigarette in the US, Britain, and many other European countries, with mean tar content of 30 mg per cigarette in the mid-1950s down to approximately 15 mg per cigarette in 1970s. The mortality from lung cancer among younger

men who have smoked low tar cigarettes for most of their smoking lives began to fall before there was any material reduction in the amount smoked, and even fell slightly in young women while the amount they smoked was still rising. *Doll & Peto (1981)* examined trends of lung cancer mortality in males in the US, Britain and other European countries, and concluded that the international differences and the the temporal trends were generally consistent with the tar yields and tar intakes across time and across countries. Judged by the rapid decrease in male lung cancer now being seen in Britain, it was estimated that about 50% of the risk reduction in lung cancer may be associated with the lower-tar cigarettes *(Lubin, et al 1984; Peto 1986).*

Cigarette smoking in China

In the past three decades, efforts at smoking control in many Western countries have produced dramatic and encouraging results. For example in US, the prevalence of smoking among adults fell from 40% in 1965 to 29% in 1987 *(Yu, et al 1990)*, and almost half of all living adults who ever smoked have quit. While smoking prevalence rates have decreased by about 1% per year in most Western populations, they have increased by 2% per year in many developing countries, and half of the global increase in tobacco consumption between 1976 and 1986 occurred in China. Manufactured cigarettes were introduced into China from Western Europe. The first factory to produce manufactured cigarettes was established in Shanghai in 1925 by a British company. A cross-sectional survey carried out in 1982 among 110,367 adults in Shanghai aged 20 years and over *(Deng & Gao 1985),* showed that 56% of male adults were smokers, and of these 12% started smoking before 20 years of age and 23% between 20-24 years of age. There was an increase in cigarette smoking with age, with the exception of people aged 20-29 years among whom the prevalence of smoking was already very high. The proportion of smokers among female adults was low at 6.6%, and most of the female smokers started to smoke after 40 years of age. The proportion

of ex-smokers who had quit smoking for at least one year was 2.6% and 0.6% in male and females subjects respectively.

The first national smoking survey conducted in 1984 provided the most comprehensive data so far for the country as a whole *(Weng, et al 1987; Yu, et al 1990)*. Overall, among the half million Chinese people over 15 years of age who were surveyed, 39% (61% of males and 7% of females) were regular smokers. This would indicate that about 227 million men and 24 million women in China are smokers. The prevalence of smoking among Chinese males resembles the findings in the United States in 1955 when 52% of American men were classified as regular smokers. However, only 3% of Chinese males described themselves as former smokers, compared with 11% of males in the United States in 1955. The 7% smoking rate among Chinese women is much lower than both the peak rate of 33% attained in 1966 and the 1987 rate of 27% among American women *(Schoenborn & Boyd, 1989)*. 75% of the male smokers started to smoke before 25 years of age, while about half of the female smokers started to smoke before 25 years of age. Among the different occupations, the prevalence of cigarette smoking was highest in the factory workers, with prevalence rates of 66% and 8% respectively for males and females. The prevalence of cigarette smoking was also high among male medical doctors, at 57%. There is only a modest geographical variation in the prevalence of smoking between different regions of China, with the prevalence ranging from 43% to 68% in males and from 2% to 24% in females.

Manufactured cigarettes are now the predominant tobacco product used in China. Most Chinese cigarettes are unfiltered and the tar yield and nicotine content have remained high in recent years. In the population as a whole, 73% of smokers were found to smoke manufactured cigarettes, but only 3% smoked filtered cigarettes *(Weng, et al 1987)*. Based on the measurements made in 1983 for some brands of cigarettes commonly sold in China *(Gao 1986)*, the tar yield

ranged from 21-33 mg per cigarette, falling within the category of "high-tar" cigarette (20 mg or more) as defined by the IARC *(1986),* and the nicotine content ranged from 0.8-1.6 mg per cigarette. On average, Chinese smokers do not smoke as many cigarettes per day as people in Western populations. Almost two thirds of Chinese smokers smoked 15 or cigarettes a day compared with about one third of American smokers who smoke that amount *(Yu, et al 1990).* However there is evidence that the number of cigarettes consumed per day in China is increasing, while the age at which smoking starts is decreasing. During the past decade per capita cigarette consumption has nearly doubled, increasing from less than 1,000 cigarettes per person per year in 1978 to 1748 cigarettes per person per year in 1987 *(World Bank, 1990).*

The proportion of diseases attributed to smoking varies from country to country as a result of variations in the amount of illness due to other causes, the prevalence of etiological agents that interact with tobacco smoke in the production of disease, and the smoking habits of the population. In Western populations, where use of tobacco has been prevalent for almost half century, cigarette smoking has been shown to be responsible for 80-90% of all lung cancer, and has also been found to be a major risk factor for CHD, stroke, COPD, oesophageal cancer and many other diseases. In China, the prevalence of cigarette smoking is now very high, but this is a relatively recent phenomenon, and direct evidence concerning the health consequences of smoking in China is sparse. The present prospective study can provide such information in a Chinese population (Shanghai) where cigarette smoking has been prevalent for longer than most other parts of China.

Chapter 2

Background and study population

This chapter describes the background and study population of a prospective study carried out in urban Shanghai among two occupational cohorts followed up for 8-13 years. In addition, a cross-sectional study is described of 1,500 middle-aged men from rural China in which the relationship between prolonged hepatitis B virus (HBV) infection and blood cholesterol levels was investigated.

2.1 Baseline examination in the two cohorts in Shanghai

1). Study populations

The study population comprised two individual cohorts (A and B) of factory workers aged 35-64 years at baseline examination from urban Shanghai. Both cohorts were designed as epidemiologic longitudinal studies to determine the prevalence and incidence of cardiovascular diseases (in particular coronary heart disease and stroke) and of the relationship of these diseases with several risk factors which had been implicated by studies carried out in Western populations *(Rose & Blackburn 1968; Li, et al 1979)*.

In cohort A, the baseline survey was conducted between September 1972 and July 1973 by the Department of Epidemiology, Shanghai Medical University and by the Institute of Cardiovascular Disease of Shanghai. The three factories selected for study had their medical needs provided for by the teaching hospitals of Shanghai Medical University, and were located close to these university hospitals. A screening clinic was set up in each factory during baseline examination. All people aged 35-64 years were identified from factory records, and invited to attend the clinics for a baseline survey. 1635 men and 1288 women (2923 people, 95% of those invited) participated in the baseline examination.

A similar protocol was adopted in cohort B, with a screening clinic set up in each factory by the Chest Hospital of Shanghai for the baseline survey. Eight factories whose medical needs were provided for by this hospital were chosen for the study. The baseline survey was conducted between March 1977 and November 1978, and all people aged between 35 to 64 years were invited to take part in the study. A total of 6428 people (4859 men and 1569 women, 93% of those invited) were screened during this period.

2). Collection of data at baseline examination

Physicians or nurses working in the university hospitals were principally involved in carrying out the study, but they received additional help from the local medical personnel employed directly by the factories. Appropriate training in interview procedure, and standardization of measurement of both blood pressure and body weight was given to all medical staff prior to the baseline examination in order to minimize inter- and intra-observer variation in data collection. Information about education, occupation, physical exercise, medical and medication history was obtained from each individual in the two cohorts, using standard questionnaires. Data on systolic and diastolic blood pressure (SBP & DBP), height, weight, cigarette smoking habits and alcohol consumption were recorded in each individual. A blood sample was taken for measurement of serum cholesterol, and a resting electrocardiogram (ECG) was performed. For the purpose of the present study, a brief description of the procedure and methods used at baseline examination is given for serum cholesterol, blood pressure and cigarette smoking:

Serum cholesterol: In both cohorts, venous blood was drawn in the morning (usually between 07:00 and 10:00) after an overnight fast with the participants in the sitting position and the tourniquet removed. 15 ml of venous blood was taken directly into a 20 ml tube without anticoagulant. Blood samples were taken daily

to the central laboratory, where the tubes were centrifuged for separation of serum. All the blood samples were assayed within two days of collection. In cohort A, serum cholesterol measurements were performed in the lipid laboratory of the Cardiovascular Disease Institute of Shanghai using the method described by Zak *(1954)*. This method produced results that were correct and reasonably reproducible and which could be used to divide Cohort A into quartiles of baseline cholesterol. In cohort B, however, cholesterol measurements were performed in the lipid laboratory of the Chest Hospital of Shanghai, using a manual version of the Libermann-Burchard method *(Pearson, et al 1953)*. This produced results that in absolute terms were too high (see below) but that also were reasonably reproducible and therefore could also be used to divide Cohort B into quartiles of baseline cholesterol. In both cohorts, serum total cholesterol was measured in milligrams per deciliter and converted to millimoles per litre with use of the conversion mmol/l=(mg/dl)x0.02586. Lipoprotein factions of cholesterol were not measured, and the samples were not retained. Internationally standardized quality control comparisons were not available in Shanghai when this study was done in the 1970s, but in both cohorts substantial efforts were made to ensure the consistency of the cholesterol measurements, and satisfactory **intra**-laboratory quality control was confirmed by blind re-measurements of selected samples. Moreover, subsequent re-measurement of cholesterol levels (using the same method as at baseline) in a sample of the subjects in cohort A and cohort B a few years after the baseline examination also confirmed these baseline values.

The absolute cholesterol values recorded at baseline were 4.2 mmol/l (or 162 mg/dl) in cohort A and 5.0 mmol/l (or 192 mg/dl) in cohort B. **Inter**-laboratory quality control with direct comparisons of cholesterol measurements on blood samples exchanged among four laboratories during the follow-up study of cohort A, indicated that cholesterol values in the cohort B laboratory were an average of about 0.8 mmol/l (or about 30 mg/dl) higher than these in the cohort A laboratory

and two other lipid laboratories (C & D) from another two hospitals. The mean serum cholesterol in 10 blood samples exchanged among these four laboratories were 4.35 mmol/l (or 168 mg/dl) in the laboratory of cohort A, whereas in the laboratory of cohort B it was 5.08 mmol/l (or 196 mg/dl) (Table 2.1). The cholesterol measurements in two other laboratories involved (C & D) indicated good agreement with that in cohort A laboratory, with mean serum cholesterol of 4.27 mmol/l (or 165 mg/dl) and 4.17 mmol/l (or 161 mg/dl) respectively.

Table 2.1. Serum cholesterol (mmol/l) in 10 samples exchanged among four laboratories

Labs	Different samples						Same samples						Mean of all 10 samples
	1	2	3	4	5	Mean	1	2	3	4	5	Mean	
A	3.42	2.49	3.42	3.94	3.70	3.39	5.31	5.34	5.34	5.31	5.23	5.31	**4.35**
B	4.04	3.54	3.89	4.38	4.38	4.04	6.01	6.17	6.01	6.17	6.17	6.09	**5.08**
C	3.34	3.58	2.59	4.25	3.89	3.52	5.10	5.13	4.82	5.00	5.18	5.03	**4.27**
D	3.16	2.38	3.24	3.63	3.55	3.19	5.18	5.18	5.18	5.18	5.05	5.16	**4.17**

Internationally validated studies (such as the WHO MONICA Project) on other urban Chinese populations reported a mean cholesterol of about 4.1 mmol/l (or 160 mg/dl) for adults in Chinese cities *(WHO Monica Project, 1989)*. By the mid-1980s, both laboratories involved in the present study had changed their methods of cholesterol measurement to that recommended and standardised by the WHO MONICA Project. Subsequent quality control checks indicated good agreement between this new method and the previous method used in the cohort A laboratory, but confirmed that the method used previously in the laboratory of cohort B had been producing results that were about 0.5-0.8 mmol/l (or about 20-30 mg/dl) too high *(Han, et al 1984)*. The baseline cholesterol values in cohort A can be used both to divide cohort A into quarters of baseline cholesterol, and to estimate directly the mean cholesterol in each group. The absolute values of cholesterol measured in cohort B cannot be used directly to estimate mean cholesterol, but they can still be used to subdivide subjects, like cohort A, into 4 similar-sized "quarter" groups of baseline cholesterol for follow-up of mortality.

Blood pressure: Casual blood pressure for each subject was measured by the physicians in the right arm using a standard mercury sphygmonanometer with regular size cuffs and a stethoscope with a bell placed on the arm. The participants were in the sitting position with the right arm at the level of the heart, and blood pressures were taken after they had been resting for at least 10 minutes. Systolic blood pressure (SBP) was taken as the point of appearance and diastolic blood pressure (DBP) as the points of disappearance of Korotkoff sounds (fifth phase). One measurement of blood pressure was made in both cohorts. Although the original protocol did not specify the accuracy of the measurement to be employed most readings were made to the nearest even number.

Cigarette smoking: Data obtained from questionnaires on cigarette smoking included number of cigarettes smoked per day and years of ever smoking up to the time of baseline examination. Current regular smokers were defined as those who had smoked at least one cigarette a day during the year preceding their baseline examination. In cohort A, the numbers of cigarette smoked per day was recorded only according to two categories: less than 20 cigarettes per day, and 20 cigarettes a day or more. In cohort B, the actual number of cigarettes smoked per day were recorded for each subjects, but for the purpose of the present analyses the data have been grouped in the same two categories as in cohort A. Cigar and pipe tobacco consumption were not asked about at baseline survey, as consumption is uncommon in urban Shanghai. No information on ex-smokers was collected.

2.2 Follow-up examination in the Shanghai cohorts

A follow-up re-survey was conducted about 3 years after the baseline examination in both cohorts. The procedure of re-examination and the collection of the data were similar to that at baseline survey *(Li 1979)*. Among 2923 subjects

studied in cohort A at baseline examination, 2392 people (82%) were re-examined three years after baseline. The data collected at this examination included blood pressure, serum cholesterol, serum triglycerides, blood glucose level, cigarette smoking, medical history since baseline examination. Blood pressure was measured with same procedure and method employed at the baseline examination. A cholesterol measurement was made at same laboratory on the follow-up visit, using the same method as that used for the baseline samples. All the blood samples were assayed within two days of collection. Resting ECG was also performed for each subjects.

In cohort B the follow-up re-examination was undertaken in the 4 factories previously studied at the baseline examination, and a total of 1804 subjects (68% of those studied in these four factories at the baseline survey) were re-examined 3 years after the baseline examination. The information obtained included cigarette smoking, alcohol consumption, medical history since baseline examination. The blood pressure was measured in the same way as that for baseline blood pressure. Blood was drawn after an overnight fast in the mornings for the determination of serum cholesterol, triglyceride and blood glucose levels. The serum cholesterol concentration was measured in the same laboratory, using the same method as that used for baseline samples.

2.3. Determination of causes of death in the Shanghai cohorts

One main reason for choosing these factory worker populations for the present study was that it was much easier to organize subsequent mortality follow-up and to minimize the number of people lost to the study. For, factory records provide detailed and complete information about vital status of their staff. The vital status for those individuals included in the study were determined annually in both cohorts through the records of the medical room, the workers' unions and the salary department in each factory. For those people who retired during the follow-up period, information about their vital status could still be obtained directly

through the pension department in each factory. Information was also obtained on those 265 individuals who had left the factory during the follow-up period prior to January 1, 1987. Vital status was known for all but 64 subjects (0.7% of the total study population in the two cohorts).

For each death occurring during the follow-up period, information on the cause of death was first sought from the official death certificates. Death certificates were customarily completed by the certified hospital doctors in charge of the medical treatment of the patients, and sent to Shanghai Sanitary and Anti-epidemic Station where specially trained persons reviewed them for completeness and consistency. The cause of each death was then coded, with if necessary, verification by the doctor or the family of deceased people. Additionally, for all deaths ascribed to malignant tumours, a separate tumour card was completed and sent to the Shanghai Institute of Tumours.

In the present study, information on the cause of death was supplemented by enquiry of hospital records. Extra information was also sought by questioning relatives and close friends of the deceased person, as well as team leaders, women leaders or medical staff in the factory who might be expected to know about the health status of people working in the factory. For deaths attributed to cancer, confirmation of the diagnosis was also sought by checking the records of the cancer registry in the Shanghai Institute of Tumours. This provided information on the degree of technical sophistication of the diagnosis, and helped distinguish between primary tumour sites and metastatic sites. All such information relating to the underlying cause of death was reviewed and coded by two certified nosologists in the Shanghai Sanitary and Anti-epidemic Station, using the 9th revision of the International Classification of Disease (ICD 9th). Particular attention was taken to distinguish causes of death which might be confused with one another (e.g., coronary heart disease as opposed to pulmonary heart disease, liver cancer and cirrhosis, stomach cancer and gastric

ulcer, lung cancer and pulmonary tuberculosis). More than 65 per cent of cancer diagnoses were based on the analysis of pathological or histological materials, (although this figure varied for different cancers) and for the remainder most of the diagnoses were based on operative findings, gross assessment of specimens, x-rays, or ultrasonography, supplemented where possible with radioisotopic, biochemical and immunological techniques. Diagnosis based merely on clinical assessment involved only a very small number of patients.

The validity of the diagnosis of the cause of death is clearly of paramount importance with regard to investigating the relationship between disease rates and risk factors. The reliability and accuracy of diagnosis differ between countries, depending on medical care and training, concepts of disease entities and classification and on the trends in diagnosis and concern for accurate reporting in the country under study. In the present study, the study populations were factory workers working in factories that were medically attached to the teaching hospital of Shanghai Medical University (cohort A) or Shanghai Chest hospital (cohort B). There were, therefore, several reasons for considering the data in the present study to be entirely adequate. Firstly, the population studies formed a reasonably uniform socioeconomic group, secondly there was good cooperation and completeness of follow-up, and finally the cause of death could be certified more accurately than might have been the case among a sample of the general population. Some misclassification of causes of death is, nevertheless, inevitable in countries such as China (but also UK and USA) where autopsies are rarely performed. But, any bias in the ascertainment of the causes of death is not likely to exist to such an extent that it would produce false results for the association of risk factors with disease rates. Moreover, for most analysis, attention is confined mainly to certain disease categories (such as total stroke) rather than to the different subtypes (such as haemorrhage vs cerebral infarction within stroke category), and so misclassification is much less likely to be a problem. For these reasons, the cause of death data in the present study are

likely to provide valid and reliable evidence about the association of risk factors and cause-specific mortality.

2.4 HBV infection and cholesterol in a rural Chinese population

In order to help understand the association of low blood cholesterol with risk of liver cancer and chronic liver disease (see results), a further study of cholesterol concentration was conducted among more than 1,500 middle-aged men in rural China, of whom 15% were known to be carriers of the hepatitis B virus (HBV).

1). Subjects and blood sample collection

These subjects were participants in a large geographical correlation survey in rural China which was conduced between September to December 1983 *(Chen, et al 1990).* Sixty-five counties throughout rural China were selected for the survey on the basis of wide variations in the mortality rates for 7 major types of cancer (including liver cancer) during the period of 1973-75 *(Li, et al 1981).* Two communes within each county were randomly selected, and then an age-stratified random sample of approximately 25 males and 25 females (aged 35-64 years) from each commune was studied.

A 10-ml fasting venous blood sample was collected from each participant into a vacutainer. On the day of collection, all blood samples were centrifuged to separate plasma from the red blood cells in the local field survey centres. For each individual, one 4 ml fraction of plasma, containing 20 mg of sodium ascorbate, was then stored at -20°C. After several weeks, the frozen samples were transferred to the study centre in Beijing where they were aliquoted and stored at -30°C. Some of the aliquots were analysed, either as individual samples or pooled samples, for a ranges of factors (including HBsAg and HBcAB on individual samples, see below) *(Chen, et al 1990).* Aliquots from 1,882 males from 46 of the 65 counties were air-freighted on dry ice to Oxford, UK in mid-1989 for analysis of *H. Pylori* antibody status and subsequent storage at -30°C

(Forman, et al 1990). Hence, prior to thawing out for the present analyses, the samples had undergone two freeze-thaw cycles.

2). Plasma hepatitis B virus and lipids assays

In the original survey *(Chen, et al 1990)*, HBV indicators were determined in individual samples (whereas plasma cholesterol and other lipid parameters had been measured only in pooled samples of 25 male and separately of 25 female participants from each commune). Plasma hepatitis B virus surface antigen (HBsAg) status was determined using a SPRIA diagnostic kit *(Ma 1984)*, and hepatitis B virus anti-core antibody (HBcAB) was determined by the enzyme-linked immunoabsorbent assay *(Engvall & Perlman 1971).* Data on plasma HBV indicators were available from the study centre in Beijing for 1564 of the 1882 males whose samples were stored in Oxford. For a further 7 individuals, insufficient sample was available for any lipid analysis. Thus it was possible to analyse lipids in 1557 samples with known HBV indicators.

Lipid analyses for each individual sample were carried out using a Cobas Fara centrifugal analyser (Roche Diagnostic, Welwyn Garden City, UK) in the Lipid Reference Laboratory, St Thomas' Hospital, London, UK. Plasma cholesterol was measured using the Kinetic colorimetric method which uses a Kinetic CHOD-PAP reagent (Boehringer-Mannheim), and apolipoproteins (apo AI and apo B) were measured by immonoturbidemetry *(Mount, et al 1988).* In all plasma samples, sodium ascorbate had previously been added, at a concentration of 5 mg/dl, as a preservative. This presented a problem for cholesterol measurements using standard enzymatic methods as these involve enzymatic oxidation, with hydrogen peroxide converting a colourless oxidised compound to its coloured reduced form. To solve this problem, all the samples were pre-treated with ascorbate oxidase to catalyse the oxidation of ascorbate before measuring cholesterol using the standard enzymatic method *(Lumb & Slavin, 1992).*

Chapter 3

Statistical methods of data analysis

The data generated from the present prospective study of various chronic diseases consists of values of a dichotomous dependent variable (i.e. alive or dead) attributed to certain diseases during the follow-up period, and of independent variables recorded at baseline examination. A number of statistical survival methods have previously been developed for the analyses of the data from longitudinal studies of the relationship of chronic diseases with risk factors.

3.1. Combination of the data from the two cohorts

Both cohorts (A and B) involved a few thousand subjects followed for 8-13 years. Individually they may lack the statistical power to establish firm associations between potential risk factors and disease rates, especially when the numbers of deaths from some particular causes are small and the strength of any association is modest. To obtain more reliable information about the association between baseline variables and subsequent disease rates, results from the two cohorts were combined. The two cohorts were carried out independently at two different times, but both were originally designed as prospective studies of cardiovascular disease, they used very similar protocols, and the populations studied were middle aged factory workers living in urban Shanghai. Moreover, the statistical methods used (log-rank and Cox's proportional hazards model) to analyse the combined data both avoid direct comparison of the baseline variables in one cohort with those in the other.

3.2. Non-parametric and parametric methods used

1). Logrank method

The logrank test has been widely recommended for statistical comparison of groups of observations of event times in which some observations may be

censored. It is the rank test with the greatest power for detecting multiplicative differences in failure rates, and has many applications in clinical trials, carcinogenesis and prospective epidemiological study of chronic diseases *(Peto & Peto 1972; Peto, et al 1977).*

The logrank test comparing two groups (A and B) during a particular period of follow-up involves calculation of the observed deaths (O_A & O_B) and the expected death (E_A & E_B) in both groups. O_A is then compared with E_A and O_B with E_B, to see if there are any marked discrepancies. For each group, the expected number of deaths in a particular period is the proportion of all subjects who are in that group multiplied by the number of deaths during that period. The total expected number of deaths in a particular group over an extended period is the sum of the separate expected number of deaths in that group in each period that comprise the extended period. If groups are equivalent in terms of risk of death, then the total number of deaths observed in each group should on average equal the sum of all the separate expected deaths in each separate time during this period. This method can be generalised instantly to the comparison of several groups of patients with each other, with the same principles used to calculate the expected number of deaths in each group, and would be equally applicable if subjects are further subdivided (e.g. into males and females, and different age groups), with calculation of the O's and E's made separately within each strata in a cohort.

The ratio O/E for a group is called the relative death rate for that group because it approximates to the ratio of the death rate in that group to the death rate among all groups combined. Therefore, the ratio of two O/E's from different groups can be used to describe the apparent ratio of the corresponding death rates. For example, in the present study, the relative death rates (O/E) among the group of individuals that smoke and the non-smoking group are 1.31 and 0.77, so that the death rate ratio is about 1.70 (i.e. very crudely, cigarette smoking is associated with a 70% excess risk of deaths.) The approximate statistical

significance of differences between observed (O) and expected numbers of death (E) can be estimated by comparing the sum of $(O-E)^2/E$ with an appropriate chi-square distribution (X^2) with k-1 degrees of freedom (where k denotes the number of groups being compared with each other).

Frequently the comparisons made involve more than 2 groups (e.g. risk of CHD in four quarter groups of serum cholesterol) where, instead of asking if there is statistically significant heterogeneity (by calculation of X^2), it is more appropriate and sensitive to examine whether there is a statistically significant trend in the relationship between risk of disease and different level of risk factors studied. In the present study, both tests of heterogeneity and trend were performed where there were 3 or more naturally ordered subgroups, but the P-value used to help infer whether the variable was related to the risk of disease were generally that the test for trend, even if the statistical significance of the heterogeneity test was slightly more extreme. The test for trend involves the following steps. Each group is assigned a number (n), starting at 1 and working upwards in natural order, with calculation within each group of $A=n(O-E)$, $B=nE$, and $C=nE^2$. All the A's in the different groups are added together to obtain "A_{sum}"; "B_{sum}" and "C_{sum}" are obtained similarly. The statistic, V, is calculated by:

$$V=C_{sum}-\left(\frac{B_{sum}*B_{sum}}{E_{sum}}\right)$$

The test statistics for trend, T, is obtained from

$$T=\frac{A_{sum}*A_{sum}}{V}$$

and this is compared with the chi-square distribution on 1 degree of freedom.

This non-parametric approach avoids any assumptions about the exact shape of the relationship between baseline variables and disease risks. Moreover, it allows the joint evaluation of the information from two different studies by analysing the data as though the separate cohorts were each retrospective strata within one large cohort, without any assumptions about compatibility of the

cohorts. The log-rank test does, however, have some limitations with respect to the analysis of continuous variables (such as serum cholesterol or blood pressure), as some information is lost by arbitrarily subdividing subjects into a few groups instead of analysing them on a continuous scale. The parametric method of Cox's proportional-hazard model avoids this limitation.

2). Cox's proportional-hazards model

Cox's proportional-hazards model *(Cox 1972)* has been widely applied to the prospective epidemiologic studies of chronic disease.This method combines the features of (i) traditional multivariate analysis, which allows estimation of the association of a specific factor with disease after consideration of the association of several other factors, and (ii) traditional life-table analysis, utilizing the exact time of failures and accommodates censoring, that allows the calculation of survival rates and cumulative survival rates, even if the periods of observation of the subjects differ. The statistical models used in the present study utilize both covariates (risk factors) measured on each individual and the time each outcome event (death) occurs. The model is given by

$$h(t;z)=h_0(t)\exp(\Sigma ß_i Z_i)$$

where Z_i , i=1$\cdots$, r are the covariates, $h_0(t)$ is the underlying hazard rate at time t when all the covariates are zero, $ß_i$, i=1$\cdots$,r are the regression coefficients, and h(t;z) is the hazard rate for an individual at time t with covariates z. Thus the ratio of the hazard functions for two individuals with different sets of covariates does not depend upon time. No parametric assumptions about the shape of survival curve are made, but the model implicitly contains two other assumptions. The first assumption is the multiplicative relationship between the underlying hazard function and the log-linear function of the covariates (the proportionality assumption). The second assumption of the model is the log-linear effect of the covariates upon the hazard function.

In the Cox regression analysis, estimation of regression coefficients (ß) and its standard error were obtained by the partial likelihood method *(Cox 1975)*. The regression coefficient indicates the relationship between the covariate and the hazard function. A positive coefficient increases the value of the hazard function and, therefore, indicates a negative relationship with survival (i.e., the higher the level of the variable the higher the risk). A negative coefficient has the reverse interpretation. Covariates can be standardized by dividing by their sample standard deviations to facilitate a comparison of the relative contribution of each independent variable to the risk of disease studied (standardized coefficients). The relative risk of disease for two levels of risk or exposure can be calculated according to regression coefficients estimated in the analysis. Let the event D be the occurrence of death from the relevant disease during a follow-up of length T with one risk factor present. Then the relative risk of disease for the two levels of risk factor, denoted by z_1 and z_2 is defined to be

$$RR=\frac{P(d|z1)}{P(d|z2)}$$

In the Cox proportional-hazards model if the disease incidence is generally low for all levels of the risk factor, the underlying hazard is exponential and a proportional effect of the risk factor is assumed. The relative risk is then approximated by the log odds ratio and defined to be $\log OR=ß(z_1-z_2)$, and, hence, the odds ratio is given by $OR=\exp[ß(z_1-z_2)]$. For the simple case of one dichotomous covariate (eg, smoker vs non-smoker), where $z_1=1$, and $z_2=0$, the hazard ratio, or relative risk is $e^{ß}$. Standard deviations and 95% confidence limits for these log odds ratios are likewise obtained by multiplying the standard deviations and confidence limits of the regression coefficients by the difference between two levels of exposure (z_1-z_2). The statistical significance of the coefficients of each independent variable may be estimated by means of the Z statistic, that is the ratio of the coefficients to its standard error. The statistical significance of the overall prediction, or discrimination, is conveniently given by

the likelihood ratio statistic (LRS) which, when the sample size is large, approximates a chi-squared distribution with the number of degrees of freedom equal to the number of independent variable considered. The Cox regression analyses for the overall data of the two cohorts combined were carried out after stratifying for which cohort (A or B) subjects were in. Another method of combining the results from two cohorts involves calculating an inverse-variance-weighted average of the slopes (regression coefficient) from Cox regression analysis of baseline variables and disease in each cohort. Both approaches give virtually identical results.

3). Other statistical methods

Analysis of covariance: In studying the possible relationship between postulated risk factors and disease rates, consideration has been given to the association of the risk factor with other variables that may be involved in disease development and that contribute to the presence and strength of the risk factor itself. To describe such associations, subjects were usually subdivided into a few groups on the basis of either conventional or arbitrary cutoff points for that variable, and comparisons for mean values of other variables of interest were made among these groups. As age and sex were related to most baseline variables, and in many cases they were not equally constituted among the groups compared, a statistical adjustment was made using analysis of covariance with age or sex as the covariates. For each group, the adjusted group mean is $u_i=y_i+\sum\beta_m(X_m-X_{mi})$ where the y_i is the unadjusted observed mean value for i^{th} group, β_m is the regression coefficients of m^{th} covariate on the factor studied, X_m is the overall mean value for the m^{th} covariate across the groups compared, and X_{mi} is the mean value for the m^{th} covariate in the i^{th} group. For the combined results from two cohorts, the weighted mean values were computed, using the inverse of the variances as weights.

Finite Population Sampling theory: This method was used in the additional study of more than 1,500 rural Chinese to investigate the association between HBV infection and cholesterol concentration. The prevalence of hepatitis B virus infection and the mean concentrations of cholesterol varied markedly among the communes studied, To compare the difference in blood cholesterol concentration between HBV carriers and non-carriers, analyses were performed within each individual commune, then pooled together across the 81 communes studied. For each commune, the total observed and expected sums of plasma cholesterol values were first calculated with respect to HBV status, under the assumption that cholesterol concentrations were unrelated to HBV infection.

Suppose that there are a total number of N_j subjects ($i=1,2,\cdots,N_j$), each with cholesterol value of X_{ij}, in one specific commune (j), and that out of these N_j subjects, there are n_j individuals who were HBV carriers. If there is no difference in cholesterol concentrations between the HBV carriers and non-carriers then, on the basis of Finite Population Sampling Theory *(Peto & Peto 1972),* the expected (E_j) sum of cholesterol values among the HBV carriers is given by $n_j(\overline{X}_j)$, where $\overline{X}_j$ is the overall mean value for that commune, and its variance (s_j^2) is given by $\sum X_{ij}^2/N_j - \overline{X}_j^2$. The observed ($O_j$) and expected ($E_j$) sums of cholesterol values for carriers in each stratum can then be added together to yield an overall observed sum ($\sum O$) and an overall expected sum ($\sum E$) for HBV carriers, with overall variance $\sum[n_j s_j^2(N_j-n_j)/(N_j-1)]$ (The absolute values of difference between $\sum O$ and $\sum E$ are the same for HBV carriers and for non-carriers, but with the opposite direction). The data can also be expressed as observed and expected mean cholesterol levels by subdividing $\sum O$ and $\sum E$ by the number of subjects with respect to the HBV status. The difference between observed mean and expected mean can then be compared between HBV carriers and non-carriers, and the percentage changes relative to overall mean values of cholesterol estimated, along with their 95% confidence intervals. This statistical procedure can be

performed within separate age strata. Data on other factors, such as apo B and apo AI, were analysed in the same way.

3.3 Correction for the underestimation produced by the "regression dilution" bias

"Regression to the mean" is the phrase used to identify the phenomenon by which a variable that is extreme on its first measurement will tend to be closer to the centre of the distribution for a later measurement. The expression was first used by *Galton (1886)* who studied the relationship between the height of parents and their adult offspring. Children of tall parents were on average shorter than their parents and children of short parents were on average taller than their parents. *Galton (1886)* called this effect "regression toward mediocrity". With biological measurements, the variability responsible for "regression to the mean" can be attributed both to inherent variation in the phenomenon being measured and to variability of the measurement itself.

In a given population, the measured values of any particular variable in individuals are normally distributed about some population mean. Among that subset of subjects with some initial values that are high relative to this mean, remeasurement of the variable would produce values somewhat lower than the initial values due to the effect of regression to the mean. This happens because there are more subjects with initial values that are really closer to the population mean (i.e., with positive measurement errors) than there are subjects with even higher true initial values (i.e., with negative measurement errors). Conversely, if subjects with low initial values are considered, the net effect of regression to the mean would be to raise the true mean changes. This phenomenon has long been recognized in the experimental trials on the effects of treatment or clinical studies of high risk subgroups (i.e. high blood pressure, reduced FEV1) *(Peto 1976)*, but its more general importance in epidemiologic studies has not been recognized until recently *(MacMahon, et al 1990).*

In most epidemiologic prospective studies, disease rates are generally related to variables measured on a single occasion at the beginning of the study. As estimates of the long-term **usual** level in an individual (i.e., the average values of an individual over several years), baseline measurements are subject to random fluctuation, due partly to the measurement process and partly to any real but temporary intra-individual biological variation at the baseline visit from their usual levels. Uncorrected use of just the baseline values can result in systematic and substantial underestimation of the strength of the real association of disease with the **usual** level of the risk factor *(Gardener & Heady 1973; Peto 1976; MacMahon, et al 1990)*. This is because the group of subjects with low baseline values include disproportionately many people whose baseline values happened to be somewhat lower than their usual values, while in the high value group there are disproportionately many people whose baseline measurements happened to be somewhat higher than their usual levels. This bias, which is a direct result of the phenomenon of "regression to the mean", systematically dilutes the importance of the risk factor whether the effects on disease rates are assessed by non-parametric analysis of simple tabulations or by multivariate regression methods.

The size of the dilution caused by this “regression dilution” bias is directly related to the extent to which the baseline measurements are subject to the phenomenon of regression to the mean. The regression dilution bias can be corrected for, and the true association estimated, in two main ways *(MacMahon, et al 1990)*.

The first is a “non-parametric” correction method: the disease rates for categories defined by their baseline measurements are plotted not against the mean baseline values in each category, but against an unbiased estimate of the mean usual values in each of those categories. Direct measures of the usual values do not exist, but remeasurements made several years after the baseline

examination among a proportion of the subjects can be used indirectly to correct the associations. The mean values at baseline and at subsequent post-baseline examination are calculated for subjects in categories defined by their baseline values alone (i.e., irrespective of the values of any subsequent remeasurements). The means of the baseline values are seriously biased estimates of the mean usual values in each category (and the biases are particularly large in the top and bottom categories) whereas the means of the remeasured values provide estimates that are substantially less subject to such bias. The remeasured values can be used as an approximate guide to the association between "usual" values and baseline values. By combining data on this association with data on the association between baseline values and the subsequent risk of disease, it is possible to estimate the real association between **usual** values of the risk factor and the subsequent risk of disease. For example, if the difference in mean systolic blood pressure (SBP) between top and bottom categories is about 60% greater for baseline SBP than for SBP remeasured 3 years later, then, when the relative risks of vascular disease are plotted against the estimates of mean usual SBP in each of the baseline categories, the slopes of the SBP/disease association will be at least 60% steeper than when the relative risks are plotted against the mean baseline SBP in each category.

The second way of estimating the true association involves a "parametric" correction method. If the association between baseline measurements and estimated usual values is assumed to be approximately straight, then the slope of the relationship can be adjusted accordingly, for example, in the case of blood pressure, the effects on vascular disease of any particular difference in usual SBP can be estimated as the effects of a difference in baseline SBP of 60% greater than the difference in usual SBP. This approximation can be used to obtain estimates of the effects of a given difference in usual SBP (eg 10 mmHg). The estimate is obtained from the log odds ratios, which are themselves obtained by multiplying by 1.6 and then by 10 mmHg the regression coefficient from the

Cox's proportional hazards analyses of the effects on disease rates of differences in baseline SBP, adjusted for various other factors. Standard deviations and 95% confidence limits for these log odds ratio are likewise obtained by multiplying the standard deviations and confidence limits of the regression coefficients by 1.6 and then by 10 mmHg. Similar procedures can be applied to the other risk factors, such as serum cholesterol and DBP.

Chapter 4

All cause and cause-specific deaths

4.1. Age and sex distribution of study populations

The study population comprises two individual cohorts (cohort A and B) of middle-aged (35-64 years of age at baseline examination) factory workers in urban Shanghai. In cohort A a total of 2923 people (1635 men and 1288 women) were screened at baseline examination during 1972-73. While in cohort B, 6428 people (4859 men and 1569 women) were screened at baseline examination in 1977-78. In Table 4.1 and 4.2 the numbers (and percentages) of subjects in each cohort respectively are shown subdivided by age and sex. In both cohorts, the male population appeared to be older than their female counterparts. The mean ages of all men were 49 and 50 years respectively in cohort A and cohort B, while women were aged 45.4 and 45.5 years respectively. Of the female subjects studied in the two cohorts, about 50 per cent were under the age of 45 years at baseline, while among males 34 per cent in cohort A and 23 per cent in cohort B were younger than 45 years of age at entry to the study.

4.2. Distribution of death by causes

In Table 4.3 the number of deaths attributed to different causes (or groups of causes) together with the corresponding frequency is shown for the two cohorts separately and combined. Separate causes of death are presented if there were more than 15 deaths in the two cohorts combined. Of 2923 people in cohort A, 334 (241 men and 93 women) were known to have died by 31 December 1986, 2580 people were known to be alive at that date, and 9 people (0.3%) could not be traced. Of 6428 subjects screened in cohort B, 286 people (259 men and 27 women) were known to be dead by 31 December 1986, 6087 people were alive at that date, and 56 (0.9%) were lost to mortality follow-up.

Overall in the two cohorts combined, 231 deaths were ascribed to any vascular disease (ICD 9th, 390-459), accounting for 37 per cent of total deaths; 44 (7% of total deaths) were from coronary heart disease (ICD 9th 410-414), 152 (25%) from stroke (ICD 9th 430-438), and 19 deaths (3%) were certified as being from pulmonary heart disease (ICD 9th 416). Cancer (ICD 9th 140-239) was the certified cause of 274 deaths in the two cohorts (44% of total deaths); including 66 (11%) from lung cancer (ICD 9th 162), 63 (10%) from stomach cancer (ICD 9th 151), 54 (9%) from primary liver cancer (ICD 9th 155), 19 (3.1%) from oesophageal cancer (ICD 9th 150) and 17 (2.7%) from colorectal cancer (ICD 9th 153, 154). There were 115 deaths (18.5% of total deaths) in the two cohorts attributed to causes other than vascular disease or cancer; 29 deaths (4.6%) were due to chronic hepatitis and cirrhosis (ICD 9th 571); 31 (5%) deaths were due to chronic lung disease (ICD 9th 490-496), and 17 (3%) deaths due to non-medicinal causes (i.e. poisoning, external injury, accidents: ICD 9th 800-999).

In Table 4.4 the number of cause-specific deaths and the corresponding relative frequencies are shown for males and females in the two cohorts together. Overall among 6494 male subjects in the two cohorts, there were 500 deaths from any cause during 8-13 years of follow-up, while among 2857 females 120 deaths occurred. Both males and females showed a similar pattern in the distribution of cause of death, except that lung cancer and chronic lung disease were less common causes of death in women than in men (about 6% versus about 18%, respectively). Overall, vascular disease caused 183 deaths (37% of total death) in men and 48 deaths (40%) in women. There were 223 (45%) deaths from cancer in men, including 60 (12%) from lung cancer, 58 (12%) from stomach cancer and 44 (9%) from liver cancer. Among women, there were 51 deaths (43%) ascribed to cancer, with 6 deaths (5.0%) from lung cancer, 5 (4.2%) from stomach cancer and 10 (8.3%) from liver cancer. Non-vascular non-cancer diseases were responsible for 94 deaths (19%) in men and 21 deaths (18%) in women.

4.3. Distribution of causes of death by age and sex

Tables 4.5 and 4.6 show the number of deaths attributed to different causes (or groups of causes), along with the corresponding death rates in successive five-year age groups for cohort A and cohort B respectively. During 8-13 years of follow-up, a total of 65 people (9 in cohort A and 56 in cohort B) were not traced, and this small group of people was presumed to be alive at 31 December, 1986. As would be expected, total death rates and cause-specific death rates increased rapidly with increasing age. In general, after age 45, death rates in each successive five-year age group are almost double those of the previous age group (although given the small numbers of deaths, smooth trends with age for any particular cause of death cannot be expected).

Overall in cohort A, among 1256 subjects aged less than 45 years at their baseline examination, 36 people died from any cause during 13-years of follow-up, and the death rate was 28.7 per thousand of the population. In contrast, among 286 subjects aged between 60 and 64 years, 124 people died and the death rate was 433.6 per thousand of the population. In the age groups of 45-49, 50-54 and 55-59, total death rates from any disease were 55.7, 136.8 and 233.3 per thousand of the population respectively. Likewise in cohort B, a similar gradient in death rates between each successive age group was also shown. During 8-years of follow-up, 31 people died from any cause among 1896 subjects aged between 35-44 years at baseline examination and the death rate was 16.4 per thousand population, while among 482 subjects aged between 60 and 64 years, the death rate was 178.4 per thousand of the population. With respect to the age groups of 45-49, 50-54 and 55-59, the death rates from any disease were 18.5, 45.0 and 88.7 per thousand of the population respectively. The annual age-standardized mortality was 8.8 per thousand in cohort A, which was, not statistically significantly higher than the 5.6 per thousand in cohort B *(z=1.78, 2P>0.05)*.

The overall patterns of age-specific deaths for the principal cancers were largely similar to those reported elsewhere in China *(Li et al 1981).* For cancer of the lung, and cancer of the stomach, death rates increased with age and were most frequent in the oldest age group studied in this population (60-64 years). For liver cancer, the death rates were already high by age 50-54, and levelled out thereafter. Age specific death rates for chronic liver disease showed very similar patterns to those for liver cancer. With respect to coronary heart disease and stroke, the death rates increased rapidly with age, and about one-third of deaths occurred among the oldest age group (60-64 years of age).

4.4 Summary

As shown in the present prospective study in Shanghai, cancer and cardiovascular disease now account for the majority of deaths in middle-aged Chinese, as in most Western populations. The particular pattern of diseases are, however, still very different in this Chinese population from that in Western countries. In general, the vascular disease rates in this Chinese population were characterized by low rates of coronary heart disease and high rates of stroke. The ratio of stroke to coronary heart disease was about 3.5 in this Chinese population, in contrast to 0.3 to 0.4 in Western populations. Lung cancer was the most frequent cause of death from cancer, with cancer of the stomach, liver and oesophageal also responsible for a large proportion of deaths in both men and women. Chronic liver disease and chronic lung disease are two other important causes of death in this middle-age Chinese population, and are much more common than in Western populations.

Table 4.1. Age and sex distribution of study populations at baseline examination in cohort A.

Age groups (years)	Male		Female		All subjects	
	No. of subjects	Percent (%)	No. of subjects	Percent (%)	No. of subjects	Percent (%)
35-39	223	13.7	269	20.9	492	16.8
40-44	330	20.2	434	33.7	764	26.1
45-49	313	19.1	279	21.7	592	20.3
50-54	307	18.8	139	10.8	446	15.3
55-59	255	15.6	88	6.8	343	11.7
60-64	207	12.7	79	6.1	286	9.8
Total ¶	1635	100.0	1288	100.0	2923	100.0

¶ The mean (SD) age in men and in women were 49.0 (8.8) years and 45.4 (7.5) years respectively, while for all subjects it was 47.7 (8.4) years.

Table 4.2. Age and sex distribution of study populations at baseline examination in cohort B.

Age groups (years)	Male		Female		All subjects	
	No. of subjects	Percent (%)	No. of subjects	Percent (%)	No. of subjects	Percent (%)
35-39	530	10.9	454	28.9	984	15.3
40-44	593	12.2	319	20.3	912	14.1
45-49	1437	29.6	513	32.7	1950	30.3
50-54	1042	21.4	224	14.3	1266	19.7
55-59	788	16.2	46	2.9	834	13.0
60-64	469	9.7	13	0.8	482	7.5
Total ¶	4859	100.0	1569	100.0	6428	100.0

¶ The mean age (SD) in males and in females were 50.1 (6.5) years and 45.5 (4.3) years respectively, while for all subjects it was 48.9 (6.4) years.

Table 4.3. Number and frequency of cause-specific deaths in cohort A and cohort B during 8-13 years of follow-up.

Causes of death	ICD 9th codes	Cohort A		Cohort B		Both cohorts	
		No. of deaths	Percent (%)	No. of deaths	Percent (%)	No. of deaths	Percent (%)
All vascular diseases	(390-459)	133	39.8	98	34.3	231	37.3
CHD	(410-414)	27	8.1	17	5.9	44	7.1
Stroke	(430-438)	86	25.7	66	23.1	152	24.5
Pulmonary heart dis.	(416)	8	2.4	11	3.8	19	3.1
Other vascular dis.		12	3.6	4	1.4	16	2.6
All cancer	(140-239)	144	43.1	130	45.4	274	44.2
Lung	(162)	34	10.2	32	11.2	66	10.6
Stomach	(151)	32	9.6	31	10.8	63	10.2
Liver	(155)	26	7.8	28	9.8	54	8.7
Oesophageal	(150)	9	2.7	10	3.5	19	3.1
Colorectal	(153,154)	12	3.6	5	1.7	17	2.7
Other sites		31	9.3	24	8.4	55	8.9
Other diseases		57	17.1	58	20.3	115	18.5
Chronic liver disease	(571)	10	3.0	19	6.6	29	4.6
Chronic lung disease	(490-496)	22	6.6	9	3.1	31	5.0
Nonmedicinal	(800-999)	5	1.5	12	4.2	17	2.7
Others		20	6.0	18	6.3	38	6.1
All causes		334	100.0	286	100.0	620	100.0

Table 4.4. Number and frequency of cause-specific deaths by sex in the two cohorts during 8-13 years of follow-up.

Causes of death	ICD 9th codes	Males		Females	
		No.of deaths	Percent (%)	No. of deaths	Percent (%)
All vascular diseases	(390-459)	183	36.6	48	40.0
CHD	(410-414)	33	6.6	11	9.2
Stroke	(430-438)	121	24.2	31	25.8
Pulmonary heart dis.	(416)	16	3.2	3	2.5
Other vascular dis.		13	2.6	3	2.5
All cancer	(140-239)	223	44.6	51	42.5
Lung	(162)	60	12.0	6	5.0
Stomach	(151)	58	11.6	5	4.2
Liver	(155)	44	8.8	10	8.3
Oesophageal	(150)	16	3.2	3	2.5
Colorectal	(153,154)	11	2.2	6	5.0
Other sites		34	6.8	21	17.5
Other diseases		94	18.8	21	17.5
Chronic liver disease	(571)	26	5.2	3	2.5
Chronic lung disease	(490-496)	30	6.0	1	0.8
Nonmedicinal	(800-999)	13	2.6	4	3.3
Others		25	5.0	13	10.8
All causes		500	100.0	120	100.0

Table 4.5. Number of deaths and death rates for cause-specific diseases by age at baseline in cohort A during 13-years of follow-up.

Causes of death	Age at baseline examination (years)											
	<45		45-49		50-54		55-59		60-64		All ages	
	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)
All vascular diseases	11	8.8	14	23.6	20	44.8	30	87.5	58	202.8	133	45.5
CHD	1	0.8	2	3.4	5	11.2	5	14.6	14	49.0	27	9.2
Stroke	8	6.4	11	18.6	12	26.9	18	52.5	37	129.4	86	29.4
Pulmonary heart dis.	0	0.0	0	0.0	0	0.0	5	14.6	3	10.5	8	2.7
Other vascular dis.	2	1.6	1	1.7	3	6.7	2	5.8	4	14.0	12	4.1
All cancer	14	11.1	14	23.6	36	80.7	39	113.7	41	143.4	144	49.3
Lung	0	0.0	4	6.8	8	17.9	10	29.2	12	42.0	34	11.6
Stomach	6	3.2	2	3.4	8	15.7	6	17.5	11	38.5	32	10.9
Liver	4	3.2	2	3.4	8	17.9	6	17.5	6	21.0	26	8.9
Oesophageal	0	0.0	0	0.0	3	6.7	4	11.7	2	7.0	9	3.1
Colorectal	1	0.8	0	0.0	1	2.2	5	14.6	5	17.5	12	4.1
Other sites	9	2.4	6	10.1	9	20.2	8	23.3	5	17.5	31	10.6
Other diseases	11	8.8	5	8.4	5	11.2	11	32.1	25	87.4	57	19.5
Chronic liver disease	6	4.8	0	0.0	2	4.5	2	5.8	0	0.0	10	3.4
Chronic lung disease	0	0.0	2	3.4	1	2.2	7	20.4	12	42.0	22	7.5
Nonmedicinal	2	1.6	1	1.7	1	2.2	1	2.9	0	0.0	5	1.7
Others	3	2.4	2	3.4	1	2.2	1	2.9	13	45.5	20	6.8
All cuases	36	28.7	33	55.7	61	136.8	80	233.3	124	433.6	334	114.3
No. of subjects	1256		592		446		343		286		2923	

Table 4.6. Number of deaths and death rates for cause-specific diseases by age at baseline in cohort B during 8-years of follow-up.

Causes of death	Age at baseline examination (years)											
	<45		45-49		50-54		55-59		60-64		All ages	
	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)	No. of deaths	Rates (1/1000)
All vascular diseases	4	2.1	12	6.2	20	15.8	32	38.4	30	62.2	98	15.2
CHD	0	0.0	4	2.0	2	1.6	4	4.8	7	14.5	17	2.6
Stroke	2	1.1	8	4.1	16	12.6	22	26.4	18	37.3	66	10.3
Pulmonary heart dis.	1	0.5	0	0.0	2	1.6	6	7.2	2	4.2	11	1.7
Other vascular dis.	1	0.5	0	0.0	0	0.0	0	0.0	3	6.2	4	0.6
All cancer	19	10.0	17	8.7	23	18.2	32	38.4	39	80.9	130	20.2
Lung	1	0.5	3	1.5	5	4.0	10	12.0	13	27.0	32	5.0
Stomach	5	2.6	1	0.5	5	4.0	6	7.2	14	29.0	31	4.8
Liver	3	1.6	8	4.1	7	5.5	5	6.0	5	10.4	28	4.4
Oesophageal	0	0.0	4	2.0	2	1.6	2	2.4	2	4.2	10	1.6
Colorectal	1	0.5	0	0.0	0	0.0	2	2.4	2	4.2	5	0.8
Other sites	9	4.7	1	0.5	4	3.2	7	8.4	3	6.2	24	3.7
Other diseases	8	4.2	7	3.6	14	11.1	12	14.4	17	35.3	58	9.0
Chronic liver disease	2	1.0	4	2.0	5	4.0	5	6.3	3	6.2	19	3.0
Chronic lung disease	0	0.0	0	0.0	1	0.8	3	3.6	5	10.4	9	1.4
Nonmedicinal	2	1.0	1	0.5	3	2.4	2	2.4	4	8.3	12	1.9
Others	4	2.1	2	1.0	5	4.0	2	2.4	5	10.4	18	2.8
All causes	31	16.4	36	18.5	57	45.0	74	88.7	86	178.4	286	44.5
No. of subjects	1896		1950		1266		834		482		6428	

Chapter 5

Serum cholesterol and cause-specific mortality

5.1 Baseline serum cholesterol distribution

1). Frequency distributions and mean concentration.

A relatively small number of subjects (30 in cohort A and 298 in cohort B) did not have their cholesterol values measured at baseline examination either because they refused to have their blood taken or because insufficient blood could be drawn from their veins. A further 2 subjects in cohort B had definite evidence of a previous myocardial infarction on the electrocardiogram recorded at baseline. These 330 individuals (274 men and 56 women) were excluded, leaving 9021 individuals for the present analysis.

The distributions of total serum cholesterol are shown in Figure 5.1 and 5.2 for cohort A and cohort B respectively. These show an approximately normal unimodal distribution, with slight skewing to the right. The mode of serum cholesterol was 3.52-3.89 mmol/l (or 136-150 mg/dl) in cohort A and 4.30-4.66 mmol/l (or 166-180 mg/dl) in cohort B. In Table 5.1 & 5.2, the mean serum cholesterol and standard deviations by age and sex are given for cohort A and cohort B respectively. In both males and females, the mean concentration of serum cholesterol appears to increase with age up to the age of 60, and then there was a slight drop. This increase with age tended to be more marked in women than in men. Over 50 years of age, female subjects had a higher mean cholesterol than males, while the opposite was true under 50 years.

The overall age-adjusted mean in cohort A was 4.2 mmol/l (or 161 mg/dl) while in cohort B it was 5.0 mmol/l (or 192.4 mg/dl). As discussed previously, the apparent difference in the mean cholesterol values between two cohorts appears to be due to difference in the methods used by the two laboratories involved in

the two studies (see chapter 2). Intra-laboratory quality control, with direct comparisons of cholesterol measurements on blood samples exchanged among four laboratories during the follow-up study of cohort A, indicated that cholesterol values obtained in the laboratory used for cohort B were an average of about 0.78 mmol/l (or 30 mg/dl) higher than those obtained in the laboratory used by cohort A (and in the other two laboratories involved). Subsequent internationally standardized quality control checks also confirmed that the method used previously in the laboratory of cohort B had been producing results that were about 0.5-0.8 mmol/l (or 20-30 mg/dl) too high *(Han et al, 1984).* The baseline cholesterol measurements in cohort B could still, however, be used to subdivide subjects reliably into four similar-sized quartiles of baseline cholesterol for follow-up of mortality, even if they cannot be used directly to estimate the mean cholesterol in each group.

2). Relation of cholesterol to other baseline variables

The relation of serum cholesterol with certain other baseline variables for the combined data from the two cohorts is shown in Table 5.3. The subjects in each separate cohort were divided into four similar-sized quartile groups on the basis of their baseline serum cholesterol. In cohort A, the cutoff points between groups I, II, III and IV were 85%, 99% and 111% respectively of the cohort A mean cholesterol (4.2 mmol/l), while in cohort B, these were 89%, 99% and 111% respectively of the mean value (5.0 mmol/l). Subjects with high cholesterol concentration were slightly older than individuals with low cholesterol, so all the data presented in the table were age adjusted. For blood pressure (both systolic and diastolic blood pressure) and body weight, the age-adjusted mean values were calculated by analysis of covariance in each separate cohort, and the overall results for the two cohorts combined were then obtained using the inverse of the variances as weights. For cigarette smoking, alcohol drinking and resting

ECG abnormality, age-adjusted overall means were calculated by direct standardization to the age distribution of the two cohorts combined.

Subjects with higher serum cholesterol levels were shown to have higher blood pressure (both SBP and DBP) and heavier body weight than those individuals with lower cholesterol concentrations. A similar increasing tendency with increasing cholesterol concentration was also seen for prevalence of hypertension and of resting ECG abnormality. Smoking was less prevalent and alcohol consumption slightly more prevalent among subjects with higher cholesterol concentrations compared with those with lower concentrations.

5.2 Association of cholesterol with coronary heart disease

1). Relationship of baseline cholesterol with risk of CHD death

Table 5.4 gives the number of observed and expected deaths from CHD along with the estimated relative risks in four quartiles of baseline cholesterol for each separate cohort and for the combined data from the two cohorts. The statistical analyses include both the log-rank and the Cox regression methods. Overall in the two cohorts together, there were 18 deaths attributed to CHD among subjects in the highest quartile group of cholesterol (IV), and the approximate risk of deaths from CHD relative to the whole study population was 1.62. In contrast among individuals with the lowest baseline cholesterol (I), there were only 4 deaths attributed to CHD, and the approximate risk was 0.38. This trend of increasing risk of death from CHD with increasing cholesterol concentrations was significant in a log-rank trend test *(X^2=8.35, 2P<0.01)* that did not take other variables into account.

To assess the independent impact of serum cholesterol on the risk of death from CHD, a Cox proportional-hazards regression analysis was performed, with serum cholesterol included as a continuous variable and with adjustment for age, sex, cigarette smoking, alcohol drinking and diastolic blood pressure. In the

adjusted Cox regression analysis, baseline serum cholesterol was an even more significant predictor of CHD mortality after taking other variables into consideration *(z=3.47, 2P<0.001)*. The estimated regression coefficient (0.463) suggested that a 10% increase in baseline serum cholesterol concentration (that is, an increase of 0.41 mmol/l, or 16 mg/dl) would be independently associated with a 21% increase in the risk of death from CHD (that is, odds ratio 1.21; 95% confidence interval: 1.09 to 1.35). This figure, however, substantially underestimates the slope of the real association between usual cholesterol concentration and CHD, due to the "regression dilution" bias (see later). The relation between cholesterol concentration and risk of fatal CHD was significant in both cohort A and cohort B when examined separately. In cohort A, with 27 deaths from CHD during 13 years of follow-up, the regression coefficient for baseline cholesterol was 0.425 *(z=2.49, 2P<0.05)*, while in cohort B, with 16 deaths from CHD during 8 years of follow-up, it was 0.579 *(z=2.37, 2P<0.05)*.

2). Relation of baseline cholesterol with CHD death in men and women

The relationship between serum cholesterol and risk of death from CHD was also examined separately for males and females in the combined data from the two cohorts. Table 5.5 gives the number of deaths from CHD and the estimated relative risks in the four quartiles of baseline cholesterol. It shows that in both men and women there was a positive relation between risk of death from CHD and cholesterol concentration. Overall among male subjects in the two cohorts together, 32 deaths were attributed to CHD, with 12 among men in the highest baseline cholesterol quartile (IV), compared with only 3 such deaths among those with the lowest cholesterol concentrations. The approximate risk of CHD were 0.39, 1.03, 1.07 and 1.46 respectively in the four quartiles of cholesterol (from lowest to highest). This trend of increasing risk of CHD with increasing concentrations of baseline cholesterol in men was statistically significant both in

the log-rank trend test *(X^2=4.14, 2P<0.05)*, and in the Cox regression analysis after taking other variables into account *(z=2.68, 2P<0.01)*.

Likewise in women, with only 11 deaths from CHD in the two cohorts, there was a positive relationship of serum cholesterol with risk of death from CHD. The approximate risks of CHD relative to the whole female population were 0.45, 0.43, 1.00 and 1.70 respectively from the lowest quartile (I) of cholesterol to the highest quartile (IV). The number of CHD deaths among women was small and this positive trend of increasing risk of fatal CHD with increasing levels of cholesterol was non-significant by log-rank trend test *(X^2=2.81, 2P>0.05)*. It became statistically significant, however, after taking other variables into account in the adjusted Cox regression analysis *(z=2.09, 2P<0.05)*.

*3). Estimation of the relationship between **usual** cholesterol and CHD*

As discussed previously, the mean of the baseline cholesterol values in each category are, due to the "regression dilution" bias, seriously biased estimates of the mean usual cholesterol concentration in each category. The means of the re-measured cholesterol values (Tables 5.6 & 5.7) made 3 years after baseline in a proportion of subject provides estimates that are substantially less subject to such bias *(MacMahon, et al 1990)*. In cohort A, the overall means of cholesterol concentrations for 2392 subjects who had both cholesterol measurements were about the same on the two occasions (4.18 mmol/l at baseline vs 4.19 mmol/l at 3 years post-baseline). The mean cholesterol in each quartile group was, however, substantially different between the two occasions, especially for the top and bottom quartile groups. The difference in the average values of serum cholesterol between the top and bottom quartile groups was 2.32 mmol/l (or 89.4 mg/dl) at baseline, while at subsequent follow-up examination 3 years later, it was only 0.80 mmol/l (or 30.8 mg/dl). Likewise in cohort B, in which the cholesterol concentrations were measured by an assay that produced results that were 0.5-0.8 mmol/l (or 20-30 mg/dl) too high, the range of mean cholesterol

concentrations between the highest and lowest quartiles of baseline cholesterol was of similar magnitude to that in cohort A, being 2.12 mmol/l (or 82.0 mg/dl) at baseline and 0.88 mmol/l (or 34.0 mg/dl) at 3 years post-baseline (Table 5.7). The data from both cohorts suggest that a 10% difference in baseline cholesterol may correspond to only about a 4% difference in usual cholesterol.

Figure 5.3 plots the relative risk of CHD, on a log scale, against the mean **usual** cholesterol in each of four quartile groups, estimated from mean values of re-measured cholesterol 3 years after baseline in cohort A. The solid squares represents the disease risk in each quartile group relative to risk in the whole study population, while the vertical line represents plus or minus one standard deviation (SD). If the slope of the association between the relative risk of CHD and the mean usual cholesterol was roughly constant, this would imply an approximately "log-linear" relationship (i.e., one in which the percent difference in risk associated with a given absolute difference in usual cholesterol is similar at all levels of serum cholesterol). Within the range of serum cholesterol studied in this population (about 3.8–4.7 mmol/l, or 145–180 mg/dl), there was no good evidence of a **threshold** level of serum cholesterol concentration below which a lower level of cholesterol was no longer associated with a lower risk of CHD. From the Cox regression analysis (Table 5.4), it was estimated that a 10% difference in baseline cholesterol would be independently associated with a 21% (SD 6) difference in the risk of subsequent CHD deaths. Combination of the results in Table 5.4 and 5.6 would suggest that a difference of about 4% (SD 1) in **usual** cholesterol might be associated with about a 21% (95% confidence interval 9% to 35%) difference in the risk of death from CHD.

5.3 Association of cholesterol with non-CHD vascular disease

The mortality from stroke was high in the Chinese population. Among 9021 subjects in the two cohorts, 146 (25%) of the deaths that occurred during 8-13 years of follow-up were attributed to stroke. A positive and highly significant trend

was seen between blood pressure (both SBP and DBP) and subsequent stroke death (see chapter 6), but there was no apparent association between baseline cholesterol and stroke mortality (Table 5.8). In the two cohorts together, there were 34 stroke deaths in the lowest quartile (I), and the risk relative to whole population was 1.01. The approximate relative risks of deaths from stroke in cholesterol quartile II, III and IV were 1.01, 0.87 and 1.11 respectively (log-rank trend test 2P>0.05). In the Cox regression analysis, after taking other variables into account, there was still no suggestion of any significant association between serum cholesterol and stroke mortality.

It had been suggested by a previous study (MRFIT) that low cholesterol levels are associated with a high risk of stroke among patients with elevated blood pressure (i.e., DBP≥90 mm Hg), and that this might be particularly important in populations (such as the present one) where mortality from haemorrhagic stroke is high *(Iso, et al 1989)*. To examine this possible interaction between serum cholesterol and blood pressure on stroke mortality, separate analyses among subjects with a raised blood pressure (DBP≥90 mmHg) and those with a normal blood pressure (DBP< 90 mmHg) were performed. There was no evidence of any association between serum cholesterol and risk of fatal stroke in either category (Table 5.9).

Overall there were 31 deaths from vascular diseases other than CHD and stroke. The risk of deaths from such diseases was not shown to be significantly associated with serum cholesterol concentrations, even after adjustment for other variables in the Cox regression analysis (Table 5.10). Death from CHD accounted for only a small proportion (20%) of vascular disease, and so the positive relationship between risk of death from all vascular disease and serum cholesterol was not statistically significant (Table 5.11).

5.4 Association of cholesterol with non-vascular deaths

1). Serum cholesterol and risk of all cancer death

Among the 9021 subjects included in the analysis, there were 263 deaths from cancer of all sites. Table 5.12 gives the numbers of observed and expected deaths from cancer along with the approximate risks in four quartile groups of baseline cholesterol. There was no significant association between serum cholesterol and risk of total cancer mortality. Overall in the two cohorts together, the approximate risks relative to the whole study population were 1.22, 0.88, 0.96 and 0.96 respectively from the lowest quartile (I) to the highest quartile (IV) of cholesterol (log-rank trend test 2P>0.05). In the Cox regression analysis after taking other variables into account, there was no suggestion of any association between serum cholesterol and risk of total cancer mortality *(z=-0.88, 2P>0.05)*.

2). Serum cholesterol and risk of non-liver cancer death

Lung cancer: In the two cohorts, there were 63 deaths from lung cancer during 8-13 years of follow-up (Table 5.13). Overall, there was no significant association between serum cholesterol and risk of death from lung cancer, but there were opposite and statistically significant patterns in the cohorts when examined separately. In cohort A there appeared to be an inverse relationship between serum cholesterol and risk of lung cancer with subjects in the lowest quartile of cholesterol (I) having a relative risk of death from lung cancer of 1.73, while for those in the quartile II, III and IV, the relative risks were 1.03, 0.51 and 0.79 respectively. This inverse trend in the risk of lung cancer from cholesterol quartile I to IV was statistically significant by the log-rank trend test *(X^2=4.30, 2P<0.05)*, but became non-significant after taking other variables into account in the adjusted Cox regression analysis (z=-1.57, 2P>0.05). Conversely, in cohort B there was a strong positive association between baseline cholesterol and risk of lung cancer in cohort B with people in the lowest quartile (I) of baseline cholesterol having a relative risk of lung cancer of 0.59, while in quartile II, III and

IV, the relative risks were 0.54, 0.89 and 1.90 respectively. This trend of increasing risk of lung cancer with increasing levels of cholesterol remained statistically significant after adjustment in the Cox regression analysis, though less strongly so *(z=2.27, 2P<0.05)*.

No clear explanation for this discrepancy is apparent. The increased risk of lung cancer with low cholesterol seen in cohort A may be explained partly by the observation that people with low cholesterol levels were more likely to smoke cigarettes. Thus, in the adjusted Cox regression analysis when cigarette smoking was taken into account, cholesterol was no longer a significant predictor of lung cancer mortality. But this is unlikely to be the case for cohort B, for the relation of serum cholesterol with lung cancer was positive, and remained significant after adjusting for other variables. The number of deaths from lung cancer is small in both cohorts, and the association with serum cholesterol in each individual cohort was only marginally significant, so it seems likely that these opposite patterns in the association between serum cholesterol and lung cancer in the two cohorts may be largely or wholly due to the play of chance. The data combined from the two cohorts may, therefore, provide results that are much less subject to the chance variation.

Other non-liver cancers: In the two cohorts, there were 62 deaths from stomach cancer during 8-13 years of follow-up. As shown in Table 5.14, no significant association between cholesterol concentration and risk of death from stomach cancer was found, even after taking other variables into account in the adjusted Cox regression analysis. Among the 9021 subjects studied in the two cohorts, there were 16 deaths from oesophageal cancer, 17 deaths from colorectal cancer, and 54 death from all other remaining non-liver cancer. Again, no significant associations with baseline serum cholesterol were evident for these cancer categories (Table 5.15 to 5.17), even after taking other variables into account.

3). Relation of cholesterol with liver cancer and other chronic liver disease

Among the 9021 subjects in the two cohorts, there were 51 deaths attributed to primary liver cancer during 8-13 years follow-up. Table 5.18 shows the number of deaths from liver cancer and the estimated relative risks in the four quartiles of baseline cholesterol. Overall, 19 deaths occurred in the lowest quartile (I) of cholesterol compared with 8 such deaths in the highest quartile of cholesterol (IV). The approximately risks relative to the whole study population were 1.60, 0.87, 0.97 and 0.62 respectively from the lowest quartile (I) to the highest quartile (IV) of baseline cholesterol. This inverse gradient in the risk of liver cancer with increasing levels of cholesterol was statistically significant by the log-rank trend test *(X^2=4.86, 2P<0.05)*, and serum cholesterol remained a significant predictor of liver cancer mortality in the Cox regression analysis *(z=2.18, 2P<0.05)*.

In view of the inverse association observed between liver cancer and serum cholesterol, deaths from chronic hepatitis and cirrhosis were also examined separately. In Table 5.19 the number of deaths from such disease along with estimated relative risks are shown in the four quartile groups of cholesterol. Overall in the two cohorts, there were 11 deaths from chronic liver disease among subjects in the lowest quartile of cholesterol compared with only 3 such deaths in the similar-sized population who had highest baseline cholesterol (IV). The approximate risks relative to the whole study population were 1.64, 1.03, 0.92 and 0.43 respectively from the lowest quartile (I) to the highest quartile (IV). As was the case for liver cancer, this inverse association of serum cholesterol with other chronic liver diseases was statistically significant in the log-trend trend test *(X^2=4.74, 2P<0.05)*. In the adjusted Cox regression analysis, the inverse association between serum cholesterol and risk of chronic liver disease persisted and the regression coefficient was -0.016 *(z=-1.97, 2P<0.05)*. When deaths from liver cancer and from other chronic liver diseases were combined, the inverse relationship with cholesterol concentration becomes more clearly significant. The

estimated relative risks were 1.61, 0.93, 0.95 and 0.55 respectively from the lowest quartile (I) to the highest quartile (IV) of baseline cholesterol, and the Cox regression coefficient for baseline cholesterol was -0.4130 *(z=2.89, 2P<0.01)*. This apparent inverse relationship between serum cholesterol and risk of liver disease was separately significant both in men and in women. Among males, with 66 deaths from liver diseases, the regression coefficient for baseline cholesterol was -0.3320 *(z=-2.15, 2P<0.05)*, while among females with 13 deaths from liver diseases, it was -0.8338 *(z=2.37, 2P<0.05)*.

In order to investigate whether the observed inverse relationship between serum cholesterol and liver disease was attributed chiefly to some short-term "preclinical effect" of liver disease that reduced cholesterol, analysis was done after exclusion of those subjects who died in the first three years after baseline examination. For the deaths from liver disease four or more years after the baseline survey the Cox regression coefficient for serum cholesterol remained negative and statistically significant *(ß=-0.4941, z=2.90, 2P<0.01)*. The baseline serum cholesterol concentration among the 57 people who died from liver disease was on average 0.36 mmol/l (95% confidence interval 0.13-0.60 mmol/l) lower than that among survivors.

4). Serum cholesterol and non-vascular non-cancer deaths

The "non-vascular non-cancer" deaths form a miscellaneous group, including all deaths from causes other than vascular, cancer, or chronic liver disease. Overall in the two cohorts combined, there were 84 such deaths, and the number of deaths and the estimated relative risks in the four quartiles of baseline cholesterol are shown in Table 5.20. There was no statistically significant association between serum cholesterol and risk of death from this group of disease, even after adjustment for other variables in the Cox regression analysis *(z=-1.77, 2P>0.05)*.

In the two cohorts, there were 17 deaths ascribed to non-medical causes (i.e. suicide, external injury and poisoning), and these were inversely associated with the level of baseline cholesterol. (Table 5.21). Overall among the subjects in the lowest quartile of cholesterol (I), there were 6 deaths from any non-medical cause compared with 1 such death in the highest quartile (IV). The approximate risks relative to whole population from quartile I to quartile IV were 1.58, 1.43, 0.85 and 0.23 respectively. This inverse trend in the risk of death from non-medical causes with serum cholesterol was statistically significant by the log-rank trend test *(X^2=4.30, 2P<0.05)*, but, after taking other variables into account in the adjusted Cox regression analysis, the inverse association became nonsignificant *(z=-1.94, 2P>0.05)*. With respect to 67 deaths from non-vascular non-cancer medical causes in the two cohorts (Table 5.22), no significant association with serum cholesterol was evident (2P>0.05).

5.5. Hepatitis B virus infection and cholesterol concentration

Overall, there was no significant association between cholesterol concentration and total mortality from cancer, but there did seem to be an inverse relation between serum cholesterol and liver cancer. This persisted even after exclusion of those subjects who died within the first three years after baseline examination, indicating that the inverse relation was not chiefly attributable to some short term preclinical effect of liver cancer reducing cholesterol concentration. An inverse association was also seen between serum cholesterol concentration and death from chronic non-malignant liver disease. In China, lifelong persistent hepatitis B virus infection of the liver is high in the population, and accounts for most of the liver cancer and for many other deaths from chronic liver disease. In many cases, infection with hepatitis B virus starts in early childhood. If chronic infection of the liver with hepatitis B virus lowers serum cholesterol concentrations then this could explain the inverse association between cholesterol concentration and deaths from liver disease observed in the

present prospective study. To test this hypothesis, we conducted a further study of the cholesterol concentration among more than 1,500 middle-aged men in rural China, of whom 15% were known to be carriers of hepatitis B virus (HBV) (see chapter 2 for subjects and methods).

In this rural Chinese population, 15% of the study population were positive for HBsAg (or HBV carrier), and 64% were positive for HBcAB. There was, however, a large regional variation across the communes, with the proportion of individuals positive for HBsAg ranging from 0% to 54%, and HBcAB positivity ranging from 9% to 100% (Table 5.23). The overall mean plasma cholesterol concentration in this population was 2.59 mmol/l, which is about half the level seen in most Western populations. Apolipoprotein B (apoB) and apoAI levels were also low, with mean values of 0.51 g/l and 1.39 g/l respectively. There was a two-fold variation among the 81 communes with respect to the mean concentrations of plasma cholesterol, apoB and apoAI (Table 5.23).

In Table 5.24, the prevalence of HBV infection and the mean concentrations of total cholesterol, apoB and apoAI, are shown by 5-year age groups for the whole study population. Overall, the prevalence of HBV infection appeared to be slightly higher among younger people than among older people. The mean concentrations of plasma cholesterol and apoB tended to increase with advancing age, especially after 50 years, but no such observation was apparent for apoAI. The observed and expected mean concentrations of total cholesterol, apoB and apoAI with respect to HBV status are shown in Table 5.25, together with statistical significance for the comparison of mean values between HBV carriers and non-carriers. Concentrations of plasma cholesterol, apoB and apoAI were generally lower among individuals who were carriers of HBV than among non-carriers after taking age and commune into account. For total cholesterol, the concentration was 4.3% lower (0.11 mmol/l, 95% confidence interval 0.6-8.0%, $P<0.05$), and for apoB it was 6.1% lower (95% confidence interval 2.4-9.8%,

P<0.001) among HBV carriers than among non-carriers. There was no apparent association of cholesterol and apoB with past HBV infection as assessed by the existence of HBV anticore antibody (HBcAB).

5.6 Discussion

1). No threshold exists between serum cholesterol and CHD

The role of high blood cholesterol as a major risk factor for CHD has been well established by several epidemiologic studies, but these were mostly conducted in Western populations that are at high risk of the disease *(The Pooling Project Research Group, 1978; Rose & Shipley 1986; Carlson, et al 1972; Dawber 1980; Martin, et al 1986).* Because there were relatively few individuals in the Western populations who really have low usual cholesterol levels after repeated measurement, the shape of the relationship between cholesterol and risk of CHD at the lower end of cholesterol distribution is less clearly described. Nevertheless, results from comparisons between different populations indicate that, throughout a wide range, the lower the mean cholesterol, the lower the risk of CHD *(McGill, et al 1968; Keys, 1980; Knuiman, et al 1982; Robertson, et al 1977; Simons 1986).* In the Seven Countries Study *(Keys 1980)* the median serum cholesterol levels in the 16 study cohorts ranged from about 4.1 mmol/l to about 6.5 mmol/l. Comparing these 16 cohorts with each other, there was a strong positive correlation between the median plasma cholesterol and the 10-year mortality from CHD, with a large proportion of the between-population variation in mortality from this disease explained by difference in plasma cholesterol concentrations. Results from another interpopulation correlation study of serum cholesterol and CHD mortality among 19 countries also demonstrated a strong positive correlation between the mean serum cholesterol level and CHD mortality rate in men (r=0.67, P<0.001) *(Simons 1986).* Evidence from the Ni-Hon-San study of migrating populations suggested that the observed international differences in CHD risk could not be attributed chiefly to genetic differences. In that study of

Japanese populations living in three different environments it was found that the differences in the mean cholesterol concentrations were a major determinant of the differences in death rates from CHD *(Robertson, et al 1977)*.

By contrast, a few of the prospective studies conducted within populations in which the mean cholesterol levels were high have failed to show a relation between cholesterol and mortality from CHD in the lower range of cholesterol concentration, where CHD is less common *(Oliver, 1981; Goldbourt, et al 1985; The Pooling Project Research Group, 1978)*. In a prospective study of 10,059 Isreali male civil servants aged 40 and above, 618 CHD deaths (37% of total deaths) were recorded during follow-up, and the risk of CHD mortality was analysed according to five quantile groups of serum cholesterol *(Goldbourt, et al 1985)*. It was found that neither mortality from all causes nor that from CHD showed any association with baseline cholesterol levels in the lowest three quantiles (216 mg/dl and below), and the increased risk of CHD with serum cholesterol was confined to the two highest quantiles. The results of these within population studies are sometimes interpreted as showing a threshold, perhaps at about 5.2 mmol/l, below which a lower cholesterol concentration is not associated with a lower risk of CHD. On the basis of this, it is suggested that there is little to be gained in the way of protection against CHD by having cholesterol lower than 5.2 mmol/l, and that the population strategy focussed on mass dietary changes in whole populations aiming at reducing population cholesterol levels and CHD rates may be premature *(Commentary 1986)*.

The real relationship at lower levels of cholesterol is, however, difficult to assess reliably in Western populations. This is partly because the risk of death from CHD is low among people who have low cholesterol concentration, so the lower end of the cholesterol-CHD relationship in each separate study is particularly affected by random fluctuations, and partly because few people in Western populations really have low cholesterol levels after repeated cholesterol

measurements. Thus even in the large prospective studies that have been conducted in Western populations (such as MRFIT study which included nearly 360,000 people) *(Stamler, et al 1986)*, the amount of information on subjects who really do have low cholesterol is limited.

In many Asian populations, the situation is different. Most of the adults really have cholesterol concentrations that by Western standards are low, so differences between the effects of different low concentrations can be compared directly. Thus in a prospective study of 16,711 Japanese subjects with mean baseline cholesterol of 4.3 mmol/l *(Szatrowski, et al 1984)* there was a significant positive relationship between risk of CHD and baseline cholesterol. During 16 years of follow-up, there were 198 CHD events recorded, and it was estimated, based on Cox regression analysis, that the relative risk of CHD for baseline cholesterol, between 3.89 and 4.65 mmol/l, between 4.66 and 5.70 mmol/l, and greater than 5.70 mmol/l were 1.30, 1.89 and 2.23 respectively as compared with the level of less than 3.89 mmol/l. The present study in Shanghai with mean baseline serum cholesterol of about 4.2 mmol/l confirmed this positive relationship, and within the range of usual cholesterol concentrations studied (about 3.8-4.7 mmol/l) there was no evidence of any apparent threshold below which a lower level of cholesterol was not associated with a lower risk of CHD.

In this study population a 10% difference in baseline serum cholesterol concentration was associated with a 21% difference in the risk of death from CHD. This difference in CHD risk is similar to that reported in prospective studies in Western populations in which the mean cholesterol levels were high *(Stamler, et al 1986)*. In all such studies, however, the reported relationship is only of baseline cholesterol measurement with CHD. This will, because of the "regression dilution bias" *(MacMahon, et al 1990)*, tend to underestimate substantially the strength of the relationship between **usual** cholesterol and CHD. Remeasurements of cholesterol in a sample of the population in the

present study allowed approximate correction for this bias, and it was then estimated that a 4 (SD 1)% difference in usual cholesterol concentration was associated with a 21% (95% confidence interval 9-35%) difference in the risk of CHD. Even if the strength of this relationship is due partly to the play of chance, it does illustrate the statistically inevitable prediction that the true relation between serum cholesterol and CHD must be substantially stronger than is suggested by standard analyses of baseline cholesterol.

2). Serum cholesterol levels and stroke mortality

It is generally known that the importance of serum cholesterol as a risk factor for stroke is much weaker and less consistent than its firmly established effect on coronary heart disease *(Tell, et al 1988)*. Several prospective observational studies, conducted mainly in Western populations reported no significant relationship of serum cholesterol to the risk of stroke, mainly cerebral infarction *(Kannel, et al 1965; Heyman, et al 1971; Salonen, et al 1982; Neaton, et al 1984; Harmsen, et al 1990)*. In contrast, a few prospective studies of Japanese in Japan and of Japanese-American men in the Honolulu Heart Study appeared to show an inverse association of serum cholesterol with the occurrence of intracerebral hemorrhage *(Ueshima, et al 1980; Kagan, et al 1980; Tanaka, et al 1982; Lin, et al 1984; Yano, et al 1989)*. In the present study of a Chinese population, there was no evidence of an inverse association between serum cholesterol and risk of total stroke mortality.

If lipids do relate to cerebral atherosclerosis, then a possible explanation for this apparent contradiction is that risk factors for symptomatic cerebrovascular disease may not necessarily be the same as those for atherosclerosis in general. That is, the factors associated with the precipitation of the clinical event may differ from those related to the underlying process of atherosclerosis *(Reed, et al 1988)*. It has been speculated that some factors may be contributing to the weak and uncertain relationship between serum cholesterol and risk of clinical stroke

observed in most Western populations *(Ostfeld 1980)*. Firstly, risk factors for CHD lose much of their importance in older age groups, and a similar situation for stroke may likewise operate, as most strokes occur in older people. Secondly, patients with higher serum cholesterol may not survive to an age at which stroke is common. This was supported by an autopsy study in the Honolulu Japanese men *(Stemmermann, et al 1984)* in which autopsy-verified cerebral infarction was found to be associated with myocardial infarction in more than half the cases and was usually not the underlying cause of death. This cannot, however, explain entirely the observation in the Asian population such as Japan, China, of low CHD rates, and high stroke rates. Thirdly, the etiology of atherosclerotic disease in the extracranial arteries may be similar to that in the coronary arteries and may be related primarily to the levels of blood lipids and secondarily to the elevated blood pressure, but intracranial arterials, particularly small-vessel may differ from extracranial arterials in their relationship with lipids *(Kuller & Reisler, 1971)*. Racial comparisons in the pattern of stroke suggest that Whites have more extracranial occlusive disease, while Chinese and Japanese tend to have more intracranial atherosclerosis (predominantly small-vessel pathology) that results in lacunar infarction and hemorrhage *(Huang, et al 1990; Feldmann, et al 1990)*. In the Honolulu Heart study *(Reed, et al 1988)*, age-adjusted mean atherosclerosis scores in the large arteries of the circle of Willis were consistently related to serum cholesterol, while no such association was found in the small arteries of the circle of Willis. Similar results were also shown in the Oslo study *(Holme, et al 1981)*, in which the percentage of the intimal surface covered with raised lesions in major intracranial arteries was positively correlated with serum cholesterol.

Recent data on 350,977 MRFIT screenees followed up for 6 years indicated a positive and significant relationship between baseline serum cholesterol levels and subsequent risk of deaths from cerebral infarction *(Iso, et al 1989)*. The relative risk of ischemic stroke was 2.57 for the highest quantile of cholesterol (≥6.74 mmol/l) compared with the lowest quantile (<4.15 mmol/l), suggesting that

cholesterol may be related to ischemic stroke in a manner similar to that for CHD. However the data from MRFIT study purported to show an excess risk of death from intracranial hemorrhage among men in the lowest serum cholesterol group at baseline. It was concluded that low cholesterol levels may cause intracranial hemorrhage, and that although its public health impact is overwhelmed by the strong positive association of serum cholesterol with death from non-hemorrhagic stroke and coronary heart disease in Western population, this may be of particular importance in countries such China and Japan, where mortality rates from hemorrhagic stroke are higher, and that from CHD are lower.

Two separate points should be made in considering the evidence of inverse association between low cholesterol and risk of haemorrhagic stroke. Firstly, although in some Asian populations death rates from hemorrhagic stroke are high, those from occlusive stroke are also quite high *(Chen, et al 1987; Li, et al 1985)*, and from a public health viewpoint, what matters is the relationship of cholesterol levels to total stroke (which was non-significantly positive in the MRFIT study). Secondly, the MRFIT prospective study does not provide strong evidence of any real inverse association–let alone a causal link–between serum cholesterol levels and intracranial hemorrhage. For, although a large number of subjects were studied for six years, only 83 deaths were certified as being due to intracranial hemorrhage, and the overall statistical test for an inverse association of death from intracranial hemorrhage with cholesterol levels yielded a P value of only 0.06. Indeed, among subjects with a baseline cholesterol level above 4.14 mmol per litre, there was no apparent relation whatever between cholesterol levels and intracranial hemorrhage, so that the only evidence for an inverse association was that 11 of the 83 deaths from intracranial hemorrhage (13 percent) occurred among the 6 percent of subjects whose baseline cholesterol level was below 4.14 mmol per litre. In discussing this, the MRFIT investigators emphasized the even higher mortality from intracranial hemorrhage among the even smaller subgroup of subjects with low cholesterol levels who also had a

baseline diastolic blood pressure of at least 90 mmHg. But, even though it may be possible to devise a biological hypothesis to explain this apparent interaction between the cholesterol level and blood pressure, it is also quite possible to suppose that it is largely or wholly due to bias produced by data-dependent subgroup analyses *(Collins, et al 1987)*, subdividing one marginally significant association between disease and cholesterol level with respect to blood pressure.

In the present study, which included about as many subjects with stroke as the MRFIT study, no association was seen between serum cholesterol concentration and death from stroke, even among subjects with diastolic blood pressure ≥90 mm Hg. The aetiology of the fatal strokes is not reliably known, but other studies in China have shown that more than half of all fatal strokes are due to haemorrhage *(Li, et al 1985; Chen, et al 1987).* So, although the present study cannot address directly the question of whether haemorrhage stroke rates are slightly increased in subjects with low cholesterol, it does indicate that no strong association is likely to exist. Furthermore, the present study provided direct evidence that even within a population where haemorrhagic stroke rates are high, low cholesterol is not associated with any appreciable increase in total stroke mortality.

A recent study of secular trends in risk factors levels and cardiovascular disease rates in rural Japan has concluded that *(Shimamoto, et al 1989)* rapid change to Western and urban eating patterns and lifestyles, as reflected by rapid increase in mean cholesterol concentration, is a major factor contributing to the substantial decrease in stroke deaths, especially for cerebral haemorrhage. But, there are many possible confounders in this relation, in particular the effects of other changes in a traditional Oriental diet (i.e. high salt, high carbohydrate, low fat, and low protein). Furthermore, there was also a substantial reduction in the mean blood pressure in the population, averaging 13 mmHg for systolic blood

pressure and 4 mmHg for diastolic blood pressure – a magnitude that appears to be compatible with 60% decrease in the incidence of stroke as would be expected from the epidemiological evidence *(MacMahon, et al 1990)*. In the Minnesota Heart Survey *(Burke, et al 1990)* of a simultaneous, long-term surveillance of health behaviour, risk factors and disease occurrence in a American population, it was found that the mean levels of blood pressure and of serum cholesterol are both declining, and that deaths from CHD, cerebral infarction and cerebral hemorrhage are falling in parallel. In the populations where the diet is a traditional Mediterranean diet (moderately high in fat, but mainly monounsaturated fat, adequate in protein, and intermediate in salt), both serum cholesterol and blood pressure levels are low and rates for both CHD and stroke are also low, providing no evidence in favour of the hypothesis that low blood cholesterol is a primary cause of cerebral hemorrhage in some Asian populations *(Keys 1970; Blackburn & Jacobs 1989)*.

3). Serum cholesterol and risk of cancer death

There continues to be substantial confusion as to whether there is any causal relationship between low serum cholesterol and risk of cancer death. The observation of an inverse association between blood cholesterol and risk of cancer was first reported in 1974 on the basis of pooled data of colon cancer from a number of European and North American prospective studies *(Rose, et al 1974)*. Such an inverse relationship between low cholesterol and subsequent risk of cancer deaths at multiple sites has since been investigated in many prospective studies *(Rose & Shipley 1980; International Collaborative Group 1982; Sherwin, et al 1987; Williams, et al 1981; Beaglehole, et al 1980; Isles, et al 1989; Dyer, et al 1981)*. The results from previous prospective studies have been inconsistent. Several studies have indicated an inverse association between serum cholesterol and risk of cancer *(Rose & Shipley 1980; International Collaborative Group 1982; Sherwin, et al 1987; Williams, et al 1981;*

Beaglehole, et al 1980; Feinleib 1981; Schatzkin, et al 1987; Smith, et al 1992), others reported no such association *(Salonen 1982; Dyer, et al 1981)* and some even reported a positive relationship *(Tornberg, et al 1986).* In several of the studies in which an inverse association has been observed, there was evidence that this is largely or wholly secondary to the metabolic consequences of cancer present at the time of entry to the study (a phenomenon referred to as the "preclinical cancer" effect) *(Rose & Shipley 1980; International Collaborative Group 1982; Sherwin, et al 1987; Hiatt & Fireman 1986; Cambien, et al 1980; Tornberg, et al 1989; Smith, et al 1992),* although some other studies have not found this *(Williams, et al 1981; Beaglehole, et al 1980; Isles, et al 1989; Schatzkin, et al 1987; Kark, et al 1980).* It is noteworthy that most of the previous studies were conducted in Western populations which are at high levels of serum cholesterol. There is much less direct evidence about the association of serum cholesterol with the risk of cancer in populations with low mean cholesterol levels.

The present study, in which the mean cholesterol concentration is unusually low provides direct evidence about any possible inverse relation between cholesterol concentration and risk of cancer. Overall, there was no apparent association between cholesterol and total mortality from cancer. After subdivision with respect to cancer sites, there was still no suggestion of any significant association with cholesterol for lung, stomach, oesophagus or colon and rectum cancer. But there did appear to be an significant inverse relationship between serum cholesterol concentration and liver cancer. An inverse association was also seen between serum cholesterol concentration and death from chronic non-malignant liver disease. This persisted even after exclusion of those subjects who died within the first three years after baseline examination, indicating that the inverse relation was not chiefly attributable to some short-term preclinical effect of liver disease reducing cholesterol. A recent report from MRFIT study has also demonstrated a significant excess risk of liver cancer among individuals with low

cholesterol *(Neaton, et al 1992)*. In that study with 100 liver cancer deaths recorded during the follow-up period, there was a 3-fold excess risk of death from liver cancer in the lowest cholesterol group (<4.1 mmol/l) compared with all other high cholesterol groups (≥4.1 mmol/l), although no consistent inverse trend was observed across different cholesterol levels.

4). The mechanism of the association between cholesterol and liver disease

The liver plays a central role in the metabolism of lipids *(Kesaniemi & Miettinen 1988)*. It is a major site of cholesterol synthesis as well as lipid uptake, catabolism, conversion and excretion. Furthermore, the liver synthesizes lipoproteins, secretes them into blood stream and is involved in their removal from the circulation. It is plausible that chronic liver disease may affect the uptake, transport, or synthesis of cholesterol resulting in reduced cholesterol concentration.

It has been well recognized that long and persistent infection of liver with HBV is the most important cause of primary liver cancer and other chronic liver diseases *(Beasley, et al 1981)*. While the prevalence of the carrier state for HBV is less than 1% in most Western populations *(McQuillan, et al 1989)*, about 15% of the population in China have lifelong HBV infection *(Jiang 1982)*, and this accounts for most of the country's liver cancer and chronic liver disease. In a large prospective study of 22,707 male Chinese in Taiwan *(Beasley, et al 1981)*, it has been shown that the carriers of HBsAg were more than 200 times as likely to develop liver cancer as non-carriers. In that study, 41 cases of liver cancer occurred during 3 years of follow-up, of which 40 were positive for HBsAg. Integration of DNA sequences of HBV has been found in tumour cells of liver cancer patients, further implicating the causal role of HBV in the development of liver cancer *(Brechot, et al 1980)*.

The present study in a rural Chinese population provides epidemiological evidence of an association between prolonged HBV infection and low concentration of blood cholesterol. Those individuals who were carriers of HBV had a significantly lower concentration of plasma cholesterol (4.3%, 0.11 mmol/l) compared with non-carriers. Furthermore, the concentration of plasma apoB, the major apoprotein of low density lipoprotein that transports the majority of cholesterol in the blood and reflects, in part, hepatic secretion of cholesterol, was also significantly lower by 6.1% among the HBV carriers. The findings of the present study are in agreement with results from another study of 3,000 Chinese adults in Taiwan *(Pan BY, personal communication)*. In that study, with mean cholesterol of 4.8 mmol/l, the mean concentration of cholesterol among HBV carriers was significantly lower than among non-carriers by 4.0% (0.19 mmol/l, $P<0.001$) after adjustment for age and body mass index, although no data were available with respect to the apolipoproteins.

The demonstration in this cross-sectional study of a significantly lower plasma cholesterol among HBV carriers does not necessarily establish that infection of the liver with HBV precedes low blood cholesterol. While it is possible that low plasma cholesterol observed among HBV carriers may be a manifestation of inadequate nutrition that predisposes to HBV infection, it is unlikely to be the case given the features of HBV transmission in China. There is strong evidence that prenatal maternal-infant transmission of HBV is an important and efficient route of infection of HBV *(Stevens, et al 1975; Beasley, et al 1977)*. Over 90 per cent of children born to women who are positive for both HBsAg and hepatitis B virus e antigen (HBeAg) will themselves become chronic carriers of the virus *(Beasley, et al 1977)*. It was estimated that prenatal infection may account for about 50-60% of all Chinese HBV carriers *(Stevens, et al 1975; Beasley, et al 1977)*. In many other cases, people become infected with HBV, mainly during early childhood, as a results of horizontal transmission of the virus. While it is evident that HBV

infection acquired at an early age of life often leads to a chronic carrier state, exposure to HBV during adulthood rarely results in persistent infection *(McMahon, et al 1985)*. So, it would appear that infection of the liver with HBV precedes low blood cholesterol. The possibility that the association is due to confounding by a difference in nutritional intake and in socio-economic status also seems unlikely. For, although the 81 communes involved in the study were very heterogeneous with respect to prevalence of HBV infection and cholesterol levels, the subjects within each individual commune were themselves selected from the same village, and are known to be very homogeneous with respect to socio-economic status, life-style and dietary patterns *(Chen, et al 1990)*. Furthermore the individuals who were carriers of HBV in this study were themselves asymptomatic "healthy" people and had no prior knowledge of their HBV infection. The most plausible biological explanations is, therefore, that prolonged infection of the liver with HBV, often starting in early childhood, chronically lowers blood cholesterol.

The 4 per cent difference in blood cholesterol observed between HBV carriers and non-carriers is, however, not a big effect. But only a modest effect of HBV infection on blood cholesterol would be expected, given the fact that HBV carriers included in this study were healthy people with no clinically apparent evidence of liver damage. This 4% difference in blood cholesterol between HBV carriers and non-carriers is only half the size of the difference (8-9%) observed in the prospective study between those who died of liver cancer and chronic non-maliganant liver disease and those who did not. Although possibly due to the play of chance (as there is overlap between the 95% confidence intervals of the two differences) it seems more likely that this discrepancy chiefly reflects differences between the study populations with respect to the extent or severity of liver damage from HBV infection at the time of blood sampling. On the other hand our current knowledge of the natural history of cancer is insufficient to dismiss completely the possibility that liver disease itself could, to some extent, also affect

cholesterol metabolism many years before the tumour becomes clinically apparent. Although the biological mechanism of the effect of HBV on the metabolism of cholesterol requires more elaboration, it would be plausible to assume that chronic liver damage associated with HBV may reduce the liver's capacity to synthesize or secrete new cholesterol and cholesterol transporting lipoproteins (consistent with a significantly lower apo B value).

The overall mean concentration of plasma cholesterol in the present study of a rural Chinese population was only 2.59 mmol/l when measured for this study of HBV infection and cholesterol. This figure is a slight underestimate, however, compared with the results of previous pooled analyses on the same samples made 7 years ago *(Chen, et al 1990).* The mean concentration of plasma cholesterol measured on pools of the same samples 7 years ago was 3.30 mmol/l, which is 27% higher than the values obtained recently. The mean apoB concentration was also 13% higher in the previous analysis as compared with present data. These decreases in cholesterol and apoB are unlikely to be attributable entirely to measurement variability. Indeed, the measurement of apoB was actually made in the same laboratory on both occasion using the same method. The storage conditions such as temperature, and sample handling procedure such as thaw-freeze may have contributed to the changes seen for cholesterol and apoB. Despite this, however, the relative difference demonstrated in this study between HBV carriers and non-carriers would remain unchanged.

Several alternative explanations of the findings of an inverse relationship between low blood cholesterol level and cancer risk have been suggested. Several studies have produced evidence supporting the proposal that a preclinical cancer effect can cause the relationship, probably by increased cholesterol catabolism resulting from enhanced low-density lipoprotein receptor activity in cancer cell *(Vitols, et al 1985; Ueyama, et al 1990)*, and in cells of other tissues *(Ueyama, et al 1990)*. There have also been some reports that the inverse

association between cholesterol and cancer may be secondary to the relationship between serum cholesterol and some factors which may be causally related to cancer such as low levels of serum retinol *(Kark, et al 1982)* or serum alpha-tocopherol *(Knekt, et a; 1988)*, and high levels of estrogen *(Vatten & Foss 1990)*. In this study we have demonstrated that prolonged infection with HBV is an additional explanation contributing to the inverse relationship between cholesterol and cancer. Prolonged HBV infection appears to lead both to a low cholesterol level and to an increased risk of death from liver cancer and from chronic liver disease, and consequently produces, as observed in the present prospective study, an inverse association between blood cholesterol and risk of death from liver disease.

5). Serum cholesterol and non-medical deaths

Non-medical deaths include many different types of deaths with a variety of behavioural, environmental and social determinants. Studies of the relationship of cholesterol with death from non-medical deaths (i.e., suicides, accidents or violence) are sparse and the results have not been consistent. A recent review *(Muldoon, et al 1990)* of six trials of cholesterol lowering purported to show an excess of such deaths in the group allocated cholesterol lowering treatment. The investigators concluded that reduction of cholesterol may have direct and sufficient consequences on neurochemical and behavioural function so as to increase the risk for suicide, accidental or violent death. However, these analyses were based on only a small selected subset of the relevant trials (and, even among those, follow-up data for a substantial number of randomized patients were excluded so that appropriately unbiased "intention to treat" analyses could not be performed), and they were not supported by a more complete and more systematic overview of all of the available data (published or not) from all randomised trials of cholesterol lowering by diet or drugs in which no such excess was seen *(Peto, et al 1985)* .

Similarly, the large prospective observational studies do not provide any consistent evidence that low cholesterol is associated with any material increase in the risk of accidental or violent deaths. In the two Finish cohorts of the Seven Countries study *(Pekkanen, et al 1989)* with 25-years of follow-up, a total of 47 men died due to accidents or violence, and no apparent association was found with baseline serum cholesterol levels. In the present study, there was a marginally significant inverse association between death attributed to non-medical causes and serum cholesterol. This group of deaths from non-medical cause included accidents (five deaths), external injury (four), suicide (five) and other causes (three). The number of such deaths was small, the association became non-significant after taking other variables into account, no single cause was predominant, other studies do not support it, and there is no biological plausible explanation for this association, so it seems that this marginally significant inverse association may largely or wholly represent a chance finding.

5.7. Conclusions

1). In the present study, the mean baseline serum cholesterol for 9021 Chinese adults was 4.2 mmol/l (or 162 mg/dl), and only 43 (7%) of the deaths that occurred during 8-13 years of follow-up were attributed to CHD.

2). In this low-cholesterol low-risk population, there was a strongly positive, and apparently independent relationship between serum cholesterol concentration and risk of death from CHD ($z=3.47$, $2P<0.001$). Within the range of serum cholesterol studied of 3.8-4.7 mmol/l (or about 145-180 mg/dl), there was no evidence of any apparent "threshold" below which a lower level of serum cholesterol was no longer associated with a lower risk of CHD.

3). It was estimated that a 10% difference in baseline serum cholesterol (about 0.41 mmol/l or 16 mg/dl) was associated independently with 21%±6 difference in subsequent CHD risk. This is about the same size percentage as

has been observed in prospective studies in Western populations where the mean cholesterol is high. After appropriate adjustment for the "regression dilution" bias, a 4%±1 difference in usual cholesterol was associated with a 21%±6 difference in CHD death.

4). There was no apparent association between serum cholesterol and total stroke mortality, even among those subjects with high blood pressure.

5). Overall there was no significant association of serum cholesterol with total mortality from cancer, but there did appear to be an inverse relationship between serum cholesterol and liver cancer. An inverse association between serum cholesterol and death from chronic hepatitis and cirrhosis was also observed. Persistent infection of liver with hepatitis B virus appears to be the cause both of a lower serum cholesterol and a higher risk of death from liver disease, explaining the inverse association.

Figures and tables

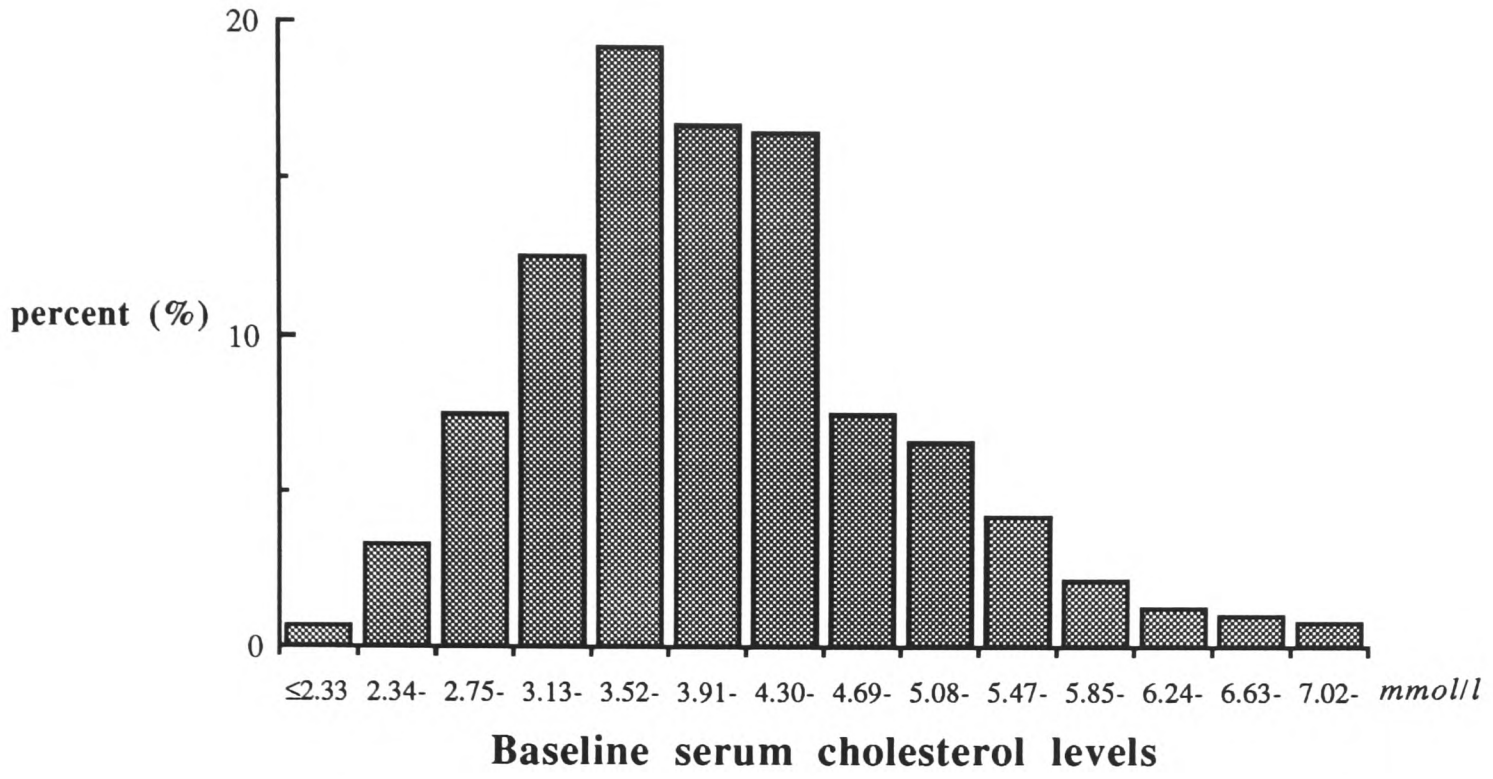


Figure 5.1. The distribution of baseline serum cholesterol concentration in cohort A.

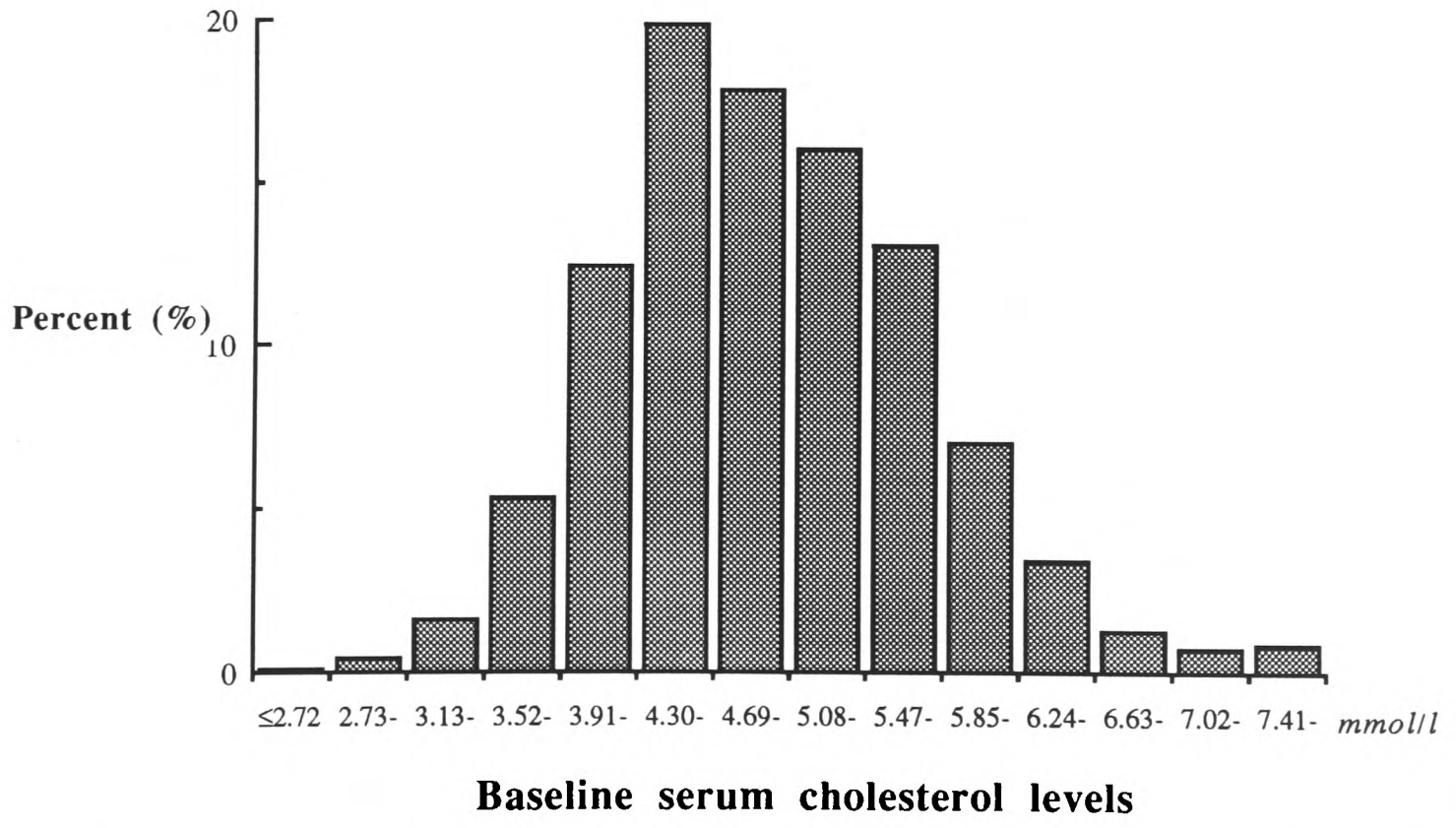


Figure 5.2. The distribution of baseline serum cholesterol concentration in cohort B

Table 5.1. Mean levels of serum cholesterol by age and sex at baseline examination in cohort A.

Age groups (years)	Male			Female			All subjects		
	No. of subjects	Mean (mmol/l)	SD	No. of subjects	Mean (mmol/l)	SD	No. of subjects	Mean (mmol/)	SD
35-39	219	4.14	0.89	268	3.99	0.90	487	4.06	0.89
40-44	324	4.11	0.96	433	4.06	0.83	757	4.08	0.89
45-49	307	4.18	0.95	277	4.33	1.01	584	4.25	0.98
50-54	304	4.25	0.92	139	4.40	1.09	443	4.30	0.98
55-59	249	4.13	0.84	88	4.41	0.96	337	4.20	0.88
60-64	206	4.13	1.01	79	4.39	1.21	285	4.21	1.07
Total ¶	1609	4.16	0.93	1284	4.19	0.96	2893	4.17	0.94

¶ The age-adjusted mean values of serum cholesterol were 4.15 mmol/l (or 160.1 mg/dl) for men and 4.20 mmol/l (or 162.3 mg/dl) for women.

Table 5.2. Mean levels of serum cholesterol by age and sex at baseline examination in cohort B.

Age groups (years)	Male			Female			All subjects		
	No. of subjects	Mean (mmol/l)	SD	No. of subjects	Mean (mmol/l)	SD	No. of subjects	Mean (mmol/l)	SD
35-39	495	4.92	0.81	436	4.90	0.73	931	4.91	0.77
40-44	562	4.90	0.74	309	4.93	0.82	871	4.91	0.77
45-49	1352	4.94	0.82	497	4.88	0.74	1849	4.92	0.80
50-54	1002	4.99	0.80	218	5.38	1.01	1220	5.06	0.85
55-59	762	5.10	0.87	45	5.52	0.89	807	5.12	0.88
60-64	438	5.07	0.81	12	5.39	0.68	450	5.07	0.81
Total ¶	4611	5.06	0.81	1517	4.99	0.82	6128	4.98	0.82

¶ The age-adjusted mean values of serum cholesterol were 4.97 mmol/l (or 191.8 mg/dl) for males and 5.04 mmol/l (or 194.4 mg/dl) for females.

Table 5.3. Mean values of baseline variables in the cholesterol quartiles in the combined data from the two cohorts.

Variables¶	Quartiles of baseline serum cholesterol			
	I (lowest)	II	III	IV (highest)
Age (years)	47.7	48.0	48.7	49.3
Males (%)	70.1	67.7	69.5	68.6
SBP (mmHg)	122.8	124.1	125.2	127.5
DBP (mmHg)	77.5	78.4	79.0	81.1
Body weight (kg)	57.2	58.3	59.0	60.0
Hypertension (%)†	11.0	12.6	13.6	17.3
Cigarette Smoking (%)	46.0	44.4	43.6	42.1
Alcohol consumption (%)	19.8	19.1	19.4	20.9
Resting ECG abnormality (%)	10.0	11.0	10.5	12.7
No. of subjects:	2162	2285	2405	2169

¶ Mean age increased slightly from cholesterol I to IV, so all other variables have been age-adjusted.
† Hypertension was defined as SBP≥160 &/or DBP≥95 (mmHg).

Table 5.4. The number of deaths from **CHD** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)¶	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	2	7.0	0.29	1443	2	3.5	0.57	**2162**	**4**	**10.5**	**0.38**
II	722	7	6.4	1.09	1563	2	3.8	0.53	**2285**	**9**	**10.2**	**0.88**
III	705	7	6.6	1.06	1700	5	4.6	1.09	**2405**	**12**	**11.2**	**1.07**
IV (highest)	747	11	7.0	1.57	1422	7	4.1	1.71	**2169**	**18**	**11.1**	**1.62**
Total	2893	27	27.0	1.00	6128	16	16.0	1.00	**9021**	**43**	**43.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)			5.46*				3.21				**8.35****	
Cox regression analysis												
Coefficients (ß)†			0.425				0.579				**0.463**	
z values (ß/s.e.)			2.49*				2.37*				**3.47*****	

¶ The expected (E) number of deaths, adjusted for age and sex by the log-rank method.

§ X^2 values less than 3.84 are not conventionally significant (i.e. 2P>0.05).

*,**,*** Statistically significant at 2P<0.05, <0.01 and <0.001 respectively.

† The regression coefficients were estimated in the Cox's proportional-harzards model, with serum cholesterol included in the model as a continuous variable together with age, sex, diastolic blood pressure, cigarette smoking and alcohol drinking.

Table 5.5. The number of deaths from **CHD** and the estimated relative risks in males and females by quartiles of baseline cholesterol in the combined data from the two cohorts.

Quartiles of baseline cholesterol	Males				Females			
	No.of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Expected deaths(O)	Observed deaths(E)	Ratios of O/E
I (lowest)	1516	3	7.6	0.39	646	1	2.2	0.45
II	1546	8	7.8	1.03	739	1	2.3	0.43
III	1671	9	8.4	1.07	734	3	3.0	1.00
IV (highest)	1487	12	8.2	1.46	682	6	3.5	1.70
Total	6220	32	32.0	1.00	2801	11	11.0	1.00
Statistical analysis								
Log-rank trend (X^2)§		4.14*				2.81		
Cox regression analysis								
Coefficients (ß)†		0.425				0.463		
z values (ß/s.e.)		2.68**				2.09*		

§ X^2 values less than 3.84 are not conventionally significant (i.e. 2P>0.05).
*,** Statistically significant at 2P<0.05 and <0.01 respectively.
† The regression coefficients were estimated in the Cox's proportional-hazards model with serum cholesterol included in the model as a continuous variable together with age, diastolic blood pressure, cigarette smoking and alcohol drinking.

Table 5.6. Mean cholesterol levels at baseline and at 3 years post-baseline for quartile groups defined by baseline cholesterol in cohort A.

Baseline cholesterol quartile (mmol/l)	No. of subjects with two measurements	Mean cholesterol at baseline (mmo/)	Mean cholesterol after 3 years (mmol/l)
I. ≤3.52	586	3.08	3.83
II. 3.53-4.09	588	3.81	4.06
III. 4.10-4.61	583	4.34	4.23
IV. ≥4.62	635	5.40	4.63
All groups	2392	4.18	4.19
Differences of mean cholesterol (IV-I)		2.32	0.80

Table 5.7. Mean cholesterol levels at baseline and at 3 years post-baseline for quartile groups defined by baseline cholesterol in cohort B.

Baseline cholesterol quartile groups	No. of subjects with two measurements	Mean cholesterol at baseline (mmol/l)	Mean cholesterol after 3 years (mmol/l)
I (lowest)	402	3.97	4.95
II	388	4.63	5.27
III	415	5.22	5.38
IV (higest)	389	6.09	5.83
All groups	1594	4.96	5.35
Differences of mean cholesterol (IV-I)		2.12	0.88

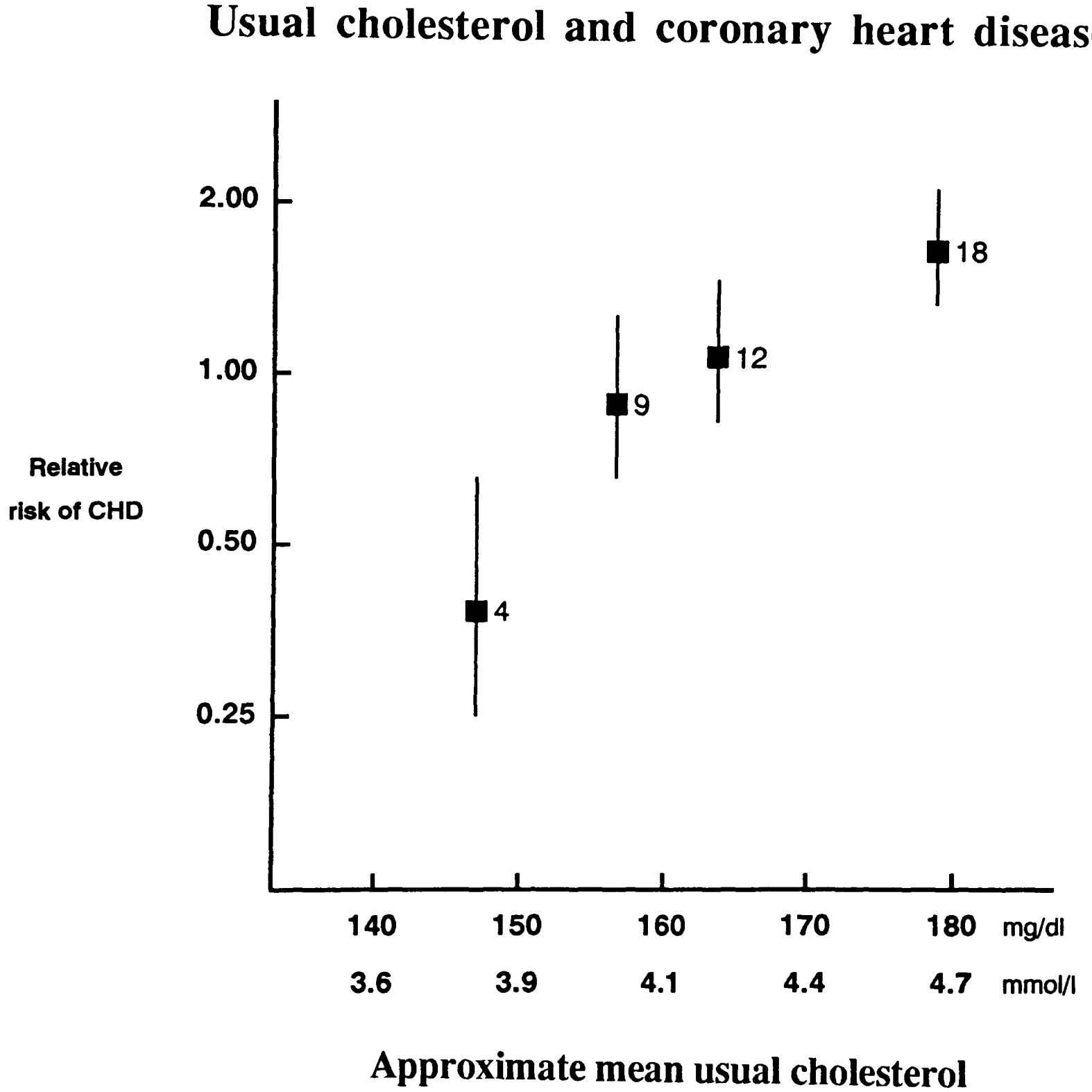


Figure 5.3. Relative risks of death from CHD by 4 quartile groups of baseline cholesterol in 9021 Chinese people with 8-13 years of follow-up. Approximate mean usual cholesterol in 4 groups are from mean values three years after baseline in Cohort A. Numbers of deaths from CHD in each group are shown with vertical lines that represent one standard deviation.

Table 5.8. The number of deaths from **stroke** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	21	20.3	1.03	1443	13	13.4	0.97	**2162**	**34**	**33.7**	**1.01**
II	722	24	20.2	1.19	1563	11	14.4	0.76	**2285**	**35**	**34.6**	**1.01**
III	705	14	21.8	0.64	1700	20	17.2	1.16	**2405**	**34**	**39.0**	**0.87**
IV (highest)	747	27	23.7	1.14	1422	16	15.0	1.06	**2169**	**43**	**38.7**	**1.11**
Total	2893	86	86.0	1.00	6128	60	60.0	1.00	**9021**	**146**	**146.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2) §		0.03				0.39					**0.06**	
Cox regression analysis												
Coefficients (ß)		0.000				-0.069					**-0.015**	
z values (ß/s.e.) §		0.00				-0.47					**-0.17**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.9. The number of deaths from **stroke** and the estimated relative risks in four quartiles of baseline cholesterol according to blood pressure in the combined data of two cohorts.

Quartiles of baseline cholesterol	DBP<90 mm Hg				DBP≥90 mmHg				**All subjects**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects¶**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	1821	11	11.0	1.00	339	23	18.7	1.23	**2160**	**34**	**29.7**	**1.14**
II	1836	10	10.6	0.94	448	25	24.6	1.02	**2284**	**35**	**35.2**	**0.99**
III	1897	10	11.4	0.88	508	24	27.1	0.89	**2405**	**34**	**38.5**	**0.88**
IV (highest)	1592	13	11.0	1.18	576	30	31.6	0.95	**2168**	**43**	**42.6**	**1.01**
Total	7146	44	44.0	1.00	1871	102	102.0	1.00	**9017**	**146**	**146.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			0.04				0.92				**0.07**	
Cox regression analysis												
Coefficients (ß)			0.077				-0.116				**-0.015**	
z values (ß/s.e.) §			0.50				-0.88				**-0.17**	

¶ 4 subjects did not have blood pressure measurements at baseline, and were excluded in the analysis.
§ X^2 values less than 3.84 or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.10. The number of deaths from **other vascular** disease and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	4	4.6	0.87	1443	3	2.4	1.25	**2162**	**7**	**7.0**	**1.00**
II	722	7	4.3	1.63	1563	1	2.7	0.37	**2285**	**8**	**7.0**	**1.14**
III	705	4	5.0	0.80	1700	5	3.5	1.43	**2405**	**9**	**8.5**	**1.06**
IV (highest)	747	4	5.1	0.78	1422	3	3.4	0.88	**2169**	**7**	**8.5**	**0.82**
Total	2893	19	19.0	1.00	6128	12	12.0	1.00	**9021**	**31**	**31.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			0.26				0.00				**0.13**	
Cox regression analysis												
Coefficients (ß)			-0.039				0.062				**0.012**	
z values (ß/s.e.) §			-0.16				0.17				**0.12**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.11. The number of deaths from **all vascular** disease and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	27	31.1	0.87	1443	18	19.3	0.93	**2162**	**45**	**50.4**	**0.89**
II	722	38	30.8	1.23	1563	14	21.0	0.67	**2285**	**52**	**51.8**	**1.00**
III	705	25	33.6	0.74	1700	30	25.3	1.19	**2405**	**55**	**58.9**	**0.93**
IV (highest)	747	42	36.5	1.15	1422	26	22.4	1.16	**2169**	**68**	**58.8**	**1.16**
Total	2893	132	132.0	1.00	6128	88	88.0	1.00	**9021**	**220**	**220.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			0.26				1.71				**1.44**	
Cox regression analysis												
Coefficients (ß)			0.089				0.039				**0.100**	
z values (ß/s.e.) §			1.05				0.21				**1.40**	

§ X^2 values less than 3.84, or z values less than1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.12. The number of deaths from **all cancers** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	43	32.7	1.32	1443	31	27.8	1.12	**2162**	**74**	**60.5**	**1.22**
II	722	26	33.5	0.78	1563	30	30.2	0.99	**2285**	**56**	**63.7**	**0.88**
III	705	32	34.6	0.92	1700	35	35.4	0.99	**2405**	**67**	**70.0**	**0.96**
IV (highest)	747	38	38.2	0.99	1422	28	30.6	0.92	**2169**	**66**	**68.8**	**0.96**
Total	2893	139	139.0	1.00	6128	124	124.0	1.00	**9021**	**263**	**263.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			1.04				0.53				**1.53**	
Cox regression analysis												
Coefficients (ß)			-0.050				-0.077				**-0.062**	
z values (ß/s.e.) §			-0.64				-0.70				**-0.88**	

§ X^2 values less than 3.84, or z values less than are not conventionally significant (i.e. 2P>0.05).

Table 5.13. The number of deaths from **lung cancer** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	13	7.5	1.73	1443	4	6.8	0.59	**2162**	**17**	**14.3**	**1.19**
II	722	8	7.8	1.03	1563	4	7.4	0.54	**2285**	**12**	**15.2**	**0.79**
III	705	4	7.8	0.51	1700	8	9.0	0.89	**2405**	**12**	**16.8**	**0.71**
IV (highest)	747	7	8.9	0.79	1422	15	7.9	1.90	**2169**	**22**	**16.8**	**1.31**
Total	2893	32	32.0	1.00	6128	31	31.0	1.00	**9021**	**63**	**63.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			4.30*				7.00**				**0.11**	
Cox regression analysis												
Coefficients (ß)			-0.313				0.432				**0.054**	
z values (ß/s.e.) §			-1.57				2.27*				**0.39**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).
*,** Statistically significant at 2P<0.05 and <0.01 respectively.

Table 5.14. The number of deaths from **stomach cancer** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	7	8.0	0.88	1443	9	6.6	1.36	**2162**	**16**	**14.6**	**1.10**
II	722	6	7.9	0.76	1563	9	7.3	1.23	**2285**	**15**	**15.2**	**0.99**
III	705	7	7.9	0.89	1700	8	8.7	0.92	**2405**	**15**	**16.6**	**0.90**
IV (highest)	747	12	8.2	1.46	1422	4	7.4	0.54	**2169**	**16**	**15.6**	**1.03**
Total	2893	32	32.0	1.00	6128	30	30.0	1.00	**9021**	**62**	**62.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			1.50				2.77				**0.06**	
Cox regression analysis												
Coefficients (ß)			0.193				-0.328				**0.004**	
z values (ß/s.e.) §			1.01				-1.34				**0.05**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.15. The number of deaths from **oesophageal cancer** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	3	1.6	1.91	1443	2	2.1	0.93	**2162**	**5**	**3.7**	**1.35**
II	722	1	1.6	0.64	1563	5	2.1	2.34	**2285**	**6**	**3.7**	**1.62**
III	705	2	1.8	1.05	1700	1	2.6	0.39	**2405**	**3**	**4.5**	**0.67**
IV (highest)	747	1	2.0	0.50	1422	1	2.2	0.46	**2169**	**2**	**4.1**	**0.48**
Total	2893	7	7.0	1.00	6128	9	9.0	1.00	**9021**	**16**	**16.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			1.24				1.29				**2.53**	
Cox regression analysis												
Coefficients (ß)			-0.575				-0.552				**-0.567**	
z values (ß/s.e.) §			-1.28				-1.20				**-1.77**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.16. The number of deaths from **colorectal cancer** and the estimated relative risks by quartiles of baseline cholesterol in two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	5	2.6	1.92	1443	2	1.1	1.82	**2162**	**7**	**3.7**	**1.89**
II	722	2	2.6	0.78	1563	1	1.2	0.85	**2285**	**3**	**3.7**	**0.80**
III	705	0	3.4	0.00	1700	2	1.5	1.35	**2405**	**2**	**4.8**	**0.41**
IV (highest)	747	5	3.4	1.45	1422	0	1.3	0.00	**2169**	**5**	**4.7**	**1.06**
Total	2893	12	12.0	1.00	6128	5	5.0	1.00	**9021**	**17**	**17.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			0.50				1.41				**1.52**	
Cox regression analysis												
Coefficients (ß)			0.077				-0.579				**-0.066**	
z values (ß/s.e.) §			0.28				-0.93				**-0.26**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.17. The number of deaths from **other non-ilver cancer** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	3	6.8	0.44	1443	7	5.1	1.36	**2162**	**10**	**11.9**	**0.84**
II	722	5	7.4	0.67	1563	4	5.9	0.68	**2285**	**9**	**13.3**	**0.68**
III	705	14	7.9	1.76	1700	8	6.4	1.25	**2405**	**22**	**14.3**	**1.54**
IV (highest)	747	9	8.9	1.02	1422	4	5.6	0.71	**2169**	**13**	**14.5**	**0.90**
Total	2893	31	31.0	1.00	6128	23	23.0	1.00	**9021**	**54**	**54.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			2.73				0.45				**0.66**	
Cox regression analysis												
Coefficients (ß)			0.270				-0.309				**0.097**	
z values (ß/s.e.) §			1.73				-1.05				**0.66**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.18. The number of deaths from **liver cancer** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	12	5.9	2.03	1443	7	6.0	1.16	**2162**	**19**	**11.9**	**1.60**
II	722	4	6.2	0.65	1563	7	6.4	1.09	**2285**	**11**	**12.6**	**0.87**
III	705	5	6.1	0.82	1700	8	7.3	1.10	**2405**	**13**	**13.4**	**0.97**
IV (highest)	747	4	6.8	0.59	1422	4	6.2	0.64	**2169**	**8**	**13.0**	**0.62**
Total	2893	25	25.0	1.00	6128	26	26.0	1.00	**9021**	**51**	**51.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			5.20*				0.72				**4.86***	
Cox regression analysis												
Coefficients (ß)			-0.567				-0.135				**-0.378**	
z values (ß/s.e.) §			-2.37*				-0.54				**-2.18***	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).
* Statistically significant at 2P<0.05.

Table 5.19. The number of deaths from **non-malignant chronic liver disease** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	5	2.5	2.00	1443	6	4.2	1.43	**2162**	**11**	**6.7**	**1.64**
II	722	2	2.4	0.83	1563	5	4.4	1.14	**2285**	**7**	**6.8**	**1.03**
III	705	3	2.5	1.20	1700	4	5.1	0.78	**2405**	**7**	**7.6**	**0.92**
IV (highest)	747	0	2.6	0.00	1422	3	4.3	0.70	**2169**	**3**	**6.9**	**0.43**
Total	2893	10	10.0	1.00	6128	18	18.0	1.00	**9021**	**28**	**28.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			4.04*				1.46				**4.47***	
Cox regression analysis												
Coefficients (ß)			-0.973				-0.208				**-0.471**	
z values (ß/s.e.) §			-2.25*				-0.68				**-1.97***	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).
* Statistically significant at 2P<0.05.

Table 5.20. The number of deaths from **all non-vascular non-cancer** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	11	11.6	0.95	1443	10	8.0	1.25	**2162**	**21**	**19.6**	**1.07**
II	722	16	10.7	1.50	1563	13	9.1	1.43	**2285**	**29**	**19.8**	**1.46**
III	705	9	12.1	0.74	1700	11	10.5	1.05	**2405**	**20**	**22.6**	**0.88**
IV (highest)	747	11	12.6	0.87	1422	3	9.4	0.32	**2169**	**14**	**22.0**	**0.64**
Total	2893	47	47.0	1.00	6128	37	37.0	1.00	**9021**	**84**	**84.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			0.54				1.47				**3.81**	
Cox regression analysis												
Coefficients (ß)			-0.077				-0.579				**-0.232**	
z values (ß/s.e.) §			-0.42				-2.52*				**-1.77**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).
* Statistically significant at 2P<0.05.

Table 5.21. The numbersof deaths from **non-medical causes** (sucides, accidental and violent deaths) and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	2	1.2	1.67	1443	4	2.6	1.54	**2162**	**6**	**3.8**	**1.58**
II	722	1	1.2	0.83	1563	5	3.0	1.67	**2285**	**6**	**4.2**	**1.43**
III	705	1	1.3	0.77	1700	3	3.4	0.88	**2405**	**4**	**4.7**	**0.85**
IV (highest)	747	1	1.3	0.77	1422	0	3.0	0.00	**2169**	**1**	**4.3**	**0.23**
Total	2893	5	5.0	1.00	6128	12	12.0	1.00	**9021**	**17**	**17.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			0.45				4.26*				**4.30***	
Cox regression analysis												
Coefficients (ß)			-0.228				-0.923				**-0.614**	
z values (ß/s.e.) §			-0.44				-2.25*				**-1.94**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).
* Statistically significant at 2P<0.05.

Table 5.22. The number of deaths from **other non-vascular non-cancer medical diseases** and the estimated relative risks by quartiles of baseline cholesterol in the two cohorts.

Quartiles of baseline cholesterol	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
I (lowest)	719	9	10.3	0.87	1443	6	5.4	1.11	**2162**	**15**	**15.7**	**0.96**
II	722	15	9.6	1.56	1563	8	6.1	1.31	**2285**	**23**	**15.7**	**1.46**
III	705	8	10.9	0.73	1700	8	7.1	1.13	**2405**	**16**	**18.0**	**0.89**
IV (highest)	747	10	11.2	0.89	1422	3	6.4	0.47	**2169**	**13**	**17.6**	**0.74**
Total	2893	42	42.0	1.00	6128	25	25.0	1.00	**9021**	**67**	**67.0**	**1.00**
Statistical analysis												
Log-rank trend (X^2)§			0.30				1.42				**1.33**	
Cox regression analysis												
Coefficients (ß)			-0.019				-0.405				**-0.127**	
z values (ß/s.e.) §			-0.13				-1.51				**-0.95**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 5.23. Mean values and ranges observed among the 81 communes.

Variables	Mean	Ranges
HBsAg *(% of positive)*	15	0~54
HBcAB *(% of positive)*	64	9~100
Cholesterol *(mmol/l)*	2.59	1.65~3.59
Apo B *(g/l)*	0.51	0.38~0.68
Apo AI *(g/l)*	1.39	1.02~2.05

Table 5.24. Prevalence of HBV infection and mean values of lipids by age group in the overall study population.

Age group	No. of subjects¶	HBsAg		Cholesterol		Apo B		Apo AI	
		No. positive	(%)	Mean *(mmol/l)*	SD	Mean *(g/l)*	SD	Mean *(g/l)*	SD
35-39	317	54	17.0	2.49	0.81	0.49	0.15	1.41	0.38
40-44	216	35	16.2	2.51	0.82	0.51	0.16	1.42	0.36
45-49	256	37	14.5	2.47	0.80	0.49	0.16	1.34	0.33
50-54	256	43	16.8	2.69	0.84	0.52	0.16	1.41	0.36
55-59	266	28	10.5	2.68	0.83	0.52	0.16	1.40	0.37
60-64	230	35	15.2	2.71	0.73	0.52	0.14	1.41	0.36
All groups	1541	232	15.1	2.59	0.81	0.51	0.16	1.39	0.36

¶ 16 individuals were not included in the table, because one of the three lipids was not measured due to insufficient sample.

Table 5.25. The mean observed and expected values of plasma cholesterol, apoB and apoAI according to hepatitis B virus infection status.

Variables	HBV(+)				HBV(-)				Difference between HBV+ & HBV-	Relative change (%)	z values
	No. of subjects	Observed mean(O)	Expected mean(E)¶	O-E	No. of subjects	Observed mean(O)	Expected mean(E)	O-E			
Cholesterol *(mmol/l)*	238	2.61	2.70	-0.09	1318	2.58	2.56	0.02	-0.11	4.3	-2.22*
Apo B *(g/l)*	233	0.50	0.53	-0.03	1316	0.51	0.50	0.01	-0.04	6.1	-3.29***
Apo AI *(g/l)*	234	1.39	1.42	-0.03	1318	1.40	1.39	0.01	-0.04	1.5	-1.45

¶ The expected mean values were estimated after adjustment for age and commune based on the finite sampling theory.
*,*** Statistical significant at 2P<0.05 and <0.001 respectively.

Chapter 6

Blood pressure and cause-specific mortality

6.1. Baseline blood pressure distribution

1). Frequency distributions and mean values

Among 9351 people studied at baseline in the two cohorts, four people (1 in cohort A and 3 in cohort B) did not have their blood pressure taken at their baseline examinations. These four subjects were excluded, leaving 9347 individuals for the present analysis.

The distributions of baseline systolic and diastolic blood pressure (SBP & DBP) in cohort A are shown in Figures 6.1 and 6.2 respectively, while in cohort B, they are shown in Figures 6.3 and 6.4 respectively. Both SBP and DBP show an approximately normal unimodal distribution, with slight skewing to the right, which was more pronounced for systolic than for diastolic. In both cohort A and cohort B, the mode of SBP was 111-120 mmHg, while for DBP it was 71-80 mmHg. Tables 6.1 and 6.2 give the mean levels of SBP and DBP for cohort A by age and sex respectively along with their standard deviations, while for cohort B the corresponding data are shown in Table 6.3 and Table 6.4 respectively. The levels of SBP and DBP increase with age in both males and females. In cohort A, the age-adjusted mean levels of SBP were 127.5 mmHg for males and 128.1 mmHg for females, while for DBP these were 82.5 mmHg and 82.2 mmHg for men and women respectively. In cohort B, the mean SBP and DBP levels were both slightly higher in males than in females. The age-adjusted mean levels of SBP were 123.6 mmHg for men and 122.4 mmHg for women, while for DBP it was 77.6 mmHg and 75.9 mmHg for males and females respectively.

2). The prevalence of isolated systolic hypertension

Table 6.5 gives the prevalence rates of isolated systolic hypertension by age in the two cohorts. The definition of isolated systolic hypertension used is diastolic blood pressure less than 90 mmHg and systolic blood pressure of 160 mmHg or above. Among the total population in the two cohorts, 1.4% had isolated systolic hypertension at baseline. The prevalence of isolated systolic hypertension increased markedly with advancing age, with a prevalence of 0.3% among individuals aged less than 50 years of age, while among those aged 60-64 years it was 7.3%.

3). Relation of blood pressure to other baseline variables

The relation of blood pressure to certain other baseline variables is shown in Table 6.6 for the combined data of two cohorts. Based on baseline blood pressure, individuals in each separate cohort were classified into one of the following three categories: normotensive, borderline hypertension and definite hypertension using the criteria defined by WHO. The definitions of three blood pressure categories were as follows: normotensive: SBP/DBP<140/90 mmHg; definite hypertension: SBP≥160 and/or DBP≥95 mmHg; borderline hypertension: all individuals who are not included in the above two categories. For mean serum cholesterol, blood pressure and body weight, the age-adjusted mean values were calculated by ANOVA in each cohort, and pooled mean values for the two cohorts together were then computed, using the inverse of the variances as weights. With respect to cigarette smoking, alcohol drinking and resting ECG abnormalities, the age-adjusted overall means were calculated by direct standardization to the age distribution of the two cohorts combined. Individuals with high blood pressure were slightly older, and after adjustment for age, there was a trend towards higher serum cholesterol and heavier body weight among hypertensive subjects compared with normotensive people. People with high baseline blood pressure were less likely to smoke cigarettes, more likely to drink

alcohol and have a significant higher proportion of resting ECG abnormalities than those with low blood pressure.

6.2. Association of baseline blood pressure with total mortality

1). Blood pressure status and risk of all cause death

Among the 9347 subjects in the two cohorts, 620 deaths were recorded from any cause during 8-13 years of follow-up. The association of blood pressure with all cause mortality was first evaluated according to the three categories of blood pressure status at baseline using the definitions described above (i.e., normotensive, borderline hypertension and definite hypertension). Table 6.7 gives the number of deaths and the estimated relative risks in three blood pressure categories, along with the statistical analyses of the log-rank trend test. There was a strong positive association between the levels of blood pressure at baseline and subsequent risk of death from all causes. Overall in the two cohorts, there were 272 deaths from any cause in the normotensive group, and the approximate risk of total mortality relative to the whole study population was 0.77. In contrast among individuals with definite hypertension, there were 222 total deaths, and the approximate risk was 1.57. This trend of increasing risk of death from all causes with increasing levels of blood pressure was highly significant in a log-rank trend test *(X^2=61.66, 2P<0.001)*. This strong association between levels of baseline blood pressure and total mortality was separately significant in both cohort A and cohort B.

2). Systolic blood pressure and risk of all cause death

To examine the relationship of systolic blood pressure with risk of total mortality, subjects in each cohort were subdivided into five categories on the basis of baseline systolic blood pressure, irrespective of each individual's baseline DBP levels. The cutoff points of 125, 140, 155 and 170 mmHg were

arbitrarily chosen to give reasonable numbers of deaths in each of the five categories for the satisfactory analyses of the data.

In Table 6.8 the number of deaths from all causes and the estimated relative risks were given in the five categories of baseline systolic blood pressure (SBP). There was a strong direct relationship between baseline levels of SBP and risk of total mortality. Overall in the two cohorts together, there were 224 deaths in the lowest SBP category with baseline SBP less than 125 mm Hg (1), and the estimated risk relative to the whole study population was 0.79. The risk of all cause mortality increased steadily with increasing levels of baseline SBP, with relative risks of 0.80, 1.12, 1.32 and 1.84 respectively from SBP category 2 to category 5 *(log-rank trend test: X^2=58.24, 2P<0.001)*. In the Cox regression analysis with baseline SBP included as a continuous variable, SBP remained a strong predictor of total mortality after adjustment for age, sex, cigarette smoking, serum cholesterol, alcohol consumption *(z=6.53, 2P<0.001)*. The estimated regression coefficient (0.011) suggested that a 10 mmHg difference in baseline SBP would be independently associated with a 12% excess risk of total mortality (i.e., odds ratio of 1.12, 95% CI: 1.08-1.15). This figure, however, substantially underestimates the slope of the real association between usual SBP levels and disease rate, due chiefly to the "regression dilution" bias (see later). The relation between baseline levels of SBP and risk of total mortality was separately significant in both cohort A and cohort B. In cohort A, with 334 deaths from all causes during 13 years of follow-up, the regression coefficient for SBP was 0.010 *(z=4.20, 2P<0.001),* while in cohort B, with 286 deaths during 8 year of follow-up, it was 0.013 (z=5.06, 2P<0.001).

3). Diastolic blood pressure and risk of all cause death

In examining the relationship between diastolic blood pressure and disease rates, individuals in each cohort were categorized, like SBP, into five groups according to their baseline DBP level, regardless of the SBP level. Cutoff points

of 80, 90, 100 and 110 mmHg were chosen to yield reasonable numbers of deaths in each group.

Table 6.9 gives the number of deaths from all causes and the estimated relative risks in the five categories of baseline DBP. As with SBP, the risk of all causes of death was strongly associated with the levels of baseline DBP. Overall in the two cohorts together, the risk of all cause mortality increased steadily from the lowest DBP group (1) to the highest group (5), with the relative risks of 0.76, 0.90, 1.01, 1.79 and 2.23 respectively *(log rank trend test: X^2=67.77, 2P<0.001)*. In the adjusted Cox regression analysis, baseline DBP remained a significant predictor of total mortality after taking other variables into account *(z=7.18, 2P<0.001)*. The estimated regression coefficient (0.024) suggested that a 7 mmHg difference in baseline DBP would be independently associated with a 18% excess of total mortality (that is odds ratio 1.18, 95% CI: 1.13-1.24). The relationship between baseline DBP and total mortality was separately significant in both cohort A and cohort B, and in both men and women. Among males in the two cohorts together, with 500 total deaths during 8-13 years of follow-up, the regression coefficient for DBP was 0.025 *(z=6.82, 2P<0.001)*, while among females with 120 deaths from any cause, it was 0.017 (z=2.21, 2P<0.05).

6.3. Association of baseline blood pressure with vascular death

1). Blood pressure status and risk of all vascular death

Table 6.10 gives the number of deaths from all vascular diseases and the estimated relative risk in three blood pressure categories at baseline. Overall in the two cohorts together, there were 58 deaths attributed to any vascular disease among the individuals with normal baseline blood pressure, and the approximate risk relative to the whole study population was 0.46. In contrast among those subjects who had definite hypertension at baseline, there were 141 deaths from any vascular disease, and the corresponding risk was 2.50. The risk of vascular

death among hypertensive subjects was more than 5 times that among subjects with normal blood pressure. This positive gradient in the risk of death from all vascular disease with increasing levels of blood pressure was highly statistically significant by the log-rank trend test *(X^2=89.25, 2P<0.001)*.

2). Systolic blood pressure and risk of all vascular deaths

Table 6.11 shows the number of deaths from all vascular diseases and the estimated relative risks in the five categories of baseline SBP. The relative risk of deaths from vascular disease increased progressively with increasing levels of SBP. Overall, among those individuals with baseline SBP less than 125 mm Hg (1), there were 49 deaths from all vascular diseases, and the estimated risk relative to the whole study population was 0.49. In contrast, among those individuals with the highest levels of baseline SBP (≥170 mm Hg), there were 77 deaths from any vascular disease, and the corresponding risk was 3.12. This trend of increasing risk of death from all vascular disease with increasing levels of SBP was highly significant by the log rank trend test *(X^2=138.63, 2P<0.001)*. In the adjusted Cox regression analysis, baseline SBP remained a significant predictor of total mortality from vascular disease after taking other variables into consideration *(z=10.47, 2P<0.001)*. The overall regression coefficient for SBP was 0.026, which suggests that a 10 mmHg difference in the baseline SBP would be independently associated with a 30% excess risk of total vascular disease (95% CI: 24-36%). The relationship between baseline levels of SBP and risk of total mortality from all vascular disease was separately significant in both cohort A and cohort B. In cohort A, with 133 deaths from all vascular disease during 13 years of follow-up, the regression coefficient for SBP was 0.022 *(z=6.41, 2P<0.001)*, while in cohort B, with 98 deaths due to all vascular diseases during 8 years of follow-up, it was 0.032 *(z=8.46, 2P<0.001)*.

3). Diastolic blood pressure and risk of all vascular death

In Table 6.12, the number of deaths from all vascular disease and the estimated relative risks are shown for five categories of baseline DBP. Like SBP, there was a strongly positive relationship between the baseline levels of DBP and risk of deaths from all vascular disease. Overall among those individuals who had the lowest DBP (<80 mm Hg) at baseline, there were 31 deaths from any vascular disease, and the approximate risk relative to the whole study population was 0.42, whereas for those individuals in the baseline DBP category 2 to category 5, the relative risks were 0.70, 0.98, 2.91 and 3.98 respectively *(log rank trend test: X^2=154.91, 2P<0.001).* In the Cox regression analysis, after adjusting for other baseline variables, the estimated regression coefficient for DBP on total mortality from vascular disease was 0.057, which suggested that a 7 mmHg difference in the baseline DBP would be independently associated with a 49% excess risk of death from all vascular diseases (95% CI: 39-60%). Like SBP, this strong association between baseline DBP and risk of death from all vascular disease was separately significant in both cohort A and cohort B (Table 6.12).

6.4. Relationship of baseline blood pressure with stroke death

1). Blood pressure status and risk of stroke death

Table 6.13 gives the number of deaths from stroke along with the estimated relative risks in the three blood pressure categories at baseline. There was a strong and positive relationship between blood pressure levels at baseline and risk of death from stroke. Overall in the two cohorts together, there were 102 stroke deaths among subjects with definite hypertension at baseline, compared with only 36.5 deaths that would be expected by the chance, and the approximate risk of stroke death relative to the whole study population was 2.8. In contrast among people with a normal blood pressure at baseline, 30 deaths were attributed to the stroke, and the risk was 0.36. The ratio of the risk for definite hypertension to the risk for normotension was 7.75, which suggests that the risk

of stroke death among people with definite hypertension is approximately eight times that of normotensive subjects. The individuals with borderline hypertension at baseline had an intermediate risk of 0.62. This gradient of increasing risk of death from stroke with increasing levels of blood pressure was highly statistically significant by the log-rank trend test *(X^2=134.02, 2P<0.001)*. The relation between blood pressure and risk of stroke was separately significant in both cohort A and cohort B. In cohort A, with 86 deaths from stroke during 13 years follow-up, the approximate relative risks of stroke death were 0.46, 0.54 and 2.27 respectively from normotensive group to the definite hypertension group *(log-rank trend test: X^2=51.44, 2P<0.001)*, while in cohort B, with 66 stroke deaths during 8 years of follow-up, the corresponding relative risks in the three groups were 0.26, 0.75 and 3.90 respectively *(log-rank trend test: X^2=112.10, 2P<0.001).*

In Table 6.14 the number of deaths from stroke and the estimated relative risks in the three categories of blood pressure were shown for three age groups in the combined data from the two cohorts. For subjects, whether young or old at baseline, elevated blood pressure was clearly associated with an increased risk of subsequent death from stroke. In all three age groups examined, the trends of increasing risk of stroke death with increasing levels of blood pressure were highly statistically significant by the log-rank trend test *(2P<0.001)*. There appeared to be a tendency towards slightly low relative risk of stroke in the older age group for hypertensive subjects compared with normotensive subjects. For those individuals aged 35-49 years at baseline, the risk of stroke death for definite hypertension was about 13 times that for normal subjects (Table 6.14), while among individuals aged 50-59 years and 60 years or over, the corresponding relative risks were 10 and 5 respectively in the group with definite hypertension compared with the normal group. A more direct comparison of stroke mortality among three different age groups in relation to blood pressure is further illustrated in Figure 6.5. Although the relative risks of stroke tended to decrease with age, the absolute risk of stroke death in each of the three blood

pressure categories was much higher in elderly people than in younger subjects. In the oldest age group, the difference in the mortality from stroke between those individuals with definite hypertension and those with normotensive was 16 per 1,000 person-years, compared with only 2 per 1,000 person-year in the youngest age group.

2). Systolic blood pressure and risk of stroke death

General analysis: In Table 6.15 the number of deaths from stroke and the estimated relative risks were shown in the five categories of baseline SBP along with the statistical analysis. There was a strong direct relationship between levels of SBP and risk of death from stroke. Overall in the two cohorts, stroke caused 57 deaths among 517 subjects with the highest SBP levels (≥170 mmHg) at baseline, compared with 15.9 deaths that would be expected, and the approximate risk relative to the whole study population was 3.6. In contrast among the subjects in the lowest baseline SBP category (<125 mmHg), there were 23 deaths due to stroke, and the approximate risk was 0.34. For those individuals in the SBP category 2, 3 and 4, the risks of death from stroke were 0.57, 1.01 and 2.15 respectively. This strong positive trend of increasing risk of death from stroke with increasing levels of SBP was highly statistically significant by the log-rank trend test *(X^2=150.31, 2P<0.001)*.

In the adjusted Cox regression analysis, baseline SBP remained a strong significant predictor of stroke mortality *(z=10.86, 2P<0.001)* after taking other variables into account. The estimated regression coefficient (0.032) suggested that a 10 mmHg difference in baseline SBP would be independently associated with a 38% excess risk of death from stroke (that is, odds ratio 1.38; 95% confidence interval: 1.30 to 1.46). The relation between SBP and stroke was separately significant in both cohort A and cohort B. In cohort A, with 86 stroke deaths during 13 years of follow-up, the regression coefficient for SBP was 0.027

(z=6.58, 2P<0.001), while in cohort B, with 66 deaths from stroke during 8 years of follow-up, it was 0.040 *(z=8.17, 2P<0.001)*.

Subgroup analysis: In Table 6.16 the number of deaths from stroke and the estimated relative risks in the five categories of SBP were given for three age groups. A more direct comparison of the stroke mortality among three different age groups in association with SBP was shown in Figure 6.6. The strong relationship between SBP and risk of stroke deaths was evident in all three age groups *(2P<0.001)*. The gradient of the relationship between baseline SBP and risk of stroke appeared to decrease with advancing age, but the absolute risk of fatal stroke was much higher in older people than in younger people. The estimated Cox regression coefficients (0.0404) among those individuals aged 35-49 years at baseline suggested that a 10 mmHg difference in the baseline SBP would be independently associated with a 50% (95% CI: 30-73%) excess risk of death from stroke, while for those people aged 50-59, and 60 or above at baseline, the corresponding excess risks of death from stroke for a 10 mm Hg difference in baseline SBP were 41% (95% CI: 31-53%), and 27% (95% CI: 15-40%) respectively.

Table 6.17 gives the number of deaths from stroke and the estimated relative risks in the five categories of SBP for both men and women. A further comparison of stroke mortality between males and females in relation to baseline SBP is illustrated in Figure 6.7. The strong, direct and apparently independent relationship between baseline SBP and risk of death from stroke was readily apparent in both males and females. Overall in the two cohorts combined, there were 121 deaths from stroke among the men, and the approximate risks of death from stroke from the lowest (1) SBP category (<125 mmHg) to the highest (5) SBP category (SBP≥170 mm Hg) were 0.28, 0.57, 1.09, 2.38 and 3.71 respectively (*log-rank trend test: X^2=137.48, 2P<0.001)*. Likewise among women, with 31 deaths from stroke during 8-13 years of follow-up, the relative risks from

the lowest SBP category (1) to the highest category (5) were 0.61, 0.60, 0.66, 1.51 and 3.14 respectively *(X^2=17.37, 2P<0.001)*.

In the adjusted Cox regression analysis the strong positive relation between baseline SBP and stroke mortality persisted after taking other variables into account. No apparent difference is evident between males and females regarding the strength of the relationship between baseline SBP and stroke, judged by the regression coefficients (both ß=0.0324), though the overall stroke mortality was somewhat higher among men than among women in each of the five SBP categories (Figure 6.7).

3). Diastolic blood pressure and risk of stroke death

General analysis: Table 6.18 shows the number of deaths from stroke and the estimated relative risks in the five categories of baseline DBP along with the statistical analysis. There was a strong direct association between levels of DBP and risk of fatal stroke. Overall in the two cohorts together, there were 13 deaths from stroke among subjects with the lowest baseline DBP (<80 mmHg), compared with about 50 deaths that would be expected, and the approximate risk relative to the whole study population was 0.26. In contrast, among 209 individuals who had the highest levels of baseline DBP (≥110 mmHg), 31 of whom died of stroke against about 6 expected deaths, the risk was 5.44. For those individuals in the DBP category 2, 3 and 4, the risks of stroke death were 0.63, 1.02 and 3.11 respectively. This strong positive gradient in the risks of stroke death with increasing level of DBP was highly statistically significant by the log-rank trend test *(X^2=168.87, 2P<0.001)*.

In the adjusted Cox regression analysis, the baseline DBP remained a highly significant predictor of stroke mortality after taking other variables into account *(z=12.02, 2P<0.001)*. The estimated regression coefficient (0.072) suggests that a 7 mmHg difference in baseline DBP would be independently associated with a

66% (95% CI: 52-80%) excess risk of fatal stroke. The relation between baseline DBP and stroke was separately significant in both cohort A and cohort B. In cohort A, with 86 deaths from stroke, the regression coefficient for DBP was 0.059 *(z=7.00, 2P<0.001)*, while in cohort B, with 66 fatal strokes it was 0.087 *(z=10.01, 2P<0.001)*.

Subgroup analysis: In Table 6.19 the number of deaths from stroke and the estimated relative risks in the five categories of DBP were shown for three individual age groups. A further comparison of stroke mortality among three different age groups in relation to DBP was illustrated in Figure 6.8. There was a consistent and strong relationship between baseline DBP and risk of fatal stroke in all three age groups *(2P<0.001)*. As with SBP, the strength of the relationship between DBP and stroke risk tended to decrease with increasing age, but the stroke mortality increased markedly with age (Figure 6.8). According to the estimated Cox regression coefficients, a 7 mmHg difference in the baseline DBP would be independently associated with a 72% (95% CI: 43-106%) excess risk of death from stroke for people aged 35-49 years, while for those people aged 50-59, and 60 years or over, these were 72% (95% CI: 54-91%) and 41% (95%CI: 21-64%) respectively.

In Table 6.20 the number of deaths from stroke and the approximate relative risks in the five categories of DBP were shown for both men and women in the combined data from the two cohorts. The age-adjusted stroke mortalities in males and females in relation to baseline DBP levels are further illustrated in Figure 6.9. As with SBP, the risk of fatal stroke increased progressively with increasing levels of DBP in both men and women. Among males with 121 stroke deaths during 8-13 years of follow-up, the relative risks of stroke from the lowest category of DBP (1) to the highest category (5) were 0.23, 0.57, 1.14, 3.24 and 6.10 respectively *(log-rank trend test: X^2=165.82, 2P<0.001)*, while among females with 31 stroke deaths, they were 0.47, 0.87, 0.65, 2.71 and 3.49 respectively *(X^2=18.76,*

2P<0.001). In the adjusted Cox regression analysis, the strong direct and apparently independent relation between baseline DBP and fatal stroke persisted in both men and women after taking other variables into account. Among males, the regression coefficient for DBP was 0.0774 *(z=11.05, 2P<0.001)*, while among females, it was 0.0646 *(z=4.83, 2P<0.001)*.

6.5. Relationship of baseline blood pressure with CHD death

1). Blood pressure status and risk of CHD death

Table 6.21 gives the number of deaths from CHD and the estimated relative risks in the three categories of blood pressure at baseline. There was a strong positive relationship between baseline blood pressure and risk of CHD death. Overall in the two cohorts, there were 28 deaths attributed to CHD among individuals who had definite hypertension at baseline, against 12 expected, and the approximate risk of CHD deaths relative to the whole study population was 2.3. In contrast, among those with normal blood pressure at baseline, only 11 deaths were due to CHD, and the relative risk was 0.49. The ratio of risk among subjects with definite hypertension to the risk for those with normal blood pressure was 4.7. This trend of increasing risk of death from CHD with increasing level of blood pressure was highly significant by the log-rank trend test *(X^2=23.30, 2P<0.001)*. The association of blood pressure with fatal CHD was separately significant in both cohort A and cohort B. In cohort A, with 27 deaths from CHD during 13 years of follow-up, the approximate risk of CHD deaths in the normotensive group was 0.52, compared with 1.91 for the definite hypertensive group *(X^2=10.05, 2P<0.01)*. Likewise in cohort B, with 17 deaths from CHD during 8 years of follow-up, the overall risks were 0.47, 0.32 and 3.44 respectively from normotensive to definite hypertensive *(X^2=18.20, 2P<0.001)*.

2). Systolic blood pressure and risk of CHD death

The number of deaths from CHD and the estimated relative risks in the 5 categories of baseline SBP were shown in Table 6.17, along with the statistical analysis. Overall in the two cohorts together, there were 14 deaths from CHD among those people with the highest baseline SBP (≥170 mmHg), compared with 5 expected deaths, and the approximate risk relative to the whole study population was 2.8. In contrast among subjects who had the lowest baseline SBP (<125 mmHg), there were 10 deaths attributed to CHD, and the relative risk was 0.55. This positive trend of increasing risk of CHD death with rising level of SBP was highly significant by the log-rank trend test *(X^2=20.92, 2P<0.001)*.

In the adjusted Cox regression analysis after taking other variables into account, baseline SBP remained a significant independent predictor of CHD mortality *(z=4.01, 2P<0.001)*. The estimated regression coefficient (0.023) suggested that a 10 mmHg difference in baseline SBP would be independently associated with a 26% (95% CI: 12-41%) excess risk of death from CHD. The relationship between baseline SBP and CHD was separately significant in both cohort A and cohort B. In cohort A, with 27 deaths from CHD during 13 years of follow-up, the regression coefficient for SBP was 0.018 *(z=2.31, 2P<0.05)*, while in cohort B, with 17 fatal CHD, it was 0.030 *(z=3.38, 2P<0.001)*. The Cox regression analysis was also performed separately for men and women in the combined data from the two cohorts. Among males, with 32 CHD deaths, the regression coefficient for SBP was 0.027 *(z=4.29, 2P<0.001)*, while among females, with 11 fatal CHD deaths, SBP was positively, but non-significantly related to CHD *(ß=0.006, z=0.39, 2P>0.05)*. This lack of a significant trend among women may be largely or wholly due to the play of chance, for the number of CHD death was small.

3). Diastolic blood pressure and risk of CHD death

Table 6.23 shows the number of deaths from CHD and the approximate relative risks in the five categories of baseline DBP. As with SBP, there was a strong direct relationship between risk of CHD and the levels of DBP at baseline. Overall in the two cohorts together, there were 7 deaths attributed to CHD among those subjects with the lowest baseline DBP (≤79 mmHg), compared with 13.5 deaths that would be expected by chance, and the approximate risk was 0.52. While for the subjects in the DBP category 2 to category 5, the risks of CHD were 0.63, 1.36, 2.83 and 1.58 respectively. This trend of increasing risk of CHD death with increasing levels of baseline DBP was highly statistically significant by the log-rank trend test *(X^2=16.04, 2P<0.001).* There were relatively small numbers of CHD deaths in the study population, which may well explain why there was no a smooth gradient in the risk of CHD between adjacent DBP categories.

In the adjusted Cox regression analysis, the significant relation of baseline DBP with CHD remained after taking other variables into consideration *(z=3.47, 2P<0.001)*. The estimated regression coefficient (0.041) suggested that a 7 mmHg difference in baseline DBP would be independently associated with a 33% (95% CI: 13-57%) excess risk of death from CHD. The relation between baseline DBP and fatal CHD was separately significant in both cohort A and cohort B. In cohort A, with 27 fatal CHD, the regression coefficient for DBP was 0.038 *(z=2.35, 2P<0.05)*, while in cohort B, with 17 CHD deaths, it was 0.045 *(z=2.50, 2P<0.05)*. As with SBP, the association of DBP with CHD was highly significant among men *(ß=0.051, z=3.75, 2P<0.001)*, but not among women, of whom only 11 deaths were due to CHD *(ß=0.008, z=0.29, 2P>0.05)*.

6.6. Relation of baseline blood pressure with other causes of death

In the whole study population, there were 35 deaths attributed to vascular disease other than stroke or CHD, and these were found not to be significantly associated with baseline blood pressure (either SBP or DBP), even in the

adjusted Cox regression analysis after taking other variables into account (Table 6.24 to 6.26).

Overall in the present study population, 389 deaths (63%) were attributed to non-vascular disease, including 274 from cancer and 115 from all other non-vascular non-cancer diseases. No association was apparent between blood pressure (either SBP or DBP) and such deaths, even after taking other variables into account in the adjusted Cox regression analyses (Table 6.27 to 6.30).

6.7. Estimation of the relationship between **usual** blood pressure and vascular disease

As discussed previously, the means of the baseline blood pressure in each category are, due to the "regression dilution" bias, seriously biased estimates of the mean usual blood pressure in each category. The means of the re-measured blood pressure values made a few years after baseline examination in a proportion of subject provides estimates that are substantially less subject to such bias *(MacMahon, et al 1990)*. In both cohort A and cohort B, the remeasurements of blood pressure made a few years after the baseline examination are available in a sample of the study population. In Table 6.31, the data are shown for individuals divided into five categories on the basis of their baseline SBP values alone (i.e. irrespective of the values of any subsequent remeasurements of blood pressure). For individuals in each category of baseline SBP, average values are given for the original baseline measurement and for the blood pressure remeasurement 3 years after baseline. The difference in mean SBP between the lowest and the highest baseline SBP categories was on average about 70 mmHg at baseline in both cohorts, while at 3 years post-baseline it was about 44 mmHg. With respect to DBP (Table 6.32), the average difference in mean DBP between the lowest and highest categories at baseline was about 44 mmHg, while at three years post-baseline it was about 26 mmHg. These data indicate that the difference in the range of mean SBP and DBP values is at least 60% greater for

baseline blood pressure than for blood pressure remeasured a few years later. So, when the relative risks of disease rates are plotted against the estimates of mean **usual** blood pressure (estimated from the mean values of the re-measured blood pressure 3 years after baseline) in each of the five categories of blood pressure, the slope will be at least 60% steeper than when the relative risks are plotted against the mean **baseline** blood pressure values.

In Figure 6.10, the overall relative risks of stroke estimated from the combined data from the two cohorts were plotted against mean **usual** systolic blood pressure and mean diastolic blood pressure values in each of the five baseline categories. The estimates of the usual systolic and diastolic blood pressure in each baseline category are taken from the mean blood pressure values at 3 years post-baseline in the two cohorts (Tables 6.31 & 6.32). The solid squares represent the disease risk in each category relative to risk in the whole study population, while the vertical lines represent one standard deviation on either side of these estimates. The corresponding figures for CHD deaths and for all vascular deaths are Figures 6.11 and 6.12 respectively. Blood pressure remeasurements in both cohorts suggest that the differences in usual blood pressure between the five blood pressure categories may be approximately equal. In plotting Figures 6.10 to 6.12 therefore, the five blood pressure categories have been spaced equally. If this is approximately appropriate, then the slope of the association between the relative risk of disease (plotted on a log scale) and the mean usual blood pressure would appear to be roughly constant, implying an approximately "log-linear" relationship (that is, one in which the percent difference in risk associated with a given difference in usual blood pressure is similar at all levels of blood pressure). In general, within the range of blood pressure studied in the present population (about 117-161 mmHg for SBP and 75-101 mmHg for DBP), there was no good evidence of a "threshold" level of SBP or DBP below which a lower level of blood pressure is no longer associated with a lower risk of stroke, CHD or of all vascular deaths. Nor was there any good

evidence of a threshold level above which the relative risk of vascular disease increased much more rapidly (although in contrast to stroke deaths and all vascular deaths, the relatively small number of CHD deaths could not be expected to result in a smooth slope).

Combination of the results in Tables 6.31 & 6.32 with the previous Cox regression analysis of baseline blood pressure with vascular deaths suggested that a 10 mmHg difference in **usual** SBP (where 10 mmHg is approximately equal to the average difference in usual SBP between two successive categories in the Figures) might be associated with a 67% (95% confidence interval: 52%-83%) difference in the risk of stroke death, with a 44% (95% confidence interval: 21%-73%) difference in CHD deaths and a 52% (95% CI: 40-64%) difference in all vascular deaths. With respect to DBP, it may be estimated that a 7 mmHg difference in **usual** DBP (where 7 mmHg is approximately equal to the average difference in usual DBP between two successive categories) might be associated with a 124% (95% confidence interval: 96%-155%) difference in the risk of stroke death, with a 58% (95% confidence interval: 22%-105%) difference in CHD deaths and a 89% (95% CI: 70-111%) difference in all vascular deaths.

6.8. The relative impacts of SBP and of DBP on vascular disease

The relative importance of systolic and diastolic blood pressure in predicting the risk of deaths from vascular disease was evaluated in the present data. Since diastolic blood pressure has a much narrower range of values than systolic blood pressure, standardised methods are needed to control for this difference. One attempt at adjustment has been to compare standardised regression coefficients, calculated by multiplying the conventional regression coefficients by the standard deviations of the systolic and diastolic blood pressure measurements. Standardised relative risks were then estimated by calculation of the exponents of the standardised regression coefficients, which indicated the relative change in risk associated with a change of one standard deviation in blood pressure. In

Table 6.33 the regression coefficients and standardised relative risks with their 95% confidence intervals are shown for stroke, CHD and all vascular disease.

After adjustment for sex, age, serum cholesterol, cigarette smoking and alcohol drinking in the Cox regression model, diastolic blood pressure appeared to be the stronger predictor of stroke mortality. The standardised relative risk of stroke was 2.38 for DBP and 2.04 for SBP when each was analysed alone. After adjustment for each other the relative risk associated with DBP was 1.87 (95% CI: 1.51-2.31), while for SBP it was 1.36 (95% CI: 1.11-1.67). With respect to coronary heart disease, systolic blood pressure appeared to be a slightly better predictor of CHD mortality than DBP. The standardised relative risks of CHD were 1.67 for SBP and 1.64 for DBP when each was evaluated alone. When each was adjusted for the other, the addition of systolic pressure after diastolic pressure significantly improved the regression estimate of risk of CHD, but the addition of diastolic pressure after systolic pressure did not. The relative risk associated with systolic blood pressure after adjustment for diastolic blood pressure was 1.49 (95% CI: 1.05-2.12), while for DBP after adjustment for SBP it was 1.20 (95% CI: 0.82-1.77). Over 60 per cent of the vascular deaths were due to stroke in this population, and DBP was shown to be more closely related to the risk of all vascular mortality than SBP. The relative risks associated with a one standard deviation difference were 1.78 for SBP and 1.98 for DBP, and after adjusting for each other these were 1.31 (95% CI: 1.11-1.54) and 1.60 (95% CI: 1.34 -1.91) respectively.

6.9. Isolated systolic hypertension and vascular disease

In individuals, elevations in systolic and diastolic pressure are usually strongly correlated. However, the phenomenon of isolated systolic hypertension (i.e., elevations of systolic blood pressure without elevated diastolic blood pressure) has long been recognized clinically. The standard definition of isolated systolic hypertension is diastolic blood pressure less than 90 mmHg with systolic blood

pressure of 160 mmHg or above. When this is applied to the present population, 1.4% of the subjects had isolated systolic hypertension (Table 6.5). For the evaluation of the relation of isolated systolic hypertension with vascular disease, individuals were divided into three groups based on the systolic blood pressure level (normotensive: ≤139 mmHg, borderline: 140-159 mmHg, definite isolated hypertension: ≥160 mmHg). Subjects with a diastolic blood pressure equal to or above 90 mmHg were not considered, leaving 7435 individuals for the analyses. Table 6.34 gives the number of deaths from stroke, CHD and all vascular disease, along with estimated relative risks in the three categories of isolated systolic hypertension. Overall among these subjects, there were 48 stroke deaths, and these were shown to be significantly related to the level of systolic blood pressure. Among individuals with definite isolated systolic hypertension, there were 9 strokes, and the approximate relative risk was 2.89. By contrast, for those individuals who were normotensive at baseline, the risk of stroke death was 0.81. This trend of increasing risk of stroke death with levels of isolated systolic pressure was statistically significant by the log-rank trend test *(X^2=12.36, 2P<0.001)*. In the adjusted Cox regression analysis, isolated systolic hypertension remained a significant predictor of stroke mortality after taking other variables into account *(ß=0.0266, z=3.61, 2P<0.001)*. There were 17 CHD deaths among these subjects, and the approximate relative risk of CHD was 2.90 for individuals with definite isolated systolic hypertension, compared with 0.89 for normotensive subjects. This trend was not statistically significant, however, perhaps due to the small number of deaths involved *(X^2=2.80, 2P>0.05)*. There were 90 deaths from any vascular disease included in the analysis, and these were shown to be strongly and positively associated with isolated systolic hypertension. The relative risks of all vascular death for those individuals who were normotensive, borderline and definite systolic hypertensive were 0.83, 1.24 and 2.47 respectively *(X^2=15.77, 2P<0.001)*. In the adjusted Cox regression analysis, the significant association of isolated systolic blood pressure with the

risk of deaths from all vascular disease persisted after taking other variables into account *(z=2.87, 2P<0.01).*

6.10. Discussion

1). Continuous positive relation between blood pressure and vascular disease

The incidence of CHD deaths is, at present, substantially lower in Chinese than in Western populations, while the mortality from stroke in China is similar to that in Japan and higher than in Western countries *(Tao, et al 1989).* A number of prospective observational studies in Western populations have demonstrated consistently that blood pressure (both systolic and diastolic blood pressure) is positively, and apparently independently, associated with the primary incidence of stroke and of CHD, particularly among those individuals who had high blood pressure at the start of the study *(Reid, et al 1976; Yano, et al 1983; Stamler, et al 1989).* There is, however, much less direct evidence about the relationship of blood pressure with vascular disease in Chinese populations. In particular, little is known about the association at lower levels of blood pressure, and about the size of the effects of prolonged differences in blood pressure on disease rates.

The present prospective study demonstrated a strong and significant correlation between blood pressure and vascular disease death rates in the Chinese population studied. The risk of death from stroke was more strongly related to blood pressure (both SBP and DBP) than CHD, as in many studies in Western populations. Those individuals with definite hypertension at baseline had risks of fatal stroke and of fatal CHD almost 8 times and 5 times, respectively higher than normotensive subjects. People with borderline hypertension also had significantly higher risks of stroke and of CHD than normotensive subjects. The present study also showed that the relationships of blood pressure (both SBP and DBP) with stroke and CHD are continuous and graded over a wide range of blood pressure, with no apparent threshold below which lower levels of blood

pressure were no longer associated with lower risks of disease. These results are in agreement with findings from many larger prospective studies conducted mainly in Western populations *(Reid, et al 1976; Yano, et al 1983; Stamler, et al 1989)*.

A few observational studies have failed to show a continuous and graded relationship between blood pressure (especially DBP) and risk of cardiovascular disease. These has been interpreted as evidence of a J-shaped relationship, with an increase in the risk of cardiovascular events at DBP levels below 85-90 mmHg. In a re-analysis of data from the Framingham study there was a continuous positive correlation between SBP and total cardiovascular events, but for DBP below 85-98 mmHg the incidence of total cardiovascular events did not decrease with pressure but if anything, tended to increase *(Anderson 1978)*. The relationship between DBP and risk of cardiovascular events appeared to be a J-shape curve with the lowest risk (or "J-point") at about 90 mmHg DBP. A similar pattern was also described in the data from the Pooling Project Group *(The Pooling Project Research Group 1978)*, which showed an even more pronounced J-shape relation of CHD with DBP. In the Seven Countries Study *(Keys 1980)*, examination of the data without assumptions about the shape of the relationship raised a similar question about linearity. In that study, taking either CHD mortality or the incidence of fatal or non-fatal CHD as end points, no significant relationship of CHD risk with blood pressure at entry was found over roughly the lower two-thirds of the distribution of the blood pressure in any of the regions. In the upper third of the blood pressure distribution the risk of CHD tended to rise sharply. A few clinical studies of hypertension treatment have also found a continuous association between treated blood pressure level and stroke, but a J-shaped relationship between treated diastolic blood pressure levels and cardiac events *(Cruickshank, et al 1987; Berglund & Samuelsson 1987; Farnett, et al 1991)*. These results have often been cited as evidence that there may be a threshold level of blood pressure, particularly for DBP at about 85-90 mmHg,

below which lower levels are not associated with lower risks of vascular disease, and that lowering blood pressure below this critical point is no longer beneficial and possibly even deleterious *(Anderson 1978; Cruickshank, et al 1987; Berglund & Samuelsson 1987)*. Several methodological considerations can help reconcile these apparent discrepancies, for most of these studies were small and some were not restricted to primary disease.

First, previous vascular disease might itself reduce blood pressure or might result in increasing use of antihypertensive treatment. Hence, even if there is a positive causal relation between blood pressure and disease (both primary and secondary), an artifactual negative association between DBP and the secondary incidence of disease might still be observed, especially at the lower end of the blood pressure range. In a large Finnish study of general population *(Aromaa A 1981),* the overall association of blood pressure with the risk of vascular mortality was shown to be J-shaped, with increased mortality at very low blood pressure and especially at low DBP levels. More detailed analysis of the data indicated, however, that increased mortality at low blood pressure levels was due chiefly to the presence of cardiac and other disease which might lower blood pressure or be subject to antihypertensive treatment. Likewise, in the MRFIT study among 5440 screenees found at baseline to have a history of myocardial infarction, there was a negative association with CHD at lower levels of DBP, whereas the association between DBP and the primary incidence of CHD in MRFIT was continuous and positive throughout the range of DBP studied *(Stamler, et al 1989)*.

The second point that needs to be considered in determining whether the association between blood pressure and the primary incidence of vascular disease is direct throughout the range of blood pressure values commonly seen in Western populations, with no evidence of any threshold, may be largely statistical. This arises because the relationship between blood pressure and

disease in particular studies may be subject to appreciable random fluctuations, especially in the "normotensive" range where the primary disease rate is small. These random fluctuations mean that different studies may give apparently different results, or even that the use of different cutoff points to subdivide study population may produce some artifactual difference regarding the shape of the relation at the lower end of blood pressure distribution, so selective emphasis on some studies and not others could introduce substantial biases.

The recent overview *(MacMahon, et al 1990)* involving 420,000 individuals from 9 major prospective observational studies of the primary incidence of vascular disease among middle-aged individuals provided reliable evidence about the association between DBP and primary incidence of stroke and of CHD. The combined results demonstrated positive, continuous and apparently independent associations between DBP and the risk of stroke and of CHD. Throughout the range of usual DBP in the populations studied (about 70-110 mmHg), there did not appear to be any threshold below which a lower level of DBP was not associated with a lower risk of stroke or CHD. The usual DBP was strongly and positively related to risk not only among those individuals who might be considered "hypertensive", but also among those who would usually be considered "normotensive". Likewise in the present study of a Chinese population, there was a strong direct and continuous relationship between blood pressure (both SBP and DBP) and risk of stroke and of CHD, with no apparent threshold within the range of usual blood pressure studied (SBP:117-161; DBP: 75-101 mmHg) below which a lower levels of blood pressure was no longer associated with a lower risk of disease. These results suggest that for the large majority of individuals, whether conventionally "hypertensive" or "normotensive", a lower blood pressure should eventually confer a lower risk of vascular disease.

*2). Strength of relationship between **usual** blood pressure and vascular disease*

As estimates of usual blood pressure the baseline blood pressure measured on a single occasion at entry to the study have limited accuracy as a result of measurement error and temporal fluctuations at baseline from individual's long-term usual blood pressure *(Peto 1976; Gardener & Heady 1973)*. Most prospective observational studies have, however, reported only the association between disease incidence and blood pressure measured just at baseline. But, because of the "regression dilution bias" resulting from such random errors *(MacMahon, et al 1990)*, uncorrected use of just the baseline blood pressure can result in systematic and substantial underestimation of the strength of the real association of disease with usual blood pressure. By combining data on the association between usual blood pressure and baseline blood pressure with data on the association between baseline blood pressure and the risks of vascular disease, it is, however, possible to correct the "regression dilution bias", and thus to estimate the real association between usual blood pressure and the subsequent risk of vascular disease *(MacMahon, et al 1990)*.

In the present study, the repeated measurements of blood pressure in a sample of population indicated that the difference in the mean blood pressure (both SBP and DBP) between successive categories was at least 60% greater at baseline than at 3 years after baseline. Hence, when the relative risks of vascular disease are plotted against the estimates of mean usual blood pressure in each of the five categories, the slope of the BP/disease associations are 60% steeper than when the relative risks are plotted against the mean baseline blood pressure in each category. Other studies in Western populations indicated a similar increase in the relationship between usual diastolic blood pressure and disease rates as compared with those between baseline DBP and vascular disease *(MacMahon, et al 1990)*, although no data were reported for SBP. In the Finnish study *(Aromaa 1981)* when the subjects were divided into 5 categories

according to baseline DBP, with the same cutoff points as those chosen in the present study, the difference in mean DBP between the top category (DBP≥110 mmHg at baseline) and the bottom category (DBP≤79 mmHg) was 45.9 mmHg at baseline examination, while at the subsequent re-measurement in the same subjects 5 years later, it was only 22.8 mmHg. In the Puerto Rico Study *(Garcia-Palmieri & Costas 1986)*, there was a similar contraction of the difference in the mean DBP. At baseline examination, the range of mean DBP between top and bottom categories was 46.1 mmHg, while at a repeated measurement 4 years later it was 28.8 mmHg. In the Framingham study *(Dawber 1980)*, the blood pressure measurements were repeated every two years after the baseline measurement, and the available data indicated that the difference in mean DBP between highest and lowest baseline DBP categories was 45.7 mmHg at baseline, whereas at 2 years and 4 years post-baseline these were 31.6 mmHg and 28.5 mmHg respectively. Similarly, in the present study of a Chinese population, the difference in mean DBP between highest and lowest baseline DBP categories was 44 mmHg at baseline, while at the repeated measurement three years after baseline examination it was about 26 mmHg. The present study also suggested a similar percentage contraction of the difference in the mean levels of SBP between baseline and repeated measurement. It would appear, therefore, that blood pressure (both SBP and DBP) is at least 60% more important as a risk factor for vascular disease than has been generally appreciated both in Western and in Chinese populations.

The strength of the relationship between prolonged differences in usual systolic and diastolic blood pressure and the risk of vascular disease may be estimated, with an adjustment factor of 1.6 (i.e. a 60% increase in steepness) for the Cox regression coefficients. The present study showed that prolonged differences in usual SBP of 10 mmHg would be associated with a 67% excess of stroke, a 44% excess of CHD and a 52% excess of total vascular disease. With respect to DBP, it was estimated that a 7 mmHg difference in usual DBP would be

associated with a 124% excess of stroke, a 58% excess of CHD and a 89% excess of all vascular disease death. It is noteworthy that the size of the percentage differences of disease rates (in particularly for stroke) associated with a given difference in diastolic blood pressure was substantially greater in the present Chinese population (124%±7) than that estimated in the Western populations (46%±2) *(MacMahon, et al 1990).* It is not clear if this apparent discrepancy in the strength of the relationship of blood pressure with stroke risk is due chiefly to the play of chance, or reflects the difference in the pathological types of stroke between Chinese and Western people. In the MRFIT study *(Neaton, et al 1984),* it was found that stroke mortality was more strongly associated with DBP among black men than among white men. In that study, a 10 mmHg difference in baseline DBP was estimated to be associated with a 86% difference in the stroke mortality among black men, while among white men it was only 45%. It was speculated that high proportion of hemorrhagic strokes observed among blacks might be a important factor contributing to this apparent difference.

The present results involve the primary incidence of disease, and so they are not significantly biased by any hypotensive effect of prior cardiac conditions. The observed associations between blood pressure and the subsequent incidence of disease rate appear too strong and independent to be accounted for entirely by other confounding factors. In view of the biological plausibility of a causal relationship *(Russell 1975),* these strong epidemiologic associations can, therefore, probably be accepted as largely causal. While non-randomised observational prospective studies may, despite the possibility of confounding by other risk factors, be more relevant to evaluate the eventual effects of prolonged differences in blood pressure, randomised trials may be more relevant to assessing how rapidly, and to what extent, the epidemiologically expected reductions in disease rates are produced by lowering blood pressure in middle age for only a few years. Evidence from randomised controlled trials have

indicated that for stroke virtually all the epidemiologically expected reduction produced by antihypertensive treatment appears rapidly within just a few years of blood pressure reduction, whereas for CHD, just over half the epidemiologically expected reduction appears rapidly. The recent overview of 14 unconfounded randomised trials of antihypertensive drugs, involving a total 37,000 individuals, provided direct and highly significant evidence that both fatal and non-fatal strokes are prevented within just a few years of blood pressure lowering, even if DBP is below 110 mmHg at the start of treatment *(Collins, et al 1990).* The reduction in the odds of stroke associated with a reduction in DBP of 5-6 mmHg for just 2-3 years was 42% (95% CI: 33-50%), which is similar in size to the difference of 35-40% that would be expected in the observational studies *(MacMahon, et al 1990).* The significant reduction in CHD seen in the trials (14%, 95% CI: 4-22%; 2P<0.01) falls somewhat short of the difference of about 20-25% suggested by the observational epidemiological evidence for a prolonged 5-6 mmHg difference in usual DBP. This apparent shortfall of CHD reduction may be due chiefly to the play of chance (since the observed reduction is not significantly different from a 20% reduction), or due to the involvement of some chronic processes (such as changes in atherosclerosis that may be accelerated by raised blood pressure) which may mediate the effects of blood pressure. The updated results from that overview, with inclusion of the data from three recent trials (SHEP, STOP and MRC Elderly), have provided more convincing evidence about the benifit of blood pressure reduction on CHD, although it is still somewhat short of that suggested by the epidemiological evidence *(Collins, personal communication).* The significant reduction in CHD associated with a reduction of DBP seen in the updated overview of 17 randomised trials is 16% (95% CI: 8-25%, 2P=0.0001). There is still a need for future trials to elucidate the controversy about the so-called "J-curve" phenomenon between treated DBP levels and cardiac events in certain high risk patients, such as those with preexisting

ischemic diseases and/or left-ventricular hypertrophy *(Cruickshank, et al 1987; Berglund & Samuelsson 1987; Farnett, et al 1991).*

3). The relative impact of systolic vs diastolic pressure on vascular disease

It has long been held that DBP is more important than SBP as a risk factor for cardiovascular disease. Textbooks and committee recommendations have tended to only briefly mention systolic blood pressure levels while focusing on the diastolic level as the primary index for making diagnostic and treatment decisions. But, while diastolic and systolic blood pressures are both predictors of death from vascular disease, epidemiologic studies have consistently suggested that in middle-aged men systolic pressure is slightly better. In the Framingham study *(Kannel, et al 1974)* with 16-year follow-up for subjects 45-74 years old, the level of SBP rather than DBP appeared to have a greater impact on the risk of CHD, cerebrovascular disease, intermittent claudication, and congestive heart failure as well as on overall mortality. The results showed that the mean differences in standard normal deviates for deaths from CHD were 0.41 for systolic pressure and 0.28 for diastolic pressure. The Western Collaborative Group study *(Rosenman, et al 1976)*, a prospective epidemiologic study of 3154 middle-aged men, showed that in subjects aged under 50 years SBP was a stronger predictor of CHD risk than DBP, while in the older age group of 50-59 years SBP and DBP were similarly predictive. *Miall et al (1982)* concluded after studying 2680 people for 17 years that, in the elderly, elevated SBP was a more important risk factor of cardiovascular mortality than DBP. In the Whitehall study *(Lichtenstein, et al 1985)*,18,403 British male civil servants aged 40-64 years were followed for 10 years. After adjusting for age, body mass index, cigarette smoking, angina pectoris and ischemic electrocardiographic findings, systolic pressure was a slightly better indicator of risk of CHD than diastolic pressure when each was considered alone. After adjusting for the other, the risk associated with systolic pressure was significantly greater than that associated

with DBP. The findings from the Honolulu Heart Program in 7610 Japanese men on Oahu *(Yano, et al 1983)* add further support to the hypothesis that CHD is more strongly related to SBP than to DBP. But, data combined from Oslo, Tromsø, and the Norweigian counties studies *(Tverdal 1987)*, showed, essentially, the opposite effect. A total of 39,207 men aged 35-49 years were followed for an average of 8.9 years, and the standardised relative risks of CHD mortality were greater for DBP than for SBP. The effects were most marked in the low age group (35-39 years), but at age 45-49 years the CHD mortality was similar in the upper quartiles of both SBP and DBP.

It has been proposed *(Lichtenstein, et al 1985)* that three factors may contribute to the observation that systolic pressure is slightly superior to diastolic pressure as a predictor of deaths from coronary heart disease. Firstly, the large range between subjects for systolic pressure may more readily identify those at risk for CHD. Secondly, as systolic levels depend partly on arterial compliance, they may provide a better reflection of the degree of underlying arterial disease. Thirdly, arterial injury may be related more to peak than to mean pressure. In the present study there were only 43 deaths from CHD, and both SBP and DBP were shown to be significant predictors of CHD when each was considered alone. When adjusted for each other, the risk associated with systolic blood pressure was significantly greater than that associated with diastolic pressure. The standardised relative risks of SBP and of DBP, after adjusting for each other, were 1.49 and 1.20 respectively. The addition of SBP after diastolic pressure significantly improved the regression estimates of CHD risk, but addition of DBP after systolic pressure did not. These results are in general agreement with findings in most other observational studies in Western populations, although the implications of this finding for the diagnosis and treatment of hypertension remain to be elucidated.

With respect to stroke, it has been suggested that the relative importance of SBP and DBP in predicting stroke risk may vary with different types of stroke *(Yano, et al 1983)*. For cerebral hemorrhage, a disease often caused by the rupture of an aneurysm of a cerebral arteriole, onset is considered to be "triggered" by a sharp elevation of blood pressure. In contrast for cerebral infarction, which is thought to develop as the result of aggravation of arteriosclerosis by high blood pressure, persistent high blood pressure is believed to be more important than a sharp increase in blood pressure *(Shimizu, et al 1984)*. It has been reported *(Yamori, et al 1975)* that in stroke-prone spontaneous hypertensive rats (SHR) cerebral hemorrhage is frequent among cases with high blood pressure of greater severity and shorter duration, whereas cerebral infarction is more frequent among cases with high blood pressure of lesser severity but slightly longer duration *(Okamoto et al 1974)*.

Epidemiological observational studies suggest that DBP is a more important risk factor than SBP in cerebral hemorrhage, while the reverse is true with respect to cerebral infarction. In the Japanese Radiation Effect Research Foundation study *(Shimizu, et al 1984)*, 20,000 Japanese have participated in biennial clinical examination since 1958. This study indicated that cerebral hemorrhage risk could be explained by diastolic blood pressure only, and systolic blood pressure did not add significantly to risk factors in the presence of diastolic pressure. On the other hand, for cerebral infarction, systolic blood pressure was a slightly more important predictor, though both SBP and DBP contributed almost equally. The Honolulu Heart Program *(Yano, et al 1983)*, using a multiple logistic regression model, showed that both SBP and DBP were important independent predictors of CHD and stroke mortality, but SBP appeared to be a stronger predictor of mortality from CHD than did DBP, whereas the opposite was true for total stroke mortality. No separate results were available for different types of stroke in relation to blood pressure, but stroke mortality cases in

that cohort consisted predominantly of hemorrhagic strokes (60%) rather than thrombo-embolic strokes (23%). In the Framingham study *(Kannel, et al 1974, 1976)*, with 14 years of follow-up, over 60% of all strokes were attributed to atherothrombotic brain infarctions, and the total stroke mortality was more strongly associated with SBP than with DBP. In a case-control study *(Abu-zeid, et al 1977)*, SBP measured prior to stroke was shown to be significantly higher among cases with cerebral infarction than among controls, but there was no significant difference in DBP between the two groups. The opposite was true among cases of cerebral hemorrhage.

In the present study of a Chinese population, the standardized relative risks of stroke for baseline SBP and DBP after adjusting for each other were 1.36 and 1.87 respectively. This suggests that DBP was more closely related to total stroke mortality than was SBP, although both were independent risk factors for stroke mortality. The aetiologies of stroke are not reliably known for subjects in this study, but other studies in Chinese populations have demonstrated that more than half of all fatal strokes are due to hemorrhagic stroke *(Wang, et al 1983; Li, et al 1985; Hu, et al 1986; Chen,et al 1987)*. It is perhaps more noteworthy, in terms of public health and clinical management of hypertension, that the relative importance of blood pressure, whether systolic or diastolic pressure, appears to be greater for stroke mortality than for CHD mortality. The absolute importance of blood pressure on stroke was even greater because in China strokes are so much more common than CHD.

4). Isolated systolic hypertension and its effect on vascular mortality

Epidemiological evidence indicates that SBP is at least as closely correlated to cardiovascular morbidity and mortality as is DBP. While in an individual, elevations in systolic and diastolic pressure are usually strongly correlated, isolated systolic hypertension is regarded as a distinct syndrome which is present when an individual's SBP is elevated in the presence of low or normal DBP. The

phenomenon is shown to be more common in women than in men, and the prevalence increases with age in both sexes, but is relatively uncommon until after 60 years. Although the definition of isolated systolic hypertension has not been well standardized, several studies have reported the prevalence of the condition. In the Hypertension Detection and Follow-up Program (HDFP), with a total of 158,906 individuals screened, isolated systolic hypertension, (using the definition of SBP≥160 and DBP<90 mmHg) was present in less than 1% of individuals aged less than 50 years, whereas it was present in 2.3% and 6.8% respectively of people aged 50-59 and 60-69 years *(Curb, et al 1985).* In the Systolic Hypertension in the Elderly Program (SHEP) study, isolated systolic hypertension ranged from 6% of individuals aged between 60 and 69 years to 18% of those aged 80 years or older *(Borhani, et al 1991).* The prevalence of isolated systolic hypertension in the present Chinese population was similar to that reported in Western populations, ranging from 0.3% for people aged under 50 years to 7% of individuals aged between 60-64 years.

Isolated systolic hypertension is an independent risk factor for the development of cerebrovascular and cardiovascular disease. In the present study, there was nearly a four-fold increase in the risk of stroke among those people with definite isolated systolic hypertension as compared with normotensive subjects (i.e. SBP<140 mmHg). The adjusted relative risk of CHD was also more than 3 times greater among subjects with definite isolated systolic hypertension than among those with normotensive. The overall trend was not statistically significant, however, perhaps because of the small numbers of CHD deaths involved in the analysis. Other prospective studies conducted in Western populations have shown that people with isolated systolic hypertension have relative risks of mortality from vascular diseases similar in direction and magnitude to those demonstrated in the present study *(Kannel, et al 1980; Garland, et al 1983; Curb, et al 1985).* In a community-based population study involving 2,636 individuals aged 60 years and older with 6 years of follow-up

(Garland, et al 1983), subjects with isolated systolic hypertension had an adjusted relative risk of 1.5 for all-cause mortality and 4.0 for stroke death. In the Framingham study *(Kannel, et al 1980)*, isolated systolic hypertension (defined as systolic pressure exceeding 160 mmHg and diastolic pressure below 95 mmHg) was associated with a substantial (two- to fivefold) excess risk of death from all causes and from cardiovascular disease. There was a pronounced excess risk of cardiovascular disease associated with isolated systolic hypertension, even after excluded those individuals who had a diastolic pressure higher than 95 mmHg at any of the biennial examinations throughout the follow-up period.

Isolated systolic hypertension is believed to result from the pathphysiology of ageing, involving mainly decreases in arterial compliance as a result of arteriosclerosis but not necessarily atherosclerosis. The increased peripheral vascular resistance, and diminished $ß_2$ receptor sensitivity resulting from arteriosclerosis is thought to lead to decreased smooth muscle relaxation. As a result the large arteries become less able to absorb pressure during systole and recoil during diastole, although systolic hypertension per se is also linked to increased cardiovascular risk whether the vessel is rigid of not *(Van, et al 1981; Staessen, et al 1990; Kannel, et al 1980)*. Because of the presumed irreversible "stiffening" of blood vessels seen with advancing age, it had been thought that systolic hypertension would be relatively unresponsive to treatment. Moreover, there was a widespread perception that elderly patients, among whom isolated systolic hypertension is most prevalent, were more prone to adverse effects from antihypertensive treatment than were younger patients. The hypothesis that medical treatment of isolated systolic hypertension might reduce morbidity and mortality in elderly patients has recently been investigated in a number of trials. The available evidence indicates that most of those concerns regarding the treatment of isolated systolic hypertension are unsubstantiated at least in the selected healthy elderly subjects that have participated in the studies. Elderly

individuals were found to tolerate antihypertensive medication as well as younger people in the HDFP study *(Curb, et al 1985)*. Moreover, the recent report from the Systolic Hypertension in the Elderly Program *(SHEP Cooperative Research Group 1991)* has demonstrated clearly the benefit of treatment of isolated systolic hypertension in the elderly. In that study, involving 4,736 persons aged 60 years and above with 5 years of follow-up, systolic blood pressure was on average 12 mmHg lower in the treatment group than that in the placebo group. The reduction of systolic blood pressure was shown to be associated with a significant 36% reduction in the incidence of total stroke, and with an absolute benefit over 5 years follow-up of 30 events per 1,000 participants. Major cardiovascular events were also significantly reduced, with a 5-year absolute benefit of 55 events per 1,000. The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) has also shown that the benefits of antihypertensive treatment are at least as striking in elderly patients as in young and middle-aged hypertensive patients *(Dahlof, et al 1991)*. In that study, involving 1627 patients aged 70-84 years with an average of two years treatment, mean blood pressure in the active treatment group was significantly reduced by 20 mm Hg for SBP and by 8 mm Hg for DBP compared with placebo group. The reduction of blood pressure in active treated group was associated with a 40% reduction in the primary endpoints from cardiovascular disease. These findings indicate a considerable potential for decreasing the incidence of, and disability from, major vascular disease by effective sustained drug treatment of hypertension (including isolated systolic hypertension). These results also have significant implications for the drug treatment of other primary hypertension in the elderly, given both the high prevalence of hypertension and the high rate of vascular disease in the elderly.

6.11. Conclusions

1). All cause mortality, in particular stroke and CHD mortality, increased with rising blood pressure, in males and females and in different age groups.

2). There was no evidence of threshold below which a lower level of blood pressure was no longer associated with lower risks of stroke or of CHD within the range of blood pressure studied (SBP: 117-161 mmHg, DBP: 75-101 mmHg).

3). Approximate correction for the "regression dilution" bias indicated that the relationship between usual blood pressure and disease rates are at least 60% more important than was previously thought.

4). Stroke mortality is more strongly associated with blood pressure than CHD.

5). SBP is likely to be an equally strong or indeed a slightly stronger predictor of CHD risk than DBP, while the reverse is true for stroke.

6). Isolated systolic hypertension is associated with more than a three-fold excess risk of death from vascular disease.

Figures and tables

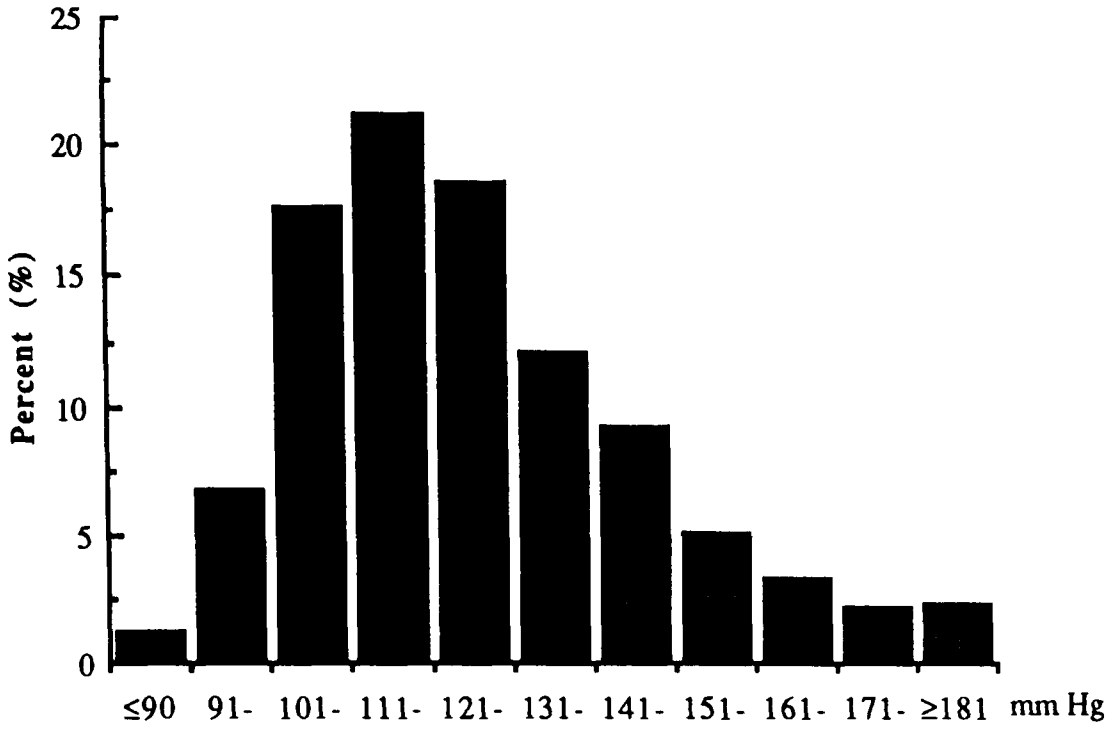


Figure 6.1. Distribution of systolic blood pressure in cohort A.

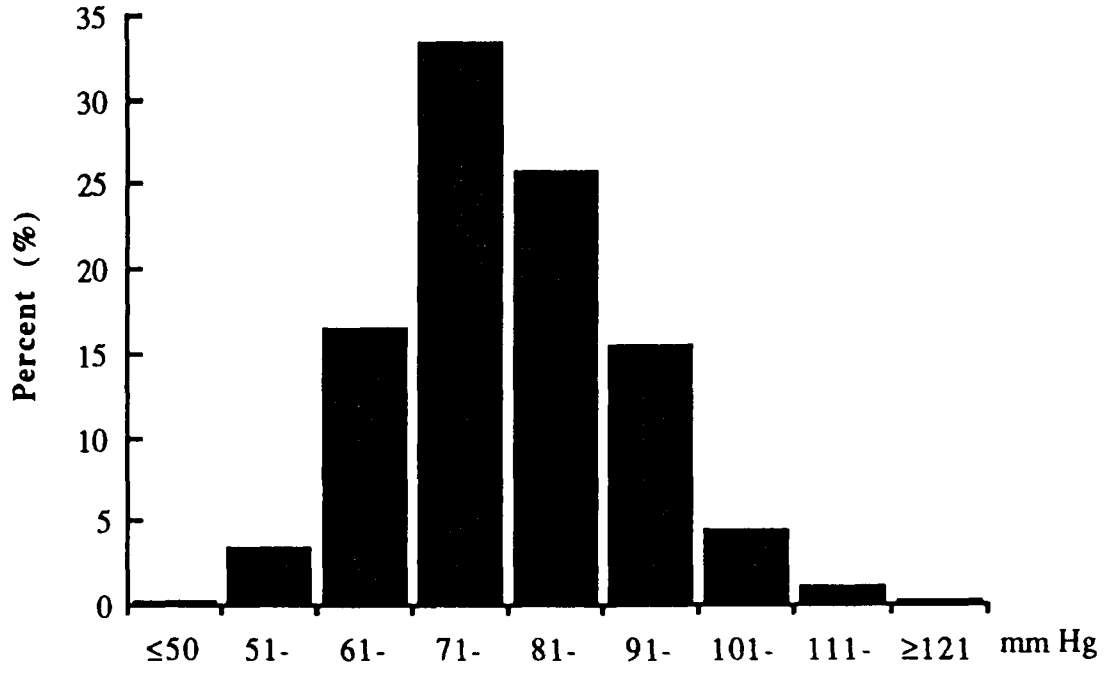


Figure 6.2. Distribution of diastolic blood pressure in cohort A.

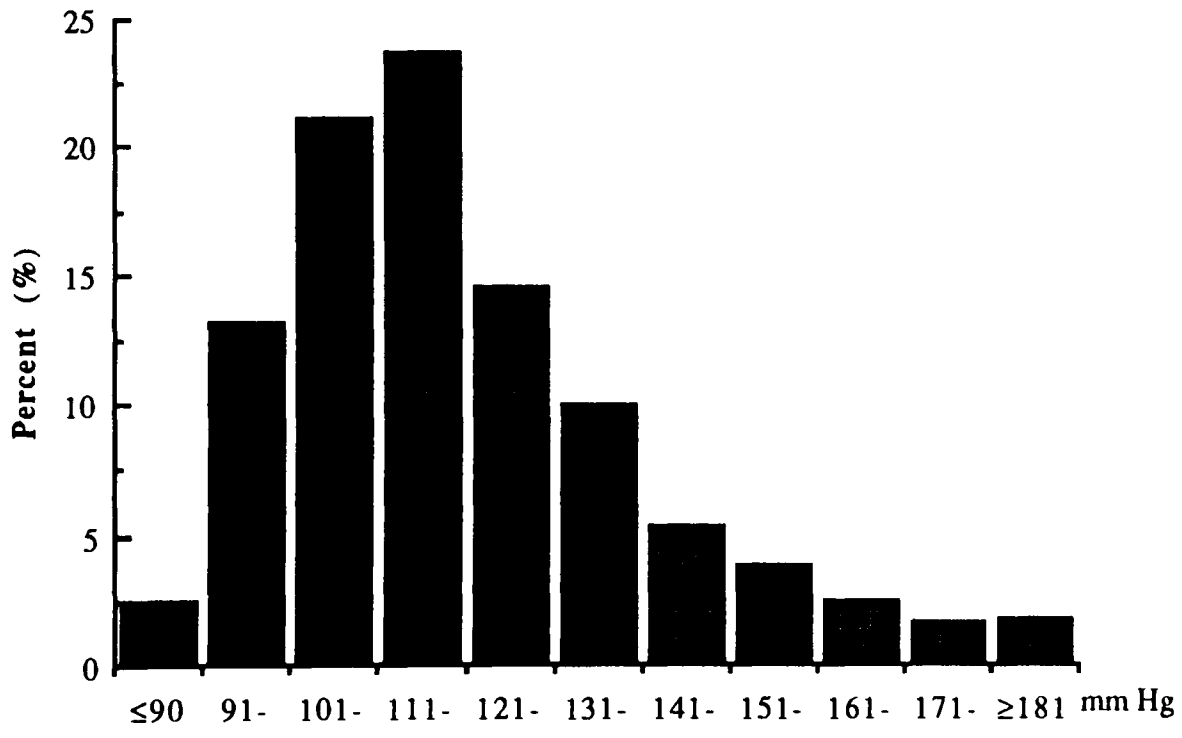


Figure 6.3. Distribution of systolic blood pressure in cohort B.

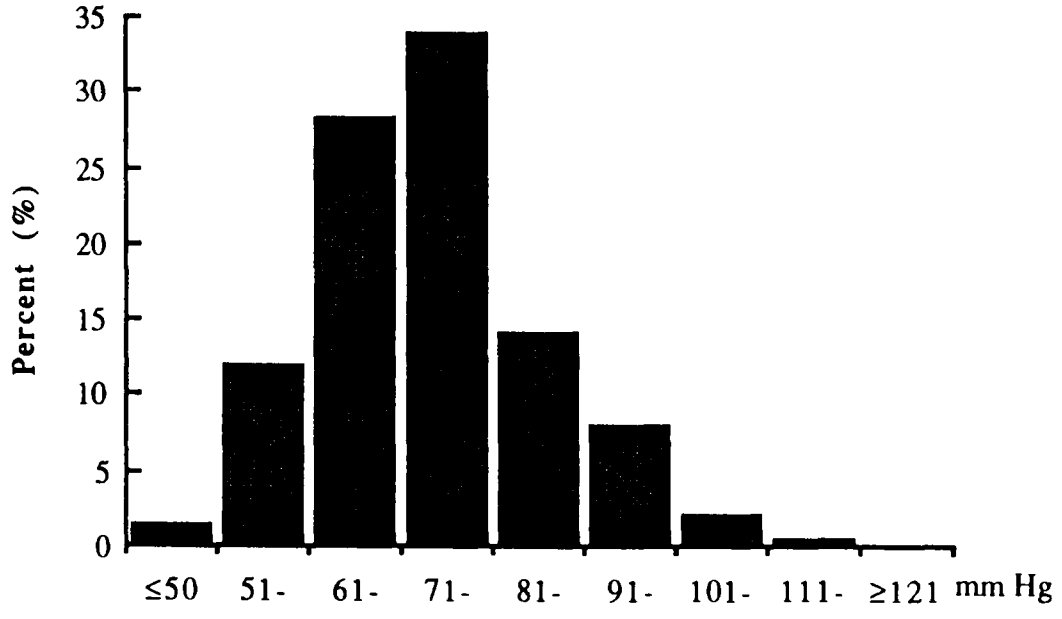


Figure 6.4. Distribution of diastolic blood pressure in cohort B.

Table 6.1. Mean levels of systolic blood pressure by age and sex at baseline examination in cohort A.

Age groups (years)	Male			Female			All subjects		
	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD
35-39	223	117.0	14.8	269	115.7	14.4	492	116.3	14.6
40-44	330	121.4	15.8	434	121.3	18.4	764	121.4	17.3
45-49	312	125.6	17.6	279	127.7	20.5	591	126.6	19.0
50-54	307	129.6	20.8	139	130.7	24.0	446	130.0	21.8
55-59	255	136.8	23.3	88	141.2	22.2	343	137.9	23.1
60-64	207	151.7	26.9	79	149.2	25.6	286	151.0	26.5
Total ¶	1634	129.4	22.5	1288	125.6	21.6	2922	127.7	22.1

¶ The age-adjusted mean SBP by analysis of covariance were 127.5 mmHg for males and 128.1 mmHg for females.

Table 6.2. Mean levels of diastolic blood pressure by age and sex at baseline examination in cohort A.

Age groups (years)	Male			Female			All subjects		
	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD
35-39	223	76.4	10.3	269	76.3	9.6	492	76.3	9.9
40-44	330	80.7	10.0	434	79.6	10.8	764	80.0	10.5
45-49	312	83.3	11.9	279	83.1	11.6	591	83.2	11.7
50-54	307	84.6	12.5	139	83.5	11.9	446	84.2	12.3
55-59	255	85.6	12.8	88	88.9	11.2	343	86.5	12.5
60-64	207	89.8	11.6	79	87.9	13.5	286	89.3	12.1
Total ¶	1634	83.2	12.1	1288	81.2	11.7	2922	82.3	12.0

¶ The age-adjusted mean DBP by analysis of covariance were 82.5 mmHg for males and 82.2 mmHg for females.

Table 6.3. Mean levels of systolic blood pressure by age and sex at baseline examination in cohort B.

Age groups (years)	Male			Female			All subjects		
	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD
35-39	530	117.8	16.3	454	116.6	18.1	984	117.3	17.1
40-44	593	117.1	15.7	319	117.6	19.0	912	117.3	16.9
45-49	1436	120.8	19.3	512	119.7	21.2	1948	120.5	19.8
50-54	1041	126.2	22.7	224	121.4	21.2	1265	125.4	22.5
55-59	788	132.3	24.8	46	125.9	22.0	834	131.9	24.7
60-64	469	138.3	27.6	13	131.5	21.3	482	138.1	27.5
Total ¶	4857	124.7	22.3	1568	118.9	20.0	6425	123.3	21.9

¶ The age-adjusted mean SBP by analysis of covariance were 123.6 mmHg for men and 122.4 mmHg for women.

Table 6.4. Mean levels of diastolic blood pressureby age and sex at baseline examination in cohort B.

Age groups (years)	Male			Female			All subjects		
	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD	No. of subjects	Mean (mmHg)	SD
35-39	530	75.7	10.6	454	73.9	11.4	984	74.9	11.0
40-44	593	75.1	11.0	319	74.5	12.1	912	74.9	11.4
45-49	1436	76.7	11.8	512	75.3	12.6	1948	76.3	12.1
50-54	1041	78.7	12.6	224	76.0	12.0	1265	78.3	12.5
55-59	788	80.5	12.3	46	76.6	10.8	834	80.3	12.3
60-64	469	81.3	13.2	13	78.8	11.1	482	81.2	13.2
Total ¶	4857	77.9	12.2	1568	74.9	12.0	6428	77.2	12.2

¶ The age-adjusted mean DBP by the analysis of covariance were 77.6 mmHg for men and 75.9 mmHg for women.

Table 6.5. Prevalence of definite isolated systolic hypertension by age groups at baseline examination in both cohort A and cohort B.

Age groups (years)	Cohort A			Cohort B			Both cohorts		
	No. of subjects	No. of hypertension¶	Prevalence (%)	No. of subjects	No. of hypertension	Prevalence (%)	No. of subjects	No. of hypertension	Prevalence (%)
35-49	1847	6	0.4	3844	11	0.3	5691	17	0.3
50-54	446	4	0.9	1265	16	1.3	1711	20	1.2
55-59	343	5	1.5	834	33	4.0	1177	35	3.0
60-64	286	22	7.7	482	34	7.1	768	56	7.3
Total	2922	37	1.3	6425	94	1.5	9347	131	1.4

¶ Definite isolated systolic hypertension was defined as DBP<90 mmHg and DBP ≥160 mmHg.

Table 6.6. Mean values of baseline variables in the three categories of blood pressure at baseline for the combined data from the two cohorts.

Variables ¶	Categories of blood pressure †		
	Normotensive	Borderline	Hypertension
Males (%)	66.6	74.5	74.1
Age (years)	47.2	50.7	52.7
SBP (mmHg)	114.4	139.2	162.5
DBP (mmHg)	73.3	86.5	99.1
Cholesterol (%) §	99.0	101.3	103.7
Body weight (kg)	57.5	60.5	62.4
Smoking (%)	45.3	43.3	42.2
Alcohol consumption (%)	18.2	23.7	21.8
Resting ECG abnormality (%)	8.3	13.6	21.7
Number of subjects:	6681	1369	1297

¶ Mean age increased slightly from normotensive to definite hypertension, so all other variables have been age-adjusted.

† Normotensive: SBP/DBP<140/90 mm Hg; Hypertension: SBP≥160 mm Hg &/or DBP≥95 mm Hg; Borderline: any others not included in the previous two categories.

§ For each cohort mean serum cholesterol values in three categories of blood pressure were expressed as the percent of the cohort mean, and an age-adjusted weighted mean then computed, using the inverse of the variances as weights.

Table 6.7. The number of deaths from **any cause** and the estimated relative risks in three categories of baseline blood pressure during 8-13 years of follow-up. .

Baseline blood pressure status	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)¶	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Normotensive	1924	125	165.5	0.76	4757	147	187.8	0.78	**6681**	**272**	**353.3**	**0.77**
Borderline	471	68	75.3	0.90	898	58	49.8	1.16	**1369**	**126**	**125.1**	**1.01**
Hypertension	527	141	93.2	1.51	770	81	48.4	1.67	**1297**	**222**	**141.6**	**1.57**
Total	2922	334	334.0	1.00	6425	286	286.0	1.00	**9347**	**620**	**620.0**	**1.00**
X^2 for trend			37.05***				34.16***				**61.66*** **	

¶ The expected (E) number of deaths, adjusted for age and sex by the log-rank method.
*** Statistically significant by the log-rank trend test at 2P <0.001.

Table 6.8. The number of deaths from **any cause** and the estimated relative risks in 5 categories of baseline SBP during 8-13 years of follow-up.

Baseline SBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤124	1547	103	127.1	0.81	4112	121	157.4	0.77	**5659**	**224**	**284.5**	**0.79**
2. 125-139	578	47	66.6	0.71	859	38	39.6	0.96	**1437**	**85**	**106.2**	**0.80**
3. 140-154	460	78	73.2	1.07	862	58	48.2	1.20	**1322**	**136**	**121.4**	**1.12**
4. 155-169	163	39	30.5	1.28	249	23	16.5	1.39	**412**	**62**	**47.0**	**1.32**
5. ≥170	174	67	36.7	1.83	343	46	24.4	1.89	**517**	**113**	**61.1**	**1.84**
Total	2922	334	334.0	1.00	6425	286	286.0	1.00	**9347**	**620**	**620.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)		36.02***				33.96***				**58.24*** **		
Cox regression analysis												
Regression coefficients (ß)†		0.010				0.013				**0.011**		
z values (ß/s.e.)		4.20***				5.06***				**6.53*** **		
Relative risks§		1.11				1.14				**1.12**		
(95% CI of relative risk)		(1.05-1.16)				(1.08-1.20)				**(1.08-1.15)**		

† Estimated in the Cox's proportional-hazards model with a linear term for SBP, adjusted simultaneously for age, sex, serum cholesterol, cigarette smoking, alcohol drinking.

*** Statistically significant at 2P<0.001.

§ Relative risk was calculated from regression coefficient, associated with a 10 mm Hg difference in baseline SBP.

Table 6.9. The number of deaths from **any cause** and the estimated relative risks in 5 categories of baseline DBP during 8-13 years of follow-up.

Baseline DBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤79	1094	67	93.0	0.72	2994	92	116.2	0.79	**4088**	**159**	**209.2**	**0.76**
2. 80-89	1045	101	119.9	0.84	2302	103	107.3	0.96	**3347**	**204**	**227.2**	**0.90**
3. 90-99	462	71	69.1	1.03	640	34	35.0	0.97	**1102**	**105**	**104.1**	**1.01**
4. 100-109	230	61	37.1	1.64	371	42	20.6	2.04	**601**	**103**	**57.7**	**1.79**
5. ≥110	91	34	15.0	2.27	118	15	7.0	2.14	**209**	**49**	**22.0**	**2.23**
Total	2922	334	334.0	1.00	6425	286	286.0	1.00	**9347**	**620**	**620.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)		45.50***				28.55***				67.77***		
Cox regression analysis												
Regression coefficients(ß)†		0.024				0.023				**0.024**		
z values (Coeff./SE)		5.25***				4.78***				**7.18*** **		
Relative risks¶		1.18				1.17				**1.18**		
(95% CI of relative risk)		(1.11-1.26)				(1.10-1.25)				**(1.13-1.24)**		

† Estimated in the Cox's proportional-hazards model with a linear term for DBP, adjusted simultaneously for age, sex, serum cholesterol, cigarette smoking, and alcohol drinking.

*** Statistically significant at 2P<0.001.

¶ Relative risk was calculated from regression coefficient, associated with a 7 mm Hg difference in baseline DBP

Table 6.10. The number of deaths from **all vascular** disease and the estimated relative risks in three categories of baseline blood pressure during 8-13 years of follow-up.

Baseline blood pressure status	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Normotensive	1924	35	62.9	0.56	4757	23	62.5	0.37	**6681**	**58**	**125.4**	**0.46**
Borderline	471	17	31.3	0.54	898	15	17.9	0.84	**1369**	**32**	**49.2**	**0.65**
Hypertension	527	81	38.8	2.09	770	60	17.7	3.39	**1297**	**141**	**56.5**	**2.50**
Total	2922	133	133.0	1.00	6425	98	98.0	1.00	**9347**	**231**	**44.0**	**1.00**
X^2 for trend			56.88***				117.86***				**89.25*** **	

*** Statistically significant by the log-rank trend test at 2P <0.001.

Table 6.11. The number of deaths from **all vascular** disease and the estimated relative risks in 5 categories of baseline SBP during 8-13 years of follow-up.

Baseline SBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤124	1547	28	48.4	0.58	4112	21	51.9	0.40	**5659**	**49**	**100.3**	**0.49**
2. 125-139	578	13	26.1	0.50	859	6	13.7	0.44	**1437**	**19**	**39.8**	**0.48**
3. 140-154	460	30	30.0	1.00	862	21	17.3	1.21	**1322**	**51**	**47.3**	**1.08**
4. 155-169	163	20	12.8	1.56	249	15	6.0	2.50	**412**	**35**	**18.8**	**1.86**
5. ≥170	174	42	15.6	2.69	343	35	9.1	3.85	**517**	**77**	**24.7**	**3.12**
Total	2922	133	133.0	1.00	6425	98	98.0	1.00	**9347**	**231**	**231.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)			59.79***				102.73***				**138.63*** **	
Cox regression analysis												
Regression coefficients(ß)			0.022				0.032				**0.026**	
z values (ß/s.e.)			6.41***				8.46***				**10.47*** **	
Relative risks			1.25				1.38				**1.30**	
(95% CI of relative risk)			(1.17-1.33)				(1.28-1.48)				**(1.24-1.36)**	

*** Statistically significant at 2P<0.001.

Table 6.12. The number of deaths from **all vascular** diseases and the estimated relative risks in 5 categories of baseline DBP during 8-13 years of follow-up.

Baseline DBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤79	1094	19	35.8	0.53	2994	12	38.4	0.31	**4088**	**31**	**74.2**	**0.42**
2. 80-89	1045	30	47.4	0.63	2302	29	37.2	0.78	**3347**	**59**	**84.6**	**0.70**
3. 90-99	462	29	28.2	1.03	640	11	12.5	0.88	**1102**	**40**	**40.7**	**0.98**
4. 100-109	230	34	15.3	2.22	371	32	7.4	4.32	**601**	**66**	**22.7**	**2.91**
5. ≥110	91	21	6.2	3.39	118	14	2.6	5.38	**209**	**35**	**8.8**	**3.98**
Total	2922	133	133.0	1.00	6425	98	98.0	1.00	**9347**	**231**	**231.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)		62.25***				116.23***				**154.91*** **		
Cox regression analysis												
Regression coefficients(ß)		0.047				0.069				**0.057**		
z values (ß/s.e.)		6.74***				9.46***				**11.34*** **		
Relative risks		1.39				1.62				**1.49**		
(95% CI of relative risk)		(1.26-1.53)				(1.47-1.79)				**(1.39-1.60)**		

*** Statistically significant at 2P<0.001.

Table 6.13. The number of deaths from **stroke** and the estimated relative risks in three categories of baseline blood pressure during 8-13 years of follow-up.

Baseline blood pressure status	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Normotensive	1924	19	41.1	0.46	4757	11	42.3	0.26	**6681**	**30**	**83.4**	**0.36**
Borderline	471	11	20.2	0.54	898	9	12.0	0.75	**1369**	**20**	**32.2**	**0.62**
Hypertension	527	56	24.7	2.27	770	46	11.8	3.90	**1297**	**102**	**36.5**	**2.79**
Total	2922	86	86.0	1.00	6425	66	66.0	1.00	**9347**	**152**	**152.0**	**1.00**
X^2 for trend			51.44***				112.10***				**134.02*** **	

*** Statistically significant by the log-rank trend test at $2P<0.001$.

Table 6.14. The number of deaths from **stroke** and the estimated relative risks in three categories of baseline blood pressure in three age groups during 8-13 years of follow-up.

Baseline blood pressure status	Age at baseline examination (years) 35-49 No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	50-59 No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	60-64 No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E
Normotensive	4543	10	22.7	0.44	1827	13	40.5	0.32	331	7	19.4	0.36
Borderline	656	4	3.5	1.13	527	9	13.3	0.68	186	7	14.5	0.48
Hypertension	492	15	2.7	5.52	534	46	14.2	3.24	271	41	21.1	1.95
Total	5691	29	29.0	1.00	2888	68	68.0	1.00	768	55	55.0	1.00
X^2 for trend			54.00***				79.10***				27.46***	

¶ Expected (E) number of deaths, adjusted for sex and cohorts by the log-rank method.
*** Statistically significant by the log-rank trend test at $2P<0.001$ respectively.

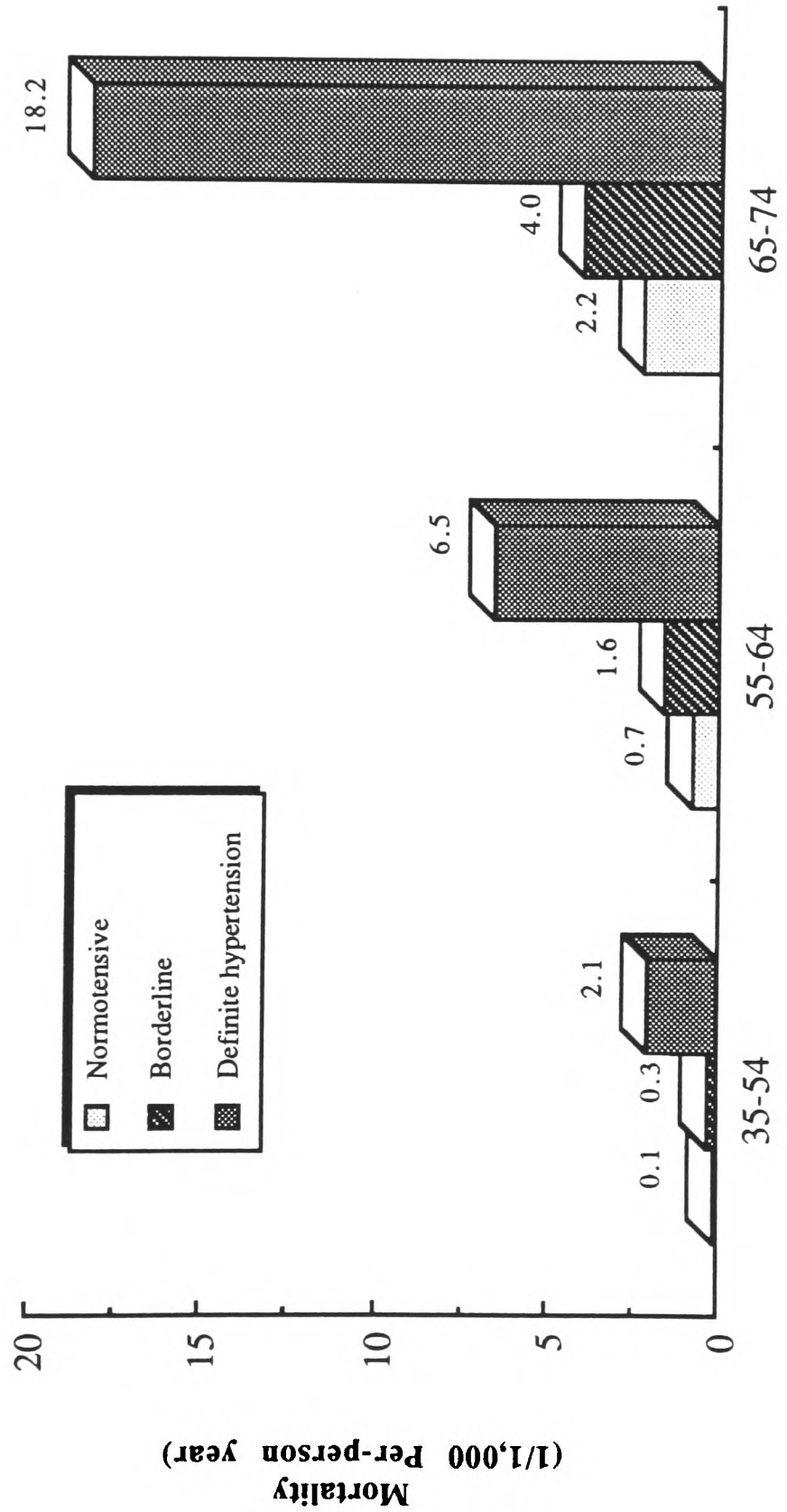


Figure 6.5. The relation of blood pressure status with stroke mortality in three age groups

Table 6.15. The number of deaths from **stroke** and the estimated relative risks in 5 categories of baseline SBP during 8-13 years of follow-up.

Baseline SBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤124	1547	14	32.0	0.44	4112	9	35.1	0.26	**5659**	**23**	**67.1**	**0.34**
2. 125-139	578	9	16.9	0.53	859	6	9.3	0.65	**1437**	**15**	**26.2**	**0.57**
3. 140-154	460	18	19.2	0.94	862	13	11.6	1.13	**1322**	**31**	**30.8**	**1.01**
4. 155-169	163	15	8.1	1.85	249	11	4.0	2.75	**412**	**26**	**12.1**	**2.15**
5. ≥170	174	30	9.8	3.06	343	27	6.1	4.43	**517**	**57**	**15.9**	**3.58**
Total	2922	86	86.0	1.00	6425	66	66.0	1.00	**9347**	**152**	**152.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)			59.56***				98.40***				**150.31*** **	
Cox regression analysis												
Regression coefficients(ß)			0.027				0.040				**0.032**	
z values (ß/s.e.)			6.58***				8.17***				**10.86*** **	
Relative risks			1.31				1.49				**1.38**	
(95% CI of relative risk)			(1.21-1.42)				(1.36-1.64)				**(1.30-1.46)**	

*** Statistically significant at 2P<0.001.

Table 6.16. The number of deaths from **stroke** and the estimated relative risks in 5 categories of baseline SBP in three age groups during 8-13 years of follow-up.

Baseline SBP categories (mm Hg)	Age at baseline examination (years) 35-49				50-59				60-64			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E
1. ≤124	3940	6	19.3	0.31	1467	11	31.3	0.35	252	6	14.9	0.40
2. 125-139	869	6	5.2	1.15	486	8	12.5	0.64	82	1	7.1	0.14
3. 140-154	610	7	3.3	2.14	520	13	13.2	0.98	192	11	14.4	0.77
4. 155-169	127	3	0.6	4.60	192	12	5.2	2.31	93	11	6.9	1.59
5. ≥170	145	7	0.6	11.15	223	24	5.8	4.14	149	26	11.8	2.21
Total	5691	29	29.0	1.00	2888	68	68.0	1.00	768	55	55.0	1.00
Statistical analysis												
Log-rank trest test (X^2)			66.33***				67.14***				28.09***	
Cox regression analysis												
Regression coefficients(ß)†			0.0404				0.0347				0.0239	
z values (ß/s.e.)			5.58***				8.44***				4.73***	
Relative risks			1.50				1.41				1.27	
(95% CI of relative risk)			(1.30-1.73)				(1.31-1.53)				(1.15-1.40)	

† Estimated in the Cox's proportional-hazards model with a linear term for SBP, adjusted simultaneously for sex, serum cholesterol, cigarette smoking and alcohol drinking.
*** Statistically significant at 2P<0.001.

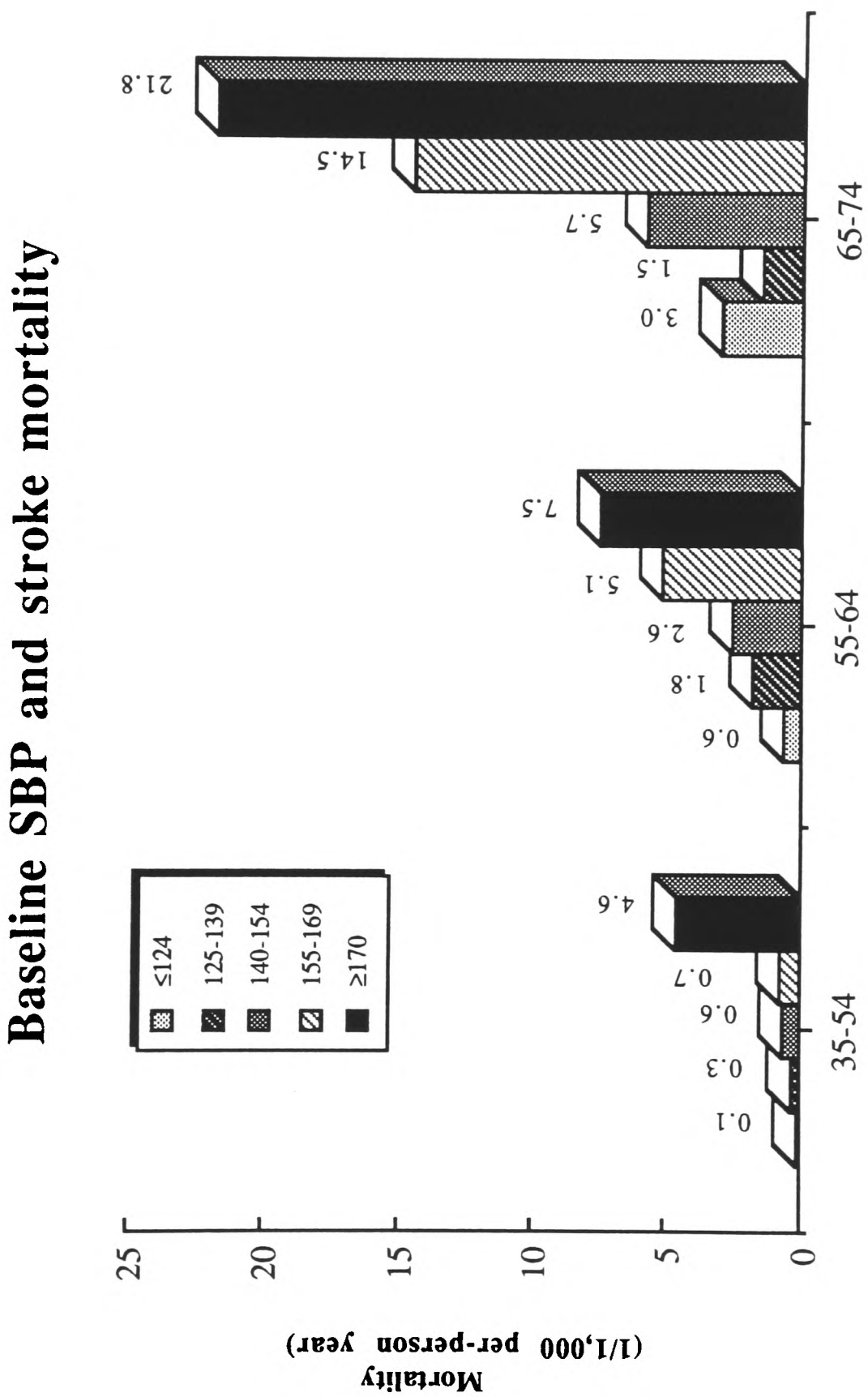


Figure 6.6. The relationship of SBP with stroke mortality in three age groups

Table 6.17. The number of deaths from **stroke** and the estimated relative risks in 5 categories of baseline SBP in males and females in the combined data from the two cohorts during 8-13 years of follow-up.

Baseline SBP categories (mmHg)	Males				Females			
	No. of subjects	Observed deaths(O)	Expected deaths(E)¶	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E
1. ≤124	3782	15	53.9	0.28	1877	8	13.2	0.61
2. 125-139	1036	12	21.2	0.57	401	3	5.0	0.60
3. 140-154	990	27	24.7	1.09	332	4	6.1	0.66
4. 155-169	288	21	8.8	2.38	124	5	3.3	1.51
5. ≥170	395	46	12.4	3.71	122	11	3.5	3.14
Total	6491	121	121.0	1.00	2856	31	31.0	1.00
Statistical analysis								
Log-rank trend test (X^2)			137.48***				17.37***	
Cox regression analysis								
Regression coefficients(ß)†			0.0324				0.0324	
z values (ß/s.e.)			9.91***				4.41***	
Relative risks			1.38				1.38	
(95% CI of relative risk)			(1.30-1.47)				(1.20-1.60)	

¶ The expected (E) number of deaths, adjusted for age and cohorts by the log-rank method.
† The regression coefficients were estimated in Cox's proportional-hazards model after adjusting for age, serum cholesterol, smoking and alcohol drinking.
*** Statistically significant at 2P<0.001.

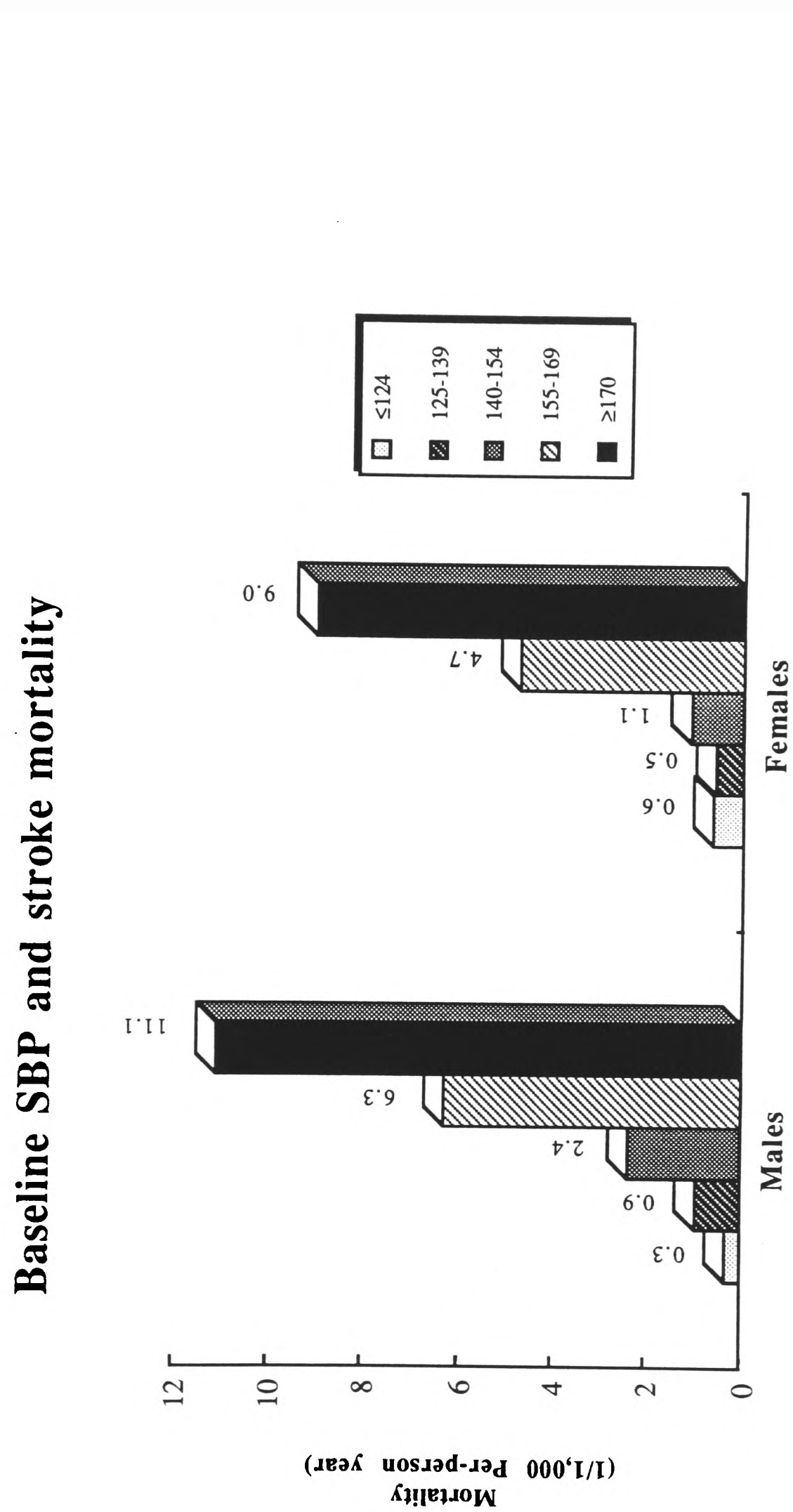


Figure 6.7. The relationship of SBP with stroke mortality in males and females

Table 6.18. The number of deaths from **stroke** and the estimated relative risks in 5 categories of baseline DBP during 8-13 years of follow-up.

Baseline DBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤79	1094	10	23.6	0.42	2994	3	25.9	0.12	**4088**	**13**	**49.5**	**0.26**
2. 80-89	1045	18	30.7	0.59	2302	17	25.0	0.68	**3347**	**35**	**55.7**	**0.63**
3. 90-99	462	18	18.0	1.00	640	9	8.4	1.07	**1102**	**27**	**26.4**	**1.02**
4. 100-109	230	21	9.8	2.14	371	25	5.0	5.00	**601**	**46**	**14.8**	**3.11**
5. ≥110	91	19	4.0	4.75	118	12	1.7	7.06	**209**	**31**	**5.7**	**5.44**
Total	2922	86	86.0	1.00	6425	66	66.0	1.00	**9347**	**152**	**152.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)		64.45***				130.25***				**168.87***		
Cox regression analysis												
Regression coefficients(ß)		0.059				0.087				**0.072**		
z values (ß/s.e.)		7.00***				10.01***				**12.02***		
Relative risks		1.51				1.84				**1.66**		
(95% CI of relative risk)		(1.35-1.70)				(1.63-2.07)				**(1.52-1.80)**		

*** Statistically significant at 2P<0.001.

Table 6.19. The number of deaths from **stroke** and the estimated relative risks in 5 categories of baseline DBP in three age groups during 8-13 years of follow-up.

Baseline DBP categories (mm Hg)		Age at baseline examination (years) 35-49 No. of subjects	35-49 Observed deaths(O)	35-49 Expected deaths(E)	35-49 Ratios of O/E	50-59 No. of subjects	50-59 Observed deaths(O)	50-59 Expected deaths(E)	50-59 Ratios of O/E	60-64 No. of subjects	60-64 Observed deaths(O)	60-64 Expected deaths(E)	60-64 Ratios of O/E
1.	≤79	2837	4	13.7	0.29	1032	4	22.2	0.18	219	5	12.9	0.39
2.	80-89	1971	6	10.3	0.58	1114	15	26.2	0.57	262	14	18.8	0.74
3.	90-99	549	6	3.3	1.85	404	10	10.9	0.92	149	11	12.8	0.86
4.	100-109	257	7	1.3	5.22	249	24	6.5	3.69	95	15	6.8	2.19
5.	≥110	77	6	0.4	15.27	89	15	2.2	6.82	43	10	3.7	2.72
Total		5691	29	29.0	1.00	2888	68	68.0	1.00	768	55	55.0	1.00
Statistical analysis													
Log-rank trend test (X^2)			68.05***				105.60***				24.21***		
Cox regression analysis													
Regression coefficients(ß)†			0.0773				0.0772				0.0491		
z values (ß/s.e.)			5.83***				9.85***				4.45***		
Relative risks			1.72				1.72				1.41		
(95% CI of relative risk)			(1.43-2.06)				(1.54-1.91)				(1.21-1.64)		

† Estimated in the Cox's proportional-hazards model with a linear term for DBP, adjusted simultaneously for sex, serum cholesterol, cigarette smoking and alcohol drinking.
*** Statistically significant at 2P<0.001.

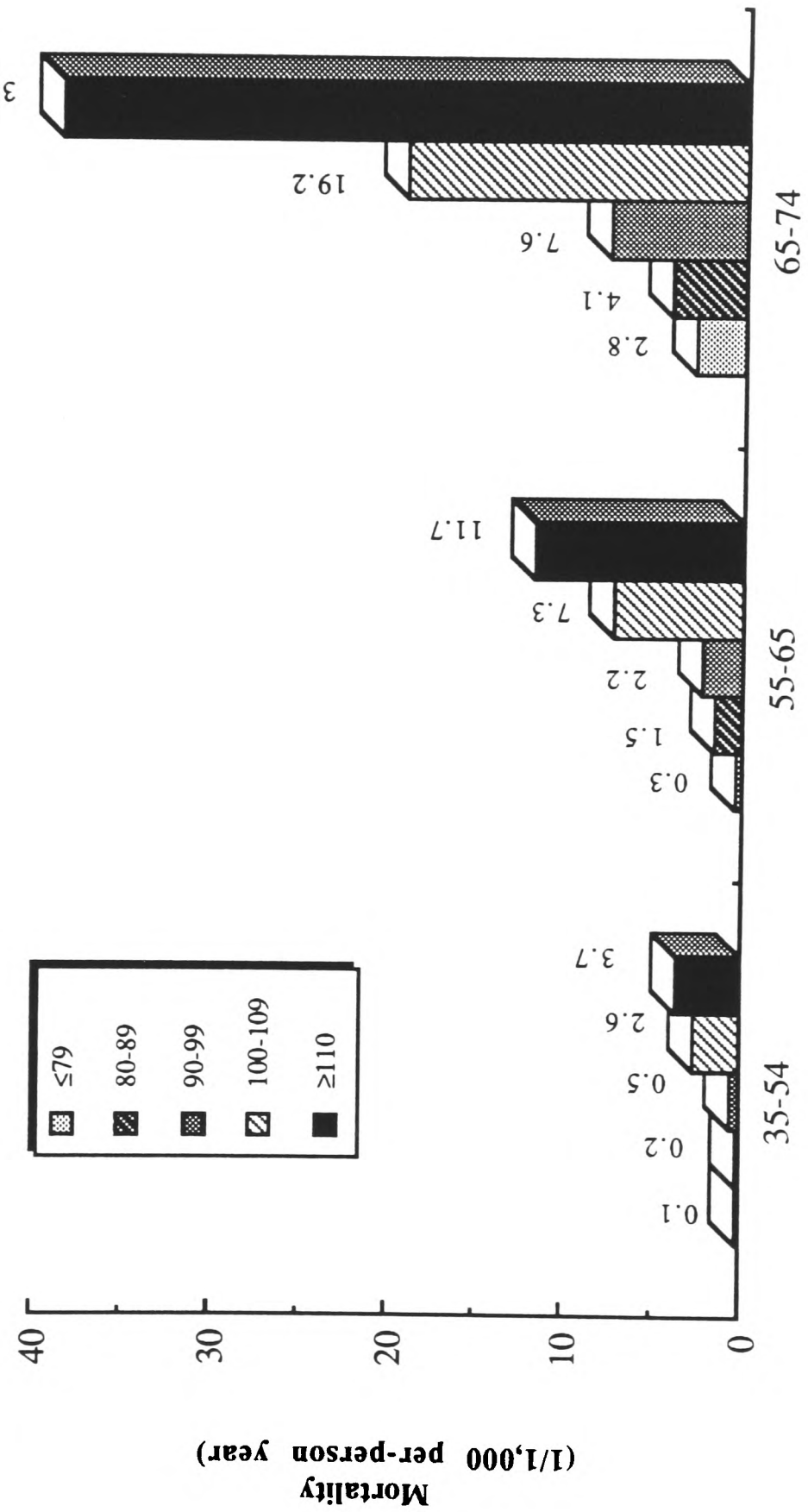


Figure 6.8. The relationship of DBP with stroke mortality in three age groups

Table 6.20. The number of deaths from **stroke** and the estimated relative risks in 5 categories of baseline DBP in males and females in the two cohorts combined during 8-13 years of follow-up.

	Baseline SBP categories (mmHg)	Males				Females			
		No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E
1.	≤79	2686	9	39.7	0.23	1402	4	9.8	0.41
2.	80-89	2401	26	45.4	0.57	946	9	10.4	0.87
3.	90-99	801	23	20.3	1.14	301	4	6.1	0.65
4.	100-109	446	37	11.4	3.24	155	9	3.3	2.71
5.	≥110	157	26	4.3	6.10	52	5	1.4	3.49
Total		6491	121	121.0	1.00	2856	31	31.0	1.00
Statistical analysis									
Log-rank trend test (X^2)			165.82***				18.76***		
Cox regression analysis									
Regression coefficients(ß)			0.0744				0.0646		
z values (ß/s.e.)			11.05***				4.83***		
Relative risks			1.68				1.58		
(95% CI of relative risk)			(1.53-1.85)				(1.31-1.89)		

*** Statistically significant at 2P<0.001.

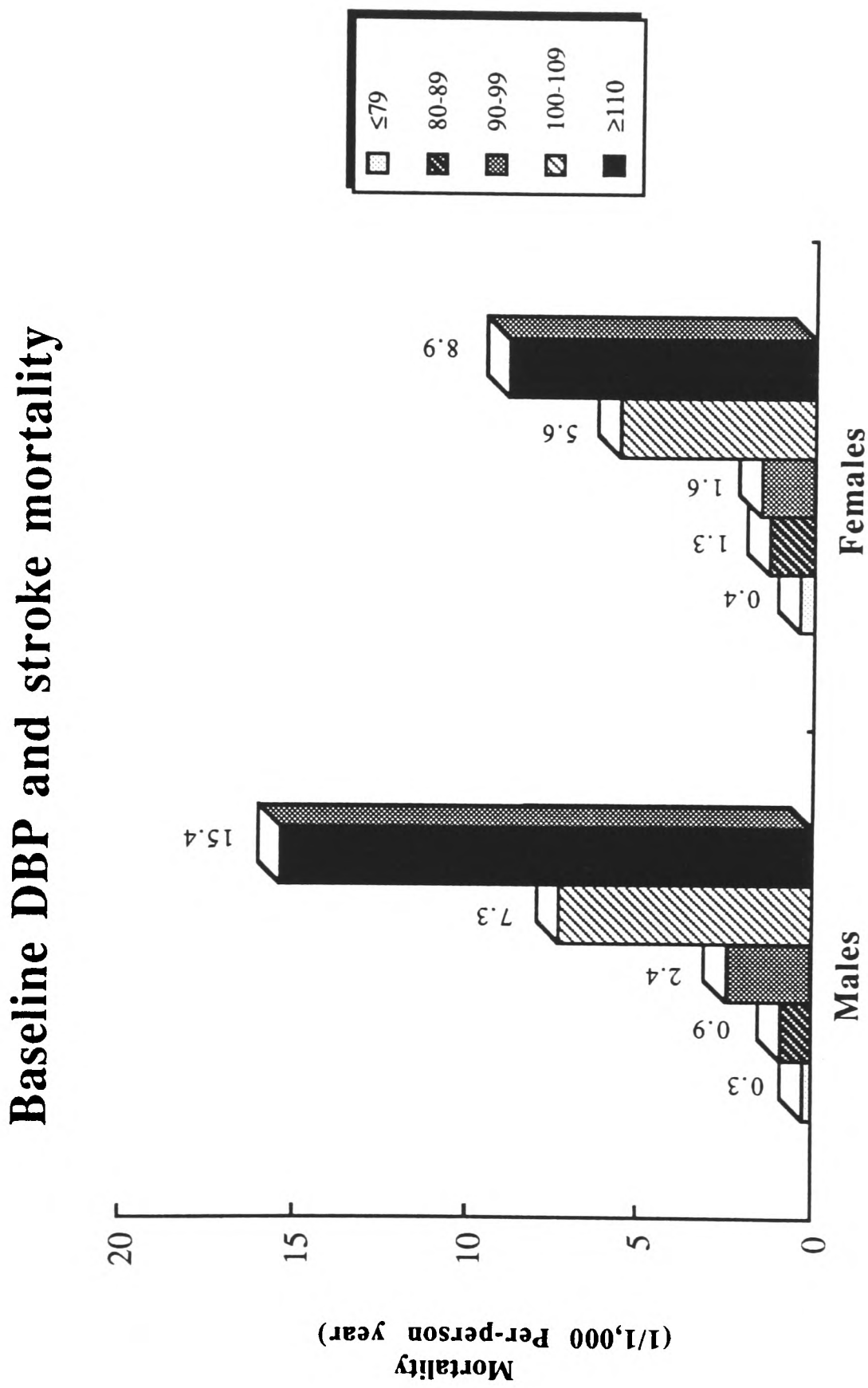


Figure 6.9. The relationship of DBP with stroke mortality in males and females

Table 6.21. The number of deaths from **CHD** and the estimated relative risks in three categories of baseline blood pressure during 8-13 years of follow-up.

Baseline blood pressure status	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Normotensive	1924	6	11.6	0.52	4757	5	10.7	0.47	**6681**	**11**	**22.3**	**0.49**
Borderline	471	4	6.5	0.62	898	1	3.1	0.32	**1369**	**5**	**9.6**	**0.52**
Hypertension	527	17	8.9	1.91	770	11	3.2	3.44	**1297**	**28**	**12.1**	**2.31**
Total	2922	27	27.0	1.00	6425	17	17.0	1.00	**9347**	**44**	**44.0**	**1.00**
X^2 for trend			10.05**				18.20***				**23.30*** **	

,* Statistically significant by the log-rank trend test at 2P<0.01, and <0.001 respectively.

Table 6.22. The number of deaths from **CHD** and the estimated relative risks in 5 categories of baseline SBP during 8-13 years of follow-up.

Baseline SBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤124	1547	5	9.3	0.54	4112	5	8.9	0.56	**5659**	**10**	**18.2**	**0.55**
2. 125-139	578	3	5.2	0.57	859	0	2.4	0.00	**1437**	**3**	**7.6**	**0.39**
3. 140-154	460	8	6.3	1.27	862	2	3.0	0.67	**1322**	**10**	**9.3**	**1.08**
4. 155-169	163	3	2.8	1.07	249	4	1.1	3.64	**412**	**7**	**3.9**	**1.79**
5. ≥170	174	8	3.4	2.35	343	6	1.6	3.75	**517**	**14**	**5.0**	**2.80**
Total	2922	27	27.0	1.00	6425	17	17.0	1.00	**9347**	**44**	**44.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)			8.74**				16.18***				**20.92*** **	
Cox regression analysis												
Regression coefficients(ß)			0.018				0.030				**0.023**	
z values (ß/s.e.)			2.31*				3.38***				**4.01*** **	
Relative risks			1.20				1.35				**1.26**	
(95% CI of relative risk)			(1.03-1.39)				(1.13-1.61)				**(1.12-1.41)**	

*,**,*** Statistically significant at 2P<0.05, <0.01 and <0.001 respectively.

Table 6.23. The number of deaths from **CHD** and the estimated relative risks in 5 categories of baseline DBP during 8-13 years of follow-up.

Baseline DBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤79	1094	3	6.9	0.43	2994	4	6.6	0.61	**4088**	**7**	**13.5**	**0.52**
2. 80-89	1045	6	9.6	0.63	2302	4	6.4	0.63	**3347**	**10**	**16.0**	**0.63**
3. 90-99	462	9	5.9	1.53	640	2	2.2	0.91	**1102**	**11**	**8.1**	**1.36**
4. 100-109	230	8	3.3	2.42	371	5	1.3	3.85	**601**	**13**	**4.6**	**2.83**
5. ≥110	91	1	1.4	0.71	118	2	0.5	4.00	**209**	**3**	**1.9**	**1.58**
Total	2922	27	27.0	1.00	6425	17	17.0	1.00	**9347**	**44**	**44.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)		6.96**				11.55***				**16.04*** **		
Cox regression analysis												
Regression coefficients(ß)		0.038				0.045				**0.041**		
z values (ß/s.e.)		2.35*				2.50*				**3.47*** **		
Relative risks		1.30				1.37				**1.33**		
(95% CI of relativer risk)		(1.05-1.63)				(1.07-1.75)				**(1.13-1.57)**		

,* Statistically significant at 2P<0.01 and <0.001 respectively.

Table 6.24. The number of deaths from **other vascular** disease and the estimated relative risks in three categories of baseline blood pressure during 8-13 years of follow-up.

Baseline blood pressure status	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Normotensive	1924	10	10.2	0.98	4757	7	9.5	0.74	**6681**	**17**	**19.7**	**0.86**
Borderline	471	2	4.6	0.43	898	5	2.8	1.79	**1369**	**7**	**7.4**	**0.95**
Hypertension	527	8	5.2	1.54	770	3	2.7	1.11	**1297**	**11**	**7.9**	**1.39**
Total	2922	20	20.0	1.00	6425	15	15.0	1.00	**9347**	**35**	**35.0**	**1.00**
X^2 for trend §			0.64				0.86				**1.42**	

§ X^2 values less than 3.84 are not conventionally significant (i.e. 2P>0.05).

Table 6.25. The numbers of deaths from **other vascular** diseases and estimated relative risk in 5 categories of baseline SBP during 8-13 years of follow-up.

Baseline SBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤124	1547	9	7.2	1.25	4112	7	7.9	0.89	**5659**	**16**	**15.1**	**1.06**
2. 125-139	578	1	4.0	0.25	859	0	2.1	0.00	**1437**	**1**	**6.1**	**0.16**
3. 140-154	460	4	4.6	0.87	862	6	2.7	2.22	**1322**	**10**	**7.3**	**1.37**
4. 155-169	163	2	1.9	1.05	249	0	1.0	0.00	**412**	**2**	**2.9**	**0.69**
5. ≥170	174	4	2.4	1.67	343	2	1.4	1.43	**517**	**6**	**3.8**	**1.58**
Total	2922	20	20.0	1.00	6425	15	15.0	1.00	**9347**	**35**	**35.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.24				0.64				**0.32**	
Cox regression analysis												
Regression coefficients(ß)			0.002				-0.010				**-0.003**	
z values (ß/s.e.) §			0.22				-0.77				**-0.36**	
Relative risks			1.02				0.90				**0.97**	
(95% CI of relative risk)			(0.85-1.22)				(0.70-1.17)				**(0.82-1.14)**	

§ X^2 values less than 3.84, or z value less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 6.26. The number of deaths from **other vascular** diseases and the estimated relative risks in 5 categories of baseline DBP during 8-13 years of follow-up.

Baseline DBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤79	1094	6	5.4	1.11	2994	5	5.9	0.85	**4088**	**11**	**11.3**	**0.97**
2. 80-89	1045	6	7.1	0.85	2302	8	5.7	1.40	**3347**	**14**	**12.8**	**1.09**
3. 90-99	462	2	4.3	0.47	640	0	1.9	0.00	**1102**	**2**	**6.2**	**0.32**
4. 100-109	230	5	2.3	2.17	371	2	1.1	1.82	**601**	**7**	**3.4**	**2.06**
5. ≥110	91	1	0.9	1.11	118	0	0.4	0.00	**209**	**1**	**1.3**	**0.77**
Total	2922	20	20.0	1.00	6425	15	15.0	1.00	**9347**	**35**	**35.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§		0.35				0.01					**0.17**	
Cox regression analysis												
Regression coefficients(ß)		0.005				-0.007					**0.002**	
z values (ß/s.e.) §		0.55				-0.56					**0.05**	
Relative risks		1.06				0.93					**1.01**	
(95% CI of relative risk)		(0.87-1.28)				(0.73-1.19)					**(0.86-1.16)**	

§ X^2 values less than 3.84 or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 6.27. The number of deaths from **all cancer** and the estimated relative risks in 5 categories of baseline SBP during 8-13 years of follow-up.

Baseline SBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤124	1547	55	56.4	0.98	4112	69	72.5	0.95	**5659**	**124**	**128.9**	**0.96**
2. 125-139	578	21	29.1	0.72	859	21	18.0	1.17	**1437**	**42**	**47.1**	**0.89**
3. 140-154	460	37	30.9	1.20	862	28	21.6	1.30	**1322**	**65**	**52.5**	**1.23**
4. 155-169	163	15	12.7	1.18	249	6	7.2	0.83	**412**	**21**	**19.9**	**1.06**
5. ≥170	174	16	15.0	1.06	343	6	10.7	0.56	**517**	**22**	**25.7**	**0.86**
Total	2922	144	144.0	1.00	6425	130	130.0	1.00	**9347**	**274**	**274.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			1.02				0.22				**0.13**	
Cox regression analysis												
Regression coefficients(ß)			0.001				-0.003				**-0.001**	
z values (ß/s.e.)§			0.23				-0.71				**-0.31**	
Relative risks			1.01				0.97				**0.99**	
(95% CI of relative risk)			(0.93-1.10)				(0.89-1.05)				**(0.93-1.05)**	

§ X^2 values less than 3.84 or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 6.28. The number of deaths from **all cancer** and the estimated relative risks in 5 categories of baseline DBP during 8-13 years of follow-up.

Baseline DBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤79	1094	37	40.5	0.91	2994	56	53.4	1.04	**4088**	**93**	**93.9**	**0.99**
2. 80-89	1045	49	52.1	0.94	2302	50	48.7	1.03	**3347**	**99**	**100.8**	**0.98**
3. 90-99	462	31	29.2	1.06	640	18	15.7	1.15	**1102**	**49**	**44.9**	**1.09**
4. 100-109	230	17	15.7	1.08	371	6	9.2	0.65	**601**	**23**	**24.9**	**0.92**
5. ≥110	91	10	6.4	1.56	118	0	3.1	0.00	**209**	**10**	**9.5**	**1.05**
Total	2922	144	144.0	1.00	6425	130	130.0	1.00	**9347**	**274**	**274.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§		2.05				1.97					**0.02**	
Cox regression analysis												
Regression coefficients(ß)		0.004				-0.010					**-0.003**	
z values (ß/s.e.) §		0.53				-1.29					**-0.46**	
Relative risks		1.03				0.93					**0.98**	
(95% CI of relative risk)		(0.93-1.14)				(0.84-1.04)					**(0.90-1.07)**	

§ X^2 values less than 3.84 or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 6.29. The number of deaths from all **non-vascular non-cancer** disease and estimated relative risks in 5 categories of baseline SBP during 8-13 years of follow-up. .

Baseline SBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤124	1547	20	22.3	0.90	4112	31	33.0	0.94	**5659**	**51**	**55.3**	**0.92**
2. 125-139	578	13	11.5	1.13	859	11	7.9	1.39	**1437**	**24**	**19.4**	**1.24**
3. 140-154	460	11	12.3	0.89	862	9	9.4	0.96	**1322**	**20**	**21.7**	**0.92**
4. 155-169	163	4	4.9	0.82	249	2	3.2	0.63	**412**	**6**	**8.1**	**0.74**
5. ≥170	174	9	6.1	1.48	343	5	4.6	1.09	**517**	**14**	**10.7**	**1.31**
Total	2922	57	57.0	1.00	6425	58	58.0	1.00	**9347**	**115**	**115.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.70				0.00				**0.35**	
Cox regression analysis												
Regression coefficients(ß)			0.001				0.001				**0.001**	
z values (ß/s.e.)§			0.18				0.11				**0.10**	
Relative risks			1.01				1.01				**1.01**	
(95% CI of relative risk)			(0.90-1.13)				(0.90-1.13)				**(093-1.09)**	

§ X^2 values less than 3.84 or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 6.30. The number of deaths from all **non-vascular non-cancer** diseases and the estimated relative risks in 5 categories of baseline DBP during 8-13 years of follow-up. .

Baseline DBP categories (mm Hg)	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
1. ≤79	1094	11	16.6	0.66	2994	24	24.4	0.98	**4088**	**35**	**41.0**	**0.85**
2. 80-89	1045	22	20.3	1.08	2302	24	21.4	1.12	**3347**	**46**	**41.7**	**1.10**
3. 90-99	462	11	11.7	0.94	640	5	6.8	0.74	**1102**	**16**	**18.5**	**0.86**
4. 100-109	230	10	6.1	1.64	371	4	4.0	1.00	**601**	**14**	**10.1**	**1.39**
5. ≥110	91	3	2.3	1.30	118	1	1.3	0.77	**209**	**4**	**3.6**	**1.11**
Total	2922	57	57.0	1.00	6425	58	58.0	1.00	**9347**	**115**	**115.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§		3.37				0.10					**1.16**	
Cox regression analysis												
Regression coefficients(ß)		0.009				0.002					**0.004**	
z values (ß/s.e.) §		0.78				0.17					**0.55**	
Relative risks		1.07				1.01					**1.03**	
(95% CI of relative risk)		(0.91-1.25)				(0.86-1.19)					**(0.93-1.14)**	

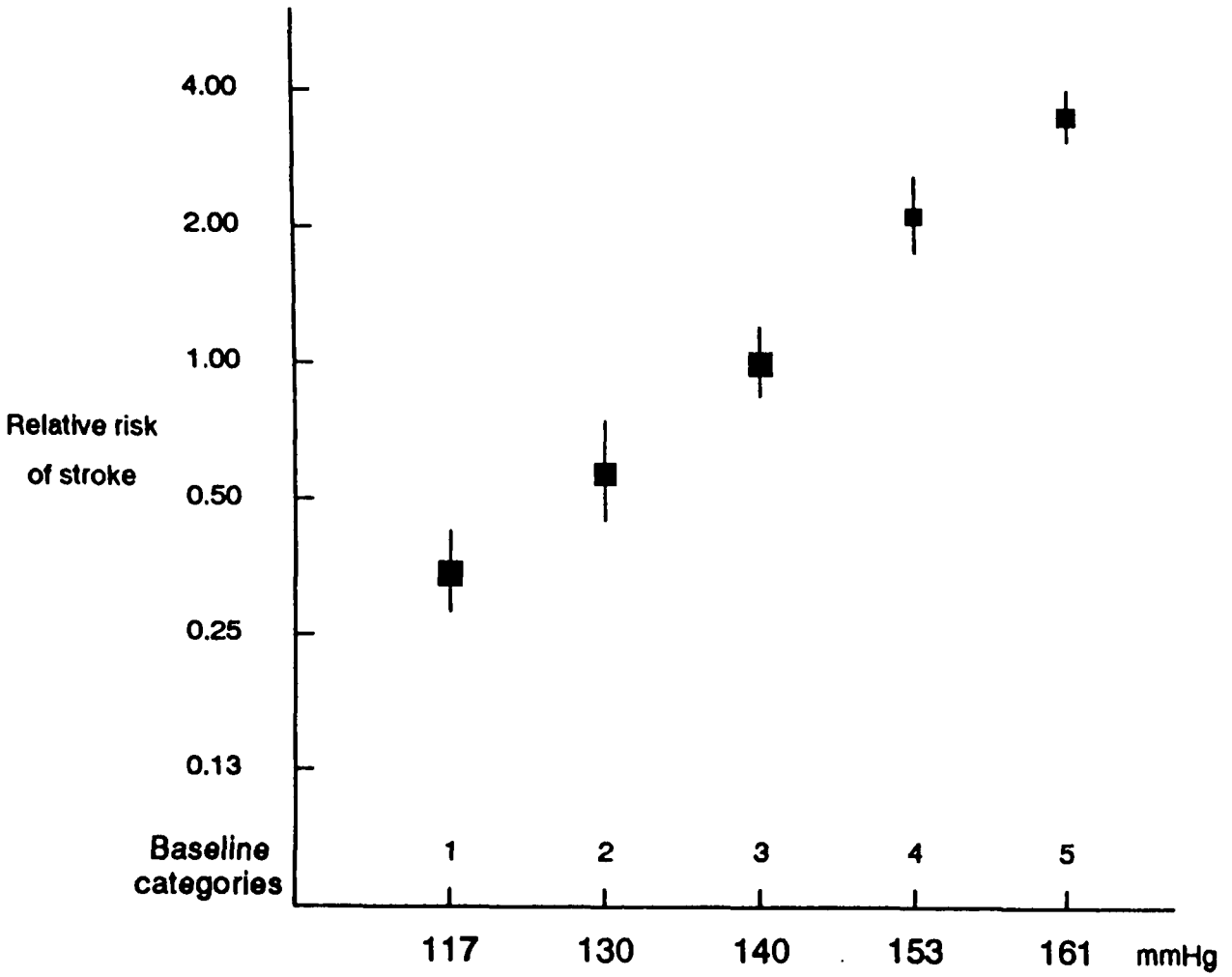
§ X^2 values less than 3.84 or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 6.31. Mean systolic blood pressure (SBP) at baseline and at 3 years post-baseline for 5 categories defined by baseline SBP in cohort A and cohort B.

Baseline SBP categories (mmHg)	Cohort A			Cohort B		
	No. of subjects	Mean SBP at baseline	Mean SBP at 3 years	No. of subjects	Mean SBP at baseline	Mean SBP at 3 years
1. ≤125	1247	111.8	118.1	1211	109.9	116.2
2. 125-139	464	131.0	129.5	191	130.5	130.2
3. 140-154	337	145.3	140.1	255	144.3	139.5
4. 155-169	104	160.9	155.5	64	160.2	151.5
5. ≥170	109	181.8	161.5	82	180.7	161.0
Total	2261	126.3	127.5	1803	122.0	124.3
Difference of mean SBP (5–1)		70.0	43.4		70.8	44.8

Table 6.32. Mean diastolic blood pressure (DBP) at baseline and at 3 years post-baseline for 5 categories defined by baseline DBP in cohort A and cohort B.

Baseline DBP categories (mmHg)	Cohort A			Cohort B		
	No. of subjects	Mean DBP at baseline	Mean DBP at 3 years	No. of subjects	Mean DBP at baseline	Mean DBP at 3 years
1. ≤79	849	71.0	74.8	868	66.2	76.2
2. 80-89	840	82.7	79.7	623	80.8	83.3
3. 90-99	350	92.8	86.0	185	91.3	91.7
4. 100-109	160	101.7	93.8	93	100.4	98.1
5. ≥110	62	114.0	96.5	34	110.9	105.8
Total	2261	82.1	80.3	1803	76.4	81.9
Difference of mean DBP (5–1)		43.0	21.7		44.7	29.6



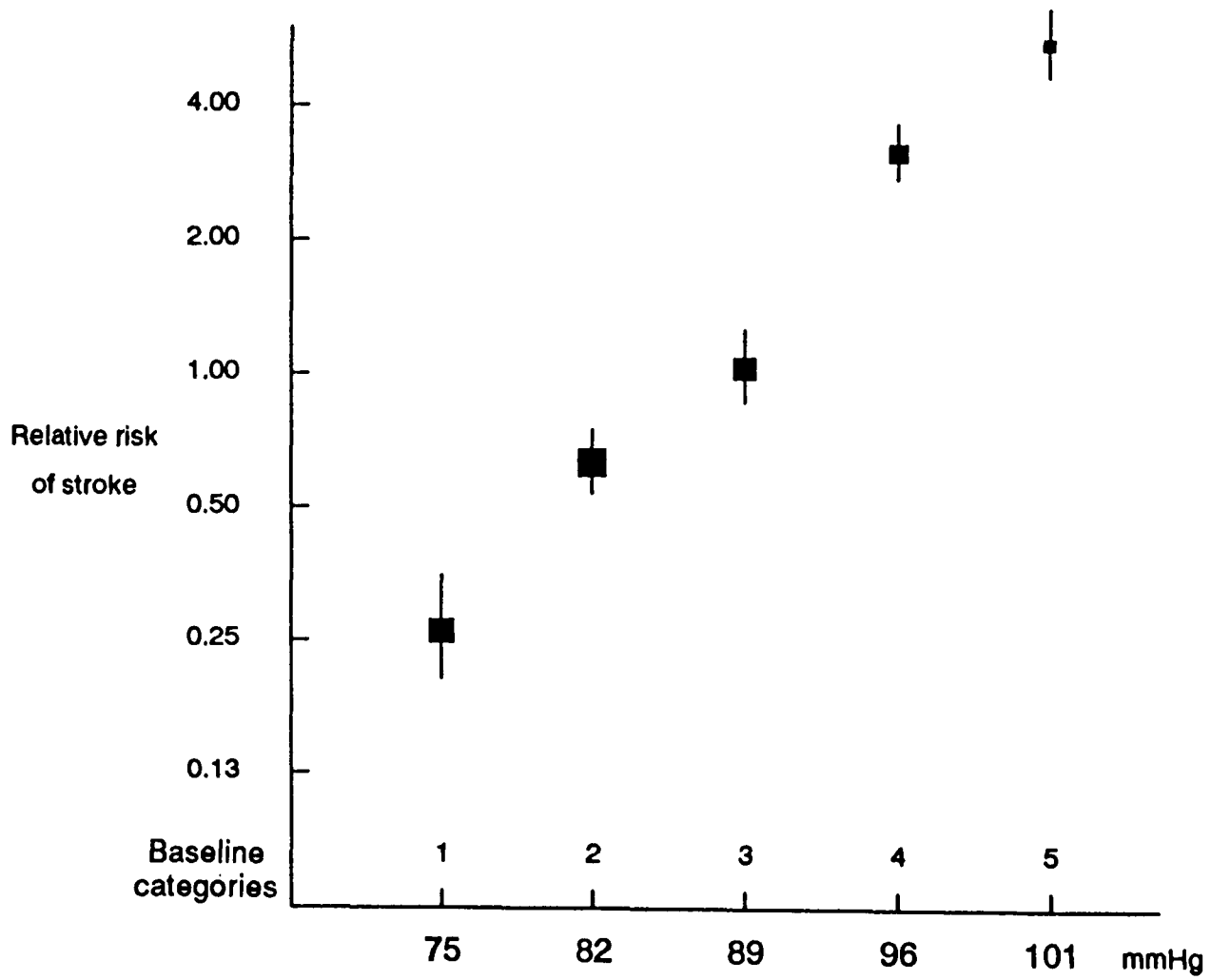
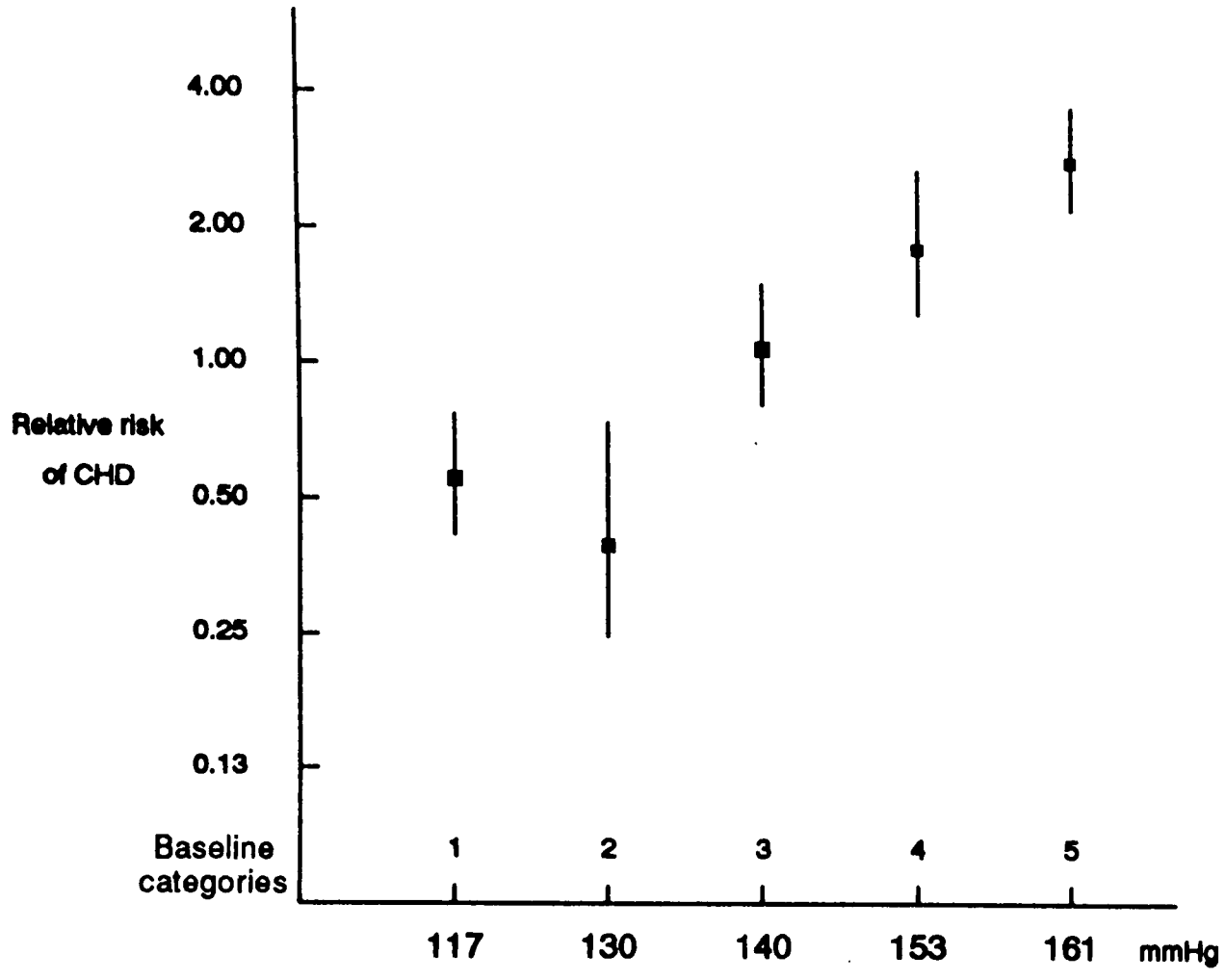


Figure 6.10. Relationship of usual systolic and diastolic blood pressure with risk of death from stroke among 9347 Chinese in Shanghai.



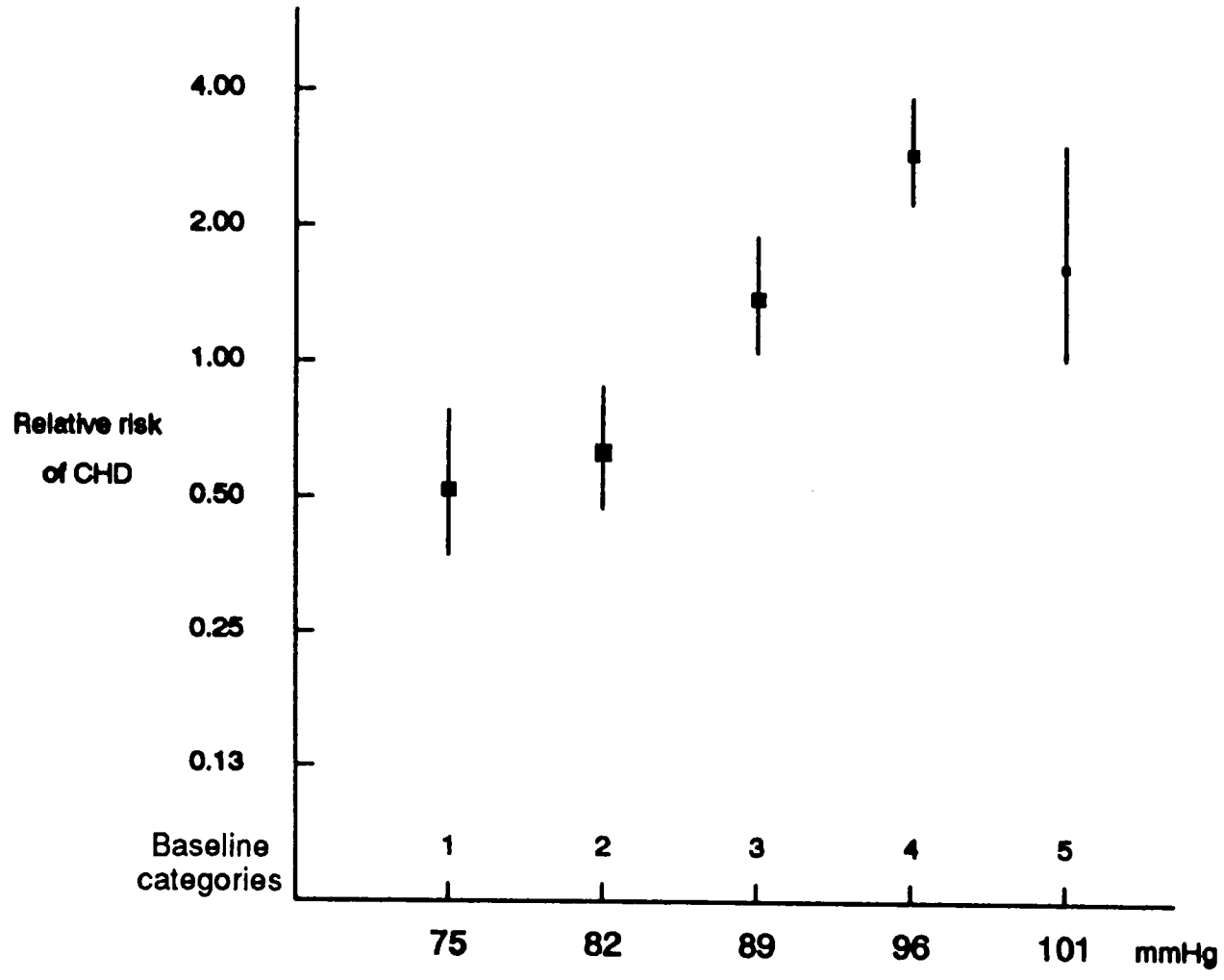
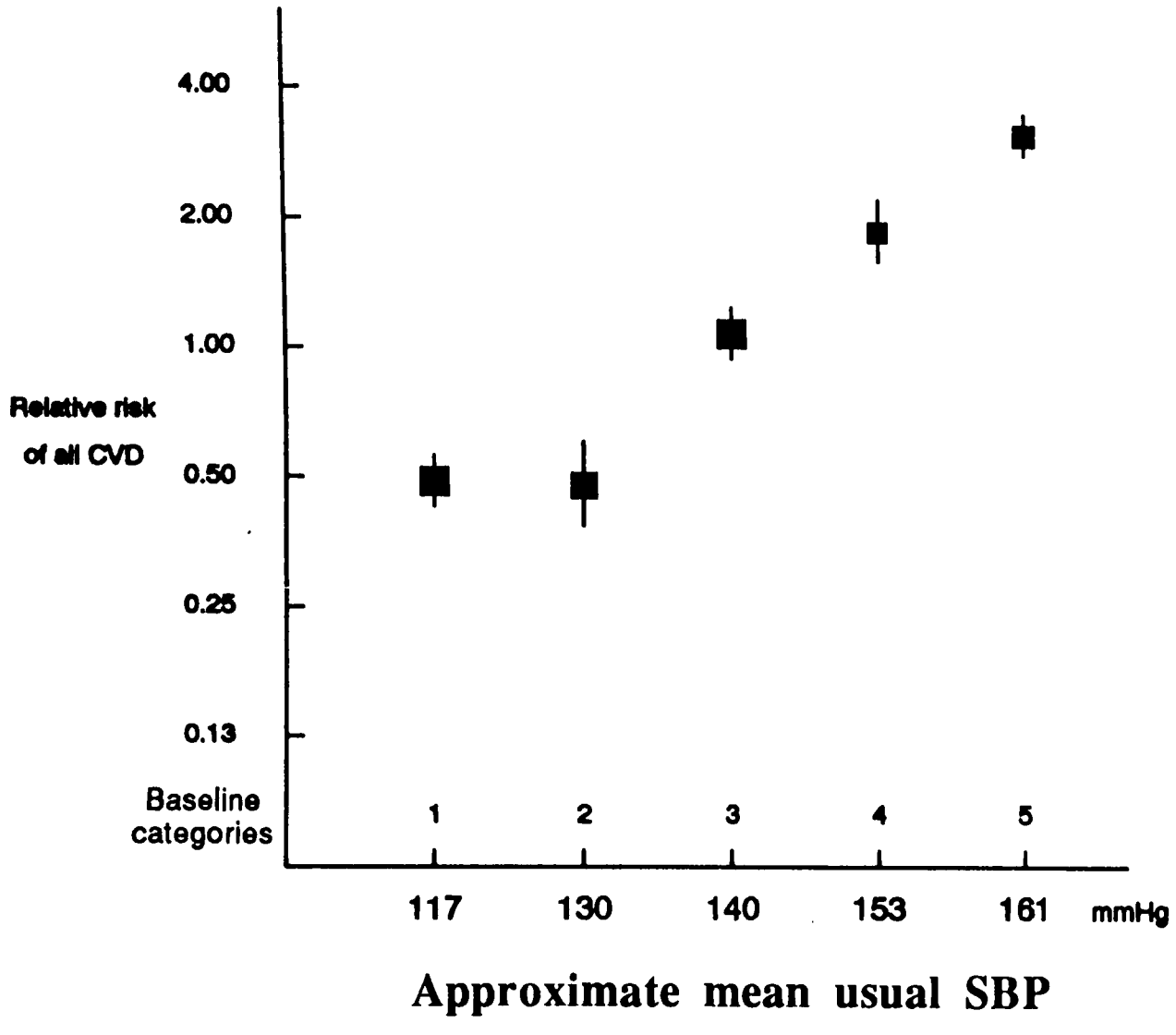


Figure 6.11. Relationship of usual systolic and diastolic blood pressure with risk of death from CHD among 9347 Chinese in Shanghai.



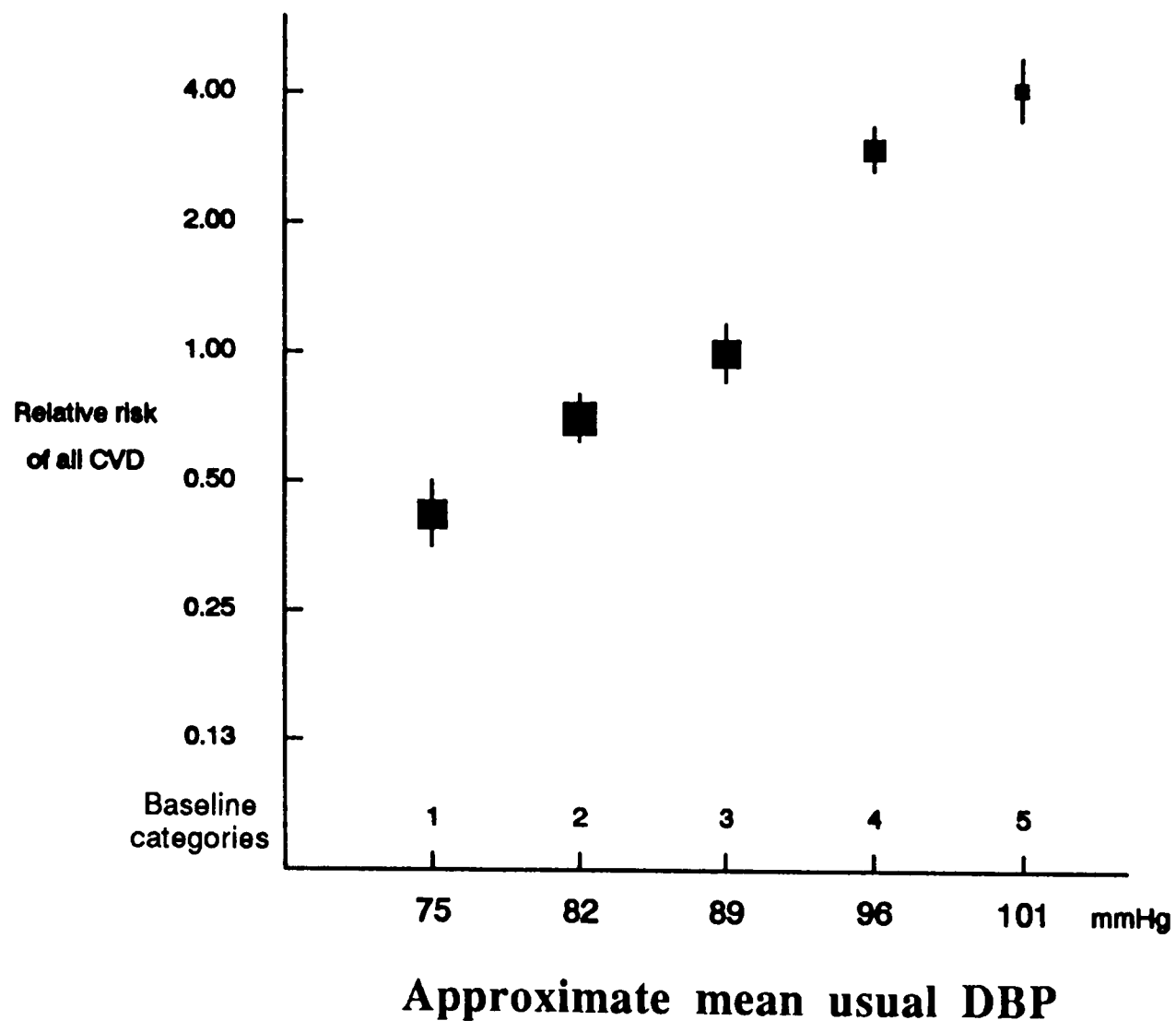


Figure 6.12. Relationship of usual systolic and diastolic blood pressure with risk of death from all vascular disease among 9347 Chinese in Shanghai.

Table 6.33. Standardised relative risks of systolic and diastolic blood pressure for deaths from coronary heart disease, stroke and all vascular disease from Cox's proportinal-hazards regression analysis in the combined data from the ztwo cohorts.

Blood pressure variables in the model	Stroke			CHD			All vascular		
	Regression coefficients¶	Standardised relative risks†	95% C.I.§	Regression coefficients	Standardised relative risks	95% C.I.	Regression coefficients	Standardised relative risks	95% C.I.
SBP alone	0.0325	2.04	1.80-2.33	0.0233	1.67	1.30-2.14	0.0261	1.78	1.59-1.98
DBP alone	0.0723	2.38	2.07-2.74	0.0413	1.64	1.24-2.17	0.0570	1.98	1.76-2.23
SBP adjusted for DBP	0.0140	1.36	1.11-1.67	0.0181	1.49	1.05-2.12	0.0122	1.31	1.11-1.54
DBP adjusted for SBP	0.0520	1.87	1.51-2.31	0.0153	1.20	0.82-1.77	0.0393	1.60	1.34-1.91
No. of deaths		**146**			**43**			**220**	

¶ The regression coefficients were estimated after adjusting for age, sex, serum cholesterol, cigarette smoking and alcohol drinking.
† The standardised relative risks indicated the relative change in risk associated with a change of one standard deviation in the SBP (22 mmHg) and DBP (12 mmHg).
§ Indicate 95% confidence interval of standardised relative risks.

Table 6.34. The number of deaths from **vascular disease** and estimated relative risks for isolated systolic hypertension in the combined data from the two cohorts during 8-13 years of follow-up.

Isolated systolic hypertension (DBP<90 mmHg)¶	Nol of subjects	Stroke			CHD			All vascular		
		Observed deaths(O)	Expected deaths(E)	Ratios of O/E	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	Observed deaths(O)	Expected deaths(E)	Ratios of O/E
Normotensive	6681	30	37.2	0.81	11	12.4	0.89	58	69.9	0.83
Borderline	623	9	7.7	1.17	2	3.2	0.63	18	14.5	1.24
Hypertension	131	9	3.11	2.89	4	1.4	2.90	14	5.66	2.47
Total	7435	48	48.0	1.00	17	17.0	1.00	90	90.0	1.00
Statistical analysis										
Log-rank trend test (X^2)§			12.36***			2.80			15.77***	
Cox regression analysis										
Regression coefficients(ß)†			0.027			0.012			0.0163	
z values (ß/s.e.)§			3.61***			0.94			2.87**	

¶ Normotensive: SBP<140 mmHg; Borderline: SBP≥140 and SBP<160 mmHg; Hypertension: SBP≥160mmHg.
§ X^2 values less than 3.84 or z values less than 1.96 are not conventionally significant, i.e. 2P>0.05.
† The regression coefficients were estimated in Cox's proportional-hazards model after adjusting for sex, age, serum cholesterol, cigarette smoking and alcohol drinking.
,* Statistically significant at 2P<0.01, and 2P<0.001 respectively.

Chapter 7

Cigarette smoking and cause-specific mortality

7.1. Characteristics of cigarette smoking at baseline

1). Proportions of current regular smokers

Information on current smoking status at baseline was available for all individuals in both cohorts. Current smokers are defined as those individuals who had smoked at least one cigarette a day during the year prior to the baseline examination. No data were collected at baseline on cigar and pipe smoking habits, as consumption of these was rare in urban Shanghai.

In Table 7.1 the proportions of current cigarette smokers at baseline are shown for cohort A according to age and sex, while corresponding data for cohort B are given in Table 7.2. Current smokers were divided into two groups according to the number of cigarettes smoked, with "light smokers" being individuals who smoked less than 20 cigarettes a day and "heavy smokers" being those who smoked 20 or more cigarettes a day. In both cohort A and cohort B, cigarette smoking was much more common in men than in women in any age group. In cohort A, 63 per cent of men were current smokers at baseline, compared with 11 per cent of women. After adjusting for differences in the age distribution, 54% of male and 12% of female were current smokers. With respect to cohort B, 60% of men were current smokers at baseline, while in contrast only 4% of women were smokers. The age adjusted proportions of current smokers were 59% for men and 5% for women.

In both cohorts, the prevalence of smoking among females increased steadily with advancing age, while among males there was an increasing trend in the smoking rate from 35-60 years old, and then the prevalence fell slightly among those aged 60-64 years. At all ages, male smokers tended to smoke more

cigarettes than did female smokers. In cohort A, 11% (119 out of 1037) of male smokers were heavy smokers compared with 7% (10/135) of female smokers. In cohort B, over half (58%) of the male smokers smoked 20 or more cigarettes a day, compared with 18% of the female smokers.

2). Age of starting to smoke among current smokers

At baseline, information was also collected on the age of starting to smoke among current regular smokers. 118 current smokers (only in cohort A) were excluded from the analyses because data on age of starting to smoke were not available. The numbers and relative frequencies of smokers subdivided by age of starting to smoke are shown in Table 7.3 and 7.4 for cohort A and cohort B respectively. In general, male smokers tended to start to smoke at younger ages than did female smokers, and heavy smokers started younger than light smokers. In cohort A, 14.5% of male smokers started to smoke before 20 years of age and 48.5% began to smoke between 20-29 years of age, while for female smokers the corresponding figures were 12.3% and 34.2% respectively. Likewise in cohort B, 13.4% of male smokers started to smoke before 20 years old, and 47.8% started between 20-29 years of age, whereas for female smokers, only 36% started to smoke before 30 years of age. In cohort A, 21% of heavy smokers started to smoke before 20 years of age, and 49.2% started between 20-29 years of age, while among light smokers, the corresponding figures were 13.3% and 46.7% respectively. As to cohort B, 16.6% and 55.2% of heavy smokers started to smoke before 20 years and between 20-29 years of age respectively, while among light smokers the corresponding percentages were 8.9% and 36.6% respectively.

3). Relation of cigarette smoking to other baseline variables

The associations of cigarette smoking with certain other baseline variables are shown in Table 7.5 for the combined data from the two cohorts. In general,

the mean age was higher among smokers than among non-smokers, and higher among heavy smokers than among light smokers. There was also a much higher proportion of male subjects among smokers than among non-smokers. Thus for all other variables presented, the mean values have been adjusted for age and sex. For blood pressure, serum cholesterol, and body weight, the age and sex adjusted mean values were calculated by ANOVA in each individual cohort separately, and weighted mean values in two cohorts together were then computed, using the inverse of the variances as weights. With respect to the prevalences of hypertension, of resting ECG abnormality and of alcohol consumption, the adjusted overall means were calculated by direct standardisation to the age and sex distributions of the two cohorts combined. It appeared that cigarette smokers had slightly lower levels of blood pressure (both systolic and diastolic pressure), of serum cholesterol and of body weight, were much more likely to drink alcohol, less likely to have hypertension and had similar prevalence of resting ECG abnormality at baseline to those who were non-smokers.

7.2. Association of cigarette smoking with total mortality

Among the study population in the two cohorts there were 620 deaths from any disease over 8-13 years of follow-up. In Table 7.6 the number of deaths from all causes along with the estimated relative risks are shown by three smoking status at baseline. Overall in the two cohorts together, there were 240 deaths from any disease among the non-smokers, and the risk relative to the whole study population was 0.87. With respect to light and heavy smoker, the risks were 1.09 and 1.13 respectively. This positive gradient in the risk of all cause deaths, from non-smokers to heavy smokers, was statistically significant by the log-rank trend test *(X^2=9.58, 2P<0.001)*.

To assess the independent impact of cigarette smoking on total mortality, a Cox regression analysis was performed, with cigarette smoking included in the

model as a binary variable (non-smoker vs smoker), adjusted simultaneously for age, sex, diastolic blood pressure, serum cholesterol and alcohol consumption. In the adjusted Cox regression analysis, cigarette smoking remained a significant predictor of total mortality after taking other variables into account. Overall among the whole study population, the regression coefficient of cigarette smoking was 0.411 *(z=4.28, 2P<0.001),* from which it may be estimated that cigarette smoking is associated with 51% (95% CI 25%-82%) excess mortality. The relation of cigarette smoking with total mortality was separately significant in both cohort A and cohort B. In cohort A, with 334 deaths from any cause during 13 years of follow-up, the relative risk associated with smoking is 1.55 (95% CI 1.20-2.00, 2P<0.001), while in cohort B, with 286 deaths from any disease during 8 years of follow-up, the smokers had 48% excess risk of mortality (95% CI 12%-95%, 2P<0.01).

The association of cigarette smoking with total mortality was also examined separately for both males and females in the combined data from the two cohorts. Table 7.7 gives the number of deaths from all causes and the estimated relative risks in the three categories of cigarette smoking at baseline. Overall among males, there were 500 deaths from all causes, and the relative risks were 0.83, 1.08 and 1.11 respectively for non-smokers, light smokers and heavy smokers *(log-rank trend test: X^2=6.78, 2P<0.0)*. Among the females, with 120 deaths from any cause during the follow-up period, the relative risks of total mortality were 0.87 for non-smokers, and 1.28 and 3.07 respectively for light smokers and heavy smokers *(X^2=5.55, 2P<0.05)* . In the adjusted Cox regression analysis, cigarette smoking remained a strong positive predictor of total mortality in both males and females after taking other variables into account. Among males the estimated excess death associated with smoking was 46% (95% CI 19%-79%, 2P<0.001), while among females it was 75% (95% CI 10%-179%, 2P<0.05).

7.3. Relationship between cigarette smoking and cancer death

1). Cigarette smoking and all cancer death

Among the 9351 subjects in the present study, 274 of the deaths that occurred during 8-13 years of follow-up were attributed to cancer. The number of deaths from any cancer, together with the estimated relative risks by smoking status at baseline are shown in Table 7.8. There was a pronounced excess of death from cancer of any site among smokers compared with non-smokers. Overall in the two cohorts together, there were 97 deaths from cancer among non-smokers, and the risk relative to the whole population was 0.80. In contrast among heavy smokers, 72 cancer deaths were observed, and the relative risk was 1.31. This trend of increasing risk of cancer death from non-smokers to light and to heavy smokers was highly statistically significant *(X^2=10.90, 2P<0.001)*.

In the adjusted Cox regression analysis, cigarette smoking remained a significant predictor of total cancer mortality after taking other variables into consideration. The regression coefficient for cigarette smoking versus total cancer mortality was 0.476 *(z=3.23, 2P<0.01)*, from which it may be estimated that smokers have a 61% (95% CI 21%-115%) excess risk of cancer death compared with non-smokers. The relationship of cigarette smoking with total cancer mortality was separately significant in both cohort A and cohort B. In cohort A, with 144 cancer deaths during 13 years of follow-up, the relative risk of cancer mortality was 1.69 *(z=2.58, 2P=0.01)* among smokers compared with non-smokers, while in cohort B, with 130 cancer deaths during 8 years of follow-up, it was 1.52 *(z=1.97, 2P<0.05)*. The excess of cancer mortality associated with smoking was seen in men, but not in women. Among male subjects with 223 cancer deaths in the combined data from the two cohorts, the relative risk of total cancer mortality for smokers was 1.77 (95% CI 1.28-2.45; 2P<0.001), while among female subjects with 51 cancer deaths during 8-13 years of follow-up, the

relative risk of total cancer mortality for current smokers was 0.74 (95% CI 0.29-1.92) (*ß= -0.294, z=-0.61, 2P>0.05).*

2). Cigarette smoking and lung cancer death

Overall in the two cohorts together, there were 27 lung cancer deaths among heavy smokers, and the risk relative to the whole population was 1.75 (Table 7.9). For light smokers and non-smokers the relative risks of lung cancer were 1.05 and 0.48 respectively. This positive gradient in the risk of lung cancer from non-smokers to light smokers to heavy smokers was highly statistically significant by the log-rank trend test *(X^2=15.40, 2P<0.001).*

In the adjusted Cox regression analysis, smoking remained a significant predictor of lung cancer mortality after taking other variables into account. Overall in the combined data from the two cohorts, the regression coefficient of cigarette smoking versus lung cancer was 1.261 *(z=3.62, 2P<0.001)*, indicating that cigarette smoking was associated with a 3.5-fold (95% CI 1.8-7.0) increase in the risk of death from lung cancer. The relationship between cigarette smoking and lung cancer was separately significant in both cohort A and cohort B. In cohort A with 34 lung cancer deaths during 13 years of follow-up, the relative risk of lung cancer for smoking was 3.0 (95% CI 1.2-7.4, 2P<0.05), while in cohort B with 32 lung cancer during 8 years of follow-up, the relative risk of lung cancer was 5.5 (95% CI 1.9-15.9, 2P<0.01). Among the male cohort, with 60 lung cancer deaths, the regression coefficient of the association between lung cancer and smoking was 1.305 *(z=3.38, 2P<0.001)*, indicating that the relative risk of lung cancer among male smokers was 3.7 times (95% CI 1.7-7.9) that among non-smokers. Based on this estimate of relative risk and on the proportion of male regular smokers (62%), it may be estimated that the population attributable risk of lung cancer was 63% (95% CI: 31-81%). That is, about two-thirds of the lung cancer deaths among males were attributed directly to smoking. Too few lung cancer

deaths were observed among women to provide a reliable estimate of the population attributable risk among women.

Table 7.10 gives the number of deaths from lung cancer according to the duration of smoking in light and heavy smokers, together with the estimated relative risks compared with non-smokers. The risk of death from lung cancer increased significantly with duration of smoking in both light and heavy smokers. Overall there were only 7 deaths from lung cancer among those individuals who had smoked less than 30 years, and using non-smokers as a reference group the risks of lung cancer were 0.52 and 1.62 respectively for light and heavy smokers. In contrast among those people who had smoked 30 years or more, 45 cases of lung cancer deaths were observed, and the relative risks compared with non-smokers were 3.86 and 4.85 respectively for light and heavy smokers.

3). Cigarette smoking and mouth, pharynx, larynx and oesophagus cancer

Overall among the study population, there were 24 deaths due to upper aero-digestive cancer (mouth (2 deaths), pharynx (2), larynx (1) and oesophagus (19)) during 8-13 years of follow-up. In Table 7.11 the number of deaths from such causes, together with the estimated relative risks, are shown according to smoking status at baseline. There was an apparent excess risk of death from this type of cancer among smokers. Overall in the two cohorts together, there were 9 such deaths among heavy smokers compared with 5.3 deaths that would be expected by chance, and the risk relative to the whole study population was 1.71. In contrast among non-smokers there were 5 such deaths, and the approximate relative risk was 0.52. This trend of increasing risk of death from upper aero-digestive cancer from non-smokers to light smokers to heavy smokers was statistically significant by the log-rank trend test *(X^2=5.70, 2P<0.05)*. In the Cox regression analysis after taking other variables into account, cigarette smoking remained a strong predictor of mortality from upper aero-digestive cancer (although for cohort A the statistical test was not significant at the 5 per cent

level). Overall in the combined data from the two cohorts, the regression coefficient of cigarette smoking was 1.210 *(z=2.08, 2P<0.05)*, from which it may be estimated that cigarette smoking was associated with a 3.4-fold increase in the risk of death from aero-digestive cancer (95% CI 1.1-11.5).

4). Cigarette smoking and other sites of cancer death

Overall among the whole study population in the two cohorts there were 63, 57 and 64 deaths attributable to stomach cancer, liver cancer and other remaining sites of cancer respectively, and their associations with cigarette smoking are presented in Table 7.12 to Table 7.14. Overall these cancers were not shown to be significantly associated with cigarette smoking, although there was a sizable association between cigarette smoking and liver cancer with risk in cigarette smokers being 1.58 times that for non-smokers after taking alcohol consumption and other variables into account (Table 7.13).

7.4. Association of cigarette smoking with vascular diseases

1). Cigarette smoking and all vascular disease

Overall in the whole study population, there were 212 deaths due to any vascular disease other than pulmonary heart disease, and Table 7.15 gives the number of deaths from such diseases and the estimated relative risks by smoking status at baseline. Overall, there was no significant association between cigarette smoking and risk of deaths from all vascular diseases, after adjusting only for age and sex in the log-rank analysis, with estimated risks of 1.00, 1.04 and 0.93 respectively for non-smokers, light smokers and heavy smokers *(log-rank trend test: X^2=0.06, 2P>0.05).* In the adjusted Cox regression analysis, cigarette smoking became a significant predictor of all vascular mortality after taking other variables into account. Overall among the whole study population in the two cohorts, the regression coefficient of cigarette smoking was 0.323 *(z=1.99,*

2P<0.05), from which it may be estimated that cigarette smoking was associated with a 38% (95% CI 1-90%) excess risk of death from all vascular disease.

2). Cigarette smoking and coronary heart disease

The number of deaths from coronary heart disease (CHD) together with estimated relative risks by smoking status at baseline are shown in Table 7.16. Overall there was no significant association between cigarette smoking and the risk of CHD. Among heavy smokers there were 8 deaths from CHD, and the estimated risk relative to the whole study population was 0.99. For light smokers and non-smokers, the CHD relative risks were 1.01 and 1.00 respectively (2P>0.05). After taking other variables into account in the adjusted Cox regression analysis, cigarette smoking was shown to be positively but non-significantly related to CHD mortality in both cohorts. Overall among the whole study population, the regression coefficient of cigarette smoking was 0.338 (z=0.96, 2P>0.05), which is consistent with current smokers having a 40% (95% CI -30%~180%) excess risk of death from CHD compared with non-smokers, although the wide confidence interval includes the possibility of no excess risk.

3). Cigarette smoking and risk of stroke death

Table 7.17 gives the number of deaths from stroke along with the estimated relative risks by smoking status at baseline. There was no significant trend in the risk of stroke with cigarette smoking after adjusting only for sex and age. Overall in the two cohorts together, there were 64 deaths from stroke among non-smokers, and the risk relative to the whole study population was 0.95. With respect to those individuals who were light and heavy smokers, the risks of stroke were 1.13 and 0.88 respectively *(trend test: X^2=0.01, 2P>0.05).* Other factors might well confound the relationship between cigarette smoking and stroke risk. For example, cigarette smoking in the present study was associated with lower blood pressure. In the adjusted Cox regression analysis, when the effects of

blood pressure and some other baseline variables were controlled for, there was an apparent positive association between cigarette smoking and risk of stroke mortality. Overall, the regression coefficient of stroke mortality to cigarette smoking was 0.465 *(z=2.40, 2P<0.05)*. From this it may be estimated that current smokers have about a 60% excess risk of stroke mortality compared with non-smokers, but with wide 95% confidence limits of 9% to 133% excess.

The data was also analysed separately for males and females (Table 7.18). A significant association between cigarette smoking and risk of death from stroke was observed among female subjects, but not among males. There were 31 deaths attributed to stroke among females, and the estimated risks of stroke were 0.80, 2.05 and 2.50 respectively for non-smokers, light smokers and heavy smokers *(X^2=6.89, 2P<0.01)*. In the Cox regression analysis after adjustment for other variables, cigarette smoking remained a strong significant predictor of stroke mortality in female subjects *(ß=1.418, z=3.42, 2P<0.001)*. The difference between males and females with respect to the relationship of smoking with stroke mortality may merely reflect the chance variation introduced by data-dependent subgroup analysis and small numbers of deaths.

7.5. Cigarette smoking and non-cancer non-vascular diseases

1). Cigarette smoking and chronic obstructive pulmonary disease (COPD)

In the present study, deaths from chronic bronchitis, emphysema and pulmonary heart disease were grouped together as chronic obstructive pulmonary disease (COPD). Overall in the two cohorts, there were 50 deaths attributed to COPD, and Table 7.19 gives the number of deaths from COPD along with the estimated relative risks according to smoking status at baseline. There was an apparent positive trend, though not statistically significant, of risk of deaths from COPD with cigarette smoking. Overall in the two cohorts together, there were 13 deaths from COPD among the heavy smokers, and the risk relative

to the whole study population was 1.28, while for for light smokers and non-smokers, the risks were 1.12 and 0.71 respectively *(Log-rank trend test: X^2=2.75, 2P>0.05)*. In the adjusted Cox regression analysis, with smoking included as a binary variable, there was a significant positive association between cigarette smoking and risk of COPD after taking other variables into account. In the combined data from the two cohorts, the regression coefficient of smoking was 0.774 *(z=2.16, 2P<0.05)*, from which it may be estimated that the risk of COPD mortality among current smokers was 2.2 times (95% CI 1.1-4.4) that for non-smokers.

2). Cigarette smoking and risk of death from cirrhosis

Overall there were 24 deaths due to cirrhosis among the whole study population, and Table 7.20 shows the number of deaths from cirrhosis and the estimated relative risks according to smoking status at baseline. There was no significant association between risk of death from cirrhosis and cigarette smoking, with the overall estimated risks being 0.88, 0.83 and 1.38 respectively for non-smoker, light smoker and heavy smoker *(X^2=0.96, 2P>0.05)*, even after adjustment in the Cox regression analysis for other variables *(z=1.28, 2P>0.05)*.

3). Cigarette smoking and other medical causes of death

Overall in the two cohorts there were 43 deaths from the remaining medical causes of death (Table 7.21). The overall relative risks for non-smokers, light smokers and heavy smokers were 0.78, 1.47 and 0.78 respectively *(X^2=0.56, 2P>0.05)*, and there was no significant association even after taking other variables into consideration.

4). Cigarette smoking and non-medical causes of death

Among the whole study population there were 17 deaths due to non-medical causes (suicides, accidental and violent deaths, Table 7.22). Overall, there was a

positive, but non-significant association of such deaths with cigarette smoking. The estimated relative risks were 0.92, 1.05 and 1.11 respectively for non-smokers, light smokers and heavy smokers *(X^2=0.14, 2P>0.05).* In the adjusted Cox regression analysis after taking other variables into account, there was no apparent association of cigarette smoking with risk of death due to non-medical causes *(ß=0.107, z=0.18, 2P>0.05).*

7.6. Discussion

1). Characteristics of smoking patterns in the present Chinese population

The present study in a Chinese population in Shanghai showed that smoking was already very prevalent in early 1970s among Shanghai adult population, especially among males. Over 60% of men surveyed were regular smokers, but the prevalence of smoking was low among women at 7%. In this study, the peak smoking prevalence rates occurred later in life, between 55 and 59 years of age among males, and between 60 and 64 years of age among females. This is in contrast to that observed in Western populations in which peak smoking rates are generally found between 25 and 44 years of age for both men and women *(Schoenborn & Boyd, 1989; Yu, et al 1990).* Moreover, the smokers in the present study began smoking regularly later in life than people in Western populations. About 13% of smokers in this study reported having started smoking regularly before 20 years of age, whereas in the United States, nearly 90% of all smokers started smoking before 20 years of age *(Schoenborn & Boyd, 1989; Yu, et al 1990).* A smoking survey among 110,000 adults in Shanghai in the early 1980s *(Deng & Gao, et al 1985)* also revealed a similar finding on the age of starting to smoke. In that study, 12% of male smokers started smoking before 20 years of age, and 23% started between 20 and 24 years of age. There is, however, evidence from recent survey in China that people are now tending to smoke earlier than before. A recent survey in Beijing indicated that 24% of males under 18 years of age are regular smokers *(Ministry of Public Health 1988).*

2). Relationship of cigarette smoking with cancer

During the past three decades there has been a sizable increase in lung cancer incidence in Shanghai, while the incidence rates for stomach cancer and many other sites of cancer have remained stable. During the period from early 1960s to middle 1980s in Shanghai, the age standardised mortality from lung cancer among men nearly doubled from 28/100,000 to 52/100,000, although it was still significantly lower than that in USA *(Gao 1986).* In 1986, the incidence of lung cancer among males in Shanghai exceeded that for stomach cancer and ranked as the leading cause of cancer mortality. The overall lung cancer rates in Shanghai exceed the Chinese national average by more than three-fold in late 1970s *(Shanghai Cancer Institute 1982).* The rapid increase in the incidence of lung cancer in Shanghai is considered to be partly due to an increased population reaching old age, but chiefly due to a higher prevalence of prolonged cigarette smoking compared with other parts of China.

Epidemiological observational studies in various part of the world have provided overwhelming evidence on the causal relationship between smoking and lung cancer. Since the early 1950s when the first epidemiological study of the relationship between smoking and lung cancer was ever conducted, eight big cohort studies covering 17.5 million person-years of experience and 90 years of follow-up in five different regions of the world have shown that the risk of developing lung cancer (as well as most other cancers associated with smoking) is dose related, i.e., the more cigarettes consumed daily, the earlier the age one initiates smoking behavior, and the more years one has smoked, the greater the risk *(Surgeon General's Report 1982).* Cessation of smoking is associated with some reduction of risk, although the degree of excess risk among former smokers is strongly dependent on total prior exposure, number of years since quitting smoking and the health status of the individual at the time of cessation *(Surgeon General's Report 1982).* Consistent results on the relationship between cigarette

smoking and lung cancer have also been shown in a number of case-control studies in Shanghai and in other parts of China, but the additional evidence from prospective studies in China is sparse. In the present prospective study in a Chinese population in Shanghai lung cancer was the most common type of cancer in the study population. Confirming previous studies, there was a strong, positive relationship between cigarette smoking and risk of lung cancer mortality. The risk of lung cancer increased with the amount of cigarettes smoked, and with the duration of smoking. Regular smokers had about a four-fold increased risk of lung cancer mortality compared with non-smokers, and it was estimated that 63% (95% CI 31-81%) of the lung cancer deaths among the male population were attributed directly to cigarette smoking. The overall strength of the relationship between cigarette smoking and lung cancer was, however, much smaller than that reported by many other studies. These indicate about an 8-fold to 20-fold increased risk of lung cancer among smokers compared with non-smokers, suggesting that smoking is responsible for over 85% of male lung cancers in the population *(Doll & Peto 1976; 1978; Shopland, et al 1991)*. It is not yet clear if this apparent discrepancy between the present study and studies in Western populations is due chiefly to the play of chance, or due to the difference in the smoking patterns in the populations. In particular, age of starting to smoke, duration of smoking, amount of cigarettes smoked and types of cigarette smoked.

These factors may differentially affect the development of the various types of lung cancer *(Devesa, et al 1991)*. It is known that although all of the principal types of lung cancer (squamous cell, oat cell carcinoma and adenocarcinoma) are strongly related to the smoking, the strength of the relationship varies by cell type, with squamous and oat cell carcinoma being most strongly associated with smoking. In a hospital-based, case-control study of lung cancer in Beijing *(Huang, et al 1981)*, in which 334 cases and 1189 controls were involved, the relative risks of squamous-cell carcinoma, adenocarcinoma and undifferentiated carcinoma of lung cancer for smokers were 11.0, 2.2 and 3.6 respectively.

Similarly, a case-control study of lung cancer with different histological types conducted in Shanghai showed that the association of squamous cell carcinoma of lung cancer with smoking was very strong, the relative risks being 12 and 7 respectively for males and females; while for adenocarcinoma the association was weak with relative risks being 1.77 and 1.10 respectively for males and females *(Zheng & Gao 1986).* In another large case-control study in Shanghai involving 1405 (733 males and 672 females) lung cancer patients and 1495 population-based controls *(Gao, et al 1988)*, squamous cell cancer (48% of total lung cancer) and adenocarcinoma (33%) were the most frequent types among males, while among females the order was reversed, with adenocarcinoma (61%) much more common than squamous cell carcinoma (22%). Less than 10% of the tumours in both sexes were oat cell carcinoma. Overall, smokers experienced a 3.9-fold (males) and 3.3-fold (females) increased risk of lung cancer. The associations with smoking in both sexes were much stronger for squamous or oat cell cancer than for adenocarcinoma (relative risks 7.5 vs 1.5). For all types of lung cancer combined, the population attributable risks were 69% for males and 24% for females. If the histological composition of lung cancers is similar in the present study, this may explain partly the relatively lower overall risk of lung cancer among smokers than that reported in many Western populations.

In the present study there were insufficient lung cancer cases in the females to allow separate analysis. Although studies in China have demonstrated a significant increased risk of lung cancer among female smokers, cigarette smoking appears to account for only about one-quarter of all lung cancers among women *(Gao, et al 1988).* The percentage of adenocarcinoma, the predominant cell type of lung cancer in Shanghai females, estimated to be due to smoking was less than 10%. In China, the incidence of lung cancer among life-long non-smoking females has been documented as one of the highest in the world for reasons that are not clear *(Shimizu, et al 1985).* A recent survey in Shanghai provides evidence that factors other than cigarette smoking, including long-term

exposure to oil vapours generated by high temperature wok cooking, contribute significantly to the elevated risks of lung cancer among women *(Gao, et al 1987).*

One of the key features of the relationship between cigarette smoking and lung cancer is the relevance of duration of regular cigarette smoking to lung cancer rates. The delay between cause and full effect may mean that the main increase in cigarette usage in a country takes place over a decade or two during which no large absolute increase in lung cancer incidence occur, and that later on a vast increase in lung cancer incidence takes place over the course of a few decades during which no further large increase in smoking is occurring. Likewise, the individual risk of lung cancer also depends more strongly on duration than on the daily dose-rate of cigarette smoking *(Peto 1986; Doll & Peto 1978).* In the American Cancer Prevention Study (CPS I & CPS II), the relative risks of lung cancer among male smokers doubled from 11 to 22 during the last three decades *(Surgeon General's Report 1989).* During the same period, the risk of lung cancer among female smokers increased more than fourfold from 2.7 to 11.9, and the mortality rates among female smokers increased from 24/100,000 in the early 1960s (CPS I) to 130/100,000 in the middle of 1980s (CPS II) *(Shopland, et al 1991).* Interestingly, the lung cancer mortality rate among life-long non-smokers has remained virtually unchanged over this time-span (about 12/100,000) *(Shopland, et al 1991).* The increased lung cancer risk observed in smokers between the two different periods most likely reflects a greater total lifetime exposure to cigarette smoking among CPS II enrollers than among CPS I enrollers. Based on the data from the British Doctors Study, *Peto (1986)* estimated that a three-fold increase in the daily dose-rate may produce about a three-fold increase in effect, while a three-fold increase in duration might produce a 100-fold increase in lung cancer risks. The present study also indicated a strong duration effect of regular smoking on the risk of lung cancer death, although the results shown in this study were not as marked as those suggested above. There was no apparent difference in the risk of lung cancer deaths

between non-smokers and those people who had smoked for less than 30 years. In contrast among those individuals who had smoked for 30 years or more, there was about a five-fold increase in the risk of lung cancer compared with non-smokers. In a case-control study of lung cancer in Shanghai *(Gao, et al 1988),* it was found that for those individuals who smoked less than 20 cigarettes a day, the odds ratio for lung cancer were 0.9, 3.2 and 3.8 respectively for a duration of smoking between 1-29, 30-39 years and over 40 years, while for heavy smokers who smoked at least 30 cigarettes a day, the odds ratio for lung cancer for the three durations of smoking were 3.0, 10.8 and 15.4 respectively.

Data from a number of case-control and cohort studies has indicated that cigarette smoking is also a major cause of cancer of the mouth, pharynx, larynx and oesophagus, although there is considerable variation in the proportions of cancer that were caused by smoking as a result of variation in the consumption of alcohol and in the prevalence of those still unknown factors which cause the extremely high incidence of oesophageal cancer in parts of Africa and Asia *(Willims & Horm 1977; Kuller & Terris 1965).* Risk ratios for oesophageal cancer from case-control studies range from 1.3 to 11.1 among heavy smokers compared with non-smokers *(Cook-Mozaffari, et al 1979; Day, et al 1980)*, while corresponding risk ratios from cohort studies range from 1.8 to 6.4, with four of the largest studies demonstrating a clear dose-response relation *(Surgeon General's Report, 1982).* In the British doctors study *(Doll & Peto 1976),* the mortality rates from cancer of the mouth, pharynx, larynx and oesophagus were closely associated with smoking, with the risk being 9 times as high in cigarette smokers as in lifelong non-smokers. In the present study about 9 percent (24 deaths) of total cancers were due to cancer of the mouth, pharynx, larynx and oesophageal. Cigarette smoking was shown to be closely related to mortality from these cancers, the risk in smokers being more than 3 times that in non-smokers. There was also a positive trend in the mortality from these four types of cancer with amount of cigarettes smoked

Overall, cancers of the stomach, liver and other remaining sites did not, in the present study, show significant associations with cigarette smoking, although there was a indication of excess risk of death from liver cancer associated with smoking. The epidemiological studies have provided inconsistent data on the association of smoking with stomach and liver cancer, but further evidence that has accumulated in the last few years now suggests that cigarette smoking is a cause for both stomach and liver cancer *(Doll, et al 1990).* Neither of these two cancers is found to be very closely associated with smoking, the risk in cigarette smokers being only about double that in non-smokers, or less. The major cohort studies on smoking have reported relative risks of the order of 1.4 to 1.5 for stomach cancer among cigarette smokers, but no dose-response relationship *(Hammond 1966; Doll & Peto 1976).* Cancer of the liver was positively associated with cigarette smoking in the American Cancer Society Study *(Hammond 1966)*, the relative risks being 2.8 for men aged 45-64 and 1.3 for men aged 65-79. No information was available on alcohol consumption, but the finding of relative risks for liver cirrhosis of 2.1 and 2.0 in the two age groups, respectively, is indicative of a major confounding effect. A number of case-control studies have not, however, found that the association of liver cancer and cigarette smoking is subject to confounding by alcohol consumption. In a case-control study in Hong kong *(Lam, et al 1982)* involving 149 cases of liver cancer, only 19 were HBsAg-negative, and the cigarette consumption of these 19 cases was compared with controls; the relative risk for smokers of >20 cigarettes/day was 3.3 (95% CI 1.0-13.4). Only one of the liver cancer patients who was a heavy smoker was also a heavy drinker, and, overall, there was no significant association between alcohol consumption and risk for liver cancer.

3). Association of cigarette smoking with coronary heart disease

The incidence of and mortality rates from coronary heart disease are known to be very low in Chinese, judged by Western standards. In the present study only

7% of total deaths were certified as being coronary heart disease compared with at least 30 per cent of total deaths normally seen among adults in most Western populations. There was no significant association in the present study between cigarette smoking and risk of CHD. But the number of CHD deaths was small and the relative risk of CHD among smokers of 1.40 is compatible with 50-70% excess risk of CHD associated with smoking that has commonly been reported *(Doll & Peto 1976; Dawber 1980).*

In populations where the mean blood cholesterol level is high and coronary heart disease is prevalent, cigarette smoking has been firmly established to be one of the most important risk factors for the development of coronary heart disease *(The Pooling Project Research Group 1978; Dawber 1980; Doll & Peto 1976).* In a study of 34,000 male British doctors followed for 20 years, coronary heart disease accounted for 3191 of the 10072 deaths *(Doll & Peto, 1976)*, and the overall risk of CHD mortality was 62% higher among cigarette smokers. There was also a significant dose-response relationship between risk of CHD death and smoking. A study in British female doctors revealed similar results *(Doll, et al 1980)*, with the risk of CHD among women who smoked 15 or more cigarettes daily double that for non-smokers. In the Framingham Heart study *(Dawber 1980)*, the incidence of CHD increased in a gradient from non-smokers, to ex-smokers, to light smokers, to more than double for smokers of 20 or more of cigarettes per day. A study of 290,000 US military veterans *(Rogot & Murray 1980)*, which spanned a time when cigarette smoking and CHD were rising, found a risk of CHD that was 58% higher for smokers than for non-smokers.

A few studies in populations in which the mean cholesterol is low and CHD is less prevalent have, however, failed to demonstrate a significant excess risk of CHD with smoking *(Robertson, et al 1977; Gordon, et al 1974).* In the Seven Countries Study *(Keys, 1980)* there was a large difference in the prevalence of cigarette smoking and in the incidence rate of CHD between different cohorts.

This variation of CHD rates in the different populations was not related to overall prevalence of smoking in the population. The relationship between individual smoking habits and their risk of CHD also varied greatly among individual cohorts. For the US and Northern Europe cohorts, there was a close association between cigarette smoking and CHD death rates, with relative risk in heavy smokers being 3-4 times that in non-smokers. For men in Southern Europe (Italy, Greece, and Yugoslavia), smoking was positively but non-significantly related to the risk of CHD deaths. Japan had the highest proportion of heavy smokers in the study, but deaths from CHD among the Japanese men were too few to allow individual analysis.

In an epidemiological study of coronary heart disease in Japanese men living in Japan and in Hawaii *(Robertson, et al 1977; Yano, et al 1988),* cigarette smoking was found to be significantly related to the risk of CHD for the Japanese in Hawaii but not in Japan where the mean cholesterol was significantly lower than that in Hawaii, but there was no statistically significant difference in the effect of cigarette smoking on CHD between the two populations. Similar reports have also been reported in some studies in China, where the situation is very similar to Japan (i.e, low mean cholesterol, high proportion of smokers especially among men and low rate of CHD). In a prospective study of 1,000 male factory workers followed for four years, cigarette smoking was found not to be significantly associated with the increased risk of CHD incidence *(Wu, et al 1983).* The lack of significant impact of cigarette smoking on CHD in these populations was sometimes cited as evidence to suggest that cigarette smoking may be less important as a risk factor for CHD in a population where the mean blood cholesterol is low.

In populations with low mean cholesterol such as Chinese and Japanese, it is difficult to determine reliably the importance of smoking as a cause of CHD because the rate of coronary heart disease is very low. In general, the

prospective studies mentioned above did not separately record enough CHD events to assess the relationship with smoking reliably, and consequently the association in a particular study may be subject to appreciable random fluctuations. Reliable evidence about the association between cigarette smoking and risk of CHD in such populations can only be established by large and long-term study involving a large number of events. In a large Japanese study, involving 250,000 men and women, 6000 people died of CHD during 13 years of follow-up, and in smokers the mortality rate from CHD was 1.7 times that in non-smokers *(Hiranama & Hamano 1981).* The proportions of CHD mortality attributed to cigarette smoking were estimated to be 34% and 9% respectively for men and women. In another large prospective study of 16,711 Japanese, there were 198 CHD events during 16 years of follow-up, and cigarette smoking was shown to be significantly associated with a 60% excess risk of CHD *(Szatrowski, et al 1984).*

The importance of smoking as a cause of CHD in individuals is abundantly clear, but its effect on national rates and trends have been hard to identify. The aetiology of CHD is multifactorial, the principal modifiable risk factors being high blood cholesterol, high blood pressure and cigarette smoking. Although cigarette smoking is a strong predictor of myocardial infarction in high-risk populations, the same is not true for uncomplicated angina pectories *(Kannel, et al 1984; Hagman, et al 1987)*, This could mean that smoking does not cause coronary heart atherogenesis per se, but rather increases risk from myocardial infarction in those who already have significant underlying coronary atherosclerosis. That some elevation of blood cholesterol levels may be a necessary prerequisite for the widespread development of CHD is suggested by the virtual absence of CHD in rural Chinese populations in which the prevalences of smoking and hypertension are often high and blood cholesterol is very low *(Chen, et al 1990).*

4). Association of cigarette smoking with risk of stroke death

Although the evidence implicating cigarette smoking in the risk of coronary heart disease is consistent and substantial, the effect of smoking on stroke is less clear. Smoking has usually been considered to be either an unlikely or a possible but uncertain risk factor *(Ostfeld 1980; Dyken et al 1984; Warlow 1987).* But further evidence that has accumulated in the last few years strongly suggests that cigarette smoking is a major risk factor for stroke, although it is still not clear whether smoking principally increases the risk of cerebral haemorrhage or cerebral thrombosis, as these two conditions are not well differentiated in most epidemiological studies. A number of case-control studies that have compared stroke patients with controls have found an increased prevalence of cigarette smoking among the cases. In one such study, involving a total of 132 cases of stroke and 1586 population-based controls, cigarette smokers had a threefold increase in the risk of stroke compared with current non-smokers *(Bonita, et al 1986).* Furthermore there was also a dose-response relationship between the number of cigarettes smoked and the risk of stroke.

In the Framingham prospective study involving 4255 men and women for 26 years of follow up *(Wolf, et al 1988)*, there was a significantly increased risk of stroke generally, and particularly of brain infarction, in cigarette smokers of both sexes even after taking age, hypertension and other factors into account. The risk of stroke increased with the numbers of cigarette smoked and, in general, women had a slightly higher relative risk than men. A strong relationship between cigarette smoking and stroke, for both hemorrhagic and thromboembolic stroke, was also demonstrated in the Honolulu Heart Program Study *(Abbott, et al 1986)* involving 7872 Hawaiian men of Japanese ancestry with 12 years of follow-up. In that study, cigarette smokers had an incidence of stroke two to three times that of non-smokers. Subjects who stopped smoking halfway through the follow-up period experienced a significant reduction in the risk of stroke compared with those subjects who continued to smoke. Cigarette smoking as a risk factor for

stroke has not, however, been consistently shown in a few prospective studies *(Paffenbarger, et al 1978; Nomura, et al 1974; Okada, et al 1976).* In Japan where stroke incidences are high and cigarette smoking is prevalent (especially in men), epidemiological evidence regarding the relationship between smoking and stroke is also contradictory. A few studies have failed to show significant associations between smoking and the risk of cerebral hemorrhage or of cerebral infarction (*Okada, et al 1976; Tanaka, et al 1982; Ueshima, et al 1980)* .

There was in the present study a 60% excess of stroke deaths among smokers compared with non-smokers, and the relationship was particularly evident among female subjects. It is not clear whether the lack of a significant relationship in men is due simply to the play of chance, or to a difference in smoking habits compared with women, or even due to other confounding factors which were not studied in the present population. A recent analysis of the Medical Research Council's trial on mild hypertension suggested significantly greater risks from smoking in women *(Medical Research Council Working Party 1988).* Reasons for the differences are speculative and may include a higher dose per unit of body mass from a single cigarette in women, the concurrent use of oral contraceptives, and even a small protective effect of the widespread use of alcohol in men who smoke. In discussing this it should be borne in mind that no emphasis should be given to the different effects of smoking in different sexes before more evidence becomes available. For even though it may be possible to devise biological hypotheses to explain this apparent interaction between cigarette smoking and sex on the risk of stroke, it is also quite possible to suppose that it is largely or wholly due to bias produced by data-dependent subgroup analysis, especially when the number of stroke cases is small and the strength of the relationship assessed is only moderate *(Collins, et al 1987).*

From existing evidence in epidemiological observational studies, the relative risks of stroke related to smoking ranged from 0.5 to 3.0. The lack of consensus

on the relationship between cigarette smoking and risk of stroke is thus not surprising, because with such relative risks random variation alone could produce non-significant results or even suggest a reverse association not reflecting the true pattern. Reliable evidence on the relationship between cigarette smoking and stroke can, therefore, only be achieved by very large studies or by a systematic overview of individual studies. In a recent overview *(Shinton & Beevers 1989)* including thirty-two available studies, the overall relative risk of total stroke associated with cigarette smoking was 1.5 (95% CI 1.4 to 1.6). There was also a dose response relationship between the number of cigarettes smoked and the relative risk of stroke. A small difference in relative risk of stroke between the sexes was also noted, with relative risks being 1.43 for men and 1.72 for women. This overview provides strong and reliable evidence of an excess risk of stroke among smokers. That smoking should be associated with about 50% excess risk of stroke is comparable with the results shown in the present study among a Chinese population. This figure is modest by epidemiological standards but reflects a large potential for preventing stroke, especially in the populations such as the Chinese where cigarette smoking is widespread and stroke rates are high. The observation in a few studies that smokers who give up smoking develop stroke at rates similar to nonsmokers may be providing a clue as to the mechanism by which cigarette smoking increases the risk of stroke and other cardiovascular disease *(Wolf, et al 1988; Rogers, et al 1985; Shaper, et al 1991)*. Cigarette smoking may act chiefly by precipitating the clinical event, possibly by increasing fibrinogen levels in the blood and by adversely affecting hemorheologica factors that promote thrombus formation *(Kannel, et al 1987)*.

5). Relationship of cigarette smoking with risk of COPD death

It has been well established by strong and consistent epidemiological evidence that cigarette smoking is the major cause of chronic obstructive

pulmonary disease (i.e. chronic bronchitis, emphysema, or pulmonary heart disease) *(Fletcher, et al 1976; Surgen General's Report, 1984).* Findings reported in the *Surgeon General's report (1984)* indicated a uniform increase in death rates from COPD among male and female smokers compared with non-smokers in eight major prospective studies. The mortality ratios vary markedly, however, from 2.2 in a Japanese study to 24.7 in the British doctors study. In the present study, the relative risk of COPD deaths among smokers was 2.2 times that among non-smokers, an association which is compatible with that of the Japanese study, but much weaker than that observed in many Western populations *(Surgeon General's report 1984).* Some of this variability can be attributed to the different patterns of certification of cause of death as well as the definition used to classify COPD in the different studies, but a number of other factors may also be important. As seen in many studies *(Surgeon General's Report, 1984),* death rates from COPD rise steeply with age, particularly over the age of 65 years. Studies of populations under age 65 may, therefore, significantly underestimate the impact of cigarette smoking on COPD because of the long duration of smoking required to damage enough lung to result in death from COPD. The population under 65 contains large numbers of individuals who have significant airflow obstruction and who will die of COPD, but who have not done so prior to age 65. This explanation was supported by the observation in the American Cancer Society Study, in which the relative risk for COPD among male smokers aged 45-64 was 6.6, but increased to 11.4 for those people aged 65-79 years *(Surgeon General's Report, 1984).*

A second reason for the relatively small risk of COPD among smokers in the present study may be attributed to the selection of a working population, and a relatively short duration of follow-up. The incremental nature of lung injury in COPD often results in a prolonged period of disability prior to death. This disability is usually incompatible with full-time work. Therefore, the study of an occupational population excluded selectively those individuals with significant

existing disability from COPD. This would tend to underestimate the subsequent COPD death rates in the population, and consequently lead to an underestimation of the relative risk of smoking, unless the follow-up period is long enough to observe the progression of COPD from its asymptomatic stages through the development of disability and finally death. This so-called "healthy worker" effect is present to varying extents in all prospective studies and is one of the reasons the studies with the longest follow-up periods also tend to have the largest COPD mortality ratios. The British Doctors study with a follow-up of 20 years revealed a mortality ratio for male smokers of 25 *(Doll & Peto, 1976).*

The third interpretation for the difference in COPD risks may be due to the variation in the smoking habits among different populations. The extent of lung injury is influenced by both the number of cigarettes smoked per day and the duration of the smoking habit. In the present study, the population selected were relatively young, and on average they had not smoked for a long period, and the average rates of cigarette consumption were also low. Only 13% of smokers in this study started smoking before 20 years of age, compared with nearly 90% in Western populations *(Yu, et al 1990).* In most Western populations, smoking is known to be the most important cause of COPD, and there is hardly any COPD occurrence in life-long non-smokers. But this is not the case in the Chinese, for the mortality rate from COPD is very high even in Chinese women, although the majority of them are non-smokers *(Chen, et al 1990).* Some unknown factors, possibly poor nutrition, respiratory infection during childhood, exposure to environmental smoke may contribute to the high COPD in Chinese. This may also help to explain why, in China, smoking is not as strongly related to COPD as it is in many Western populations.

6). Cigarette smoking and other causes of death

There are conditions that may be associated with smoking only because smoking is associated with another factor that is the primary cause *(Doll, et al*

1990). In the British doctor study *(Doll & Peto 1976)* cigarette smoking was found to be associated with a five-fold increase in death from cirrhosis of the liver. Although it is possible that some chemicals in tobacco smoke are toxic to the liver, the most plausible explanation of at least part of this greatly increased risk from cirrhosis in smokers is that smoking is closely related to alcohol drinking, which is responsible for most of the liver cirrhosis in Western populations. In many Asian populations the situation is, however, different, most of cirrhosis being caused primarily by prolonged infection of the liver with hepatitis B virus. There were 24 deaths due to cirrhosis in the present study, and they were positively but non-significantly associated with smoking after taking alcohol drinking and other variables into account.

Suicide is regularly found to be more common in cigarette smokers than in non-smokers. In the British Doctors study there was a 2.5 fold excess of deaths from suicide in heavy smokers. The risk of death from poisoning, many of whom can be classed as suicide, was also increased 4-fold among the heavy smokers. These associations may be largely or wholly due to personality features that lead both to the continuation of the smoking habit and to suicide. In the present study, the association of smoking with deaths from all non-medical causes (including suicide and poisoning) was analysed, but the number of such deaths was too small to produce reliable estimation of any association.

7.7. Conclusions

1). There is a high prevalence of cigarette smoking in Shanghai, especially in men. However, smokers in the present study began smoking regularly later in life than people in Western populations. Only 13% of smokers started smoking before 20 years of age.

2). Cigarette smoking was significantly associated with an increased risk of total mortality in both males and females. Regular smokers had a 51% excess death from any disease compared with non-smokers.

3). There was a strong direct relationship between cigarette smoking and risk of all cancer in general, and lung cancer and cancer of mouth, pharynx,larynx and oesophagus specifically. The risk of lung cancer increased steadily with the amount of cigarettes smoked and with the duration of smoking.

4). Smokers had a 3.5-fold increased risk of lung cancer mortality compared with non-smokers, and among the male population 63% of the lung cancer deaths were attributed directly to smoking.

5). There was a 60% excess risk of death from stroke among regular smokers.

6). There was evidence that risk of chronic obstructive lung disease was significantly increased among smokers.

Tables

Table 7.1. Proportions of current regular smokers by age and sex at baseline examination in cohort A.

Age group (years)	Male				Female				All subjects			
	No. of subjects	Light smoker (%)	Heavy smoker (%)	All smokers (%)	No. of subjects	Light smoker (%)	Heavy smoker (%)	All smokers (%)	No. of subjects	Light smoker (%)	Heavy smoker (%)	All smokers (%)
35-39	223	98 (43.9)	5 (2.2)	103 (46.2)	269	7 (2.6)	0 (0.0)	7 (2.6)	492	105 (21.3)	5 (1.0)	110 (22.4)
40-44	330	166 (50.3)	17 (5.2)	183 (55.5)	434	26 (6.0)	1 (0.2)	27 (6.2)	764	192 (25.1)	18 (2.4)	210 (27.5)
45-49	313	191 (61.0)	23 (7.3)	214 (68.4)	279	34 (12.2)	2 (0.7)	36 (12.9)	592	225 (38.0)	25 (4.2)	250 (42.2)
50-54	307	181 (59.0)	28 (9.1)	209 (68.1)	139	24 (17.3)	3 (2.2)	27 (19.4)	446	205 (46.0)	31 (7.0)	236 (52.9)
55-59	255	155 (60.8)	34 (13.3)	189 (74.1)	88	14 (15.9)	3 (3.4)	17 (19.3)	343	169 (49.3)	37 (10.8)	206 (60.1)
60-64	207	127 (61.4)	12 (5.8)	139 (67.1)	79	20 (25.3)	1 (1.3)	21 (26.6)	286	147 (51.4)	13 (4.5)	160 (55.9)
Total ¶	1635	918 (56.1)	119 (7.3)	1037 (63.4)	1288	125 (9.7)	10 (0.8)	135 (10.5)	2923	1043 (35.7)	129 (4.4)	1172 (40.1)

¶ The age-standardised proportions of regular smokers were 54% and 12% for males and females respectively.

Table 7.2. Proportions of current regular smokers by age and sex at baseline examination in cohort B.

Age group (years)	Male				Female				All subjects			
	No. of subjects	Light smoker (%)	Heavy smoker (%)	All smokers (%)	No. of subjects	Light smoker (%)	Heavy smoker (%)	All smokers (%)	No. of subjects	Light smoker (%)	Heavy smoker (%)	All smokers (%)
35-39	530	163 (30.8)	105 (19.8)	268 (50.6)	454	5 (1.1)	2 (0.4)	7 (1.5)	984	168 (17.1)	107 (10.9)	275 (27.9)
40-44	593	156 (26.3)	160 (27.0)	316 (53.3)	319	6 (1.9)	3 (0.9)	9 (2.8)	912	162 (17.8)	163 (17.9)	325 (35.6)
45-49	1437	345 (24.0)	490 (34.1)	835 (58.1)	513	23 (4.5)	4 (0.8)	27 (5.3)	1950	368 (18.9)	494 (25.3)	862 (44.2)
50-54	1042	249 (23.9)	411 (39.4)	660 (63.3)	224	15 (6.7)	2 (0.9)	17 (7.6)	1266	264 (20.9)	413 (32.6)	677 (53.5)
55-59	788	194 (24.6)	337 (42.8)	531 (67.4)	46	2 (4.3)	1 (2.2)	3 (6.5)	834	196 (23.5)	338 (40.5)	534 (64.0)
60-64	469	116 (24.7)	187 (39.9)	303 (64.6)	13	2 (15.4)	0 (0.0)	2 (15.4)	482	118 (24.5)	187 (38.8)	305 (63.3)
Total ¶	4859	1223 (25.2)	1690 (34.8)	2913 (60.0)	1569	53 (3.4)	12 (0.8)	65 (4.1)	6428	1276 (19.9)	1702 (26.5)	2978 (46.3)

¶ The age-standardised proportions of regular smokers were 59% and 5% respectively for males and females.

Table 7.3. Number and relative frequency of regular smokers according to age of starting smoking for males and females in cohort A.

Age of starting smoking (years)	Male smokers						Female smokers						All smokers					
	Light		Heavy		All		Light		Heavy		All		Light		Heavy		All	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<20	113	13.7	23	20.2	136	14.5	11	10.6	3	30.0	14	12.3	124	13.3	26	21.0	150	14.2
20-	401	48.5	55	48.2	456	48.5	33	31.7	6	60.0	39	34.2	434	46.7	61	49.2	495	47.0
30-	312	37.8	36	31.6	348	37.0	60	57.7	1	10.0	61	53.5	372	40.0	37	29.8	409	38.8
Total ¶	826	100.0	114	100.0	940	100.0	104	100.0	10	100.0	114	100.0	930	100.0	124	100.0	1054	100.0

¶ 118 subjects without information on age of starting smoking were excluded.

Table 7.4. Number and relative frequency of regular smokers according to age of starting smoking for males and females in cohort B.

Age of starting smoking (years)	Male smokers						Female smokers						All smokers					
	Light		Heavy		All		Light		Heavy		All		Light		Heavy		All	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<20	108	8.8	281	16.6	389	13.4	6	11.3	2	16.7	8	12.3	114	8.9	283	16.6	397	13.3
20-	457	37.4	934	55.2	1391	47.8	10	18.9	6	50.0	16	24.6	467	36.6	940	55.2	1407	47.2
30-	658	53.8	476	28.1	1134	38.9	37	69.8	4	33.3	41	63.1	695	54.4	480	28.2	1175	39.5
Total	1223	100.0	1690	100.0	2913	100.0	53	100.0	12	100.0	65	100.0	1276	100.0	1702	100.0	2978	100.0

Table 7.5. Mean values of baseline variables according to cigarette smoking status at baseline in the combined data from the two cohorts.

Variables ¶	Cigarette smoking status at baseline		
	Non-smoker	Light smoker	Heavy smoker
Age (years)	46.9	49.7	51.2
Males (%)	48.9	92.3	98.8
Systolic blood pressure (mmHg)	125.5	124.7	122.9
Diastolic blood pressure (mmHg)	79.4	79.2	77.0
Hypertension (%) †	15.0	14.8	11.3
Cholesterol (%) §	100.5	99.0	98.6
Body weight (kg)	59.3	57.8	58.3
Alcohol consumption (%)	9.5	31.9	31.8
Resting ECG abnormality (%)	11.8	12.3	10.0
Number of subjects	5201	2319	1831

¶ Mean age increased slightly from non-smoker to heavy smoker, so all other variables have been age-adjusted.
† Hypertension: SBP≥160 &/or DBP≥95 mmHg.
§ For each cohort mean serum cholesterol values in each of the three categories of cigarette smoking were expressed as the percent of the cohort mean, and an age-adjusted weighted mean then computed, using the inverse of the variance as weights.

Table 7.6. The number of deaths from **all diseases** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)¶	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	139	155.2	0.90	3450	101	121.3	0.83	**5201**	**240**	**276.5**	**0.87**
Light smoker	1043	177	155.7	1.14	1276	64	65.1	0.98	**2319**	**241**	**220.8**	**1.09**
Heavy smoker	129	18	23.1	0.78	1702	121	99.6	1.21	**1831**	**139**	**122.7**	**1.13**
Total	2923	334	334.0	1.00	6428	286	286.0	1.00	**9351**	**620**	**620.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2) §			1.25				9.04**				**9.58****	
Cox regression analysis												
Regression coefficients (ß)†			0.437				0.390				**0.411**	
z values (ß/s.e.)			3.34***				2.74**				**4.28*****	
Relative risks			1.55				1.48				**1.51**	
(95% CI of relative risk)			(1.20-2.00)				(1.12-1.95)				**(1.25-1.82)**	

¶ The expected (E) number of deaths, adjusted for age and sex by the log-rank method.

§ X^2 values less than 3.84 are not conventionally significant (i.e. 2P>0.05).

,* Statistically significant at 2P<0.05, <0.01 and <0.001 respectively.

† The regression coefficients were estimated in the Cox's proportional-hazards model with cigarette smoking as a binary variable, adjusting simultaneously for sex, age, DBP, serum cholesterol and alcohol drinking.

Table 7.7. The number of deaths from **all diseases** and the estimated relative risks by smoking status at baseline among males and females.

Smoking status at baseline	Males				Females				**All subjects**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)¶	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	2544	144	173.5	0.83	2657	96	103.0	0.93	**5201**	**240**	**276.5**	**0.87**
Light smoker	2141	221	205.1	1.08	178	20	15.7	1.28	**2319**	**241**	**220.8**	**1.09**
Heavy smoker	1809	135	121.4	1.11	22	4	1.3	3.07	**1831**	**139**	**122.7**	**1.13**
Total	6494	500	500.0	1.00	2857	120	120.0	1.00	**9351**	**620**	**620.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)			6.78**				5.55*				**9.58****	
Cox Regression analysis												
Regression coefficients (ß)†			0.379				0.562				**0.411**	
z values (ß/s.e.)			3.65***				2.37*				**4.28*****	
Relative risks			1.46				1.75				**1.51**	
(95% CI of relative risk)			(1.19-1.79)				(1.10-2.79)				**(1.25-1.82)**	

¶ The expected (E) number of deaths, adjusted for age and cohorts by the log-rank method.
*,**,*** Statistically significant at 2P<0.05, <0.01 and <0.001 respectively.
† The regression coefficients were estimated in the Cox's proportional-harzards model with cigarette smoking as a binary variable, adjusting simultaneously for age, DBP, serum cholesterol and alcohol drinking.

Table 7.8. The number of deaths from **all cancers** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	55	66.7	0.82	3450	42	55.0	0.76	**5201**	**97**	**121.7**	**0.80**
Light smoker	1043	81	67.4	1.20	1276	24	30.0	0.80	**2319**	**105**	**97.4**	**1.08**
Heavy smoker	129	8	9.9	0.81	1702	64	45.0	1.42	**1831**	**72**	**54.9**	**1.31**
Total	2923	144	144.0	1.00	6428	130	130.0	1.00	**9351**	**274**	**274.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2) §			2.25				11.62***				**10.90*** **	
Cox regression analysis												
Regression coefficients (ß)			0.527				0.417				**0.476**	
z values (ß/s.e.)			2.58**				1.97*				**3.23** **	
Relative risks			1.69				1.52				**1.61**	
(95% CI of relative risk)			(1.14-2.53)				(1.00-2.30)				**(1.21-2.15)**	

§ X^2 values less than 3.84 are not conventionally significant (i.e. 2P>0.05).
*,**,*** Statistically significant at 2P<0.05, <0.01 and <0.001 respectively.

Table 7.9. The number of deaths from **lung cancer** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	8	13.4	0.60	3450	4	11.5	0.35	**5201**	**12**	**24.9**	**0.48**
Light smoker	1043	23	17.8	1.29	1276	4	7.9	0.51	**2319**	**27**	**25.7**	**1.05**
Heavy smoker	129	3	2.8	1.07	1702	24	12.6	1.90	**1831**	**27**	**15.4**	**1.75**
Total	2923	34	34.0	1.00	6428	32	32.0	1.00	**9351**	**66**	**66.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			2.88				14.95***				**15.40*** **	
Cox regression analysis												
Regression coefficients (ß)			1.099				1.698				**1.261**	
z values (ß/s.e.)			2.40*				3.11**				**3.62*** **	
Relative risks			3.00				5.46				**3.53**	
(95% CI of relative risk)			(1.22-7.36)				(1.87-15.93)				**(1.78-6.98)**	

§ X^2 values less than 3.84 are not conventionally significant (i.e. 2P>0.05).
*,**,*** Statistically significant at 2P<0.05, <0.01 and <0.001 respectively.

Table 7.10. Relationship between risk of death from **lung cancer** and duration of smoking among the light and heavy smoker in the two cohorts.

Duration of smoking (years)	Light smoker					Heavy smoker				
	No. of subjects	Observed deaths (O)§	Expected deaths (E)¶	Ratios of O/E	Relative risk†	No. of subjects	Observed deaths (O)	Expected deaths (E)	Ratios of O/E	Relative risk
1-29	1601	3	12.1	0.25	0.52	1044	4	5.2	0.78	1.62
≥30	605	22	11.9	1.85	3.86	782	23	9.9	2.33	4.85

§ Two deaths from lung cancer were not included in the analysis, because data on duration of smoking were not available.
¶ The expected numbers of deaths were calculated by the log-rank method after adjustment for age, sex and cohort among the whole study population.
† The relative risk was calculated using the risk of lung cancer among non-smokers as baseline.

Table 7.11. The number of deaths from cancer of the **mouth, pharynx, larynx and oesphageal** and the estimated relative risks by smoking status at baseline examination during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	4	5.6	0.72	3450	1	4.1	0.24	**5201**	**5**	**9.7**	**0.52**
Light smoker	1043	8	6.4	1.25	1276	2	2.7	0.75	**2319**	**10**	**9.1**	**1.10**
Heavy smoker	129	1	1.0	0.98	1702	8	4.2	1.88	**1831**	**9**	**5.3**	**1.71**
Total	2923	13	13.0	1.00	6428	11	11.0	1.00	**9351**	**24**	**24.0**	**1.00**
Statistical analysis												
Log-rand trend test (X^2)§			0.59				5.65*				**5.70***	
Cox regression analysis												
Regression coefficients (ß)			0.734				2.223				**1.210**	
z values (ß/s.e.) §			1.01				2.08*				**2.08***	
Relative risks			2.08				9.23				**3.35**	
(95% CI of relative risk)			(0.50-8.66)				(1.14-74.81)				**(1.07-10.49)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).
* Statistically significant at 2P<0.05.

Table 7.12. The number of deaths from **stomach cancer** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	11	12.8	0.86	3450	12	12.1	0.99	**5201**	**23**	**24.9**	**0.92**
Light smoker	1043	20	16.8	1.19	1276	6	7.6	0.79	**2319**	**26**	**24.4**	**1.07**
Heavy smoker	129	1	2.5	0.40	1702	13	11.2	1.16	**1831**	**14**	**13.7**	**1.02**
Total	2923	32	32.0	1.00	6428	31	31.0	1.00	**9351**	**63**	**63.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.01				0.17				**0.13**	
Cox regression analysis												
Regression coefficients (ß)			0.242				-0.294				**-0.031**	
z values (ß/s.e.) §			0.58				-0.75				**-0.11**	
Relative risks			1.27				0.75				**0.97**	
(95% CI of relative risk)			(0.56-2.89)				(0.35-1.61)				**(0.55-1.68)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 7.13 The number of deaths from **liver cancer** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	9	12.2	0.74	3450	11	12.3	0.89	**5201**	**20**	**24.5**	**0.82**
Light smoker	1043	16	12.1	1.32	1276	8	6.3	1.27	**2319**	**24**	**18.4**	**1.30**
Heavy smoker	129	1	1.7	0.59	1702	9	9.4	0.96	**1831**	**10**	**11.1**	**0.90**
Total	2923	26	26.0	1.00	6428	28	28.0	1.00	**9351**	**54**	**54.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.81				0.05				**0.36**	
Cox regression analysis												
Regression coefficients (ß)			0.662				0.308				**0.455**	
z values (ß/s.e.) §			1.30				0.68				**1.34**	
Relative risks			1.94				1.36				**1.58**	
(95% CI of relative risk)			(0.71-5.56)				(0.56-3.31)				**(0.81-3.67)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 7.14. The number of deaths from **other cancers** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	23	22.7	1.01	3450	14	14.9	0.94	**5201**	**37**	**37.6**	**0.98**
Light smoker	1043	14	14.3	0.98	1276	4	5.6	0.71	**2319**	**18**	**19.9**	**0.90**
Heavy smoker	129	1	2.0	1.00	1702	10	7.5	1.33	**1831**	**12**	**19.5**	**1.26**
Total	2923	39	39.0	1.00	6428	28	28.0	1.00	**9351**	**67**	**67.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.01				0.85				**0.40**	
Cox regression analysis												
Regression coefficients (ß)			0.237				-0.001				**0.135**	
z values (ß/s.e.) §			0.61				0.00				**0.45**	
Relative risks			1.26				1.00				**1.14**	
(95% CI of relative risk)			(0.59-2.71)				–				**(0.64-2.06)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 7.15. The number of deaths from **all vascular diseases** other than pulmonary heart disease and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	60	60.7	0.99	3450	35	33.8	1.03	**5201**	**95**	**94.5**	**1.01**
Light smoker	1043	59	55.9	1.05	1276	22	20.4	1.08	**2319**	**81**	**76.3**	**1.06**
Heavy smoker	129	6	8.3	0.72	1702	30	32.7	0.92	**1831**	**36**	**41.0**	**0.89**
Total	2923	125	133.0	1.00	6428	87	87.0	1.00	**9351**	**212**	**212.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.07				0.24				**0.06**	
Cox regression analysis												
Regression coefficients (ß)			0.396				0.208				**0.323**	
z values (ß/s.e.)§			1.87				0.85				**1.99***	
Relative risks			1.49				1.23				**1.38**	
(95% CI of relative risk)			(0.98-2.25)				(0.76-1.99)				**(1.01-1.90)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).
*. Statistically significant at 2P<0.05.

Table 7.16. The number of deaths from CHD and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	14	13.4	1.04	3450	6	6.7	0.90	**5201**	**20**	**20.1**	**1.00**
Light smoker	1043	12	11.8	1.02	1276	4	4.0	1.00	**2319**	**16**	**15.8**	**1.01**
Heavy smoker	129	1	1.7	0.59	1702	7	6.4	1.09	**1831**	**8**	**8.1**	**0.99**
Total	2923	27	27.0	1.00	6428	17	17.0	1.00	**9351**	**44**	**44.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.23				0.14				**0.00**	
Cox regression analysis												
Regression coefficients (ß)			0.358				0.297				**0.338**	
z values (ß/s.e.)§			0.79				0.54				**0.96**	
Relative risks			1.43				1.35				**1.40**	
(95% CI of relative risk)			(0.59-3.48)				(0.46-3.96)				**(0.70-2.80)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 7.17. The number of deaths from **stroke** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	38	41.7	0.91	3450	26	25.7	1.01	**5201**	**64**	**67.4**	**0.95**
Light smoker	1043	44	38.5	1.14	1276	17	15.4	1.10	**2319**	**61**	**53.9**	**1.13**
Heavy smoker	129	4	5.8	0.67	1702	23	24.9	0.92	**1831**	**27**	**30.7**	**0.88**
Total	2923	86	86.0	1.00	6428	66	66.0	1.00	**9351**	**152**	**152.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2)§			0.15				0.10				**0.01**	
Cox regression analysis												
Regression coefficients (ß)			0.597				0.293				**0.465**	
z values (ß/s.e.)§			2.30*				1.03				**2.40***	
Relative risks			1.82				1.34				**1.59**	
(95% CI of relative risk)			(1.09-3.02)				(0.77-2.34)				**(1.09-2.33)**	

§ X^2 values less than 3.84 are not conventionally significant (i.e. 2P>0.05).
*. Statistically significant at 2P<0.05.
† z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 7.18. The number of deaths from **stroke** and the estimated relative risks by smoking status at baseline examination for males and females in the combined data of two cohorts.

Smoking status at baseline	Males				Females			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E
Non-smoker	2545	43	41.2	1.04	2656	21	26.2	0.80
Light smoker	2141	52	49.5	1.05	178	9	4.4	2.05
Heavy smoker	1809	26	30.3	0.86	22	1	0.4	2.50
Total	6495	121	121.0	1.00	2856	31	31.0	1.00
Statistical analysis								
Log-rank trend test (X^2) §			0.53				6.89**	
Cox regression analysis								
Regression coefficients(ß)†			0.274				1.418	
z values (ß/s.e.) §			1.34				3.43***	
Relative risks			1.32				4.13	
(95% CI of relative risk)			(0.88-1.96)				(1.84-9.28)	

¶ The expected (E) number of deaths, adjusted for age and cohort by the log-rank method.

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

,* Statistically significant at 2P<0.01 and <0.001 respectively.

† The regression coefficients were estimated in the Cox's proportional-harzards model with cigarette smoking as a binary variable, adjusting simultaneously for age, DBP, serum cholesterol, alcohol concumption.

Table 7.19. The number of deaths from **chronic obstructive pulmonary diseases¶** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	8	10.1	0.79	3450	5	8.2	0.61	**5201**	**13**	**18.3**	**0.71**
Light smoker	1043	20	17.0	1.18	1276	4	4.5	0.89	**2319**	**24**	**21.5**	**1.12**
Heavy smoker	129	2	2.9	0.70	1702	11	7.3	1.51	**1831**	**13**	**10.2**	**1.28**
Total	2923	30	30.0	1.00	6428	20	20.0	1.00	**9351**	**50**	**50.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2) §			0.15				3.49				**2.75**	
Cox regression analysis												
Regression coefficients (ß)			0.705				0.956				**0.774**	
z values (ß/s.e.)§			1.56				1.54				**2.16***	
Relative risks			2.03				2.60				**2.17**	
(95% CI of relative risk)			(0.83-4.91)				(0.77-8.78)				**(1.07-4.38)**	

¶ Refers to chronic bronchitis, emphysema and pulmonary heart disease.

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

* Statistically significant at 2P<0.05.

Table 7.20. The number of deaths from **cirrhosis** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	5	3.3	1.51	3450	4	6.9	0.58	**5201**	**9**	**10.2**	**0.88**
Light smoker	1043	2	3.3	0.61	1276	4	4.0	1.00	**2319**	**6**	**7.3**	**0.83**
Heavy smoker	129	0	0.4	0.00	1702	9	6.1	1.47	**1831**	**9**	**6.5**	**1.38**
Total	2923	7	7.0	1.00	6428	17	17.0	1.00	**9351**	**24**	**24.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2) §			1.93				2.79				**0.96**	
Cox regression analysis												
Regression coefficients (ß)			-0.226				0.863				**0.580**	
z values (ß/s.e.)§			-0.25				1.36				**1.28**	
Relative risks			0.80				2.37				**1.78**	
(95% CI of relative risk)			(0.14-4.69)				(0.68-8.22)				**(0.73-4.34)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 7.21. The number of deaths from **other medical diseases** and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	9	11.9	0.76	3450	9	10.7	0.84	**5201**	**18**	**23.0**	**0.78**
Light smoker	1043	13	9.8	1.33	1276	7	3.8	1.84	**2319**	**20**	**13.6**	**1.47**
Heavy smoker	129	1	1.3	0.77	1702	4	5.5	0.73	**1831**	**5**	**6.4**	**0.78**
Total	2923	23	23.0	1.00	6428	20	20.0	1.00	**9351**	**43**	**43.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2) §			0.88				0.00				**0.56**	
Cox regression analysis												
Regression coefficients (ß)			0.495				0.589				**0.511**	
z values (ß/s.e.)§			0.96				1.00				**1.35**	
Relative risks			1.64				1.80				**1.67**	
(95% CI of relative risk)			(0.60-4.51)				(0.57-5.72)				**(0.79-3.50)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Table 7.22. The number of deaths from **non-medical causes** (suicides, accidental and violent deaths) and the estimated relative risks by smoking status at baseline during 8-13 years of follow-up.

Smoking status at baseline	Cohort A				Cohort B				**Both cohorts**			
	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	No. of subjects	Observed deaths(O)	Expected deaths(E)	Ratios of O/E	**No. of subjects**	**Observed deaths(O)**	**Expected deaths(E)**	**Ratios of O/E**
Non-smoker	1751	2	2.4	0.83	3450	6	6.3	0.96	**5201**	**8**	**8.7**	**0.92**
Light smoker	1043	2	2.3	0.87	1276	3	2.4	1.23	**2319**	**5**	**4.7**	**1.05**
Heavy smoker	129	1	0.3	3.22	1702	3	3.3	0.91	**1831**	**4**	**3.6**	**1.11**
Total	2923	5	5.0	1.00	6428	12	12.0	1.00	**9351**	**17**	**17.0**	**1.00**
Statistical analysis												
Log-rank trend test (X^2) §			0.76				0.00				**0.14**	
Cox regression analysis												
Regression coefficients (ß)			0.101				0.174				**0.107**	
z values (ß/s.e.)§			0.13				0.53				**0.18**	
Relative risks			1.11				1.19				**1.11**	
(95% CI of relative risk)			(0.24-5.07)				(0.63-2.26)				**(0.35-3.57)**	

§ X^2 values less than 3.84, or z values less than 1.96 are not conventionally significant (i.e. 2P>0.05).

Chapter 8

Summary and implications

8.1 Introduction

The present study examined the relationship of three factors (i.e., serum cholesterol, blood pressure and cigarette smoking) with certain chronic diseases in an urban Chinese population. This chapter summarises the main findings in the present study, along with their implications for public health, clinical medicine and future research. As shown in other populations, elevated serum cholesterol, high blood pressure and cigarette smoking were important risk factors for a wide range of chronic diseases in the Chinese population studied (Table 8.1). Moreover for CHD and stroke, these risk factors appeared to have additive effects (Table 8.2), although the small number of deaths from certain diseases (e.g., CHD) and the weakness of certain associations (e.g., between smoking and stroke) mean that it is not possible to determine reliably the degree of additivity. No direct estimates were made about how much of the difference in the risk of disease between individuals can be explained by differences in these risk factors, since the associations of risk factors with disease are continuous without any threshold, while for smoking associations with various chronic diseases are subject to substantially delayed effects.

8.2 Serum cholesterol and disease

The question of what constitutes a desirable blood cholesterol level is an important public health issue. Cholesterol concentrations (and CHD rates) vary widely between populations. The laboratory definition of "normality" in terms of a range (for example ±2 standard deviations) around the population average is often interpreted as being a biological definition of "normality". This has led to the, perhaps, mistaken, view that what is normal in the sense of common is also

Table 8.1. Summary of observed associations of serum cholesterol, blood pressure and smoking with chronic disease deaths

Causes of death	Cholesterol		SBP		Smoking	
	Relative risks†	95% CI	Relative risks†	95% CI	Relative risks†	95% CI
Vascular diseases						
CHD	1.21	1.09-1.35*	1.44	1.21-1.73*	1.40	0.70-2.80
Stroke	0.99	0.93-1.07	1.67	1.52-1.83*	1.59	1.09-2.33*
Cancer						
Lung cancer	1.02	0.91-1.14	0.99	0.95-1.06	3.53	1.78-6.98*
Aero-digestive cancer	0.80	0.62-1.04	0.98	0.95-1.04	3.35	1.07-10.49*
Chronic liver disease¶	0.84	0.75-0.95*	1.01	0.98-1.05	1.65	0.93-2.92
Chronic lung disease	0.94	0.84-1.06	1.02	0.98-1.06	2.17	1.07-4.38*
All disease	**0.99**	**0.95-1.03**	**1.19**	**1.13-1.26***	**1.51**	**1.25-1.82***

† The relative risks were estimated by Cox regression coefficients after adjusting for other variables, and for the regression dilution bias in the case of serum cholesterol and SBP. For cholesterol, the relative risk estimated was associated with a 4% difference in usual cholesterol, while for SBP, it was associated with a 10 mmHg difference in usual SBP. The relative risks for smoking were for smoker versus nonsmoker.

* The results are statistically significant, at least at $2P<0.05$.

¶ Refers to primary liver cancer and chronic hepatitis and cirrhosis.

Table 8.2. Estimated relative risks¶ of CHD by serum cholesterol and SBP

SBP groups	Quartiles of serum cholesterol				
	I	II	III	IV	All
<140	0.53	0.35	0.79	0.50	**0.55**
140-169	0.35	1.42	0.61	2.29	**1.28**
≥170	0.00	2.34	2.97	3.18	**2.19**
Total	**0.41**	**0.91**	**1.07**	**1.51**	**1.00**

¶ The relative risks estimated were adjusted for age and sex. The risk of CHD death in the whole study population was used as a reference group, ie a relative risk of 1.00.

normal in the sense of good *(Rose 1985)*. Previous comparisons with populations in which cholesterol concentrations are low and CHD is rare, suggest that few people in Western populations have a biologically "normal" (as opposed to population average normal) cholesterol concentration. Hence, the fundamental lipid problem underlying coronary heart disease in Western populations should probably be seen as the majority of the population having cholesterol levels that are too high rather than as a small proportion of the population with "high" values.

The present study indicated that cholesterol may be an important cause of coronary heart disease not only in individuals with a high mean cholesterol concentration, but also in those with what is, by Western standards, a normal or low cholesterol concentration. In this Chinese population, there was a strong positive and apparently independent relationship of serum cholesterol level with CHD death ($2P<0.001$). Within the range of usual serum cholesterol studied (3.8–4.7 mmol/l), there was no evidence of any apparent "threshold" below which a lower level of serum cholesterol was no longer associated with a lower risk of CHD. This implies that even for the majority of individuals in an urban Chinese population with a serum cholesterol concentration of about 4.1 mmol/l, a lower cholesterol concentration should eventually confer a lower risk of CHD, and that this would be still more so for most people in Western populations. On the other hand, our study provides no direct evidence that at the lower end of the cholesterol distribution seen in Western populations, lower cholesterol concentration would cause any material increase in deaths from other causes.

The International Multidisciplinary Workshop *(Blackburn, et al 1979)* addressed the question of population desirable mean cholesterol levels, and proposed that the mean blood cholesterol of an adult population above 5.2 mmol/l is incompatible with optimal cardiovascular health for populations, and that a population mean cholesterol of the order of 4.7-5.2 mmol/l is associated with substantially lower atherosclerosis and CHD rates, and also with generally

favourable experience with respect to other diseases. Population mean plasma cholesterol levels of the order of 3.6-4.7 mmol/l are consistently related to the lowest atherosclerosis and CHD rates. An expert committee convened by The World Health Organization *(1982)* recommended a lowering of the population distribution for blood cholesterol, in countries with high CHD incidence, through progressive changes in habitual dietary patterns, and a population mean blood cholesterol level below 5.2 mmol/l for adults was set as a desirable goal. This recommendation has since then been reinforced by other expert meetings convened by the WHO *(1986)*, by the NIH consensus Development Conference *(1985)*, and by the Study Group of the European Atherosclerosis Society *(1987)*. Such recommendations emphasize not only the importance of cholesterol reduction in Western countries but also the importance of avoiding a large increase of cholesterol with economic development in populations who at present have very low cholesterol levels.

Dietary (especially animal) fat consumption is an important contributor to overweight and obesity, which are causes of hypertension and the major risk factors for diabetes. Moreover, dietary fat, in particular saturated fat, consumption directly affects blood concentrations of total cholesterol, which is the most important cause of vascular disease in the population. Although current levels of fat consumption in China are well below Western levels, there is evidence that animal fat consumption appears to be increasing markedly with economic development. Recent dietary surveys of urban adults in China have already provided some cause for such concern. Avoidance of large increase in animal fat consumption should be an important element in China's food strategy for control of chronic disease. It will not only avoid large increases in certain chronic diseases in the population, but also help to contain agricultural costs, since plant-based diets require much less agricultural land than animal-based diets do§ .

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§ It is generally assumed that the cost of producing a kilogram of animal protein is 7-10 times as great as the cost of directly consuming the original kilogram of plant protein.

The absolute benefits of a lower blood cholesterol would be greatest for large countries with high CHD rates (eg, USA, USSR, UK). Indeed, some practicable methods of reducing the mean blood cholesterol in such populations by even just a few per cent might avoid large numbers of premature deaths from cardiovascular diseases. In countries such as the US and Finland, CHD mortality has clearly been declining over the last 15 years, and this improvement has been preceded and paralleled by lifestyle changes related to major CHD risk factors. Improvement in habitual dietary patterns have occurred in these countries and this has led to a decreasing trend in population mean levels of blood cholesterol *(Pyorala, et al 1985; Collaborative Lipid Group 1987)*. The existence in rural China of adult populations in which the mean serum cholesterol levels are below 3 mmol/l, and in which people have virtually no CHD, compared with Western populations *(Chen, et al 1990)*, provides an interesting context for speculation as to what might eventually be achievable in the West, if practicable methods could be devised to reduce cholesterol levels on a population basis.

8.3 Blood pressure and vascular disease

The results of this prospective study in a Chinese population clearly demonstrate that both systolic and diastolic blood pressure, are strongly and positively associated with the risk of stroke and of CHD not only among those individuals who might be considered "hypertensive", but also among those would usually be considered "normotensive". Approximate correction for "regression dilution" bias has indicated that these relationships are at least 60% stronger than previously thought. The substantial differences between the corrected and uncorrected results underline the importance in all prospective observational studies of remeasuring risk factors at a later follow-up in at least a representative proportion of survivors, so that correction for regression dilution can be made directly. The need to adjust for the "regression dilution" bias is importantly relevant not just to blood pressure, but also to serum cholesterol (as shown in this

study), and to many other risk factors that may be subject to substantial measurement error, such as dietary characteristics, blood glucose, and among smokers, the amount smoked.

Throughout the range of usual blood pressure that was studied (SBP: 117-161 mm Hg; DBP: 75-101 mm Hg), there was no threshold below which a lower level of blood pressure was no longer associated with a lower risk of vascular disease. For populations where stroke or CHD are common, a lower mean blood pressure should eventually confer a substantially lower risk of vascular disease. The absolute benefits of lower blood pressure would be greatest for large counties with high stroke (e.g. China), or CHD rates (e.g. US, USSR). A number of studies *(Stamler, et al 1987, Australian Dietary Salt Study Committee 1989)* suggest that several methods exist that, collectively, might lower population blood pressure substantially. A recent overview of 45 trials of dietary salt reduction suggested that a reduction in daily sodium intake of 50 mmol (about 3 g of salt), attainable by moderate dietary salt reduction would lower systolic blood pressure by an average of 5 mmHg; and diastolic blood pressure would be lowered by about half as much *(Law, et al 1991)*. It is estimated that such a reduction in salt intake by a whole Western population would reduce the incidence of stroke by 26% and of CHD by 15%. This might be of particular importance in China, where both salt intake and stroke mortality are much higher than in Western populations. The average daily salt intake in China is estimated to be about 15 g, which is twice that for people in most Western populations *(Chen, et al 1990)*. Given the strong relationship between blood pressure and vascular disease shown in the present Chinese population, universal moderate dietary salt reduction could result in a substantial reduction in mortality from vascular disease in the population. If, in the long term, the average daily salt intake in China can be halved, then it can be estimated that this would prevent more than half a million stroke deaths each year, and many other deaths from CHD and hypertensive disease.

From an individual patient's viewpoint, mild or moderate hypertension is less important than severe or malignant hypertension. In public health terms, however, it may be more important, for it is much more common and so accounts for a greater proportion of the deaths and serious non-fatal vascular events associated with hypertension. In the present study, nearly half of all vascular deaths in the population occurred among those who may be considered as "normotensive". The present study indicated that both for stroke and for CHD, the proportional differences in risk associated with a given difference in blood pressure were similar among "hypertensive" and "normotensive" individuals. Moreover, evidence from unpublished analysis of one study *(UK-TIA Study Group, 1988)* show that even after a stroke or TIA, the relationship between blood pressure and stroke recurrence rates still remains strongly positive throughout the "normal" range of blood pressure. This would suggest that the eventual reduction in risk of vascular disease produced by moderate blood pressure reduction (e.g., with some current antihypertensive treatment regiments) may well be medically worthwhile not only among certain "hypertensive" individuals, as already indicated in the previous trials *(HDFP Cooperative Group 1979; Collins, et al 1990)*, but also among certain individuals who, although considered "normotensive", are for some other reasons (e.g. a history of stroke, TIA or of myocardial infarction) at high risk. Indeed a clinical trial of blood pressure reduction in post-stroke patients is currently under way in China to evaluate if blood pressure reduction is of substantial value among "normotensive" patients at high risk of stroke *(Liu, personal communication)*.

8.4 Cigarette smoking and disease

Cigarette smoking is an important cause of chronic disability and death from a wide range of neoplastic, vascular and respiratory diseases. The present study provides no evidence that Chinese people tolerate cigarette smoking better than other populations where smoking has been shown to be responsible for a large

proportion of all deaths. Cigarette smoking was shown to be associated with a 50% excess total mortality in both men and women, and 18% of deaths in the population are directly attributed to smoking. There was a significantly increased risk of death from cancer in general, and specifically from lung cancer and cancer of the mouth, pharynx, larynx and oesophageal cancer among smokers. Cardiovascular diseases and COPD were also found to be closely related to cigarette smoking.

In Britain and North America, smoking causes about one-third of all deaths in middle age (35-69 years). By 1985 in the US there were about 400,000 tobacco induced deaths each year. Findings from the American Cancer Society prospective study of over 1 million men and women indicate that smoking causes 22% of all cancer deaths in women, but 45% of all cancer deaths in men *(Shopland, et al 1991)*. Furthermore, about 22% of CHD deaths in the USA are estimated to be directly attributed to smoking. Even in those Western countries, the proportion of deaths due to smoking may increase further in future. It is estimated *(Peto et al, 1992)* that at present just under 20% of all deaths in developed countries are attributable to smoking, but this percentage is still rising. In developed countries alone, it is estimated that the total number of deaths caused by smoking will increase from 1.65 million in 1985 to about 2.13 million in 1995 *(Peto, et al 1992)*. More than half of these deaths would be expected to occur between the age of 35 to 69 years, thus losing an average of more than 20 years of life.

In China more than 60 per cent of men aged 15 or greater smoke. In general, Chinese smokers have tended to start smoking later in life than in other populations. In Western populations such as USA, nearly 90% of smokers started smoking before 20 years of age, compared with only about 13% in the present study of a Chinese population. There is, however, evidence that in China people are now tending to start smoking at a younger age than before. Moreover,

although low smoking prevalence among Chinese women probably reflects cultural values which make smoking less acceptable for women, this may change markedly as it has in other countries, especially among teenage women. Probably because of the long delay between the adoption of a particular smoking habit and the emergence of its full effect on disease risks, cigarette smoking at present may account for only a relative small percentage of all deaths in China compared with other populations where the widespread use of cigarettes has lasted for many decades. In future decades, however, smoking can be expected to account for a much higher proportion of deaths.

Evidence that has accumulated in the last several decades about the health effects of smoking in Western countries can help predict the future risk from the recent large increase of smoking consumption in China. Chinese smokers may be less susceptible to arterial disease than Western smokers are, because of the lower mean blood cholesterol, but more susceptible to chronic lung disease (which can itself cause heart disease) and to stroke. So even if details differ, the total proportion of deaths attributed to smoking may eventually be about as great in China as it has been elsewhere. It has been estimated *(Peto, personal communication)* that the number of deaths from tobacco in China will increase from about 100,000 a year in the early 1980s to about two million a year in the next century. In particular, the estimated number of deaths from lung cancer among Chinese males would increase from 300,000 in 1975 to about 1 million in 2025. There are two reasons for the increase, and each multiplies up the effect of the other. There will be a fourfold increase in the number of deaths just because there will be more people in 2025 who have reached middle age or old age and so are at substantial risk of death. Moreover, there will be at least a 5-7 fold increase in the number of deaths because at each specific age a greater proportion will have smoked cigarettes regularly throughout adult life. In China, there are about 420 million people aged less than 20 years. On the present smoking rates, about 40% of them are going to be smokers at 25 years of age,

making the total number of smokers around 150-200 million for this young generation. If present smoking patterns continue, and if one in four people who smoke manufactured cigarettes regularly throughout adult life are killed by tobacco (as already happens in Britain and North America), then about 50 million of today's children in China may eventually be killed by smoking, and many more will become disabled by smoking-related diseases. This would mean that, by 2025, smoking will cause about 2 million deaths each year in China. Large prospective studies, preferably among representative populations in China, are needed to monitor the future trends in tobacco-attributable mortality, and to seek co-factors that might influence the patterns and trends of tobacco-related diseases in China.

The future vast numbers of deaths caused by smoking in China are not, however, inevitable. Practicable options for limiting this amount do exist, including a decrease in the amount of "tar" yield in the smoke of Chinese cigarettes, and avoidance of further increases in consumption, particularly among women (by, for example avoidance of all foreign cigarette promotion in China, clear information on the risks of cigarette smoking on cigarette packets and elsewhere, and an increase in the total tax payable on cigarettes). If these practicable measures could be adopted to halt the increase in smoking, then tens of millions of premature deaths could be prevented in the next century.

8.5 Control of future large increase of chronic diseases in China

China has, over the last few decades, experienced an epidemiological transition, with a shift from deaths mainly due to infectious disease to deaths being mainly from chronic and non-communicable diseases. A major element in China's past success in fulfilling such transition within just three decades has been the integration of primary prevention efforts with the primary health care system. Risk factors for the chronic diseases are often multifactorial, synergistic, and socially complex. In future, demographic changes in the population and

changes in lifestyle, dietary, environmental, occupational and exposure to other risk factors, will inevitably result in large increases in deaths from various chronic diseases in China. In particular, the large delayed effects of current smoking patterns will materialize. The type and magnitude of the health problems ahead for China will require considerable reorientation and strengthening of traditional public health approaches and principles. By far, the most important of all these efforts, from public health viewpoint, will involve control of cigarette smoking, HBV vaccination and dietary changes (in particular, restriction of salt intake, and avoidance of a large intake of animal fat). Even if the changes achieved were only moderate, collectively, such measures could have a profound impact on the prevention of chronic diseases in China. In addition, increased use of randomised trials and careful targeting of those activities for which potential reductions in risks and burden of illness are greatest could have significant effects on deaths from chronic diseases.

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