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SEVEN COUNTRIES

Ancel Keys

*A Multivariate
Analysis of Death
and Coronary
Heart Disease*

with

Christ Aravanis

Henry Blackburn

Ratko Buzina

B. S. Djordjević

A. S. Dostas

Flaminio Fidanza

Martti J. Karvonen

Noboru Kimura

Alessandro Menotti

Ivan Molaček

S. Nedeljković

Vittorio Puddu

Sven Punsar

Henry L. Taylor

F. S. P. van Buchem

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1 | Introduction

The prospective research program known as the Seven Countries Study was a logical outgrowth of explorations on the epidemiology of coronary heart disease (CHD) that began early in 1952 in Italy and Spain (Keys 1952, 1953a). Those international studies, in turn, had their inspiration in a prospective study on Minnesota business and professional men that started in 1947. The aim of this study was to find individual characteristics in apparently healthy middle-aged men related to future tendency to develop CHD, an aim based on the conviction that "the physico-chemical characteristics of the individual should have predictive value" (Keys 1949). It was believed that the discovery of predictive variables—what we now call *risk factors*—should point the way to preventive efforts (Keys 1953b).

The results of the early work in Italy and Spain stimulated an international group to join in larger surveys in Italy in 1954 (Keys 1956; White 1956). The findings in Naples, Cagliari, and Bologna, compared with similar hospital surveys in the United States, confirmed the belief in marked differences among populations in the frequency of CHD. The feasibility of organizing international teams of clinicians and medical scientists to produce comparable measurements and diagnoses in different populations was further demonstrated in South Africa in 1955 (Bronte-Stewart, Keys, and Brock 1955) and in Japan and Finland in 1956 (Keys 1957a; Keys et al. 1958; Roine et al. 1958; Keys, Karvonen, and Fidanza 1958). Those studies also indicated that populations differing in the fats in the diet also differ in the concentration of cholesterol in the blood serum, and these two features are associated with contrasts in the frequency of CHD. By that time, too, follow-up studies in Framingham, Massachusetts, Albany, and Los Angeles were clearly pointing to the importance of arterial blood pressure and serum

cholesterol as risk factors (Chapman et al. 1957; Dawber, Moore, and Mann 1957; Doyle et al. 1957).

Clearly it would be important to extend to samples of populations in other countries similar examination and follow-up studies, assuring comparability with international teams using a common protocol, standardized methods and criteria, and exchanging professional personnel between the countries concerned. Further to assure comparability, it seemed essential to concentrate at a single center the evaluation of electrocardiograms, measurement of cholesterol in blood serum, review of diagnoses, and all data processing. The Laboratory of Physiological Hygiene at the University of Minnesota was designated as the central headquarters.

Aims

One aim of such a collaborative international study was to discover to what extent the incidence rates of the various cohorts could be predicted from the experience of earlier follow-up studies in the United States, taking into account the characteristics of the cohorts in regard to the risk factors stressed in the American studies. A high degree of consistency in the experience of major prospective studies in the United States had become evident from the Pooling Project analysis of data from Albany, Chicago, Framingham, Los Angeles, Minnesota, and Tecumseh, Michigan, but that fact was not known until recently. Moreover, the samples of men in the Pooling Project analysis did not differ enough in regard to socioeconomic, ethnic, cultural, and genetic characteristics to allow universal conclusions for other populations.

A broader aim was to attempt to relate differences in incidence among cohorts to the average or general characteristics of the men in the cohorts, including their living habits. Does the incidence of CHD and of death in the various cohorts differ from that in the United States? Does the incidence vary among the cohorts? Are the differences, if any, from experience in the United States explained by the risk factors as weighted according to the experience of studies in the United States? To what extent can differences in incidence among the cohorts be explained by a multivariate analysis of characteristics of the makeup of those cohorts as indicated by the variables recorded for the subjects?

Some of the populations sampled differed markedly in the average diet, so dietary characteristics could be treated as a variable in comparisons between cohorts. Another aim of this study was to see whether consideration of dietary variables could help explain differences among the cohorts in their disease experience.

Definition of the Cohorts

For practical reasons the study is confined to men aged 40 through 59 at the entry examination. Women or younger men would yield relatively low incidence rates and therefore would require much larger numbers. Moreover, younger men are generally less stable in residence and therefore more difficult to follow. Men over 60 at entry would yield higher incidence rates, but a large proportion of them would have excluding prevalence conditions at entry. Also, considering possible future preventive efforts, relationships that might be found in old age seemed likely to be less relevant to younger ages when, presumably, the prospects for prevention would be better. Similar considerations have dictated the selection of middle-aged men as the subjects in most other prospective studies.

We wished to keep self-selection of the subjects to a minimum and to strive for near-zero loss to follow-up. Both goals were achieved by concentrating on rural areas. Rural men aged 40 or more are less likely than urban and younger men to change occupation, habits, or residence. Community spirit and cohesiveness tend to be inversely related to the size of the community, thus assuring good response in small communities if we had the cooperation of local leaders. It was decided to invite all men aged 40-59 in the selected areas to participate because an attempt to sample within an age class might be divisive.

Elsewhere we have reported details of the selection of the areas for study, the organization of the study teams, and the general characteristics of the cohorts at the entry examinations (Keys et al. 1967; Keys 1970), and only brief notes are given here. For each cohort a roster was compiled of men eligible because of age and geographical location of residence. At the entry examinations, some men not on these rosters presented themselves for examination, and in some cases they were examined. However, they were not enrolled in the cohort unless the original omission of their names had been in error.

Rural men. Of the sixteen cohorts, eleven were strictly rural; they lived and worked in areas of low population density where agriculture, forestry, and fishing are the only industries. Forestry is an important activity only in the two areas of east and west Finland, and only for the Japanese men of Ushibuka, Japan, is fishery the major activity, though a few of the men in Dalmatia were fishermen.

The rosters of men eligible for the study in the eleven rural areas included all men then 40-59 permanently residing in geographically defined regions. The lists were compiled from local registers and tax and voting lists and were checked against church, police, and other records. In Japan and the Euro-

pean countries, all adults have identity documents that are locally registered. For five cohorts the geographical areas consisted of single large villages: in Italy, Crevalcore in the Po Valley and Montegiorgio in the Region of Marche near the Adriatic Coast; in Japan, Tanushimaru and Ushibuka on the big southern island of Kyushu; in Serbia, Velika Krsna south of Belgrade, Yugoslavia. For each of the other six rural areas the geographical definition embraced a number of villages clustered in a limited area. Dalmatia refers to a series of villages strung along 60 kilometers on the Dalmatian coast of Yugoslavia, with Makarska the nearest town. Slavonia comprises Dalj and nearby small villages near the Danube River and the Hungarian frontier, with Ossiek the nearest town of any size. East Finland was represented by villages in north Karelia near the Russian border centering on the town of Joensuu. West Finland comprises villages of similar character not far from Turku; Crete, eleven villages southeast of Heraklion on the Greek island of Crete; Corfu, seven villages in the northeast part of the island of Corfu, Greece.

Railroad men. In the United States it was not considered feasible to establish rural cohorts comparable to those organized in Europe and Japan because of the geographic and occupational mobility characteristic of many men in the United States. However, men employed by the railroad industry are relatively stable in these respects and are very rarely lost to follow-up, because the pensions, death, and disability benefits of the Railroad Retirement Board provide powerful incentives to maintain contact with the board. Accordingly, with the cooperation of the board and the railroad unions and management, a statistical sample was drawn of men employed in specified occupations by the major American railroad companies in the northwest sector of the country, roughly defined by the quadrangle of Green Bay, Wisconsin, Saint Louis, San Francisco, and Seattle. Sampling took account of the size of the community and the geographic region and attempted to provide subsamples defined by occupation so as to afford contrasts between sedentary and more physically active men. Sedentary railroad men were represented by executives, dispatchers, and sedentary clerks (not all clerks in the lists of railroad employees are sedentary in their work). Physically active men were represented by switchmen.

Details of sampling the American railroad men and a discussion of the question of self-selection have been published by Taylor et al. (1966). Self-selection is particularly important for the American railroad men because their rate of response to participate in the study was lower than in the other cohorts. Of those invited, only 75 percent came in for examination (the 68 percent figure given in Taylor et al., p. 1-22, refers to the least responsive

group, the switchmen). Apparently, some switchmen refused examination because they feared that revealing a disability would mean transfer to a less active job with lower pay. However, detailed analysis of the data on the railroad men failed to indicate any significant difference between the occupational classes in either risk factors or subsequent incidence of disease. Accordingly, in the present report the railroad occupations have been pooled in most of the analyses.

To provide a European sample to compare with the American railroad men, all men aged 40-59 in specified occupations employed by the Italian State Railroad in the Rome division were invited to join the study. The Rome division extends 318 kilometers along the west coast of Italy. As in the United States, railroad men in Italy are stable in their occupations, and their status is easy to follow because of the provisions for disability, retirement, and death benefits. Although the response of the Italian railroad men to the invitation to participate was better than that of their American counterparts, it did not approach the nearly perfect response of the rural Italians. Not all men who failed to present themselves for examination actually selected themselves out of the study of Italian railroad men. Unlike the relatively convenient arrangements for the other cohorts, the examinations of the Italian railroad men were made at the main Rome railroad station, and for many of the men it was difficult to adjust work schedules for a long trip to and from Rome.

Lack of funds prevented ten-year examinations for the American railroad men. However, with the help of the Railroad Retirement Board, a careful check was made of mortality in the ten years after the entry examinations. For the Italian railroad cohort it was not possible to examine all survivors at precisely ten years after the entry examination; men were examined over a span of about ten to eleven years after entry, some examinations being made in their homes.

Zutphen, the Netherlands. In the Netherlands the Dutch investigators selected the small commercial market town of Zutphen in the eastern part of the country because it offered practical advantages of local hospitals and physicians and had been the site of earlier health surveys. Because Zutphen had more men aged 40-59 than could be covered with the resources available, a statistical sample was drawn of four out of nine men of the eligible age. That roster took so long to prepare that when the examinations were made only one man remained in the age 40 category; men listed as that age in the roster had graduated to the age 41 class.

At Zutphen only 84.3 percent of the invited men presented themselves for examination. This response, much lower than in the rural areas, bears out

the rule that cohesiveness diminishes as the size of the community increases. However, a check on the subsequent disease and mortality experience of the no-shows with the local physicians and hospitals failed to show that they were, in this respect, different from the men who formed the active cohort. It does not seem, therefore, that self-selection at Zutphen created a bias in regard to future disease in the cohort actually enrolled for examination and follow-up.

Serbia: Zrenjanin and the Belgrade University faculty. Zrenjanin, in Serbia north of Belgrade, is an agricultural town with a little light industry. A cohort of men 40-59 for the Seven Countries Study was organized in a large cooperative in Zrenjanin that operates farms, a slaughterhouse, processing plants for foods, and other agricultural products, and a small packaging factory for chemicals and cosmetics. Of the men aged 40-59 associated with the cooperative, 98 percent agreed to form the Zrenjanin cohort.

Of the sixteen cohorts for which ten-year results are reported here, the last to be formed comprised members of the faculty of the University of Belgrade who were 40 through 59 years old in 1964. Because of some questions about which men in the employ of the university should be classed as faculty, there is some uncertainty about the precise percentage response to invitation, but it was at least 80 percent. Although university professors are not representative of the general population, the relationships between their entry characteristics and subsequent disease experience was examined.

Selection of the Areas

Opportunity and practicability determined the selection of the several areas for inclusion in the Seven Countries Study. The decision to work in Italy reflected personal contacts made in our first explorations in that country. In the absence of any detailed information about the incidence of disease, the diet, and the characteristics of the men of Crevalcore and Montegiorgio, it was enough to have the assurance of our colleague Flaminio Fidanza that we would have good cooperation in those rural areas and that the cost of the work would be within our resources. It was suggested that the two areas might differ much in the diet, but this was not borne out by the dietary surveys.

Friendship with our colleague Ratko Buzina led to selection of areas of Dalmatia and Slavonia where he had friends to help and where, again, we could expect low cost and high cooperation. Although the two areas were expected to offer a dietary contrast, almost nothing was known about the incidence of CHD and other disease.

Japan was a natural selection because, of all countries with anything like

credible vital statistics, it seemed to be the lowest in CHD. The compelling practical reason was that Noboru Kimura, who had once worked with us in Minnesota, offered enthusiastic help at little cost. The farming village of Tanushimaru and the fishing village of Ushibuka were selected because local physicians in those areas offered to help.

Similarly, collaboration with Martti J. Karvonen, initiated during work on committees of the World Health Organization and the Food and Agriculture Organization of the United Nations, led to the choice of Finland, which had the appeal of the world's highest CHD mortality according to vital statistics, very competent clinical help, and a cooperative population.

In Greece, friends A. S. Dontas and Christ Aravanis led us to Crete where the diet was said to be remarkably high in olive oil but where there were no reliable data on the incidence of CHD. The island of Corfu was selected because the Greeks consider it to be far more "European" than Crete.

Personal contacts with M. J. L. Dols of The Hague, developed during joint work on United Nations committees, resulted in the presence of a Dutch observer at the international trials of protocol and methods for the Seven Countries Study. As a result, the Dutch government proposed that the Netherlands be represented in the study.

B. S. Djordjevic, then president of the Yugoslav Society of Cardiology, was an observer at the entry examinations at Corfu in 1961. He returned to Belgrade determined to organize Serbian cohorts to be included in the study. Because little was known of the frequency of CHD or the character of the diet, these variables were not involved in the selection of the areas in Serbia. As elsewhere, the determining factors were proffered aid, little expense, and assurance of cooperation.

The foregoing information about the selection of the areas for the Seven Countries Study is offered to counter unfounded suggestions that the cohorts were chosen on the basis of prior knowledge that promised to support a hypothesis of a causal link between diet and incidence of CHD.

Entry Examinations

In 1957 full-dress trials of the protocol, methods, and organization proposed for the present study were carried out in the village of Nicotera near Reggio Calabria on the Italian boot and in a number of villages on the island of Crete in Greece. Physicians and medical scientists from England, Finland, France, Japan, the Netherlands, the United States, and Yugoslavia joined the Italian and Greek teams. Most of the key persons in the later long-term study took part in the preliminary work in Italy and Greece.

After refinements of protocol, methods, and organization, the present

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long-term study was started in 1958 with the establishment of rosters and entry examinations for two areas of Croatia, Yugoslavia, the farming village of Tanushimaru, in the northern part of the island of Kyushu in Japan, and railroad workers in the northwestern part of the United States. As indicated in table 1.1, over the next six years the program was extended to cover a total of 12,763 men aged 40 through 59 at the time of their examinations. There were sixteen cohorts in seven countries enrolled by 1964. The next year the program was extended to Hungary with the leadership of George Lamm, then on the faculty of the medical school of the University of Budapest, now in the European office in Copenhagen of the World Health Organization. Three rural areas of southern Hungary near Szeged were represented by 1,041 men examined in 1965 and 1966. In 1976 ten-year re-examinations were begun in those areas with Dr. Ivan Gyarfás in charge, but a full report on the ten-year experience must await receipt and analysis of the data.

Table 1.1 shows that, in general, a high proportion of the men eligible to participate responded to the invitation for the entry examinations. For all sixteen cohorts combined, 90.4 percent of men invited appeared for examination. We have already discussed the relatively low response rates of the railroad men, the men on the faculty of the University of Belgrade, and the men of Zutphen. Except in the case of the United States railroad men, there is no reason to suggest that self-selection in regard to response might have biased the rates of prevalence of CHD and of cardiovascular disease (CVD) including CHD indicated by the entry examinations. The present report focuses on the incidence of disease and death among men found to be CHD- and CVD-free at entry. In view of the high response rate in the present study, it seems unreasonable to suggest that the men found to be CHD- and CVD-free might not be representative of all men similarly free of these diseases in the eligible sample. In any case the findings on incidence of disease and death among sizable groups of men in ethnically diverse cultures are of independent interest, regardless of whether these findings can be generalized to the entire population of the countries concerned.

Ten-year Follow-up

Of the 1,512 deaths in the ten years following the entry examinations, 413 were attributed to coronary heart disease, or a total mortality of 11.85 percent, and a CHD mortality of 3.23 percent. In the fourteen cohorts fully covered by ten-year reexaminations (9,424 men at entry), 435 men suffered hard CHD, that is, either dying from CHD or having a definite nonfatal infarction, making a ten-year incidence of 4.62 percent.

Table 1.1 indicates the magnitude of the data available for the present

Table 1.1. Definition of the sixteen cohorts (CHD-free = number free of coronary heart disease; CVD-free = number free of cardiovascular disease; N = number of men, aged 40-59, examined).

Entry year	Cohort	Response rate (%)	N (men examined)	CHD-free	CVD-free
1958-60	U.S. railroad	75.0	2,571	2,454	2,315
1958	Dalmatia, Yugoslavia (Croatia)	98.0	671	670	662
1958	Slavonia, Yugoslavia (Croatia)	91.0	696	692	681
1958	Tanushimaru, Japan	100.0	508	506	504
1959	East Finland	99.3	817	775	728
1959	West Finland	97.0	860	845	806
1960	Ushibuka, Japan	99.6	502	498	496
1960	Crevalcore, Italy	98.5	993	982	956
1960	Montegiorgio, Italy	99.0	719	713	708
1960	Zutphen, Netherlands	84.3	878	864	845
1960	Crete, Greece	97.6	686	682	655
1961	Corfu, Greece	95.3	529	526	525
1962	Rome railroad	80.6 ^a	768	758	736
1962	Velika Krsna, Yugoslavia (Serbia)	96.7	511	504	487
1963	Zrenjanin, Yugoslavia (Serbia)	98.0	516	508	476
1964	Belgrade, Yugoslavia (Serbia)	80.0	538	532	516
	Total	90.4	12,763	12,509	12,096

a. Only about half of the men missed were refusals; work schedules prevented many men from keeping appointments.

report. Crude incidence rates can be calculated from the figures in table 1.2, but in the detailed analyses to follow all rates are age-standardized, as explained in chapter 2.

Other Prospective Studies

Prospective studies covering substantial numbers of middle-aged men began in 1948. Table 1.3 lists sixteen major studies with the common purpose of attempting to identify and measure characteristics that predispose to or hinder the development of the disease. The study of longshoremen was

Table 1.2. The Seven Countries Study: Ten-Year Incidence (hard CHD = CHD death or definite myocardial infarction).

Cohort	N	All-causes deaths	CHD deaths	Hard CHD
U.S. railroad ^a	2,571	294	146	—
Dalmatia	671	61	7	14
Slavonia	696	124	15	22
Tanushimaru	508	58	5	9
East Finland	817	147	78	115
West Finland	860	127	30	61
Ushibuka	502	70	4	13
Crevalcore	993	136	24	51
Montegiorgio	719	74	10	27
Zutphen	878	109	38	59
Crete	686	42	1	4
Corfu	529	43	8	19
Rome railroad ^b	768	77	22	31
Velika Krsna	511	63	4	8
Zrenjanin	516	60	8	14
Belgrade	538	27	13	19
Total	12,763	1,512	413	466

a. No 10-year examinations.

b. Ten-year examinations incomplete.

primarily an analysis of death records of men for whom employment and some examination data were recorded in 1951, but in the other studies the methodology was essentially the same as in the present work: selection of a target sample or population, examination with standardized methods of as many of the eligible men as were willing, reexamination at set intervals of follow-up, and diligent search for information about the status of all men who could not be reexamined with the prescribed protocol.

In these studies, as in the present work, questions arise about the relevance of the findings to groups or populations other than the men actually studied. In most of the studies the target sample was preselected according to employment. Are men in particular occupations representative of men of like age in the area and in general? Because men whose activities are limited by disease are underrepresented in samples of full-time regular employees, prevalence data on such men have limited applicability. Another limitation concerns all studies in which a substantial number of men in the target sample failed to appear for examination. The effect of nonresponse to the

Table 1.3. Follow-up studies on men aged 40-59 (except where noted).

Study	Year of entry	N	Response rate (%)
1. Minnesota business, professional men 45-55 (Keys et al. 1963)	1948	300	92
2. Framingham residents, 40-60+ (Dawber, Kannel, and Lyell 1963) ^a	1948-50	1,379	66
3. Los Angeles civil servants (Chapman and Massey 1964) ^b	1950-51	1,092	75
4. San Francisco longshoremen, 35-64 (Borhani, Hechter, and Breslow 1963)	1951	3,263	67
5. Albany, N.Y., civil servants (Doyle et al. 1957)	1953-54	1,829	89
6. Chicago Western Electric Co. employees (Paul et al. 1963)	1957	2,080	67
7. Chicago Peoples Gas Co. employees (Stamler 1973; Stamler et al. 1968) ^c	1958	1,465	92
8. Tecumseh, Michigan, residents (Johnson, Epstein, and Kjelsberg 1965) ^d	1959-60	798	88
9. California corporation employees, 39-59 (Rosenman et al. 1975)	1960	3,524	66
10. Oslo, Norway, employees, 40-49 (Westlund and Nicolaysen 1972)	1960	3,751	?
11. Evans County, Georgia, residents, 45-64 (McDonough et al. 1965) ^e	1960-62	646	92
12. Gothenburg, Sweden, men born 1913, aged 50 (Tiblin, Wilhelmssen, and Werko 1975)	1963	855	88
13. Israel civil servants (Medallie et al. 1968)	1963	7,666	86
14. Two areas of Yugoslavia, residents, 35-62 (Kozarević et al. 1976)	1964-68	11,121	93
15. Puerto Rico residents, 45-59 (Gordon et al. 1974)	1965-68	6,954	81
16. Japanese in Honolulu, residents, 45-59 (Gordon et al. 1974)	1965-68	6,217	81

a. About 15 percent of the 1,379 men were volunteers not on the original invited list.

b. One-fourth of the 1,092 men were alternates to replace men who refused examination.

c. Reported on 667 men in the gas company whose medical records started in 1954.

d. A response rate of 88 percent was reported for the total of both sexes and all ages 15 and over at Tecumseh.

e. Combining sexes and ages, 92 percent response rate.

invitation for examination is considered further in chapter 3. A major bias could result from men who refuse examination because they know or suspect they are abnormal or diseased. The converse situation, men who refuse examination because they believe they are perfectly healthy and do not need examination, is of less concern because the true prevalence of detectable serious disease is low in samples, such as in these studies, and it is unlikely to be higher among men who feel particularly healthy.

The studies listed in table 1.3 were concerned with incidence, and the real question concerns the relationship between entry characteristics and the future appearance of disease. Whether the men in the follow-up study are representative of some larger population in regard to particular characteristics at entry is not the issue. We are interested in relationships. The mean blood pressure in the sample may differ from that of all men of the same age in the community, but that does not necessarily mean that a relationship between blood pressure and the frequency of later CHD found in the sample is irrelevant to the men in the community or in some other community. So we conclude that the significance of relationships emerging from the studies listed in table 1.3, and those found in the present study, is not limited to the particular studies, provided, of course, that other things are equal or at least comparable. Multivariate analysis is a powerful method in the attempt to satisfy this last stipulation.

The studies listed in table 1.3 cover something like half a million man-years of follow-up of men middle-aged at the start. Unfortunately, it is not possible to pool that great mass of data for a giant analysis extending to six countries and the United States. Data from eight of the American studies have been pooled to some extent (Pooling Project Research Group 1978). Those studies are numbers 1, 2, 3, 5, 6, 7, and 8 in table 1.3; some data from the United States railroad men in the Seven Countries Study were also included in the Pooling Project. It should be noted that the numbers of men in table 1.3 for the studies in the Pooling Project are somewhat larger than the numbers actually included in the analyses in the project because men with coronary heart disease at the entry examinations were excluded from the analyses.

Although useful, the results from the Pooling Project present many problems. In general, the methods and criteria in the several studies were similar but not identical because the studies were independently planned and operated; pooling was attempted long after the work was finished. Furthermore, with the exception of the Framingham and Tecumseh studies, the men in the Pooling Project are not samples of ordinary populations; they are somewhat self-selected samples of particular work forces. That limitation also

applies to the studies on the San Francisco longshoremen, the California corporation employees, the Oslo employees, and the Israeli civil servants.

Because the studies focused on the incidence of coronary heart disease and not total mortality, comparison of death rates and of the ratio of coronary to other deaths is not possible from the published reports. Another point of interest is the fact that a substantial number of eligible, invited men did not participate in the studies. An average of 82 percent of the men invited for examination responded. In the Seven Countries Study the average response rate to the invitation to participate was 90.4 percent; excluding the United States railroad men, the response rate was 93 percent. However, as will be shown in chapter 3, even that high level of response does not guarantee a good estimate of the prevalence of disease in the target population. Unless the response rate is extremely poor, there is little danger of an overestimation of prevalence, but unless substantially 100 percent response is obtained an important underestimation of prevalence is possible.

Accordingly, we do not emphasize comparisons among samples or populations in regard to prevalence. Moreover, all men given a diagnosis of coronary heart disease at the entry examination were excluded from all analyses of incidence. However, the subsequent experience of men found to have coronary heart disease at entry is of interest in regard to prognosis (see chapter 3).

Any attempt to compare incidence rates among these studies must raise serious questions about diagnostic comparability. Recognition of that difficulty led the collaborators in the Pooling Project to confine the analyses to myocardial infarction and death as manifestations of coronary heart disease. In this book we also concentrate on the incidence of myocardial infarction and death from coronary heart disease, that is, hard CHD. As will be seen, the incidence of angina pectoris and other soft diagnoses is much less closely related to the risk factors than diagnoses of coronary heart disease that involve electrocardiographic criteria. Furthermore, the experience of this study is that, although uncomplicated angina pectoris carries the risk of future more serious manifestations, the prognosis is much less ominous than that of myocardial infarction, even when the infarct survivor has no clinical signs of disability after the acute episode.

In many reports on the epidemiology of coronary heart disease, the various manifestations of the disease are combined. This is understandable in view of the desire to offer a significant number of cases, but it also means that reported incidence rates are often of uncertain comparability. Another reason why it is generally difficult to compare incidence rates of different studies is the common practice of reporting incidence by ten-year or even

twenty-year age groups. As will be emphasized in chapter 6, age is the most important of the risk factors, and incidence rates for ten-year age groups are not comparable unless the age distributions are essentially identical. Even though the age distributions of the men in the sixteen cohorts of the Seven Countries Study are closely similar, we have used age-standardized rates in all cohort comparisons. Furthermore, because some important characteristics, notably blood pressure, respiratory function, and smoking habits, are related to age, age must be allowed for in evaluating risk factors; here, also, age groupings may confound age and the risk factors of concern.

Death from coronary heart disease generally raises fewer questions about comparability than diagnoses of angina pectoris, coronary insufficiency, and many cases of previous infarction. Thus it might seem reasonable to compare coronary death rates in various studies. However, for the studies listed in table 1.3, death rates standardized by single years of age are not available.

Summary

Prospective studies on the epidemiology of coronary heart disease began in the late 1940s in the belief that, if clinically healthy persons were examined, queried, and followed over the years, it would be possible to identify characteristics associated with the development of clinical coronary heart disease. It was hoped that such knowledge would provide a basis for preventive measures. These programs started in the United States because the coronary problem seemed most serious there, but it was soon realized that comparisons with other populations would be instructive. Are there, as rumored, large differences among populations in the frequency of the disease? If so, what are the characteristics of the populations, including their mode of life, associated with differing rates of incidence of the disease? The cholesterol hypothesis, then being revived, needed test of the idea, derived from animal experiments but rejected by leaders of clinical medicine in the 1930s, that the diet of a population would be reflected in the level of cholesterol in the blood which, in turn, would affect susceptibility to coronary heart disease. Finally, questions were asked about the natural history of the disease. Are there population differences in the manifestations or in the force of what, years later, would be called risk factors?

In 1952 explorations in Italy and Spain showed marked differences in the average blood cholesterol level of men subsisting on the contrasting diets of working men in Naples and Madrid, (Keys 1953a; Keys 1956). Local physicians insisted that coronary heart disease was very rare in the working class of Naples and Madrid. Still greater contrasts were found when the explorations were extended to South Africa, Hawaii, Japan, California, and Fin-

land. Obviously, a systematic international prospective study, with common protocol and fixed criteria, was needed.

In 1957, full-scale trials were made in Italy and Greece to test methods and work out the organization of international teams and a common center for all data and analyses. Medical scientists participating in that work in 1957 came from England and France and the seven countries—Finland, Greece, Italy, Japan, the Netherlands, the United States, and Yugoslavia—in which the long-time collaborative study was organized. The prospective program began in 1958 with the establishment of rosters and entry examinations of men 40–59 years old in the two rural areas of Croatia, Yugoslavia, a farming center in Japan, and the start of examinations of men employed by railroad companies in the northwestern sector of the United States. The last entrants into the study, members of the faculty of the University of Belgrade, were examined in 1964.

The study concerns sixteen cohorts of men in areas suggested as affording a wide range of contrasts in the mode of life. All men aged 40–59 in the specified areas, or in the designated samples, were invited to participate. The phrase *designated samples* refers to men in certain railroad occupations in specific regions in the United States and Italy and a randomly selected 44.4 percent sample of all men 40–59 in the small town of Zutphen, the Netherlands. All men 40–59 on the faculty of the University of Belgrade and in a big cooperative at Zrenjanin, a Serbian agricultural center, were invited to make up two cohorts. The other eleven cohorts comprised the responders to invitations to participate in geographically defined rural areas in Croatia, Finland, Italy, Japan, Greece, and Serbia. A total of 12,763 men, over 90 percent of those invited, are covered by this study. Deaths and major illnesses were checked annually. Reexaminations were made yearly at Zutphen and at the five- and ten-year anniversaries of the other cohorts except for the American railroad men who were reexamined at five years; at ten years finances permitted only a thorough review of mortality.

All examination records, medical histories, electrocardiograms, and copies of death certificates were sent to the University of Minnesota for central processing and diagnostic review. Measured samples of blood serum, dried, were analyzed at the University of Minnesota, as were the lyophilized samples of the diets. Professional personnel were exchanged among the areas, and representatives of the area teams worked from time to time at the University of Minnesota center so as to assure standardization of methods and criteria.

The present book reports characteristics of the men in the sixteen cohorts at entry, intercorrelations among the several entry variables, and the dif-

ferences among the cohorts. The major focus of the book is the ten-year experience of death and the incidence of coronary heart disease and the relationships of the incidence rates to the characteristics recorded at entry. During the ten years, 1,512 men died, 413 from coronary heart disease. Most of the analyses concern the 12,095 men who showed no evidence of cardiovascular disease at the entry examinations.