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The Seven Countries Study: 2,289 Deaths in 15 Years*

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Among 11,579 men ages 40–59 without evidence of cardiovascular disease, 2,289 died in 15 years, 618 from coronary heart disease. The 15 cohorts in seven countries (four regions) differed in all-causes death rate, mainly reflecting great differences in coronary mortality. Among characteristics of entry, only mean blood pressure helped to explain cohort differences in all-causes death rate. Three-quarters of the variance in coronary death rate was accounted for by differences in mean serum cholesterol and blood pressure of the cohorts. The mortality risk for individuals was examined in each of the regions. For coronary death, age, serum cholesterol, blood pressure, and smoking were highly significant in all regions except Japan, where coronary deaths were too few for evaluation. Relative weight was not significant anywhere. Physical activity was significant only in southern Europe, where differences are associated with socioeconomic status. For all-causes death, age and blood pressure were highly significant risk factors in all regions as was smoking habit, except in Japan. Relative body weight tended to be a negative risk factor everywhere, significantly so in southern Europe. Expectations for coronary death from the experience in the United States and northern Europe greatly exceeded observed deaths in southern Europe for men of their age, serum cholesterol, blood pressure, smoking habits, physical activity, and relative weight. The reverse, prediction of coronary deaths in America and in northern Europe from the southern European experience, greatly underestimated the deaths observed. Sim-

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ilar cross-predictions between the United States and northern Europe were good for all-causes deaths, excellent for coronary deaths. Analysis of time trends in relationships of mortality to entry characteristics showed continued importance of age, blood pressure, and smoking and a tendency for the importance of cholesterol to fall in the last 5 years of follow-up.

INTRODUCTION

Prospective studies on the epidemiology of coronary heart disease (CHD) have shown that the prevalence, incidence, and mortality of the disease differs greatly among populations, that at least some of those differences are associated with contrasts in the mode of life and characteristics of the subjects at the start of follow-up, and that mathematical analysis of relationships between the entry characteristics, "risk factors," and subsequent disease can give useful estimates of the force of the various risk factors and the probability of future disorders and can suggest possibilities for prevention. But many questions remain.

Prospective studies in this area commonly concern a particular sample of a population; this leaves uncertainty about their relevance to other populations and doubt about the universality of any relationships that may be found. Comparison of findings reported from different populations is difficult when there are questions about study methods and criteria. The common protocol and methods of the Seven Countries Study sought to obviate such questions and to allow proper comparison of samples of men in differing populations with regard to the incidence of and mortality from CHD and to examine the applicability of findings in one population to other population samples. Moreover, although the initial concentration was on CHD, it was later recognized that attention also should be given to total mortality and its possible relationship to the risk factors emphasized for CHD.

Many findings in the entry examinations of the Seven Countries Study, and the experience in the follow-up through 10 years, have been reported (5–8), but obviously, much more could be learned by extension of the follow-up to cover more events. So, despite lack of central financing after 10 years, local efforts allowed collection of data on deaths and their causes to cover 5 additional years for all but 1 of the original 16 cohorts. The University of Belgrade cohort is omitted from the present report because death data after the first 10 years are incomplete.

COHORTS, SUBJECTS, METHODS, AND FOLLOW-UP

The entry examinations covered 12,225 men ages 40–59 in the 15 cohorts. Men in the full-time employ of U.S. railroads in specified occupations numbered 2,571 and a cohort of 768 men in the Rome Division of the Italian State Railroads was their counterpart in Italy. In Europe and in Japan 7,492 men in 11 cohorts comprised over 95% of all men ages 40–59 in geographically defined rural areas. A statistically defined four-ninths sample of all men ages 40–59 resident in Zutphen, a small town in east-central Netherlands, made a cohort of 878 men. A large cooperative at Zrenjanin, Serbia, provided a cohort of 516 men ages 40–59. Among the 12,225 men at the entry examinations, 646 showed evidence of cardiovascular disease. The present report excludes these men and thus concerns

11,579 "healthy" men among whom there were 2,289 deaths in 15 years, 618 of these being attributed to CHD.

The procedure, methods, and criteria at the entry and the 5- and 10-year examinations have been described in detail (5–8), but a brief summary here may be useful. The men came for examination by appointment with instructions to report in the fasting state or at least to have had no substantial food within the previous 2 hr. Almost all of the men were indeed in the fasting state—no hardship in most of these areas where little or no breakfast is customary. They refrained from smoking and exercise for 30 min before starting an interview covering age, family status, occupation, physical activity, smoking, and eating habits. Standing height was measured barefoot and weight taken wearing only light underclothes. The relative weight was expressed as the body mass index: weight in kilograms divided by the square of the height in meters. A physician fluent in the local language and knowledgeable about local ideas on health and disease took the medical history and made a standard physical examination with arterial blood pressure being recorded twice in quiet rest, using the auscultatory method and standardized manometer. A 12-lead electrocardiogram was recorded in supine rest and again, except when contraindicated in a few cases, after a 3-min 2-step exercise test.

Blood was drawn with minimal stasis from an antecubital vein. After clotting, serum was separated by slow-speed centrifugation and precision micropipets were used to put duplicate 0.1-ml samples on filter-paper strips to be dried in air and sent to the central laboratory for cholesterol measurement at the University of Minnesota with a modification of the Liebermann–Burchard method of Anderson and Keys (1).

Occupation was the main basis for classifying the American railroad men with regard to physical activity. Executives, dispatchers, and most of the men listed as "clerks" were considered sedentary and were assigned to class 1. Switchmen were coded class 2, moderately active; their work is not strenuous but they walk on the poor footing of the railroad yards, climb freight cars, and are otherwise not sedentary. About 15% of the men identified as clerks by the union do not have sedentary jobs, and they also were considered as class 2 in physical activity. In Europe and Japan, the range of physical activity was greater and, in fact, a great many men habitually did work demanding strenuous exertion. From the occupation and the personal description of physical activity, it was seldom difficult to decide the proper class for physical activity. Most of the men were in class 3, very active, that is, commonly engaged in heavy work much of the time. None of the American men could be put in that class.

For the 15 cohorts considered here, ascertainment of vital status after 10 years was satisfactorily completed for all but the men of Velika Krsna, Serbia, where the search is continuing to check the possibility that deaths might have been missed late in the follow-up. It is possible that the 73 deaths recorded could be as many as 10 or 12 short of the true total, although this would have only a trivial effect on the analysis of over 1,000 deaths in southern Europe, including Velika Krsna.

Death certificates in the files of local registry offices, or elsewhere for men who had migrated, were used to begin the inquiry into causes of death, but the final ascription of cause was made only after considering information from many sources. Frequent visits to each of the areas were made to learn about deaths with a minimum of delay; the circumstances of death were learned from family doctors and other physicians, hospitals, relatives, friends, and other possible informants. Data recorded on the decedents at entry and at 5- and 10-year examinations were also considered. Two of the present authors, A.M. and H.B., agreed on a final decision about cause of death. The descending rank of priorities adopted in cases of apparent multiple causes of death was violence, cancer in an advanced stage, CHD, other causes. Actually, multiple causes of death were recorded but not used in the present analysis. Final causes of death were classified according to the eighth revision of the International Classification of Causes of Death.

The collection of information on deaths and their causes in the U.S. railroad cohort, where the insurance provisions of the U.S. Railroad Retirement Board assured completeness of follow-up, was slightly different. Notices of death and copies of the death certificates were provided by the Board. The certificates were coded by a nosologist and checked by a physician long experienced in such work. In a subsample of deaths, there was excellent agreement between causes classified in this way and independent ascription of cause of death after review of hospital discharge records (6). The death rates in this report are adjusted by single years of age to the age distribution of all cohorts combined.

The major purpose of this report is evaluation of the significance for premature death of characteristics of men judged to be "healthy" at the outset. Men with recognized cardiovascular disease differ from their healthy counterparts not only in the evidence of disease, but because of responses to their condition, including changes in activity, in the diet, and in the use of drugs. The present report does not cover the 587 men with cardiovascular disease at entry.

Initially, the Seven Countries Study, like other prospective studies started in the 1950s, was pointed to CHD and its risk factors. With that focus, little attention was given to longevity or total mortality. The ultimate interest being prevention, it seemed reasonable to suppose that measures controlling coronary risk factors would improve the outlook for longevity as well as for heart attacks, at least in the population of middle-aged men in the United States for whom CHD is the outstanding cause of premature death.

In the present study, the large number of deaths accumulated over the years forced attention to total mortality when it was found that CHD accounted for less than one-third of all deaths. So, relationships of coronary risk factors to the larger issue of total mortality as well as to coronary deaths were examined. A distinction was made between regions: While CHD accounted for 46% of all deaths of the Americans and 40% of the northern Europeans deaths, it accounted for only 17% of all deaths among the southern Europeans and less than 5% among the Japanese in this study.

There were important differences among the cohorts in death rates, especially from CHD, so the first question concerns the extent to which the differences in death rates were related to differences among the cohorts in the mean values of their characteristics at entry. Death rates of the 15 cohorts plotted against the

TABLE 1

DEATHS IN 15 YEARS, ALL CAUSES AND CORONARY HEART DISEASE, PER 10,000, STANDARDIZED BY SINGLE YEARS OF AGE, OF MEN AGES 40–59 AND FREE FROM EVIDENCE OF CARDIOVASCULAR DISEASE AT ENTRY

Cohort, area	*N* at risk	All causes		CHD		Ratio CHD/all
		Rate	SE[a]	Rate	SE	
U.S. railroad	2,315	1,679	74	773	53	0.46
East Finland	728	2,460	153	1,202	117	0.48
West Finland	806	2,263	140	741	88	0.33
Zutphen, Netherlands	845	1,878	127	637	80	0.34
Crevalcore, Italy	956	2,263	128	425	64	0.19
Montegiorgio, Italy	708	2,067	149	447	78	0.22
Rome railroad, Italy	736	1,624	133	516	84	0.32
Dalmatia, Yugoslavia	662	1,681	152	216	54	0.13
Slavonia, Yugoslavia	680	2,625	162	389	72	0.15
V. Krsna, Yugoslavia	487	1,516	161	67	40	0.04
Zrenjanin, Yugoslavia	476	1,671	179	298	73	0.18
Crete, Greece	655	968	126	38	23	0.04
Corfu, Greece	525	1,409	154	202	58	0.14
Tanushimaru, Japan	504	1,711	165	144	50	0.08
Ushibuka, Japan	496	2,250	182	128	48	0.06
Northern Europe[b]	2,379	2,195	81	843	55	0.38
Southern Europe[c]	5,885	1,808	47	313	22	0.17
Japan	1,000	1,958	120	144	36	0.07

[a] SE = standard error.

[b] West and east Finland and Zutphen.

[c] Crevalcore, Montegiorgio, Rome railroad, Dalmatia, Slavonia, Velika Krsna, Zrenjanin, Crete, and Corfu.

means of each entry characteristic showed no peculiar distributions, so the relationship of death rate to averages for the entry variables was examined by solving the univariate regression equation both for all-causes and for coronary death rates for each entry variable.

Within each area, the men, classified by 15-year vital status, were compared with regard to each of the entry characteristics. For multivariate analysis, the relationship of the probability of death to the independent variables of age, blood pressure, serum cholesterol, relative body weight, smoking habit, and occupational physical activity was examined with the multiple logistic model, using the iterative method of Walker and Duncan (14). The statistical significance of the independent variables was judged from the *t* values, the ratios of the coefficients to their standard errors.

DEATH RATES AND ENTRY CHARACTERISTICS OF THE COHORTS

Table 1 shows age-standardized 15-year coronary and all-causes death rates. The 15-year all-causes death rate proved to be correlated with the coronary death rate, the coefficient being $r = 0.52$, reflecting the fact that 27% of all deaths in this material were due to CHD. There is no significant correlation between the coronary death rate and the rate of deaths from other causes. The coronary

TABLE 2
REGRESSION ($y = a + bx$) OF AGE-STANDARDIZED DEATH RATE (y) PER 10,000, ON MEAN VALUES OF THE ENTRY VARIABLES (x), FOR 15 COHORTS, COEFFICIENT OF CORRELATION (r_{xy}), AND ITS 95% CONFIDENCE LIMITS

Death entry variable	a	b	SE_b	r_{xy}	95% CL
CHD					
Cholesterol (mg/dl)	−1258	8.2	1.3	0.87	0.65, 0.96
Systolic B.P.	−5513	42.9	13.5	0.66	0.22, 0.88
Cigarettes per day	558	−13.0	34.1	−0.11	−0.59, 0.43
Body mass index	−1855	95.8	56.1	0.43	−0.11, 0.77
Physical activity	914	−208.0	310.2	−0.26	−0.68, 0.29
All					
Cholesterol (mg/dl)	1149	3.5	3.5	0.27	−0.28, 0.69
Systolic B.P.	−4662	47.3	21.2	0.53	0.02, 0.82
Cigarettes per day	1987	−10.5	47.5	−0.06	−0.55, 0.46
Body mass index	1344	22.2	86.0	0.07	−0.46, 0.56
Physical activity	1178	289.0	292.0	0.26	−0.29, 0.68

death rate is much more variable than the rate of death from other causes. This is shown by the coefficient of variability, the standard deviation divided by the mean. For coronary death, the coefficient is 0.77, while for noncoronary deaths, the figure is 0.27, a threefold difference in variability.

In addition to showing the comparison of the cohorts, Table 1 compares the four regions. The coronary death rate was highest in northern Europe, but the difference from the U.S. rate is not statistically significant, as is evident from the 95% confidence limits of 731 and 935 for the northern Europeans and 664 and 882 for the Americans. In contrast, the coronary death rate of the southern Europeans was only 37% that of the northern Europeans, or 40% that of the Americans. The coronary death rate of the Japanese was, as expected from the experience of the first 10 years of follow-up, much lower than the rates for the other regions. On the other hand, the rate of death of the Japanese from causes other than CHD was so high that their all-causes death rate was higher than the rate for the southern Europeans and not significantly different from the all-causes death rate of the northern Europeans, the difference of 237 deaths per 10,000 having a standard error of 154, $t = 1.5$. The Americans had the lowest death rate from all causes, but it was not significantly lower than the rate of the southern Europeans, the t value being -1.4.

The first question is whether the differences among the cohorts in death rate are related to the average entry characteristics of the men in those cohorts. Age was not a factor; the cohorts were closely matched in age, and death rates are age-standardized. For the other characteristics, one approach is regression–correlation as summarized in Table 2. The indication is that the coronary death rate is significantly related to serum cholesterol and blood pressure but not to the other characteristics considered. The fact that relative weight, smoking habit, and physical activity of occupation do not help to explain differences in coronary death rate does not imply that those characteristics are unimportant for the risk of individuals. Individual risk is examined in the next section.

For all-causes death rates, only blood pressure seeemed to be significant with $P = 0.05$. Univariate analyses gave the same general picture; $P = 0.07$ for blood pressure with none of the other variables coming close to significance.

It may be objected that the regression approach requires bivariate normality, and we cannot show that this stipulation is met. Alternatively, rank order correlation was calculated. Here again relative weight, smoking, and activity were not significantly related to coronary death rate, while serum cholesterol and blood pressure showed coefficients of correlation of $r = 0.73$ and 0.67, respectively. Judged by rank order correlation, only blood pressure came close to significance for all-causes deaths with $P = 0.08$.

RISK FACTORS FOR CORONARY DEATH FOR INDIVIDUALS

For individual risk, the multiple logistic equation was solved with the iterative method of Walker and Duncan (14) as one means of evaluating the power of the several entry characteristics in differentiating the men who died during the 15 years of follow-up from the survivors and estimating the probability of death from the risk factor values. The six characteristics at entry taken as independent variables in the logistic equation were age, serum cholesterol, systolic blood pressure, cigarette smoking, the body mass index, and habitual physical activity. With the probability of coronary death in 15 years as the dependent variable, the equation was solved separately for each of the four geographic areas. The results are summarized in Table 3.

In spite of the differences in the coronary death rate among the areas, within the separate areas the Americans, the northern Europeans, and the southern Europeans were much alike in the significance of four of the risk factors. Age, serum cholesterol, systolic blood pressure, and cigarette smoking habit were very important risk factors in all three areas, and for probability of coronary death the coefficients were similar in significance as is indicated by their t values, although age and blood pressure tended to be slightly more important than cholesterol and smoking. Those three geographic areas were also alike in that relative body weight, expressed as body mass index, showed no relevance to coronary death.

The Americans and northern Europeans were similar in regard to absence of any indication that physical activity was a risk factor. On the other hand, physical activity class of occupation seemed to be important for the southern Europeans; the probability of dying from CHD was inversely related to activity. It is hazardous to draw conclusions from these data on activity and coronary death because in Europe, especially in southern Europe, physical activity level is related to socioeconomic status and other important lifestyle features.

Table 4 summarizes the results of the corresponding multiple logistic analysis for all-causes deaths. In all areas, age and systolic blood pressure were significantly related to 15-year total mortality. Cigarette smoking was highly significant in all areas except Japan. Serum cholesterol was important for all-causes deaths only for the Americans; the t value for the northern Europeans indicates a probability of positive risk associated with cholesterol of $P = 0.06$ (one-tailed because

TABLE 3

CORONARY DEATH. COEFFICIENTS (C), TIMES 100, FROM SOLUTION OF THE MULTIPLE LOGISTIC EQUATION, AND *t* VALUES FOR PROBABILITY OF CORONARY DEATH IN 15 YEARS

	U.S.A.		N. Europe		S. Europe		Japan[a]	
Characteristic	C	*t*	C	*t*	C	*t*	C	*t*
Age (years)	9.6	6.4	7.9	5.4	9.8	6.2	10.7	1.6
	(54.8)		(42.9)		(51.9)		(59.3)	
Cholesterol[b]	0.68	4.1	0.62	4.4	0.60	3.4	−0.52	−0.5
	(31.0)		(31.4)		(25.6)		(−18.8)	
Systolic B.P.	2.4	6.2	2.3	6.0	1.9	5.3	1.3	1.1
	(44.9)		(42.2)		(36.1)		(29.8)	
Cigarettes/day	3.2	5.7	3.4	4.2	3.2	4.3	2.5	0.7
	(42.9)		(31.6)		(32.0)		(23.6)	
Body mass index	0.10	0.1	0.56	0.2	1.7	0.8	−27.4	−1.7
	(0.3)		(1.7)		(6.0)		(−64.8)	
Physical activity	10.1	0.6	8.2	0.8	−33.0	−3.3	−65.3	−1.4
	(5.1)		(5.8)		(−24.1)		(−37.1)	
Intercept[c]	−12.77	−11.8	−11.71	−10.1	−12.14	−10.8	−3.67	−0.7

Note. Standardized coefficients, coefficient × SD in parentheses.

[a] Only 10 coronary deaths of men with all entry characteristics recorded.

[b] In mg/dl; 100 mg/dl = 2.59 mmol/l.

[c] Not standardized and not times 100.

TABLE 4

ALL-CAUSES DEATH. COEFFICIENTS (C), TIMES 100, FROM SOLUTION OF THE MULTIPLE LOGISTIC EQUATION AND *t* VALUES FOR PROBABILITY OF DEATH IN 15 YEARS

	U.S.A.		N. Europe		S. Europe		Japan	
Characteristic	C	*t*	C	*t*	C	*t*	C	*t*
Age (years)	10.6	9.7	8.9	8.9	10.6	14.4	64.5	5.8
	(60.7)		(49.0)		(56.6)		(58.2)	
Cholesterol[a]	0.39	3.1	0.16	1.6	0.03	0.3	−5.6	−0.6
	(17.7)		(8.3)		(1.1)		(−7.8)	
Systolic B.P.	1.9	6.4	1.6	6.1	1.7	9.4	27.5	3.0
	(35.8)		(31.6)		(33.6)		(32.3)	
Cigarettes/day	3.3	7.9	2.9	5.1	2.0	5.7	6.3	0.7
	(44.2)		(26.8)		(20.5)		(3.4)	
Body mass index	−3.6	−1.9	−3.1	−1.8	−4.3	−4.0	−16.6	−1.7
	(−11.4)		(−9.4)		(−15.8)		(−15.8)	
Physical activity	23.3	2.2	−2.2	−0.3	−18.6	−3.9	−4.0	−0.4
	(12.6)		(−1.6)		(−13.7)		(−7.7)	
Intercept[b]	−10.33	−12.1	−7.98	−10.3	−8.04	−15.6	−7.07	−4.7

Note. Standardized coefficients, coefficient × SD in parentheses.

[a] In mg/dl; 100 mg/dl = 2.591 mmol/l.

[b] Not standardized and not times 100.

the prior hypothesis was a positive association). Relative body weight was a *negative* risk factor in all areas, meaning the higher the relative weight, the lower the probability of death in 15 years.

Physical activity was far from being a significant risk factor in the northern European and Japanese men but was a positive risk factor for all-causes deaths for the Americans and a negative risk factor for the southern European men, the logistic coefficients being statistically significant but in opposite directions in those two areas. The finding of a poorer 15-year survival of the men physically more active in the American railroads is accounted for by an excess of violent deaths among the more active men. The finding that the risk of all-causes death was increased in the least active southern European men calls for the same comment as that made about the increased risk of coronary death for the less active southern European men. In these southern European men, the physical activity of the occupation is strongly related, inversely, to socioeconomic status, which, in turn, is reflected in the diet and other aspects of the mode of life.

It has been noted in Tables 3 and 4 that the coefficients and their t values for some of the entry variables differ substantially in the solutions for all-causes deaths as compared with coronary deaths. In spite of those differences, the total discrimination by those variables is good for all causes as well as for coronary deaths. For the Americans, the upper 20% of the distribution of risk probability for coronary deaths contains 51% of the observed coronary deaths. The corresponding top 20% of the distribution of risk probability for all-causes death contains 42% of the observed all-causes deaths. For the northern Europeans, the corresponding figures are 42 and 35% of coronary and all-causes deaths in the top quintile of risk. For the southern European men, the figures are 54 and 39%. The coefficient of correlation between observed and expected numbers of deaths in the decile classes of risk probability for all-causes and for coronary deaths are, respectively, $r = 0.98$ and $r = 0.97$ for the Americans; $r = 0.99$ and $r = 0.96$ for the northern Europeans; and the same for the southern Europeans. With only 10 pairs of values, none of these coefficients differ from one another; the 95% confidence limits for $r = 0.96$ with $N = 10$ are 0.84 and 0.99.

In Japan only 12 men died from CHD in 15 years, and cholesterol values are lacking for 2 of them. With only 10 coronary deaths in 15 years for the logistic solution, it is not surprising that none of the risk factor variables are statistically significant; the numbers are insufficient for useful analysis.

PREDICTING DEATHS IN ONE REGION FROM EXPERIENCE IN ANOTHER REGION

With the exception of Japan, the solutions of the logistic equation gave satisfactory classification of the men in regard to the probability of death in 15 years from all causes as well as from CHD in the different regions. The question then arises as to the applicability of the logistic coefficients for one region to the prediction of risk of death in another region. To what extent may these coefficients have general applicability? Table 5 summarizes the results from the examination of that question.

TABLE 5
PREDICTION OF ALL DEATHS AND CORONARY DEATHS (CHD) IN ONE REGION FROM LOGISTIC COEFFICIENTS FROM ANOTHER REGION

Solution from	Predicting deaths in	O/E, all deaths	O/E, CHD deaths
South Europe	North Europe	1.15	1.89
South Europe	U.S.A.	0.89	1.32
South Europe	Japan	0.89	0.46
North Europe	South Europe	0.90	0.53
North Europe	U.S.A.	0.84	1.01
North Europe	Japan	0.81	0.22
U.S.A.	South Europe	0.95	0.52
U.S.A.	North Europe	0.97	0.96
U.S.A.	Japan	0.86	0.22
Japan	South Europe	1.19	4.95
Japan	North Europe	1.52	16.08
Japan	U.S.A.	1.31	11.18

Note. O/E is the ratio of observed to expected number of deaths. For all logistic solutions the independent variables were age, serum cholesterol, systolic pressure, cigarettes per day, body mass index, and physical activity.

For all-causes deaths, the predictions from one region to another are not bad. Except for the Japanese, the ratio of observed to expected deaths, O/E, varies only from 0.84 to 1.15. For coronary deaths the discrepancies are much greater. The 15-year coronary deaths among the northern Europeans were almost twice (189%) the number expected for men of their entry characteristics from the experience of the men in southern Europe. The coronary deaths expected among the southern European men from the coefficients for the Americans and the northern Europeans were almost double the number actually observed. On the other hand, the number of coronary deaths predicted for the Americans from the coefficients for northern Europe was almost the same as the number observed and the reverse prediction, coronary death among the northern Europeans from the American coefficients, is almost as good. The southern European men differ sharply from the Americans and the northern Europeans in the force of the coronary risk factors as well as in coronary death rate.

MORTALITY TRENDS OVER TIME

We reported elsewhere the experience from the first 10 years of follow-up of the 10,579 men in these 15 cohorts who showed no signs of cardiovascular disease at entry. The average yearly death rate in the first 10 years was 12.82 per thousand; for the next 5 years the figure was 19.47. The corresponding figures for coronary death rate were 2.66 and 7.61, so mortality from CHD increased much more than the mortality from the total of all other causes, but the changes in death rates were not the same in all areas. For the Americans, the ratio of the yearly death rate of the third 5-year period to that of the first 10 years was 2.14 for all-causes deaths and 2.30 for coronary deaths. For the northern Europeans,

TABLE 6
SIGNIFICANCE OF RISK FACTORS IN DISCRIMINATING MEN DYING IN 10 AND 15 YEARS AS INDICATED BY THE t VALUES IN THE SOLUTIONS TO THE MULTIPLE LOGISTIC EQUATION FOR FIRST 10 AND ALL 15 YEARS

Characteristic	Period (years)	U.S.A.		N. Europe		S. Europe	
		CHD	All	CHD	All	CHD	All
Age at entry	10	3.6	6.3	3.4	6.4	3.4	12.6
Age at entry	15	6.4	9.7	5.4	8.9	6.2	14.4
Systolic B.P.	10	3.4	3.3	3.6	4.2	3.0	4.2
Systolic B.P.	15	6.2	6.4	6.0	6.1	5.2	9.4
Serum cholesterol	10	3.9	1.5	4.6	0.7	2.1	−3.1
Serum cholesterol	15	4.1	3.1	4.4	1.6	3.4	0.3
Cigarette smoking	10	4.8	6.0	3.9	4.2	1.8	3.0
Cigarette smoking	15	5.7	7.9	4.2	5.1	4.2	5.7

the corresponding ratios were 1.93 and 2.92. For the southern Europeans the all-causes death rate rose less in the third 5-year period, the ratio being only 1.21, but for deaths from CHD the ratio was 3.38. From a very low coronary death rate in the first 10 years, the southern Europeans were beginning to catch up with the Americans and the northern Europeans in coronary mortality, but, even so, their coronary death rate in the third 5 years of follow-up was only about half that for the American and the northern European men.

A somewhat related question is that of the significance of the risk factors over the years. Table 6 compares the significance of risk factors as indicated by their t values, the coefficients divided by their standard errors, in the logistic solutions from the 10-year data and again from the 15-year data for all-causes and for coronary deaths. In all cases except all-causes deaths in southern Europe, the risk factors became more significant at 15 years. For all-causes deaths in southern Europe, serum cholesterol was a significant negative risk factor, meaning the higher the better, for 10 years, but after 15 years the negativity disappeared.

Table 6 indicates that the actuarial importance of the risk factors was considerably more secure with 15 years of experience than with only 10 years. This reflects the fact that the 15-year calculations are based on close to twice the number of deaths and that there was no important reversal of the risk relations. But, it is instructive to examine separately the relations of the risk factors to death in the last 5 years as summarized in Table 7.

For deaths in the third 5-year period of follow-up, the age and smoking habits of the men at entry were significant risk factors for both coronary and non-coronary death in both areas of Europe and in the United States. The systolic blood pressure at entry was also an important risk factor for coronary death 10 to 15 years later in all areas and for noncoronary deaths in northern and southern Europe, but it was not a significant risk factor for the late noncoronary deaths among the Americans. Curiously, the concentration of cholesterol in the blood serum at entry was a significant risk factor for late coronary deaths in both areas of Europe but not for the Americans. On the other hand, serum cholesterol was

TABLE 7

THE PERSISTENCE OF RISK—LATE MORTALITY. STANDARDIZED COEFFICIENTS (TIMES 100) AND THEIR *t* VALUES IN PARENTHESES FROM SOLUTION OF THE MULTIPLE LOGISTIC USING ENTRY CHARACTERISTICS COMPARING 15-YEAR SURVIVORS WITH MEN DYING IN THE PERIOD 10–15 YEARS AFTER ENTRY

	U.S.A.		N. Europe		S. Europe	
Variable	CHD	NON-CHD	CHD	NON-CHD	CHD	NON-CHD
Age	55.0	65.5	45.0	47.1	49.0	45.0
	(4.7)	(6.0)	(4.3)	(4.9)	(4.4)	(7.0)
Systolic B.P.	45.9	13.4	35.1	18.0	36.7	33.1
	(5.0)	(1.4)	(4.0)	(2.1)	(3.9)	(6.2)
Cholesterol	11.1	20.8	25.6	−30.9	23.1	77.1
	(1.0)	(2.2)	(2.5)	(−0.3)	(2.3)	(1.3)
Smoking	42.0	41.7	24.3	24.2	49.4	26.3
	(3.8)	(4.0)	(2.4)	(2.5)	(4.6)	(4.6)
Relative weight	13.4	−50.0	−87.8	−12.3	73.0	−99.7
	(1.3)	(−0.5)	(−0.9)	(−1.3)	(0.7)	(−1.6)
Intercept[a]	−13.8	−11.1	−10.7	−76.5	−13.8	−92.1
	(−8.9)	(−7.7)	(−7.2)	(−5.6)	(−9.7)	(−12.0)

[a] Not standardized.

a significant risk factor for noncoronary deaths among the Americans but not for the Europeans. These findings represent the solution of a multiple logistic equation using death in the last 5 of the 15 years of follow-up as the dependent endpoint and the characteristics at entry as the independent variables.

With these multiple logistic solutions for risk of death in the last 5 years based on the entry characteristics, discrimination between those late deaths and the 15-year survivors is good. For example, 40% of all deaths in that period were in the top quintile of estimated risk probability, only 6% in the bottom quintile. For the 98 late deaths among the Americans, 48% were in the top quintile of the solution for coronary death, 5% in the bottom quintile.

In addition, univariate analysis compared the mean entry values of men alive after 15 years and the men who died during the period 10–15 years. In all areas the entry blood pressure was higher in the men who died from all causes than from CHD, the t values ranging from 4.7 to 10.0. Serum cholesterol at entry was also important for all-causes deaths among the Americans and the southern Europeans (t = 3.1 and 3.5, respectively) and for coronary deaths among the northern Europeans (t = 2.6). Serum cholesterol was of borderline significance for the 98 coronary deaths among the Americans in the period 10–15 years (t = 1.9) and was less significant for the late all-causes deaths among the northern Europeans (t = 1.3).

THE JAPANESE COHORTS

The smaller number of coronary deaths in Japan might account for failure to find significant risk factors for coronary death in the analysis of the Japanese data, but a larger question remains. Why is the number of coronary deaths so much smaller than the number predicted by the logistic coefficients from each of the other regions for men of the same age, blood pressure, serum cholesterol, and smoking habits as the Japanese men in this study?

Racial differences in metabolism cannot be ruled out, but a small dietary experiment on Japanese men indicated that when some rice calories in the typical low-fat diet are replaced with butter fat, the serum cholesterol response is similar to that expected from controlled dietary experiments on white men in Minnesota (9). More direct evidence opposing the idea of a racial immunity to CHD concerns Japanese who migrate from Japan to Hawaii and to California. As they become increasingly Americanized in lifestyle, including the diet, the average serum cholesterol level rises, and they become much more prone to heart attacks (2, 13). While this argues against a racial peculiarity it should be observed that the Japanese men in the Seven Countries Study suffered even fewer coronary deaths than would be expected for men with their low cholesterol levels. The vital statistics for Japanese in the United States (the great majority having been born in the United States) indicate their coronary death rate, though much higher than the figures in Japan, is still low by American standards. So an effect of a persisting racial difference cannot be entirely excluded.

Another possibility concerns missed diagnoses of coronary death, a relatively new diagnosis in Japan, especially in such rural areas as provided the two Japanese cohorts in this study. All deaths in those areas were reviewed by Japanese cardiologists with full knowledge of the criteria used by their American colleagues, but in some cases, they might have been misled by the local physicians who signed the death certificates and provided details. Finally, in spite of greatly increased awareness of the coronary problem in the past two decades and many surveys showing a substantial rise in the average serum cholesterol associated with a trend toward "westernization" of the diet in Japan, vital statistics mortality from CHD has increased little and is still very low by American and European standards. The 15-year experience of CHD in Japan remains puzzling.

RELATIVE BODY WEIGHT AS A RISK FACTOR

The risk for all-causes or CHD death did not increase with increasing relative body weight in any of the regions in this study. The only area in which relative weight was significant was southern Europe where the probability of all-causes death *decreased* with increasing body mass index. These findings are contrary to the popular view, based on American insurance company reports, that the risk of premature death increases with increasing relative weight. However, the experience in the Seven Countries Study conforms to that of almost all prospective studies on unselected middle-aged men whose heights and weights were actually measured by professional personnel with no interest in the insurance industry (2–5, 12).

This is not to say, however, that relative weight is unimportant at the extremes of the population distribution. It appears that both extreme obesity and extreme emaciation carry excessive risk of premature death. A report by insurance company actuaries on persons other than insurance applicants stated that early death was associated with relative weight (11). The data reported only indicate a risk associated with relative weight for persons in the top 1.6% of the distribution.

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