

TABLE 2.—National Cooperative Pooling Project. Analysis of the risk of CHD by smoking behavior from the pooled data of the five cohorts* observed with comparable methodology (Pool 5). Average annual risk of first major coronary event, standardized incidence ratio (SIR), risk ratio >1 pack per day/nonsmokers, and number of first events, by age group

Smoking pattern	Age group					SIR
	40-44	45-49	50-54	55-59	60-64	
	Average annual risk (per 1,000 man-years)					SIR
All	3.1	6.4	8.0	22.6	19.9	100
Nonsmoker	(1.5)	3.0	3.6	7.3	15.5	58
Never smoked	(1.9)	(0.7)	(2.5)	8.7	11.4	54
Past smoker	(0.9)	5.5	4.3	6.1	15.5	63
<1/2 pack/day	(1.7)	(4.7)	(5.9)	(6.4)	(7.5)	55
Cigar and pipe only	(2.1)	(2.2)	(2.1)	12.1	19.5	71
Cigarette smokers						
About 1/2 pack/day	(3.1)	(5.0)	(6.2)	15.5	24.3	104
About 1 pack/day	3.9	8.4	10.3	13.8	22.0	120
>1 pack/day	4.9	12.2	17.4	22.5	26.8	183
Risk ratio						
> pack/day/nonsmokers ()		4.1	4.8	3.1	1.7	3.2 ¹
	Number of first events					SIR
All	34	113	158	194	145	644
Never smoked	3	2	8	21	21	55
Past smoker	1	11	10	13	18	53
<1/2 pack/day	1	4	6	6	4	21
Cigar and pipe only	2	4	5	26	33	60
About 1/2 pack/day	3	7	9	19	15	53
About 1 pack/day	14	49	64	61	42	230
>1 pack/day	10	36	56	48	22	172

* See footnote of Table 1 for names of the five study groups.

¹ Approximate 95% confidence interval: 2.6-4.2.

NOTE: () based on fewer than 10 first events.

SOURCE: Pooling Project Research Group (214).

each 5-year age group between 45 and 64, and the differences were progressively greater with age up to 60. For those smoking about one pack per day and about one-half pack per day, the excess risks were sizable, but of a lower magnitude. Because of the relatively smaller numbers, the data were not sufficient for evaluation of differences in risks among those who had never smoked, those who had smoked less than one-half pack per day, and former smokers.

In the Pooling Project data, the risk for cigar and pipe smokers was not significantly different from either the nonsmoker group or

the half-pack per day smokers, but it was significantly lower than that for men who smoked a pack of cigarettes per day (Table 2). However, the position of cigar and pipe smokers on the continuum of risk could not be adequately evaluated from these data because of small numbers.

In summary, detailed prospective studies of the incidence of CHD in white males in the U.S. population have demonstrated a clear, strong, dose-related relationship between cigarette smoking and acute myocardial infarction and death from CHD. This cigarette smoking effect was proportionally greater in younger populations, but was present in all age groups examined in these studies. Cigarette smokers in the Framingham study had a high incidence of angina pectoris among the younger age groups, but this relationship was not as strong as the relationship between smoking and myocardial infarction. Pipe and cigar smokers had a risk that was not statistically different from the risk of nonsmokers.

Ethnic Groups in the United States With Lower Risk of CHD

CHD mortality in blacks is lower than in whites in the United States (75, 76, 197, 225, 236, 259). A case-control study of the incidence of CHD during World War II in young Army men observed a risk ratio of 0.61 in black men relative to white men (120). Reasons for lower rates in black men are not adequately understood, although the smoking habits of blacks have been found to differ from those of whites. Blacks have tended to smoke cigarettes with higher tar and nicotine content, but they have also tended to smoke fewer cigarettes (262). Hypertension is also more prevalent in blacks than in whites (142). On the other hand, plasma lipid levels were reported to be more favorable; high density lipoprotein cholesterol levels (HDL-C) were higher and low density lipoprotein cholesterol levels (LDL-C) were lower in black men than in white men aged 20 to 49 (259). HDL-C has been negatively associated with CHD, and LDL-C has been positively associated with CHD (80, 84, 217).

The Evans County, Georgia, study was initiated in 1960 to investigate differences in coronary heart disease incidence and risk between blacks and whites for an entire community in a rural, principally agricultural setting (107). All residents of Evans County over age 40 and a 50 percent subsample of those aged 15 to 39 years were eligible; 92 percent of those eligible were examined between 1960 and 1962. Followup examinations from 1967 through 1969 provided a mean followup period of 7 1/4 years. Reexamination for evidence of new CHD was obtained in 91 percent of the 3,102 initially examined members of the population, including 537 black males and 947 white males (83 percent and 93 percent, respectively, of those initially available). In addition, community and mortality

surveillance was used to ascertain the incidence cases of fatal and nonfatal CHD.

During the 7 1/4 years of followup, 13.6 percent of the black males and 12.7 percent of the white males died. The onset of CHD was observed in 6 surviving and 7 decedent black men and in 40 surviving and 32 decedent white men. The age-adjusted incidence rate for white men was 3.5 times the rate in black men. There were few cases in women, but the incidence rates in black women and in white women appeared to be similar. CHD incidence was higher in smokers than in nonsmokers for the black and the white populations.

Beginning in 1965, 9,824 men aged 45 to 64 years who were residents of four rural and three urban areas of Puerto Rico were examined at a clinic in San Juan. The methods used were comparable to those used by the Framingham study (85). Of the targeted population samples, over 80 percent attended the medical examination, and over 90 percent of the examined cohort participated in four followup examinations at 2 1/2-year to 3-year intervals. The average followup was 8 1/4 years (246).

In comparison with men in Framingham, fewer men in Puerto Rico were smokers, and the Puerto Rican smokers consumed fewer cigarettes per day (85). After 2 1/2 years of observation, the incidence of CHD in Puerto Rican men was only half that observed in Framingham, and the difference between smokers and nonsmokers was not significant (222). However, after 8 1/4 years of observation and the accumulation of approximately four times as many cases, cigarette smokers had a significantly higher incidence of MI than did nonsmokers; this was true both for those living in the rural areas and for those in the urban areas when considered separately (246).

Japanese Americans have an incidence and mortality from CHD that is intermediate between the very low rates in Japan and the high rates in white Americans (83, 222, 284). The explanation for this gradient of CHD with migration has been investigated by the Ni-Hon-San study centering on a cohort of Japanese Americans living in Hawaii (14, 221).

The target cohort of the Honolulu heart study was all noninstitutionalized men of Japanese ancestry born between 1900 and 1919 who were living on the Island of Oahu in 1965 (130). Initial examinations were conducted between 1965 and 1968, and participation was obtained from 72 percent of the identified men who were eligible (7,705 men aged 45-69 years and free of CHD). CHD incidence was observed by followup examination (at 2 and 6 years) and by intensive community and mortality surveillance activities. The 2-year incidence of MI and death from CHD was only half of that observed in Framingham men, but was significantly higher in

cigarette smokers (85). The relative risk for those smoking 21 or more cigarettes per day was six times higher than for nonsmokers (221). At 6 years of followup, the risk of MI and death from CHD, but not of angina pectoris, was strongly related to cigarette smoking, and the risk increased in proportion to the number of cigarettes smoked per day (130).

CHD death rates are lower in Great Britain than in the United States by about one-fourth, and those in Norway are substantially lower than either. In 1962 the National Heart Institute and the National Cancer Institute in the United States, the London School of Hygiene and Tropical Medicine, and the Norwegian Cancer Registry undertook a study to examine differences in death rates among migrant populations to the United States (223). Native-born Americans were included in the study for comparison. Approximately 32,000 British migrants and 18,000 Norwegian migrants aged 30 to 74, residing in 12 States, were sent questionnaires. For native-born Americans, similar questionnaires were sent to a subsample of 23,000 white persons drawn from a 1961 National Health Survey sample covering the same geographic areas. A total of 7,895 CHD deaths occurred (3,193 British, 1,213 Norwegian, and 3,489 native-born deaths). Norwegian migrants exhibited the lowest CHD death rates. British migrants' rates were about equal to those for native-born Americans.

The decedent's cigarette smoking status as of October 1962 was requested from the next of kin. Smoking status from October to the end of the study period (1963–1966) was presumed not to be altered. Mortality ratios for CHD were significantly elevated among smokers compared with nonsmokers, particularly at the younger ages. The ratios were 1.9 or greater for both males and females at age 45 to 54 years and decreased somewhat with age. CHD death rates among smokers demonstrated little difference between the three groups, and ratios were greater for female than male smokers in all but two instances. Table 3 provides a summary of these mortality ratios by migrant class, age, and sex.

In summary, a number of ethnic groups in the United States have lower rates of CHD, but even in these populations, the risk of MI and CHD death are significantly higher in smokers than in nonsmokers.

Studies in Other Countries

Cigarette smoking has been found to be related to the incidence of CHD in other countries where long-term followup of large, defined cohorts has been performed. For some cohorts, early data analyses with relatively few cases have not shown significant differences, but later followup analyses with large numbers of cases have usually demonstrated a positive relationship between cigarette smoking and CHD.

TABLE 3.—Coronary heart disease mortality ratios (smoker versus nonsmoker) of British and Norwegian migrants to the United States and native-born Americans by age, sex, and cigarette smoking status

Group	Age and mortality ratio (smoker vs. nonsmoker)		
	45-54	55-64	65-74
British migrants			
Males	1.9	1.3	1.3
Females	2.9	2.4	1.7
Norwegian migrants			
Males	2.3	1.5	1.6
Females	— ¹	2.3	2.0
Native-born Americans			
Males	2.3	2.7	1.4
Females	2.8	2.0	1.3

NOTE: All nonsmoker ratios are 1.0.

¹ Less than 10 deaths.

SOURCE: Rogot (223).

An international study conducted in seven countries observed large differences in CHD incidence and mortality among 16 cohorts of men aged 40 to 59 at baseline examination in the United States, Europe, and Japan (143). The United States cohort was the railroad men described above in the Pooling Project (214). This cohort experienced a relative risk of CHD with cigarette smoking that was similar to that of other U.S. cohorts of white men (Table 1). The other cohorts of men were residents of Yugoslavia (Dalmatia, Slovenia, Velika Krsna, Zrenjanin, and Belgrade), Japan (Ushibuka and Tanushimaru), Finland (districts in the east and west), Italy (Crevalcore, Montegiorgio, and railroad men in Rome), the Netherlands (Zutphen), and Greece (Crete and Corfu). In all, 12,763 men were examined, of whom 12,509 were free of evidence of coronary heart disease at baseline examination. During the 10 years of followup, 1,512 deaths occurred from all causes, and 413 were attributed to coronary heart disease.

Ten-year CHD death rates were less than 75 per 10,000 for the cohorts living in Crete (Greece) and in Croatia (Yugoslavia) and for the two cohorts in Japan; however, for the cohorts of east and west Finland, the U.S. railroad men, Zutphen (the Netherlands), and Belgrade (Yugoslavia), the CHD death rates were 250 per 10,000 or higher. Although the cohorts participating in the Seven Countries study were not selected as representative of their countries, the CHD death rates of cohorts grouped by country were highly correlated

with the CHD death rates for men of the same ages reported in the vital statistics of these countries.

Cigarette smoking was strongly related to CHD mortality in those cohorts with both high CHD death rates and relatively large numbers of cases for analysis. For example, among U.S. railroad men, CHD death rates were about three times as high in men who smoked 20 or more cigarettes per day compared with men who had never smoked or men who had stopped smoking. Furthermore, the association between CHD and number of cigarettes smoked daily was stronger in the cohorts with high CHD mortality than in the cohorts with low CHD mortality. Among northern European men as well as United States railroad men, the 10-year age-standardized CHD death rates increased significantly with the level of cigarette smoking, and the risk for northern European men smoking 20 or more cigarettes per day was more than four times greater than for men who had never smoked (Figure 2). For the southern Europeans, however, differences were only twofold and not statistically significant. Age-standardized rates for death from all causes, respiratory tract cancer, and neoplasms were also more closely related to the number of cigarettes consumed in northern Europe than in southern Europe, and for all deaths the differences were significant in both regions.

The 10-year incidence data provide a larger number of cases for analysis, as deaths from CHD represented only about 20 percent of the total CHD incidence in the Japanese and European cohorts. Definite CHD was observed in 351 of the 9,780 men during the followup period. The highest rate (11 percent) was observed in east Finland, and the lowest (0.3 percent) was observed in Crete (Table 4). Rates within countries were similar in general, but in Greece the rates were higher in Corfu than in Crete; in Finland the rate in the eastern district was double that in the western district; in Yugoslavia, the Serbian cohorts in Belgrade and Zrenjanin were similar, but in the farming village of Velika Krsna the rate was only half as high. The Japanese cohorts were small and the incidence too low for evaluation of the influence of smoking. Only 19 men in the two Japanese cohorts were observed to develop definite coronary heart disease during the 10 years of followup.

To provide greater stability in analyses, the European cohorts were grouped together by region: the three cohorts in Finland and the Netherlands, the five cohorts in Yugoslavia, and the three Italian cohorts with the two Greek cohorts. The 10-year CHD incidence in Finland and the Netherlands was significantly related to the number of cigarettes currently smoked, and former smokers had a CHD incidence that was twice that of those who had never smoked (Figure 3). In Yugoslavia, the CHD incidence in smokers was nearly twice that of those who had never smoked. Also in Yugoslavia, the CHD incidence was nearly three times higher for those

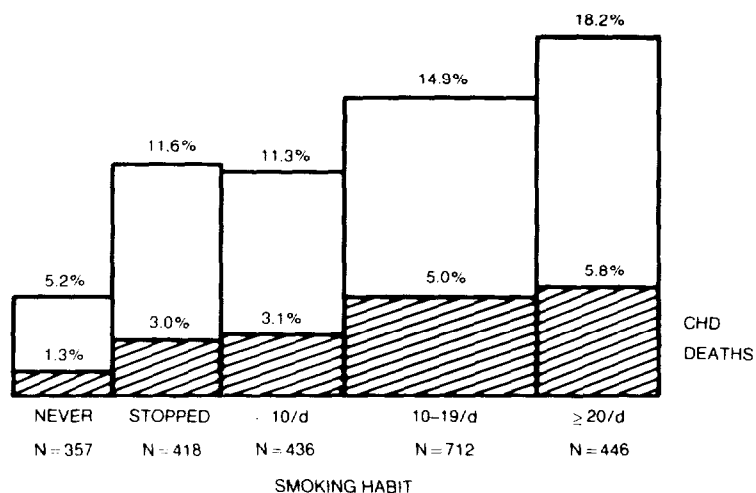


FIGURE 2.—Age-standardized 10-year death rates from all causes and from coronary heart disease of men in northern Europe (east and west Finland and Zutphen), classified by smoking habit at entry; all free of cardiovascular disease at entry

SOURCE: Keys (143).

smoking 20 or more cigarettes per day at entry compared with those who had never smoked, but no significant differences were observed between former smokers and never smokers (Figure 4). In the Italian and the Greek cohorts, the contrasts were less marked (Figure 5). The incidence of CHD was significantly higher in those northern Europeans and Yugoslavs smoking 10 or more cigarettes per day compared with lighter smokers, never smokers, or ex-smokers. The rates were also higher in the Italian and Greek cohorts, but were not statistically significant.

Observation of the Italian cohorts has continued, and 20-year followup data were recently reported (126). With the substantially larger number of cases, a significantly higher incidence of CHD was observed in cigarette smokers than in nonsmokers. The 20-year incidence of CHD increased from 90 per 1,000 in those who had never smoked to 159 per 1,000 in those smoking 10 to 19 cigarettes per day. The incidence in the highest smoking category (20+ cigarettes per day) was slightly lower (140 per 1,000) than the rate in those smoking from 10 to 19 cigarettes per day.

A number of prospective studies of CHD have been performed in the United Kingdom. Those with mortality followup—for example,

TABLE 4.—Ten-year incidence of coronary heart disease among men free of cardiovascular disease at entry (age-standardized rate per 10,000)

Cohort	N	Hard CHD			Any CHD		
		N	Rate	SE	N	Rate	SE
Dalmatia	662	13	185	52	40	629	94
Slavonia	680	18	253	60	40	561	88
Tanushimaru	504	8	148	54	20	354	82
East Finland	728	71	1,074	115	201	2,868	168
West Finland	806	45	539	80	129	1,582	129
Crevalcore	956	43	450	67	105	1,080	100
Montegiorgio	708	22	353	69	64	966	111
Zutphen	845	45	513	76	91	1,066	106
Ushibuka	496	11	204	63	23	458	94
Crete	655	2	26	20	13	210	56
Corfu	525	17	337	79	37	686	110
Rome railroad	736	25	357	68	57	786	99
Velika Krana	487	6	132	52	21	452	94
Zrenjanin	476	12	239	70	37	715	118
Total	9,780	351	369.9 ¹	19.1	913	943.8 ¹	29.6

¹ Mean of the cohort rates weighted by the number at risk in each cohort.

SOURCE: Keys (143).

the British physicians study and the Whitehall study—are reviewed below under the heading Prospective Mortality Studies.

Morris and Kagan and associates (185) investigated differences in CHD in drivers and conductors working on London buses. Among other positive associations, those who smoked were found to have a higher 5-year incidence of CHD than those who did not smoke.

In 1977 Morris, Marr, and Clayton (186) reported followup on workers who were 30 to 67 years of age at examination. The sample was of 337 men living in London and in southeast England who had participated in a 7-day individual dietary survey. By 1976, 45 of these men had developed clinical CHD. Among the CHD cases, cigarette smoking was significantly more frequent than expected, and this was true for each occupational group: bank staff, bus drivers, and bus conductors. Estimated relative risks (compared with nonsmokers) were 3.5 for those smoking 11 to 20 cigarettes and 4.7 for those smoking more than 20 cigarettes (88).

The Belfast practitioner's study was initiated in 1964, using experienced, self-selected practitioners to observe the operation of risk factors in middle-aged men who were community residents (88). The sample comprised all men born in the 10-year period 1909–1918 (age 45 to 54 at the beginning of the study) who were registered in six cooperating group practices. Examinations were performed in 69 percent of the designated population sample. Among the 1,202 subjects free of CHD at the initial examination, 104 developed CHD

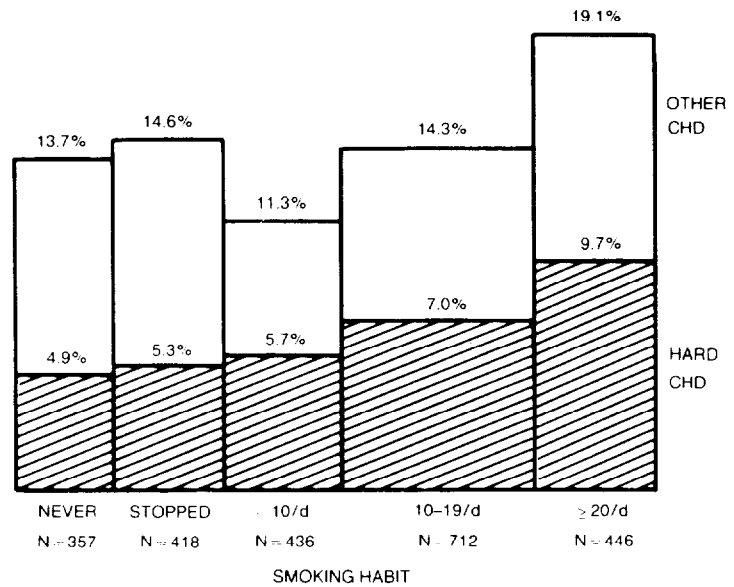


FIGURE 3.—Age-standardized 10-year incidence rate of coronary heart disease of 2,369 men in northern Europe (east and west Finland and Zutphen), classified by smoking habit at entry and then free of cardiovascular disease

SOURCE: Keys (143).

during the 5-year period of followup. MI occurred in 55 (15 fatal), cardiac ischemia in 5, and angina pectoris in 49. Current tobacco consumption, total years of smoking, and total tobacco consumption were significantly higher in the cases with CHD than in the overall population sample.

The Stockholm prospective study examined and followed men and women attending a health survey center in 1961 and 1962 (26). This sample was not a randomly selected population sample of Stockholm, but the incidence of myocardial infarction was similar to that of the Stockholm county population (27). A principal objective was to examine the relationships of fasting plasma triglyceride and cholesterol values to the future development of CHD. In analysis of 9-year followup data for 3,168 men, the incidence of MI and death from CHD with all ages combined was about fourfold higher for smokers than for nonsmokers (26). The difference was statistically significant. Risk factors for MI were evaluated in 3,189 men, among whom 130 experienced myocardial infarction during 14 years of followup; cigarette smokers experienced nearly three times the incidence of

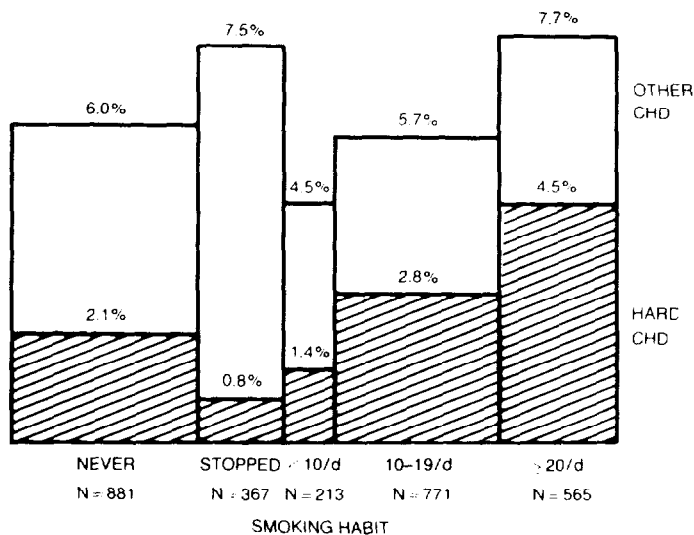


FIGURE 4.—Age-standardized 10-year incidence rate of coronary heart disease of 2,797 men in Yugoslavia (Dalmatia, Slavonia, Velika Krsna, Zrenjanin, and Belgrade), classified by smoking habit at entry and then free of cardiovascular disease

SOURCE: Keys (149).

MI experienced by nonsmokers (27). In analysis of risk factors and death during 14.5 years of followup of 3,486 men and 2,738 women, death due to ischemic vascular disease (principally CHD and stroke) was significantly related to smoking in men and in women (22).

The Section for Preventive Medicine at the University of Göteborg has observed the relationship of smoking and other risk factors to the incidence and the mortality from CHD in several studies of the Göteborg population (278). In 1963 a 30 percent sample of men born in 1913 was examined (at age 50) and followed; 88 percent participation was obtained, and 834 were found to be free of CHD. In 1970 a primary prevention trial was begun for examination of 10,000 intervention and 20,000 control subjects 47 to 54 years of age.

The 1913 birth cohort experienced a markedly excessive risk of MI with smoking during its first 4 years of observation (275); more than 90 percent of those who had myocardial infarctions were current smokers in comparison with 55 percent of those who did not. Subsequent analyses with 13-year followup have confirmed this strong relationship between smoking and CHD; the incidence of fatal

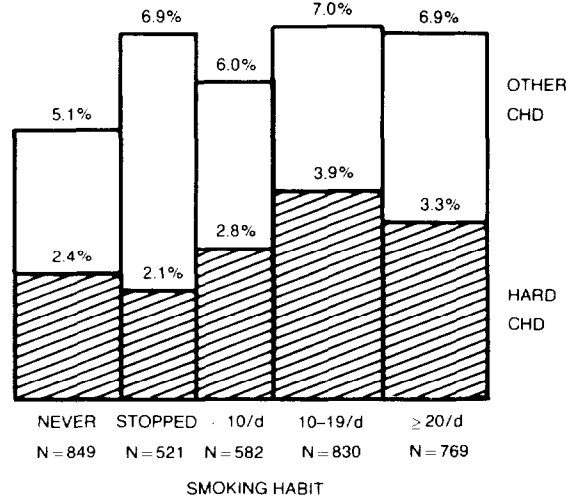


FIGURE 5.—Age-standardized 10-year incidence rate of coronary heart disease of 3,551 men in Italy and Greece (Crevalcore, Montegiorgio, Rome railroad, Crete, and Corfu), classified by smoking habit at entry and then free of cardiovascular disease

SOURCE: Keys (143).

and nonfatal MI increased with the quantity of daily tobacco consumption. Pipe and cigar smokers experienced an increased risk similar to cigarette smokers (278). No significant difference was observed for angina pectoris by smoking status.

Prospective data obtained in the Norwegian Vegetable Oil workers study beginning in 1965 have been analyzed with respect to risk factors measured at the baseline examination and the incidence of CHD during the following year (199). The defined sample comprised 16,608 men born between 1905 and 1916 who were employed in industries throughout Norway. Randomization to a control group or to a group receiving linolenic acid was performed in 13,000 men 50 to 59 years of age who were well and agreed to participate. Industrial physicians participated in the provision of baseline data and in the ascertainment of cases.

Fewer than the expected number of deaths occurred, but the number of deaths from CHD was intermediate between that expected on the basis of the Oslo and the total Norwegian populations. MI was observed in 162 men during the followup; there were no significant differences in CHD incidence attributable to treatment with linolenic acid.

TABLE 5.—First diagnosed myocardial infarction (probable + possible) in relation to cigarette consumption

Cigarettes per day	5 percent sample		Men at risk ¹	Infarctions diagnosed in observ. yr	Rates percentage		
	No.	Mean cholesterol			Unadjusted	Adjusted for age and	
					Weight/height ratio	Elevated sedim-entation rate	
None	228	239.8	5,693	37	.65	.63	.68
1-4	40	244.1	1,094	6	.55	.57	.57
5-14	162	245.2	3,679	56	1.52	1.59	1.46
15-24	47	240.7	1,214	13	1.07	1.11	1.00
25+	9	236.3	191	8	4.19	4.15	3.80
Unknown	126	237.0	4,304	42	.96		
	612	241.0	16,175	162	1.00		

¹ Men with no previous infarction diagnosis.

SOURCE: Natvig et al. (199).

The incidence of MI increased markedly with the level of cigarette smoking; the relative risk of MI for men smoking 25 cigarettes or more per day was over six times that of nonsmokers (Table 5). Smoking was less strongly related to angina pectoris (199).

The Oslo study examined and followed 14,000 men aged 40 to 49 who were free of cardiovascular disease and diabetes mellitus at examinations in 1972 and 1973. During 4 2/3 years of followup, searches of discharge records of Oslo hospitals and of death registration by the Oslo health department were used to identify nonfatal and fatal first MIs; sudden deaths without confirmation of MI were excluded (117). The incidence of MI in nonsmokers (never and ex-smokers) was only 40 percent of that in cigarette smokers (117).

A 10-year prospective study of men examined in 1964 at age 50 in Glostrup County, Denmark, was reported by Schroll and Hagerup (240). Out of a total population sample of 514 men, 436 were examined; followup for mortality and myocardial infarction was obtained in virtually all patients. This population resided in a middle-class suburb in the western part of Copenhagen and was thought to reflect the change in Danish society from principally agricultural to industrial and to be representative of the total Danish population in 1964. During the 10-year followup, 31 men developed first myocardial infarctions, an incidence of 7.1 percent. Fatal MI occurred in 16, and 15 experienced a nonfatal MI. A significantly higher risk of myocardial infarction was observed in those who smoked tobacco at baseline examination. The incidence was as follows: nonsmokers, 6 percent; smokers of 1-14 g per day, 6 percent; smokers of 15-24 g per day, 14 percent; smokers of 25 g or

TABLE 6.—Seven-year incidence of fatal and nonfatal first myocardial infarction in 3,772 smokers by category of smoking habit and 440 men who have never smoked

	Myocardial infarction per 1,000 men	Relative risk
Never smokers	17	1.0
Cigarette smokers		
Total	36	2.1
>10/day	43	2.5
Cigar smokers		
Total	42	2.4
>3/day	35	2.1
Cheroot smokers		
Total	48	2.8
>6/day	72	4.2
Pipe smokers		
Total	26	1.5
>6/day	34	2.0

SOURCE: Gyntelberg et al. (91).

more per day, 19 percent. Thus, the heavy smokers experienced an incidence of MI that was three times that of nonsmokers.

The incidence of fatal and nonfatal first myocardial infarctions in men was observed in 3,772 smokers and 1,440 nonsmokers who had baseline examinations in 1970 and 1971, were aged 40 to 59, and were employed in public and private Copenhagen companies (91). The initial response rate was 87 percent. Fatal MI was ascertained during 7 years of followup from death certificates; nonfatal MI was ascertained from 5-year followup by questionnaires (79 percent response rate) and from hospital records. Myocardial infarction among the nonresponders was included if recorded in the Copenhagen heart register, which registered all inpatient cases of myocardial infarction in the Copenhagen area.

During the followup period, 41 men free of coronary heart disease at baseline examination died from a first myocardial infarction and 129 men had a nonfatal first myocardial infarction. Overall, the relative risk of myocardial infarction was twice as high in smokers as in nonsmokers. The relative risk of fatal and nonfatal first MI in smokers compared with never smokers was as follows: cigarette smokers of more than 10 per day, 2.5; cigar smokers of more than 3 per day, 2.1; cheroot smokers of more than 6 per day, 4.2; and pipe smokers smoking more than six times per day, 2.0 (Table 6). In this study heavy cheroot smokers experienced the highest risk of MI.

Finnish men aged 50 to 53 years, insured for 10 or more years with a large Finnish life insurance company, were examined in 1965 and

1966; the examined cohort (1,648 men) consisted of 40 percent of those respondents who had complete data (207). Risk factor data included serum lipids after a 12-hour overnight fast. A smoker was a person who smoked cigarettes regularly every day; pipe and cigar smokers as well as ex-smokers were excluded from the analysis of smoking effects. With these criteria, 567 men were smokers and 982 were nonsmokers. During 7 years of followup, all deaths were identified, and cause of death was determined from death certificate files. Cardiovascular deaths included those due to coronary heart disease, heart failure, cardiac arrhythmia, cerebrovascular accidents, and sudden deaths. Cigarette smoking was associated with increased cardiovascular mortality independently of other risk factors.

The North Karelia, Finland, project was started in 1972 to mobilize community intervention for health promotion and disease prevention (235). Substantial risk factor data were obtained from random population samples of two rural counties in eastern Finland. Analysis showed a strong relationship between the major risk factors at the baseline examination (smoking, hypertension, and serum cholesterol) and the subsequent development of CHD. The relationship of smoking to the incidence of acute myocardial infarction was independent of the other risk factors (235). Eastern Finland had the highest incidence and mortality from CHD in the world, but the rates have declined substantially coincident with decreasing prevalence of these risk factors (235).

A large defined cohort of men aged 42 to 53 years, born in France and employed in the Paris civil service, was observed for an average of 4 years (range, 2-7 years) following a baseline examination for risk factors in 1965 (218). Those with definite Q waves on initial examination were excluded, leaving 7,453 men at risk. Criteria for CHD were based on those of the Pooling Project and the London Whitehall study (51, 218).

The overall incidence of CHD was 5.1 per 1,000; MI and CHD deaths accounted for 60 percent of the cases, while 40 percent of the cases were due to angina pectoris. Cigarette consumption, hypertension, hypercholesterolemia, and clinical diabetes mellitus were independently related to the incidence of coronary heart disease. Men in their fifties had a strikingly lower incidence of CHD than men in the United States; this is consistent with French mortality statistics. In univariate analysis, the incidence of CHD was progressively higher with increasing number of cigarettes smoked per day among inhalers; noninhalers had an intermediate risk (Figure 6) (218).

A defined cohort of 10,232 Israeli civil servants and municipal workers (86 percent of the defined sample) aged 40 years and above were first examined in 1963 and followed for fatal and nonfatal MI

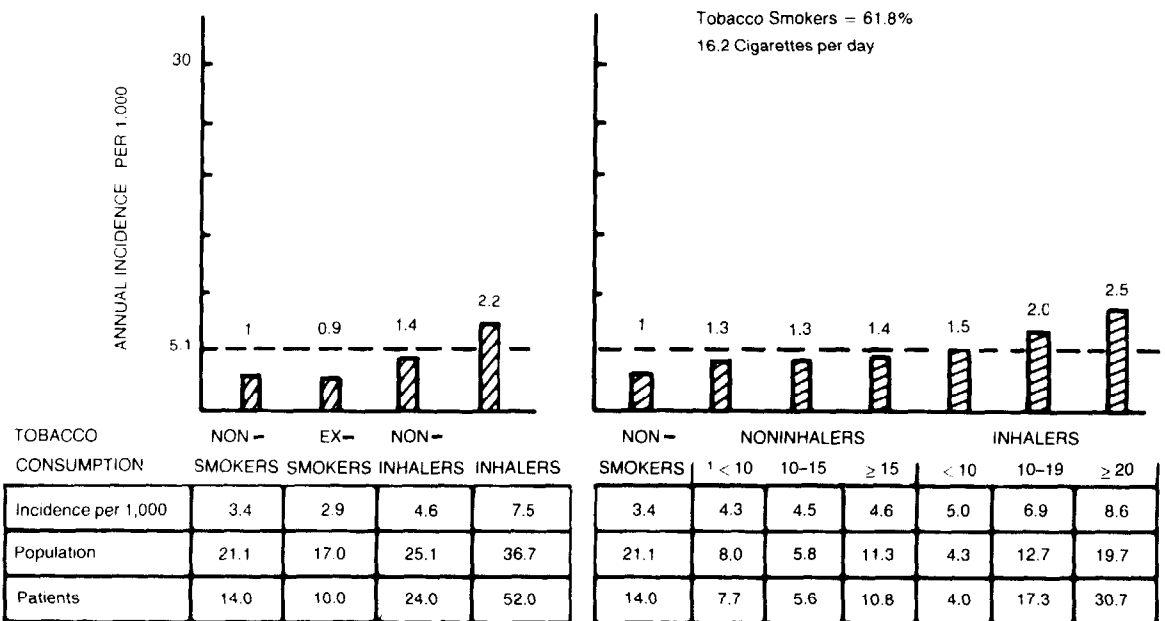


FIGURE 6.—Risk of ischemic heart disease as a function of tobacco consumption (average observation, 4 years)

¹ Cigarettes per day.
SOURCE: Richard et al. (27).

and sudden cardiac death (177). Reexaminations were performed in 1965 (97.5 percent reexamination rate) and again in 1968 (98 percent reexamination rate). After 5 years of followup, 9,764 were found to be free of myocardial infarction and there were 427 incidence cases (44 per 1,000). Of these 170 (40 percent) were unrecognized myocardial infarctions, half of which had been asymptomatic. The incidence of CHD was significantly related to the daily use of cigarettes, and the relative risk was greater at younger age (81, 176). In multivariate analysis the relationship of smoking to CHD became stronger when other variables were taken into account (81).

In summary, there were marked differences in CHD rates for the populations in different countries and different geographic locations. The relationship between cigarette smoking and CHD was more pronounced in those countries with high CHD rates. However, even in those countries with low CHD rates the evidence increasingly suggests a relationship between cigarette smoking and CHD.

Cigarette Smoking and Other Risk Factors

The strong relationship between cigarette smoking and CHD has been shown to be independent of the other major risk factors in a number of well-designed epidemiologic studies. A number of other factors have also been described as having an influence on CHD risk (119, 124, 133, 159, 214, 251). The magnitude of excess risk observed with these minor risk factors has usually been small in comparison with the excess risk observed with the major risk factors (40, 68, 143, 214).

The independence of the relationship between cigarette smoking and CHD risk has been observed in a straightforward fashion. The excess risk of CHD in smokers compared with nonsmokers exists at both high and low levels of the other risk characteristics associated with CHD. Also, extensive experience has shown that confounding influences can be separated out with multiple logistic analysis (147). Such analyses with adjustment for potentially confounding influences have been made for many characteristics in many of the studies cited in this Report. They include hypertension, elevated serum cholesterol, obesity, family history of CHD, diabetes mellitus, physical inactivity, certain personality characteristics, psychological stress, socioeconomic status, and intake of alcohol and coffee. When the data have been sufficient for adequate analysis, excess risk of CHD has been observed in cigarette smokers independent of the presence (or absence) of other CHD-risk-conferring characteristics. Such observations, made in a very large number of studies, indicate that it is the cigarette smoking habit itself that confers high risk of CHD rather than an associated characteristic (18, 40, 43, 45, 67, 94, 96, 143, 214, 244, 257).

Behavioral characteristics other than cigarette smoking have been considered important in relation to CHD, but relatively few studies of behavioral characteristics have been conducted in the context of standardized examinations of defined cohorts with consideration of potentially confounding variables. The Western Collaborative Group Study (WCGS) in California met these conditions, and therefore this study will be considered in some detail (24, 66, 71).

In the WCGS (229), 3,154 employed men examined in 1960–1961 and found to be free of CHD were characterized for behavioral pattern by a structured interview developed for this purpose and administered by trained interviewers. From tape recordings of interviews, reviewers who had no knowledge of the subjects' history or other characteristics classified the men as Type A personalities according to their manifestation of enhanced aggressiveness, ambitiousness, competitive drive, and chronic sense of time urgency. The men were classified as Type B personalities if they manifested less of the Type A characteristics and were more calm and relaxed. The Type A pattern was determined in 1,067 and the Type B pattern in 1,182 of the subjects at risk. Previously recognized risk factors were also measured. Mortality surveillance was obtained, and final followup examinations were performed for this population in 1969.

With an average followup of 8.5 years, there were 140 deaths; 31 were attributed to an initial CHD event, 19 to a recurrent CHD event, and 90 to non-CHD causes, including 7 who had developed CHD prior to the onset of the non-CHD terminal illness. CHD incidence was observed in 257 cases. Autopsy examination was performed in 24 of 31 decedent cases; acute coronary thrombosis or acute myocardial infarction was observed in 23, and severe diffuse coronary atherosclerosis was observed in 1 case.

CHD death was ascertained in 34 Type A and 16 Type B subjects. The CHD death rate per 1,000 person-years was 2.92 for Type A and 1.32 for Type B subjects.

As would be expected from other studies, the CHD incidence cases were older, smoked more cigarettes, were heavier, and had higher systolic and diastolic blood pressures, higher serum cholesterol and triglyceride levels, and higher ratios of beta to alpha lipoproteins. Other positive associations were a history of diabetes mellitus, parental history of CHD, low level of education, and low level of leisure time activity. Occupational physical activity and annual income were not significantly related to CHD incidence.

Cigarette smoking was significantly related to the incidence of CHD, and the risk was higher with increasing numbers of cigarettes smoked at the time of the baseline examination; the relative risk with smoking in older men was as great as in the younger men.

By personality patterns, those who had been characterized as Type A had an incidence of CHD that was twice as high as the incidence in

those who had been characterized as Type B. This difference persisted after adjustment for the other risk factors. In both deciles of age at entry (39–49 and 50–59), the relative risks for current cigarette smokers were higher than for nonsmokers in both Type A and Type B personalities (Table 7) (229).

A multiple logistic equation describing the relationships of the conventional risk factors to the incidence of CHD in this study was similar to the Framingham study equation (25). The coefficients for the two studies were not significantly different. Cigarette smoking, serum cholesterol, and systolic blood pressure were independent risk factors and were significantly related to the CHD incidence. The total number of cases and the number by decile of risk were similar, using the equation developed from the WCGS data and the equation from the Framingham study, indicating good relative agreement in risk prediction. In the WCGS analysis, the Type A behavior pattern was found to predict the incidence of CHD independently of the other risk factors. The additional predictive power of the Type A characteristic in the multiple logistic equation was related to some extent to higher levels of the conventional risk factors in Type A individuals.

Evidence for the importance of personality characteristics was also observed in the Framingham cohort and in studies by the French-Belgian Collaborative Group (66, 104). In these studies as well, the effect of cigarette smoking on CHD remained independent of personality characteristics.

In summary, the evidence from studies with adequate data have clearly demonstrated that cigarette smokers experience higher risk of CHD regardless of their other behavioral characteristics.

Interaction of Cigarette Smoking and Other Risk Factors

A number of pharmacologically active substances are present in tobacco smoke, and a number of direct physiologic effects have been observed (262) and are reviewed elsewhere in this Report. Recently, evidence has accumulated of an effect of smoking on lipoproteins. Recent population studies have demonstrated an inverse relationship between high density lipoprotein cholesterol (HDL-C) and the incidence of CHD (80, 84, 217). Population groups known to be at lower risk for CHD have been observed to have relatively high levels of HDL-C. Thus, HDL-C levels have been higher in women in comparison with men, in black men in comparison with white men, and in men in Japan in comparison with men in the United States (5, 106, 146, 260). An adverse influence of cigarette smoking on the levels of HDL-C and other plasma or serum lipoprotein components has been observed in a number of populations. The several classes, or fractions, of these lipid-protein complexes have different functions

TABLE 7.—Prospective history and findings by behavior pattern

	Age 39-49 years						Age 50-59 years					
	Subjects at risk		Subjects with CHD ¹		Rate of CHD ²		Subjects at risk		Subjects with CHD		Rate of CHD ²	
	Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B	Type A	Type B
Number of subjects	1,067	1,182	95	50	10.5	5.0	522	383	83	29	18.7	8.9
Parental history of CHD												
Yes	214	197	23	15	12.6	9.0	103	64	20	7	22.8	12.9
No	853	935	72	35	9.9	4.2	419	319	63	22	17.7	8.1
Smoking habits												
Never smoked	221	315	11	8	5.9	3.0	90	89	10	5	13.1	6.6
Pipe or cigar	191	216	11	6	6.8	3.3	81	78	17	2	24.7	3.0
Former cigarette	110	129	11	5	11.8	4.6	91	41	10	2	12.9	5.7
Current cigarette	545	522	62	31	13.4	7.0	260	175	46	20	20.8	13.4
Current cigarette usage												
None	522	660	33	19	7.4	3.4	262	208	37	9	16.6	5.1
1-15/day	95	119	3	8	3.7	7.9	65	43	8	1	14.5	2.7
≥16/day	450	403	59	23	15.4	11.4	195	132	38	19	22.9	16.9
Systolic blood pressure, mm Hg												
<120	264	328	17	4	7.6	1.4	95	80	7	4	8.7	5.9
120-159	771	826	69	43	10.5	6.1	381	283	64	21	19.8	8.7
≥160	32	28	9	3	33.1	12.6	46	20	12	4	30.7	23.5
Diastolic blood pressure, mm Hg												
<95	970	1,100	81	45	9.8	4.8	448	344	64	25	16.8	8.5
≥95	97	82	14	5	17.0	7.2	74	39	19	4	30.2	12.1

TABLE 7.—Continued.

	Age 39-49 years						Age 50-59 years					
Serum cholesterol, mg/100 ml												
< 220	486	607	24	11	5.8	2.1	211	148	20	6	11.2	4.8
220-259	352	376	32	20	10.7	6.3	179	142	36	10	23.7	8.3
≥ 260	226	195	39	19	20.3	11.5	130	90	27	13	24.4	17.0
Fasting serum triglycerides, mg/100 ml												
< 100	252	348	12	7	5.6	2.4	151	99	16	5	12.5	5.9
100-176	500	538	48	22	11.3	4.8	238	170	37	11	18.3	7.6
≥ 177	247	249	30	20	14.3	9.6	114	98	26	9	26.8	10.8
Serum β/a-lipoprotein ratio												
< 2.36	733	836	57	24	9.1	3.4	323	263	43	18	15.7	8.1
≥ 2.36	331	343	38	26	13.5	8.9	196	117	39	11	23.4	11.1

¹ Coronary heart disease.

² Average annual rate/1,000 subjects at risk. Difference in rates between type A and type B was tested for significance by Mantel-Haenszel χ^2 , with adjustment for factors indicated. For each factor, the adjusted association between behavior pattern and CHD incidence is significant at $p < .001$.

SOURCE: Rosenman et al. (229).

in lipid metabolism (41, 78, 213). Most of the cholesterol in the plasma is complexed in the low density lipoprotein cholesterol (LDL-C) fraction, which appears to have atherogenic properties, while a lesser proportion of cholesterol is complexed with high density lipoprotein cholesterol (HDL-C), which appears to have antiatherogenic properties (82, 100, 180, 230).

The HDL-C levels in the cigarette smokers in the studies cited above have been found to be significantly lower than in nonsmokers, and in some studies the concentration of HDL-C has been found to correlate inversely with daily cigarette consumption. This relationship does not appear to be confounded by other factors. Thus, HDL-C is inversely correlated with indices of obesity, such as relative weight, and positively correlated with alcohol intake; adjustment for these characteristics increases the difference in HDL-C between cigarette smokers and nonsmokers (79, 99, 105, 212). Additional studies are needed to investigate the complex mechanisms whereby cigarette smoking depresses HDL-C levels and increases the risk for CHD.

Blood pressure increases transiently after smoking, mediated by an adrenergic mechanism (37); however, most surveys have demonstrated a small negative association between smoking and blood pressure (263). Recent investigations of this relationship have adjusted for the covariables of weight and alcohol.

In an examination of the offspring of Framingham heart study patients and their spouses, multivariate analysis demonstrated a negative correlation between smoking and blood pressure, especially diastolic blood pressure, that was similar to the original Framingham cohort (102). A cross-sectional survey of employed men in Australia also demonstrated that, adjusted for weight and alcohol, diastolic blood pressures were slightly lower in smokers (5). In the cohort of the Lipid Research Clinics prevalence study, the small negative correlation between smoking and blood pressure was more apparent for systolic blood pressure (36). In the cross-sectional and prospective analyses of several study populations in Chicago, however, smoking was associated with higher blood pressure, especially systolic blood pressure (52, 53). Alcohol consumption was not included in these multivariate analyses.

If smoking is associated with a slightly lower blood pressure, a rise in blood pressure might be predicted after smoking cessation, especially if smoking cessation is followed by weight gain, but recent studies have not supported this concern. In the Kaiser population, smoking cessation has been associated with only a small weight gain (70). Effects on blood pressure were also small and inconsistent among subgroups. In the Multiple Risk Factor Intervention Trial, smokers who quit lost less weight than those who did not quit (239); controlling for weight, there was no increase in blood pressure with

smoking cessation. These studies show that there is little, if any, adverse effect on risk factors following smoking cessation. The benefits of smoking cessation for health in general, and cardiovascular health in particular, far outweigh any objectively observed disadvantageous effect.

Although epidemiologic studies do not suggest that smoking causes high blood pressure, concern has been expressed that it may exacerbate the clinical course. Two case-control studies in Great Britain (20, 125) and one in New Zealand (57) compared smoking patterns in patients with malignant or accelerated hypertension with those with benign hypertension. In all three, statistically significant associations between smoking and the more severe manifestations of hypertension were demonstrated.

A recent clinical study directly observed the blood pressure effects of smoking in mild hypertensives (65). When 16 habitual smokers abstained from cigarettes, their blood pressure was significantly lower than usual. Smoking two cigarettes resulted in a blood pressure increase of 10/8 mm Hg that lasted approximately 15 minutes. Combining coffee drinking with smoking led to an increase in blood pressure to their usual levels that lasted 2 hours.

For the most part, recent surveys have supported the traditional finding of a small negative association between smoking and blood pressure. Smoking cessation is not associated with a significant increase in blood pressure, especially if weight gain is avoided. Preliminary studies suggest that smoking increases the likelihood of developing malignant hypertension. Prospective and intervention studies are indicated to further investigate this phenomenon.

These findings can be translated into clinical recommendations: (1) nonhypertensive smokers can be assured that smoking cessation will not lead to high blood pressure, especially if weight gain is avoided, and (2) hypertensive smokers should be warned that these two risk factors are synergistic for cardiovascular disease and that the need for risk reduction is increased. Smoking cessation will not complicate the management of high blood pressure, and may reduce hypertensive complications. Concomitant monitoring of weight during and after smoking cessation is indicated.

Synergistic Effects of Cigarette Smoking When Associated With Other Risk Factors

Evidence that the increase in CHD risk associated with smoking may be greater when other risk factors are present than when they are absent has been observed in several investigations. Figure 7 presents the data from the Framingham 12-year followup. The CHD risk increases with increasing levels of blood pressure or serum cholesterol, and at each level of these two risk factors the risk in

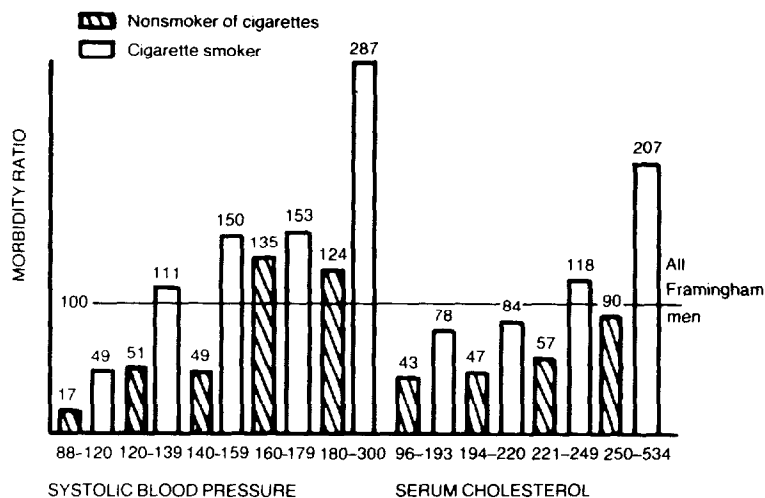


FIGURE 7.—Cigarette smoking at levels of blood pressure and serum cholesterol, 12-year incidence

NOTE: The contribution of cigarette smoking to risk of coronary heart disease appears to be independent of other demonstrated risk factors. At any level of blood pressure or serum cholesterol, cigarette smokers had an excess risk, 12-year incidence.

SOURCE: Kannel (132).

smokers is greater than the risk in nonsmokers. However, the increment of risk with smoking is not constant, but rather increases with increasing levels of blood pressure or cholesterol. For example, in Figure 7 the increment in risk in smokers with a systolic blood pressure of 80-120 mm Hg is 32 (49 minus 17), while the increment for smokers with a systolic blood pressure of 140-159 is 101 (150 minus 49). These data suggest that cigarette smoking interacts with the other two major risk factors to produce a combined risk that is greater than the sum of the risks that would have been produced by the same risk factors acting separately.

Pooling Project data are also consistent with a synergistic effect of cigarette smoking with hypertension and hypercholesterolemia (Figure 8) (19). Evidence of synergism has been found in other studies as well. In the Ni-Hon-San study, the effect of cigarette smoking on CHD incidence in the presence of high serum cholesterol appeared to be more than additive in Japanese Americans living in Hawaii. The same effect was not observed in Japanese men living in Japan, who in general had substantially lower serum cholesterol levels (221). Evidence of synergism was observed in the Stockholm prospective study and the Göteborg studies (Figure 9) (27, 278).

The synergistic interaction between the major risk factors may also explain the observation that the actual incidence of CHD in

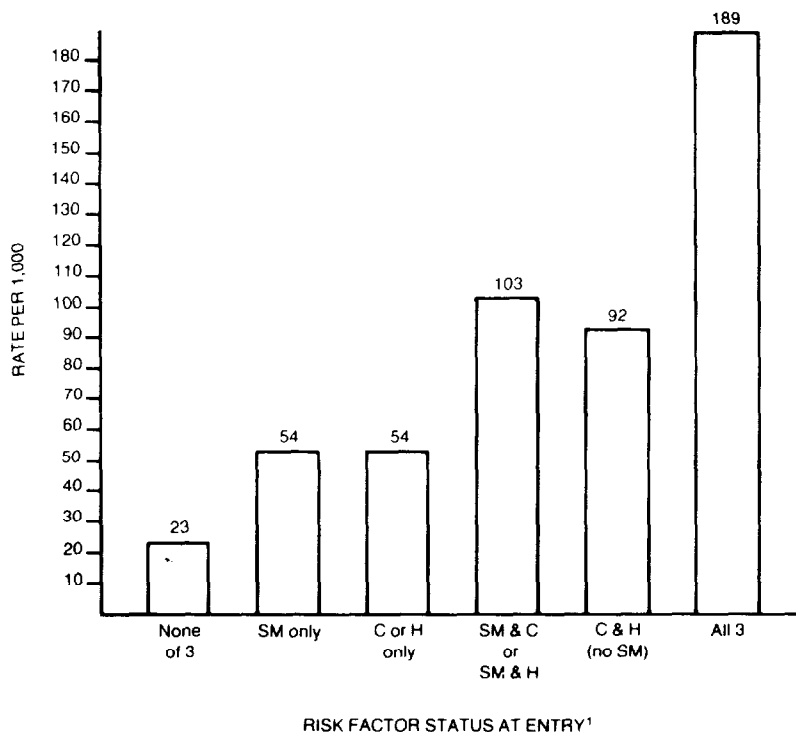


FIGURE 8.—Major risk factor combinations, 10-year incidence of first major coronary events, men age 30–59 at entry, Pooling project

¹ Definitions of the three major risk factors and their symbols: hypercholesterolemia (C), ≥ 250 mg/dh; elevated blood pressure (H), diastolic pressure ≥ 90 mm Hg; cigarette smoking (SM), any current use of cigarettes at entry. NOTE: All rates were age adjusted by 10-year age groups to the U.S. white male population, 1980. SOURCE: The Pooling Project Research Group (214).

populations with low levels of serum cholesterol is substantially lower than the incidence predicted by the multiple logistic equations derived from the Framingham population (85, 91, 124, 143, 146). If the synergistic interaction is present at low levels of the major risk factors to the same degree as at high levels of risk factors, then the impact of cigarette smoking on blood pressure in a low cholesterol population would be expected to be smaller than that measured in high cholesterol populations such as in the United States and Western Europe. The multiple logistic equations do not separate out effects that are due to synergistic interactions, and they distribute the synergistic effects to the separate risk factors as though there were no interaction among the risk factors in producing CHD. These equations treat the risk factors as though the effects of the risk

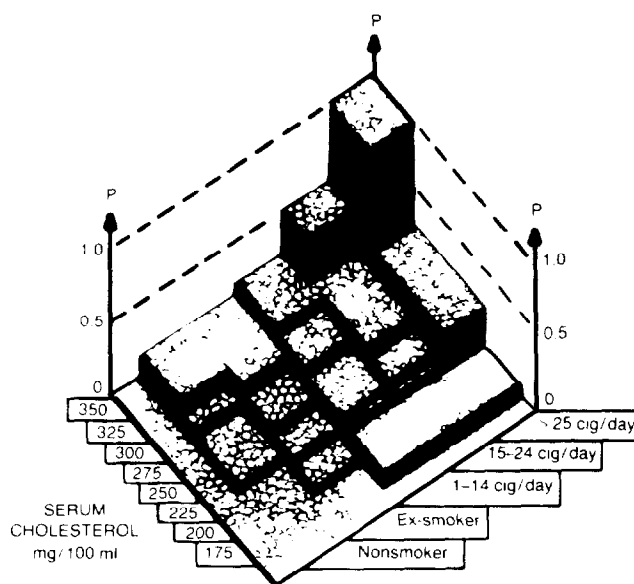


FIGURE 9.—Risk factors for disease according to population studies

NOTE: P = probability of nonfatal and fatal myocardial infarction for a 50-year-old man during 13 years' followup, 855 men born in 1913.
SOURCE: Wilhelmsen (278).

factors were additive. This limitation of the multiple logistic equation technique leads to an overprediction of the number of CHD cases to be expected in a population on the basis of smoking habits when that population has very low levels of another major risk factor such as serum cholesterol levels. Therefore, the very low levels of CHD observed in cigarette smokers from populations with very low serum cholesterol levels may reflect the synergistic nature of the interaction among the major risk factors rather than the absence of a CHD risk associated with cigarette smoking in those populations. The possibility also exists that the cigarette smokers in some of these populations have not been smoking for a sufficient duration or with a sufficient intensity to manifest an effect on coronary artery disease.

Analytical and methodological refinements appear to be needed for better understanding of the biological significance of synergism (147). Nevertheless, the evidence is clear that cigarette smoking greatly increases the risk of CHD in individuals already at increased risk because of other risk factors.