Major Risk Factors as Antecedents of Fatal and Nonfatal Coronary Heart Disease Events

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Context A frequently cited concept is that individual major risk factors for coronary heart disease (CHD) are absent in many patients (perhaps >50%) with CHD. However, prior studies have not systematically evaluated the extent to which CHD patients have previous exposure to at least 1 risk factor, including diabetes, cigarette smoking, or clinically elevated levels of cholesterol or blood pressure.

Objective To determine the frequency of exposure to major CHD risk factors.

Design, Setting, and Participants Three prospective cohort studies were included: the Chicago Heart Association Detection Project in Industry, with a population sample of 35642 employed men and women aged 18 to 59 years; screenees for the Multiple Risk Factor Intervention Trial, including 347978 men aged 35 to 57 years; and a population-based sample of 3295 men and women aged 34 to 59 years from the Framingham Heart Study (FHS). Follow-up lasted 21 to 30 years across the studies.

Main Outcome Measures Fatal CHD in all cohorts and nonfatal myocardial infarction (MI) in the FHS, compared by exposure to major CHD risk factors, defined as total cholesterol of at least 240 mg/dL (≥6.22 mmol/L), systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, cigarette smoking, and diabetes. Participants were stratified by sex and age (18-39 vs 40-59 years).

Results For fatal CHD (n=20995), exposure to at least 1 clinically elevated major risk factor ranged from 87% to 100%. Among those aged 40 to 59 years at baseline with fatal CHD (n=19263), exposure to at least 1 major risk factor ranged from 87% to 94%. For nonfatal MI, prior exposure was documented in 92% (95% CI, 87%-96%) (n=167) of men aged 40 to 59 years at baseline and in 87% (95% CI, 80%-94%) (n=94) of women in this age group.

Conclusions Antecedent major CHD risk factor exposures were very common among those who developed CHD, emphasizing the importance of considering all major risk factors in determining CHD risk estimation and in attempting to prevent clinical CHD. These results challenge claims that CHD events commonly occur in persons without exposure to at least 1 major CHD risk factor.

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PRECURSORS OF CORONARY HEART disease (CHD) have been extensively studied, and causal risk factors have been identified. Among the many risk factor associations that have been described, the best established CHD risk factors are unfavorable levels of blood cholesterol (especially total and low-density lipoprotein cholesterol) and blood pressure, cigarette smoking, diabetes, and adverse dietary habits.[1,2] These characteristics have been designated major risk factors for CHD given their relatively high prevalence in CHD-prone populations, causal relations to CHD, dominance in risk prediction over other putative risk factors, and amenability to prevention and control.[3-5] Clinical practice guidelines recommend that clinicians focus attention on all major risk factors in attempting to predict and prevent CHD.[6,7]

Although the major CHD risk factors are widely recognized as the primary causes of CHD, many studies have demonstrated that clinically elevated cholesterol levels, for example, are often absent in persons who develop CHD.[8-12] Since elevated cholesterol is regarded as a leading risk factor for CHD, the lack of evidence of exposure to elevated cholesterol levels has been linked with the proposition that a large percentage of CHD, perhaps as much as 50%, is not attributable to major CHD risk factors.[11,12] A related concept, also frequently cited, is that CHD often (≥50% of the time) occurs in the absence of any major risk factor.[13,14] If clinical CHD occurs in a large fraction of cases in the absence of prior exposure to any major CHD risk factor, this finding would justify the search for new or currently unrecognized factors accounting for CHD causation.[14] Conversely, if prior exposure to major risk factors is more common than many reports have suggested,[8-12] the concept that major risk factors are often absent in CHD may be erroneous.

To address the question of how frequently CHD events are preceded by ex-

See also pp 898, 932, and 947 and Patient Page.

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posure to major CHD risk factors, we assembled data from 3 large prospective US cohorts followed up for 21 to 30 years. We assessed the prevalence and consistency of major risk factor exposures across the 3 studies, which included both sexes and a spectrum of adult ages, and, where available, nonfatal as well as fatal CHD events.

METHODS

Data from 3 cohorts were examined: the Chicago Heart Association Detection Project in Industry (CHA), the screening component of the Multiple Risk Factor Intervention Trial (MRFIT), and the Framingham Heart Study (FHS). Cohorts were selected for these analyses because data on CHD mortality (and nonfatal CHD in the FHS) were available with extensive and complete follow-up and for men and women (in the CHA and the FHS). Analyses reported here encompassed persons aged 18 to 59 years at baseline.

Chicago Heart Association Detection Project in Industry

The CHA cohort enrolled 22 400 men and 17 122 women aged 18 years or older between late 1967 and early 1973. Approximately 10% of participants were black and 87% were non-Hispanic white. All employees at 84 Chicago-area companies and organizations received survey invitations; the response rate was 53%. Research teams trained in standardized methods of data collection performed all measurements. Age, sex, race/ethnicity, education, blood pressure, serum total cholesterol level, smoking status, height, weight, medical history, and current treatment for hypertension and diabetes were collected from each participant only once. Blood pressure was measured as a single supine reading with a standard mercury sphygmomanometer. Serum total cholesterol was measured by the Levine-Zak method.[15] Of 36 294 participants aged 18 to 59 years, those missing risk factor data (n = 314) or with prior or current CHD (n = 338) were excluded.

Deaths were ascertained using local procedures, Social Security Administration records, and the National Death Index. Cause of death was coded by trained staff according to the *International Classification of Diseases, Eighth Revision*. Death due to CHD was defined as codes 410-414. Detailed survey methods and follow-up procedures have been described.[4,15] Information on nonfatal events was not available in this cohort. The analysis is based on up to 30 years of follow-up (through December 31, 1997).

MRFIT Screenees

Screening took place from 1973 to 1975 in 18 US cities for enrollment of men aged 35 to 57 years into MRFIT. Approximately 90% of screenees were non-Hispanic white, 7% black, 2% Hispanic, 1% Asian, and less than 1% Native American or other race/ethnicity. Among 361 662 men screened, 8322 with missing systolic blood pressure data and 5362 with prior hospitalization for myocardial infarction (MI) were excluded. Data presented herein are from the remaining 347 978 men.

Measurements included blood pressure, measured with a standard mercury sphygmomanometer while the patient was seated; serum total cholesterol (determined by 1 of 14 laboratories that met the standardization requirements of the Centers for Disease Control[16]), smoking status, and history of drug treatment for diabetes. Deaths prior to 1979 were ascertained using Social Security Administration records, followed by use of the National Death Index or National Death Index Plus. Cause of death was determined from the death certificate by a nosologist using the *International Classification of Diseases, Ninth Revision*, with CHD death defined as codes 410-414 and 429.2. Analyses encompassed 21 to 23 years of follow-up (through December 31, 1996).

Framingham Heart Study

The FHS began in 1948 and involved 5209 noninstitutionalized white men and women from Framingham, Mass, aged 30 to 62 years. Measurements have been repeated in this cohort every 2 years. Multiple baseline measurements were available; to reduce misclassification bias, data from 3 examinations (visits 2-4) were averaged to obtain a mean baseline value for serum cholesterol and blood pressure. Visit 1 data were not used because blood cholesterol was measured in only 61% of participants. Those who reported cigarette use at any visit from 1 to 4 were classified as current smokers. Diabetes was defined as treatment by a physician (insulin therapy or oral hypoglycemic agents), a record of an abnormal glucose tolerance test result, or a casual blood glucose level of at least 150 mg/dL (8.33 mmol/L) on at least 2 examinations (per the method of Nelson[17]) at or before visit 4. Serum cholesterol was measured by the method of Abell et al.[18] Blood pressure was measured using mercury sphygmomanometers in seated participants.[19] The second of 3 blood pressure measurements taken at each examination was used for analyses. Age at visit 4 (approximately 6 years after baseline) was used to stratify participants.

Of 3758 people aged 34 to 59 years, persons with missing data on risk factors at all visits from 2 through 4 (n = 20), those with prior or current cardiovascular disease (n = 157 with clinical diagnoses and n = 286 with electrocardiographic abnormalities), and those taking digitalis (n = 9) were excluded. Follow-up (dating from visit 4) was limited to 30 years (through December 31, 1988) for comparability with the CHA cohort. A staff physician panel reviewed all outcome events. Cause of death was determined from death certificates, hospital records, attending physicians, pathologists, medical examiners, and family members. Nonfatal MI was detected using medical history, physical examination at follow-up, hospitalization records, and communication with personal physicians.

Risk Factor Definitions

Presence of a clinically elevated major risk factor was defined as presence of 1 or more of the following: cholesterol level of at least 240 mg/dL (≥6.22 mmol/L), diastolic blood pressure of at least 90 mm Hg or systolic blood pressure of at

least 140 mm Hg, current medication with cholesterol- or blood pressure–lowering drugs (<1% and <8% in all age-sex groups, respectively), current cigarette use, and clinical report of diabetes.

A secondary analysis was performed with risk factor cut points at higher-than-favorable levels for cholesterol (≥200 mg/dL [≥5.18 mmol/L]) and blood pressure (diastolic >80 mm Hg or systolic >120 mm Hg). These cut points were selected based on prior analysis showing that men and women aged 18 to 74 years at baseline in 5 large cohorts with none of these risk factors had relative risks of CHD death that were substantially lower (by 80%-90%) than all others in long-term follow-up.[20]

Outcome Definitions

A CHD event was defined as death due to CHD in the CHA cohort and MRFIT and as death due to CHD or nonfatal MI in the FHS. Participants who did not develop CHD were defined in the CHA cohort and MRFIT as those who did not die during follow-up or who died of causes other than CHD; in the FHS, they were defined as those who did not have fatal CHD or nonfatal MI.

Data Analyses

Men and women were analyzed separately by baseline age group (18-39 vs 40-59 years). The proportion (95% confidence interval [CI]) who had at least 1 risk factor was calculated by outcome (CHD death vs all others [those who did not die or who died of other causes during follow-up] for the CHA and MRFIT, and CHD death and nonfatal MI, separately, vs all others for the FHS) for each stratum within each cohort. The proportion with 2 or more risk factors at higher-than-favorable levels was also calculated, as was the proportion with each single risk factor considered separately. Comparisons of proportions between those with a CHD event and all others were assessed by χ^2 or Fisher exact test. The normal approximation to the binomial was used to calculate 95% CIs, except where the proportion was 100%, in which case the lower bound was estimated as $(0.025)^{1/n}$, where n is the sample size.[21] Analyses were performed using SAS version 8.02 (SAS Institute Inc, Cary, NC). All *P* values are 2-sided and significant at $P<.05$.

RESULTS

Analyses were based on 1798 CHD deaths in the CHA, 18858 CHD deaths in MRFIT, and 642 CHD events (339 CHD deaths and 303 nonfatal MI events) in the FHS. Deaths due to unknown causes numbered 53 in the CHA, 611 in MRFIT (381 coded as unknown cause on death certificate and 230 with no death certificate), and 97 in the FHS; these deaths were excluded from the analyses. For CHA men aged 18 to 39 years, median time to CHD death was 18.9 years (interquartile range [IQR], 14.5-23.2 years); for men aged 40 to 59 years, it was 16.7 years (IQR, 10.3-22.0 years); for women aged 18 to 39 years, it was 23.5 years (IQR, 21.1-24.9 years); and for women aged 40 to 59 years, it was 19.9 years (IQR, 14.8-23.9 years). For MRFIT, median time to CHD death for men aged 35 to 39 years was 15.4 years (IQR, 10.7-19.0 years) and for men aged 40 to 57 years was 14.2 years (IQR, 9.0-18.4 years). For FHS men aged 34 to 39 years, median time to CHD event was 19.1 years (IQR, 13.0-25.4 years); for men aged 40 to 59 years, it was 17.2 years (IQR, 9.6-23.5 years); for women aged 34 to 39 years, it was 24.4 years (IQR, 20.3-27.6 years); and for women aged 40 to 59, it was 19.3 years (IQR, 13.8-25.2 years).

Presence of 1 or More Clinically Elevated Major CHD Risk Factors at Baseline

TABLE 1 shows proportions of men and women with at least 1 clinically elevated major risk factor among those who died of CHD: for young adult men, CHA, 95.0%; MRFIT, 88.0%; and FHS, 89.5%; for young adult women, CHA, 92.0% and FHS, 100%; for middle-aged men, CHA, 92.7%; MRFIT, 87.0%; and FHS, 90.1%; and for middle-aged women, CHA, 93.8% and FHS, 90.2%. For nonfatal MI in the FHS, proportions ranged from 69.2% in young adult women to 91.6% in middle-aged men. In strata with 19 or more events, the lowest bound for the 95% CIs was 73%. Lower 95% CI bounds in remaining strata (younger FHS women) were 54% (6 events) for fatal CHD and 43% (13 events) for nonfatal MI.

Predictably, prior exposure to at least 1 major risk factor at higher-than-favorable levels (cholesterol ≥200 mg/dL [≥5.18 mmol/L], blood pressure >120/80 mm Hg, smoking, or diabetes) was more prevalent than described above (TABLE 2). Ranges in the proportion exposed among all age-sex groups who experienced CHD death were 96% to 99% (CHA), 98% to 99% (MRFIT), and 99% to 100% (FHS). For nonfatal MI in the FHS, exposure ranged from 85% to 100%. When events were frequent (>19 events), for either fatal or nonfatal CHD, lower bounds for 95% CIs were 82% or higher for this secondary analysis.

Among those who did not experience CHD, exposure to at least 1 risk factor in the clinically elevated range occurred in 58% to 85% (Table 1).

Estimates of the proportions of men and women with 2 or more major risk factors at higher-than-favorable levels at baseline were also substantial, ranging from 64% to 100% for those experiencing fatal CHD and 46% to 88% for those experiencing nonfatal MI (TABLE 3).

Presence of Individual Risk Factors

Among those who experienced a CHD event, the proportions who had a baseline serum cholesterol level of at least 240 mg/dL (≥6.22 mmol/L) in both age groups ranged from 16% in younger women for fatal CHD in the CHA cohort to 63% among older FHS women for CHD death. Exposure rates were similar within the FHS for fatal CHD and nonfatal MI (TABLE 4). Proportions with systolic blood pressure of at least 140 or diastolic blood pressure of at least 90 mm Hg at baseline ranged from 7.7% for nonfatal MI in younger FHS women to more than 70% in older CHA men and women. For men and women in all 3 cohorts who later experienced CHD, smoking was more

prevalent in the younger age group (62%-100%) but was also highly prevalent in the older age group (45%-75%).

Among those who did not develop CHD, individual risk factors at higher-than-optimal levels were less prevalent at baseline but were still common (Table 4).

COMMENT

This study demonstrated a high prevalence of exposure to 1 or more major CHD risk factors before a CHD event. This finding held true whether we used the primary analysis definition of exposure as clinically elevated levels of at least 1 major risk factor (cholesterol ≥240 mg/dL [≥6.22 mmol/L], arterial blood pressure ≥140/90 mm Hg, medication use for hypertension or high cholesterol, cigarette smoking, or clinical diabetes) or the secondary analysis definition of unfavorable cholesterol levels (≥200 mg/dL [≥5.18 mmol/L]) or blood pressure levels (>120/80 mm Hg), medi-

Table 1. Men and Women With at Least 1 Clinically Elevated Major CHD Risk Factor by Cohort, CHD Outcome, Sex, and Baseline Age*

	CHA†			MRFIT†			FHS				
	CHD Death	No CHD Death‡	*P* Value§	CHD Death	No CHD Death‡	*P* Value§	CHD Death	*P* Value§	Nonfatal MI	*P* Value§	No CHD Death‡
Men Aged 18-39 Years											
No.	240	10 862		1442	71 124		19		29		185
% (95% CI)	95.0 (92.2-97.8)	72.7 (71.9-73.6)	<.001	88.0 (86.3-89.7)	61.3 (60.9-61.6)	<.001	89.5 (75.3-100)	.38	86.2 (73.4-99.0)	.40	79.5 (73.6-85.3)
Men Aged 40-59 Years											
No.	1068	8026		17 416	257 996		212		167		767
% (95% CI)	92.7 (91.1-94.3)	80.6 (79.7-81.4)	<.001	87.0 (86.5-87.5)	67.8 (67.6-69.0)	<.001	90.1 (86.1-94.1)	.07	91.6 (87.4-95.8)	.03	85.3 (82.8-87.8)
Women Aged 18-39 Years											
No.	25	7715		NA	NA	NA	6		13		265
% (95% CI)	92.0 (81.1-100)	57.5 (56.4-58.6)	<.001	NA	NA	NA	100 (54.1-100)	.09	69.2 (43.1-95.3)	.77	62.3 (56.4-68.1)
Women Aged 40-59 Years											
No.	465	7188		NA	NA	NA	102		94		1330
% (95% CI)	93.8 (91.6-96.0)	75.9 (74.9-76.9)	<.001	NA	NA	NA	90.2 (84.4-96.0)	<.001	87.2 (80.4-94.0)	.005	74.4 (72.0-76.7)

Abbreviations: CHA, Chicago Heart Association Detection Project in Industry; CHD, coronary heart disease; CI, confidence interval; FHS, Framingham Heart Study; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; NA, not applicable.
*Data are expressed as those in each indicated CHD outcome stratum with at least 1 clinically elevated risk factor (serum cholesterol ≥240 mg/dL [≥6.22 mmol/L], diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg, current antihypertensive or cholesterol-lowering medication, current smoking, or diabetes). Age range in the FHS is 34 to 59 years and in MRFIT is 35 to 57 years.
†Nonfatal events were not measured in the CHA or MRFIT cohorts.
‡Includes participants who did not die or who died of other causes during follow-up; excludes nonfatal MI in the FHS.
§Calculated by χ^2 or Fisher exact test comparing those with a CHD event vs all others within the sex-cohort-age stratum.

Table 2. Men and Women With at Least 1 Major CHD Risk Factor at Higher-Than-Favorable Levels by Cohort, CHD Outcome, Sex, and Baseline Age*

	CHA†			MRFIT†			FHS				
	CHD Death	No CHD Death‡	*P* Value§	CHD Death	No CHD Death‡	*P* Value§	CHD Death	*P* Value§	Nonfatal MI	*P* Value§	No CHD Death‡
Men Aged 18-39 Years											
No.	240	10 862		1442	71 124		19		29		185
% (95% CI)	99.6 (98.8-100)	90.8 (90.3-91.3)	<.001	98.1 (97.4-98.8)	90.0 (89.8-90.2)	<.001	100 (82.4-100)	>.99	96.6 (89.8-100)	>.99	96.8 (94.2-99.3)
Men Aged 40-59 Years											
No.	1068	8026		17 416	257 996		212		167		767
% (95% CI)	98.9 (98.2-99.5)	95.3 (94.9-95.8)	<.001	98.7 (98.5-98.9)	93.8 (93.7-93.9)	<.001	99.1 (97.8-100)	.19	100 (97.8-100)	.03	97.4 (96.3-98.5)
Women Aged 18-39 Years											
No.	25	7715		NA	NA	NA	6		13		265
% (95% CI)	96.0 (88.2-100)	77.2 (76.3-78.2)	.03	NA	NA	NA	100 (54.1-100)	.59	84.6 (64.2-100)	>.99	84.2 (79.7-88.6)
Women Aged 40-59 Years											
No.	465	7188		NA	NA	NA	102		94		1330
% (95% CI)	99.1 (98.3-100)	93.5 (92.9-94.0)	<.001	NA	NA	NA	100 (96.4-94.1)	.02	98.9 (96.9-100)	.08	94.6 (93.4-95.8)

Abbreviations: CHA, Chicago Heart Association Detection Project in Industry; CHD, coronary heart disease; CI, confidence interval; FHS, Framingham Heart Study; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; NA, not applicable.
*Data are expressed as those in each indicated CHD outcome stratum with at least 1 risk factor at higher-than-favorable levels (serum cholesterol ≥200 mg/dL [≥5.18 mmol/L], diastolic blood pressure >80 mm Hg or systolic blood pressure >120 mm Hg, current antihypertensive or cholesterol-lowering medication, current smoking, or diabetes). Age range in the FHS is 34 to 59 years and in MRFIT is 35 to 57 years.
†Nonfatal events were not measured in the CHA or MRFIT cohorts.
‡Includes participants who did not die or who died of other causes during follow-up; excludes nonfatal MI in the FHS.
§Calculated by χ^2 or Fisher exact test comparing those with a CHD event vs all others within the sex-cohort-age stratum.

cation use for hypertension or high cholesterol, current cigarette use, or diabetes. For fatal CHD, in all 3 of these large, long-term prospective cohort studies, prior exposure to at least 1 clinically elevated major CHD risk factor ranged from 87% to 100%. For nonfatal MI in the FHS, in both older men and older women, prior risk factor exposures in the clinically elevated range were 92% and 87%, respectively. In younger FHS participants, estimates were less stable due to a small number of events, but they were still in the range of 69% to 86%.

Results were consistent among the 3 cohorts, in both sexes, and across a range of baseline ages under 60 years. High proportions of CHD events also occurred in persons exposed to 2 or more major CHD risk factors at higher-than-favorable levels (64%-100% for fatal CHD and 46%-88% for nonfatal MI). These results challenge claims in the medical literature that CHD events commonly occur (as often as 50% of the time) in persons who have not been exposed to at least 1 major risk factor.[8-12]

Although the high prevalence of antecedent CHD risk factor exposures found in the 3 cohorts here may seem unexpected, findings in 2 clinical CHD studies provide support for the high prevalence of major lipid risk factors at higher-than-favorable levels among CHD patients. Specifically, total cholesterol measured in men and women who had developed clinical CHD was at a higher-than-favorable level (≥200 mg/dL [≥5.18 mmol/L]) in approximately 75%.[22,23] Only 7% of persons with CHD in these 2 studies had desirable levels of 2 major cholesterol fractions (low-density lipoprotein <100 mg/dL [<2.59 mmol/L] and high-density lipoprotein ≥35 mg/dL [≥0.91 mmol/L]). To our knowledge, there are no prior reports of the magnitude of exposures to clinically elevated levels of all major CHD risk factors in cohorts followed up over a long term for CHD events.

Unfavorable levels of blood cholesterol and blood pressure, cigarette smoking, overweight/obesity, and diabetes are well established as the major causal factors for CHD.[1-7] These 5 factors, along with adverse dietary habits that also promote CHD risk, are highly prevalent in populations with epidemic CHD; for several of these factors, clinical trials have demonstrated lowered CHD event rates when the factor is treated and reduced.[2,6,7]

A critically important feature of these risk factors is that each has a continuous, dose-dependent impact on CHD risk. In particular, for cholesterol, blood pressure, smoking, and overweight, higher levels of the risk factors translate into greater CHD risk.[3,6,7,24] Thus, cut points for intervention at clinically elevated levels (eg, hyperlipidemic vs normolipidemic) have been adopted to define a high-risk clinical intervention strategy, but this approach underestimates the true effects of these factors on CHD risk. Because these risk factors have a continuous relationship to risk of CHD, in this study we evaluated 2 different cut points for defining risk factor exposures. Even with application of the higher cut points for cholesterol and blood pressure levels, prior exposure to 1 or more major CHD risk factor in CHD cases was common.

This study also suggested that, in these large US cohorts, exposure to 1 or more of the major CHD risk factors was also highly prevalent among individuals who did not develop clinical CHD during lengthy periods of follow-up. Various explanations for this paradox can be considered. First, the study only dealt with clinically apparent CHD; therefore, we

Table 3. Men and Women With at Least 2 Major CHD Risk Factors at Higher-Than-Favorable Levels by Cohort, CHD Outcome, Sex, and Baseline Age*

	CHA†			MRFIT†			FHS				
	CHD Death	No CHD Death‡	*P* Value§	CHD Death	No CHD Death‡	*P* Value§	CHD Death	*P* Value§	Nonfatal MI	*P* Value§	No CHD Death‡
Men Aged 18-39 Years											
No.	240	10 862		1442	71 124		19		29		185
% (95% CI)	85.8 (81.4-90.3)	54.9 (54.0-55.9)	<.001	82.8 (80.9-84.7)	57.8 (57.4-58.2)	<.001	94.7 (84.4-100)	.03	82.8 (68.8-96.8)	.22	71.9 (65.4-78.4)
Men Aged 40-59 Years											
No.	1068	8026		17 416	257 996		212		167		767
% (95% CI)	83.3 (81.1-85.6)	69.0 (68.0-70.0)	<.001	84.0 (83.5-84.6)	65.9 (65.7-66.1)	<.001	94.3 (91.2-97.5)	<.001	88.0 (83.1-93.0)	.01	79.8 (76.9-82.6)
Women Aged 18-39 Years											
No.	25	7715		NA	NA	NA	6		13		265
% (95% CI)	64.0 (44.8-83.2)	35.0 (34.0-36.1)	.002	NA	NA	NA	100 (54.1-100)	.006	46.1 (17.9-74.4)	.78	42.3 (36.3-48.2)
Women Aged 40-59 Years											
No.	465	7188		NA	NA	NA	102		94		1330
% (95% CI)	85.6 (82.4-88.8)	64.5 (63.4-65.6)	<.001	NA	NA	NA	94.1 (89.5-98.7)	<.001	79.8 (71.6-87.9)	.02	68.3 (65.8-70.8)

Abbreviations: CHA, Chicago Heart Association Detection Project in Industry; CHD, coronary heart disease; CI, confidence interval; FHS, Framingham Heart Study; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; NA, not applicable.

*Data are expressed as those in each indicated CHD outcome stratum with at least 2 risk factors at higher-than-favorable levels (serum cholesterol ≥200 mg/dL [≥5.18 mmol/L], diastolic blood pressure >80 mm Hg or systolic blood pressure >120 mm Hg, current antihypertensive or cholesterol-lowering medication, current smoking, or diabetes). Age range in the FHS is 34 to 59 years and in MRFIT is 35 to 57 years.

†Nonfatal events were not measured in the CHA or MRFIT cohorts.

‡Includes participants who did not die or who died of other causes during follow-up; excludes nonfatal MI in the FHS.

§Calculated by χ^2 or Fisher exact test comparing those with a CHD event vs all others within the sex-cohort-age stratum.

cannot determine how many individuals in each of the 3 cohorts had subclinical CHD following risk factor exposure. In addition, as with most diseases, exposure to the etiologic agents for CHD is necessary but not sufficient to cause the clinical disease in all persons. Host factors, which might include genetic characteristics, environmental exposures, or both, undoubtedly protect certain exposed persons from becoming diseased. High-density lipoprotein cholesterol,[2,3] for example, has well-known mitigating effects on CHD risk, even in the presence of adverse levels of major risk factors. Other protective factors are emerging, such as cholesteryl ester transfer protein, which has been reported to have antiatherogenic effects.[25] Alternatively, major CHD risk factors are also associated with competing causes of death, such as lung cancer and stroke.

On the basis of our findings and those considered elsewhere by others,[13,20,24] it is apparent that clinically elevated levels of 1 or more of the major causal CHD risk factors precede a very high proportion of fatal or nonfatal CHD events. Women aged 34 to 39 years at baseline in the FHS did not follow this pattern,

Table 4. Men and Women With Individual CHD Risk Factors at Higher-Than-Favorable or Clinically Elevated Levels by Cohort, CHD Outcome, Sex, and Baseline Age*

	CHA†			MRFIT†‡		FHS				
Risk Factors	CHD Death	No CHD Death§	*P* Value‡	CHD Death	No CHD Death§	CHD Death	*P* Value‡	Nonfatal MI	*P* Value‡	No CHD Death§
Men Aged 18-39 Years										
No.	240	10 862	<.001	1442	71 124	19		29		185
Cholesterol ≥200 mg/dL (≥5.18 mmol/L)‖	66.7	36.8	<.001	71.7	53.2	78.9	.43	69.0	.89	70.3
DBP >80 mm Hg or SBP >120 mm Hg¶	86.2	76.0	<.001	83.6	71.8	94.7	.01	89.7	.01	67.0
Current smoking	72.1	46.9	<.001	66.1	39.5	73.7	.50	72.4	.49	66.0
Diabetes	3.3	1.0	<.001	3.0	0.5	5.3	.09	0	NA	0
Cholesterol ≥240 mg/dL (≥6.22 mmol/L)‖	27.1	8.5	<.001	35.8	17.1	47.4	.16	51.7	.03	16.2
DBP ≥90 mm Hg or SBP ≥140 mm Hg¶	62.9	4.8	<.001	44.3	26.0	31.6	.21	24.1	.42	17.8
Men Aged 40-59 Years										
No.	1068	8026	<.001	17 416	257 996	212		167		767
Cholesterol ≥200 mg/dL (≥5.18 mmol/L)‖	72.4	61.5	<.001	76.5	64.7	91.5	<.001	86.8	.001	75.1
DBP >80 mm Hg or SBP >120 mm Hg¶	90.6	83.1	<.001	88.7	77.8	87.4	<.001	79.0	.06	72.0
Current smoking	52.1	40.1	<.001	48.9	34.5	67.5	.57	75.4	.13	69.5
Diabetes	7.1	3.0	<.001	5.6	1.5	4.3	.06	2.4	.76	2.0
Cholesterol ≥240 mg/dL (≥6.22 mmol/L)‖	30.3	21.0	<.001	36.5	24.3	46.7	<.001	45.5	<.001	31.6
DBP ≥90 mm Hg or SBP ≥140 mm Hg¶	73.4	60.0	<.001	55.5	36.2	39.2	<.001	26.9	.66	25.3
Women Aged 18-39 Years										
No.	25	7715		NA	NA	6		13		265
Cholesterol ≥200 mg/dL (≥5.18 mmol/L)‖	52.0	26.8	.005	NA	NA	100	.01	46.2	.88	48.3
DBP >80 mm Hg or SBP >120 mm Hg¶	48.0	46.7	.89	NA	NA	66.7	.18	46.2	.38	34.0
Current smoking	80.0	44.6	<.001	NA	NA	100	.03	61.5	.54	52.8
Diabetes	0	0.9	.64	NA	NA	16.7	.07	0	>.99	0.7
Cholesterol ≥240 mg/dL (≥6.22 mmol/L)‖	16.0	5.0	.01	NA	NA	50.0	.03	30.8	.07	12.1
DBP ≥90 mm Hg or SBP ≥140 mm Hg¶	32.0	19.6	.13	NA	NA	33.3	.07	7.7	>.99	6.8
Women Aged 40-59 Years										
No.	465	7188		NA	NA	102		94		1330
Cholesterol ≥200 mg/dL (≥5.18 mmol/L)‖	76.8	67.1	<.001	NA	NA	94.1	<.001	84.0	.05	74.9
DBP >80 mm Hg or SBP >120 mm Hg¶	86.9	72.3	<.001	NA	NA	88.2	<.001	76.6	.004	61.9
Current smoking	51.8	35.2	<.001	NA	NA	45.1	.80	51.1	.38	46.4
Diabetes	5.6	2.1	<.001	NA	NA	7.8	<.001	4.3	.008	0.7
Cholesterol ≥240 mg/dL (≥6.22 mmol/L)‖	38.9	27.2	<.001	NA	NA	62.7	<.001	58.5	<.001	34.1
DBP ≥90 mm Hg or SBP ≥140 mm Hg¶	71.4	47.4	<.001	NA	NA	44.1	<.001	40.4	<.001	24.6

Abbreviations: CHA, Chicago Heart Association Detection Project in Industry; CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; FHS, Framingham Heart Study; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; NA, not applicable; SBP, systolic blood pressure.
*Data are expressed as percentages in each indicated CHD outcome stratum with risk factor. Age range in the FHS is 34 to 59 years and in MRFIT is 35 to 57 years.
†Nonfatal events were not measured in the CHA or MRFIT cohorts.
‡Calculated by χ^2 or Fisher exact test comparing percentages with the indicated number of risk factors among those with a CHD event vs all others within the sex-cohort-age stratum. All $P<.001$ for the MRFIT cohort.
§Includes participants who did not die or who died of other causes during follow-up; excludes nonfatal MI in the FHS.
‖Or taking cholesterol-lowering medication (in the CHA cohort).
¶Or taking antihypertensive medication (in the CHA and FHS cohorts).

and they experienced reduced exposures to major risk factors compared with the other cohorts studied. However, in FHS women in this stratum, only 13 events took place during the 30 years of follow-up, and 95% CIs were wide (43%-95%). Overall, these data indicate that prior estimates of the relative infrequency of major risk factor exposures among CHD cases were probably incorrect.

Several factors may have led to inappropriately low prior estimates of the frequency of major risk factor exposures in CHD. These include effects of regression dilution bias causing underestimation of risk impact in most observational studies[26]; lag or incubation effect from onset of exposure to development of disease, necessitating an exploration of prior exposures using long-term follow-up, as was feasible in this study[27]; and inability to recognize or quantify exposures in apparently unexposed groups.[24] Another contributing factor is the cumulative effect of major risk factors throughout an individual's life.[28] For example, the FHS recently reported that remote antecedent blood pressure predicted cardiovascular disease risk more strongly than proximal blood pressures.[29] Accordingly, recent risk factor measurements probably underestimate prevalence and impact of risk factor exposures.

These data underscore the importance of considering all major risk factors in CHD risk estimation and in attempting to prevent clinical CHD. Based on these and related findings concerning the major risk factors,[13,20,24] we suggest that preventing development of unfavorable levels of blood cholesterol and blood pressure, cigarette smoking, diabetes, and unfavorable body weight (as a precursor of unfavorable blood lipid and blood pressure levels and diabetes) should be given even greater priority than is presently the case. Although blood lipid levels are important major CHD risk factors, a 1-sided focus on cholesterol as the major CHD risk factor[11,12,14] cannot be justified. Rather, these data provide an important reminder that attention must be accorded to all major risk factor exposures to address the continuing CHD epidemic.[6,7,13,20]

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