

Relative Importance of Borderline and Elevated Levels of Coronary Heart Disease Risk Factors

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Background: Clinical trials indicate that a sizable proportion of adults have multiple borderline coronary risk factors and may benefit from treatment.

Objective: To estimate the relative and absolute contributions of borderline and elevated risk factors to the population burden of coronary heart disease (CHD) events.

Design: A prospective cohort study and a national cross-sectional survey.

Setting: The Framingham Study and the Third National Health and Nutrition Examination Survey (NHANES III).

Participants: White non-Hispanic persons in the Framingham Study and in NHANES III who were between 35 to 74 years of age and had no CHD.

Measurements: Occurrence of first CHD events according to 5 major CHD risk factors: blood pressure, low-density lipoprotein and high-density lipoprotein cholesterol levels, glucose intolerance, and smoking. Three categories—optimal, borderline, and elevated—were defined for each risk factor per national guide-

lines. Sex-specific 10-year CHD event rates from the Framingham Study were applied to numbers of at-risk individuals estimated from NHANES III and the 2000 U.S. Census.

Results: Twenty-six percent of men and 41% of women had at least 1 borderline risk factor in NHANES III. According to estimates, more than 90% of CHD events will occur in individuals with at least 1 elevated risk factor, and approximately 8% will occur in people with only borderline levels of multiple risk factors. Absolute 10-year CHD risk exceeded 10% in men older than age 45 years who had 1 elevated risk factor and 4 or more borderline risk factors and in those who had at least 2 elevated risk factors. In women, absolute CHD risk exceeded 10% only in those older than age 55 years who had at least 3 elevated risk factors.

Limitations: The generalizability of the findings to persons of other ethnic backgrounds is unknown.

Conclusions: Borderline CHD risk factors alone account for a small proportion of CHD events.

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Several recent studies have emphasized that known risk factors account for more than three quarters of cases of coronary heart disease (CHD) in the United States (1–4). These studies have demonstrated that most individuals with CHD have at least 1 or more antecedent risk factors for CHD (1–3, 5) and that optimal levels of known risk factors are associated with very low vascular risk (4). These data support measuring vascular risk factors to screen for CHD risk, which would allow higher-risk individuals to be targeted for appropriate treatment (6–8).

Law and colleagues (9), however, have suggested that risk factors make poor screening tools. They highlighted the continuous relationship between levels of most risk factors and CHD risk (9–11) and concluded that screening based on conventional definitions of high risk factor levels would be ineffective because “the 10% in the population with the most extreme values . . . experience only about 20% of the disease events” (9). Since the proportional treatment benefits are similar over a continuous range of risk factor values (12, 13), Law and colleagues have proposed that the entire adult population older than age 55 years should receive mass treatment with a combination “polypill” (containing a statin, aspirin, 3 blood pressure-lowering medications, and folic acid) without any risk factor screening. According to Law and colleagues, such treatment would lower average levels of several risk factors simultaneously to prevent cardiovascular disease events (14). Their proposal is based on the premise that popula-

tion attributable risk associated with a certain level of a risk factor (borderline or elevated) depends not only on the relative risk but also on the risk factor’s prevalence (15). Average risk factor levels may contribute substantially to CHD burden because of their high prevalence. Indeed, some data support the notion that people with average levels of risk factors (below recognized intervention thresholds) account for a sizable proportion of individuals with vascular disease (16).

We investigated the relative contributions of borderline (suboptimal but below current treatment thresholds) and elevated vascular risk factors to CHD burden in the United States. To do this, we first examined the absolute rates of CHD events associated with borderline risk factors

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Context

Are borderline levels of risk factors responsible for much coronary heart disease (CHD)?

Contribution

These researchers applied 10-year CHD event rates from the Framingham Study to risk factor levels measured in a recent national probability sample. Twenty-six percent of men and 41% of women age 35 to 74 years had borderline risk factors, but only one tenth of the projected CHD events were attributed to borderline levels. Most events were attributable to elevated risk factors; among men, nearly one sixth occurred before age 55 years.

Implications

In the United States, borderline levels of risk factors probably account for a small proportion of CHD events.

—The Editors

in a community-based sample. We then estimated the absolute burden of CHD in the United States arising from borderline risk factors by applying these event rates to a national probability sample for which the risk factor prevalence has been well characterized.

METHODS**The Framingham Study Sample**

The selection criteria and study design of the Framingham Heart Study and the Framingham Offspring Study have been described previously (17, 18). Participants in the Framingham Heart Study who attended original cohort examination 11 from 1968 to 1972 ($n = 2995$) and participants in the Framingham Offspring Study who attended examination 1 from 1971 to 1974 ($n = 5124$) or examination 3 from 1984 to 1987 ($n = 3873$) were eligible for this study. These examinations are referred to as the baseline examinations. Of the 11 952 attendees, we excluded those with prevalent cardiovascular disease ($n = 1483$ [12%]), those with missing risk factor data ($n = 492$ [5%]), and those who were younger than age 35 years or older than age 74 years at the baseline examinations. After exclusions, 7391 participants, 3973 of whom were women, remained eligible for this investigation. Persons from the offspring cohort who were eligible at examination 1 remained eligible at examination 3 if they reached that examination free of cardiovascular disease.

Measurement of Risk Factors and Classification

At the baseline examinations, all participants underwent a physical examination (with a medical history), laboratory assessment of cardiovascular disease risk factors, and routine electrocardiography. A physician using a mercury column sphygmomanometer measured systolic and diastolic blood pressure twice while participants were seated; the 2 readings were averaged to determine the exami-

nation blood pressure. Levels of each of 5 established and modifiable CHD risk factors were classified as optimal, borderline, or elevated (or low in the case of high-density lipoprotein cholesterol) according to national guidelines. Blood pressure was considered optimal if the systolic pressure was less than 120 mm Hg and diastolic pressure was less than 80 mm Hg (referent), borderline if the systolic pressure was 120 to 139 mm Hg or diastolic pressure was 80 to 89 mm Hg, and elevated if the participant had hypertension (19). Low-density lipoprotein cholesterol level was considered optimal at less than 2.59 mmol/L (<100 mg/dL) (referent), borderline at 2.59 to 4.12 mmol/L (100 to 159 mg/dL), and high at greater than 4.12 mmol/L (>159 mg/dL) (7). High-density lipoprotein cholesterol level was considered optimal at more than 1.53 mmol/L (>59 mg/dL) (referent), borderline at 1.04 to 1.53 mmol/L (40 to 59 mg/dL), and low at less than 1.04 mmol/L (<40 mg/dL) (7). Glucose tolerance was classified as normal, borderline if the participant had impaired fasting glucose or impaired glucose tolerance, or elevated if the participant had diabetes (20). Smoking status was categorized as optimal if the participant was a nonsmoker, borderline if the participant was a former smoker, and elevated if the participant was a current smoker. Former smokers were considered borderline in terms of risk prediction because data show that they remain at increased CHD risk compared with nonsmokers for a few years after smoking cessation (21).

Participants were categorized according to the number of optimal, borderline, and elevated risk factors. The categories were all optimal, 1 or more borderline risk factors but no elevated risk factors, and 1 or more elevated risk factors. The third category was further stratified by numbers of borderline risk factors. Although the relationship between risk factors and CHD is continuous, we chose to analyze categories because our study focused on borderline risk factor levels.

Follow-up and Outcome Events

All study participants were under continuous surveillance for CHD events and death. We obtained information about CHD events at follow-up with the aid of medical histories, physical examinations at the Framingham Heart Study (biennially for the original cohort and every 4 years for the offspring cohort), hospitalization records, and communication with personal physicians. All suspected new events were reviewed by a panel of 3 experienced investigators, who evaluated all pertinent medical records while blinded to risk factor data. Our primary outcome of interest was the time to occurrence of a first "hard" CHD event (recognized or unrecognized myocardial infarction or coronary death) during 12 years of follow-up. A diagnosis of recognized acute myocardial infarction required the simultaneous presence of at least 2 of the following 3 criteria: symptoms consistent with myocardial infarction, diagnostic electrocardiographic changes, and diagnostic

elevation of biomarkers (22). Unrecognized myocardial infarction was diagnosed when an electrocardiogram revealed new pathologic Q waves compared with the participant's last available tracing and myocardial infarction was not known to have occurred in the interim (22). Hard CHD events have been used previously as an outcome for Framingham-based risk prediction algorithms (23, 24).

Risk Factor Distribution in the Third National Health and Nutrition Examination Survey Sample

Since the distribution of risk factors in the Framingham Study sample may differ from that in the U.S. population, we chose to examine the distributions of risk factors using data from the Third National Health and Nutrition Examination Survey (NHANES III), a national probability sample of noninstitutionalized persons (25). In addition, to permit comparisons with the Framingham Study sample and to facilitate extrapolations of Framingham CHD event rates to the U.S. population, we examined data for non-Hispanic white persons in NHANES III who were between the ages of 35 to 74 years and who did not have a history of a previous vascular event (self-reported myocardial infarction, angina, stroke, heart failure, or intermittent claudication). Furthermore, we included only persons who had a morning examination and who had been fasting for at least 9 hours; this restriction permitted us to use 1 weighting variable for all risk factors (individual and combinations). Although this restriction excluded approximately 60% of the participants, there was no evidence of selection bias. The distributions of sex, blood pressure, and smoking status among participants who were excluded because of a nonfasting state or missing risk factors were similar to those in the included participants ($P > 0.2$ for all [data not shown]).

Data on risk factors for eligible individuals from NHANES III were categorized by using the same criteria noted for the Framingham Study sample. The laboratory methods for NHANES III have been detailed elsewhere (26). The prevalence of risk factor categories was examined for the overall sample and for 4 age groups defined a priori (35 to 44 years, 45 to 54 years, 55 to 64 years, and 65 to 74 years).

Statistical Analysis

Our objective was to develop internally consistent estimates of first hard CHD event rates in the United States by age, sex, and risk factor groups. We also sought to estimate the fraction of hard CHD events that occurred in men and women according to the number of borderline and elevated risk factors (and their combinations). We estimated the number of white persons in the United States with incident hard CHD events over a 10-year period in each of the risk factor combinations by using the following 7 steps.

1. We estimated sex-specific Cox proportional hazards regression functions that related the various risk factor combinations to the incidence of a first hard CHD event in the Framingham Study sample. Ten-year CHD event

rates, age-adjusted to the 2000 standard population, were estimated for each risk factor combination in the Framingham Study sample on the basis of 12-year follow-up. We modeled the different risk factor combinations using a set of dummy variables that accounted for the number of optimal, borderline, and elevated risk factors, not the specific risk factors that made up each combination (Appendix, available at www.annals.org). This classification scheme assumes that the hazards posed by borderline or elevated levels of the 5 CHD risk factors are similar. We chose this analytic strategy to facilitate simple yet meaningful interpretation of results. In Cox models incorporating categories of risk factors, with the optimal category serving as the referent, parameter estimates for different elevated risk factors were very similar, and parameter estimates for various borderline risk factors were equivalent, thereby providing support for our strategy. For example, regression coefficients (\pm SE) for high blood pressure, high levels of low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol, smoking, and diabetes were 0.75 ± 0.19 , 0.79 ± 0.22 , 0.75 ± 0.22 , 0.66 ± 0.15 , and 0.62 ± 0.17 , respectively, in men. Consequently, absolute CHD event rates were consistent for a given number of borderline and elevated risk factors regardless of the specific combinations of risk factor levels that yielded the number (data not shown). These observations are consistent with our previous report showing that summing the number of risk factors predicts CHD risk reasonably well (23).

2. We estimated 10-year CHD event rates for each risk factor combination in specific age strata in the Framingham Study sample by substituting the midpoint for the age group into the sex-specific regression equation. For example, we used the model developed in men (pooling men of all ages) and estimated event rates for men 45 to 54 years of age by considering age 50 years in the model (Appendix, available at www.annals.org).

3. We estimated the prevalence of various risk factor combinations in different age strata for the NHANES III sample and then applied them to 2000 U.S. Census data (27) to estimate the numbers of individuals at risk for CHD in each risk factor combination in each age stratum.

4. We estimated the number of individuals who would be considered to have a high global risk (defined as an absolute hard CHD event rate of $\geq 10\%$) by summing the numbers of individuals in strata in the NHANES III sample that corresponded to categories associated with a 10-year hard CHD event rate exceeding 10% in the Framingham Study sample. While the threshold of absolute event rates that defines high risk varies across guidelines (5% for fatal cardiovascular disease in European guidelines [28] to 20% for CHD events in a recent U.S. report [29]), we empirically chose a 10% threshold for global risk because the outcome of interest was hard CHD events.

5. We then applied estimates of the 10-year hard CHD event rates derived in step 2 (in the Framingham Study sample) to the population estimates of the numbers of

Table 1. Distribution of Individual CHD Risk Factors in Framingham Heart Study Participants and in the Third National Health and Nutrition Examination Survey*

Risk Factors	Definitions	Framingham Heart Study		NHANES III†	
		Men (n = 3418)	Women (n = 3973)	Men (n = 681)	Women (n = 807)
Mean age, y		50.2	51.1	50.3	51.5
Blood pressure, %					
Optimal	Systolic < 120 mm Hg; diastolic < 80 mm Hg	19	31	31	48
Borderline	Systolic 120–139 mm Hg or diastolic 80–89 mm Hg	43	36	43	27
High	Systolic ≥140 mm Hg, diastolic ≥90 mm Hg, or treatment for hypertension	38	33	26	25
Serum LDL cholesterol level, %					
Optimal	<2.59 mmol/L (<100 mg/dL)	12	16	14	22
Borderline	2.59–4.12 mmol/L (100–159 mg/dL)	62	57	60	58
High	4.12 mmol/L (>159 mg/dL)	26	27	26	20
Serum HDL cholesterol level, %					
Optimal	>1.53 mmol/L (>59 mg/dL)	11	41	10	34
Borderline	1.04–1.53 mmol/L (40–59 mg/dL)	53	49	50	53
Low	<1.04 mmol/L (<40 mg/dL)	36	10	40	13
Glucose tolerance, %					
Optimal	Fasting glucose level < 6.11 mmol/L (<110 mg/dL) or 2-h glucose level < 7.77 mmol/L (<140 mg/dL)	81	90	82	87
Borderline	Fasting glucose level 6.11–6.94 mmol/L (110–125 mg/dL) or 2-h glucose level 7.77–11.04 mmol/L (140–199 mg/dL)	13	6	10	7
High	Known diabetes or fasting glucose level > 6.94 mmol/L (>125 mg/dL) or 2-h glucose level >11.04 mmol/L (>199 mg/dL)	6	4	8	6
Smoking, %					
Optimal	Never	26	42	30	50
Borderline	Former	39	25	42	30
High	Current	35	33	28	20

* HDL = high-density lipoprotein; LDL = low-density lipoprotein; NHANES III = Third National Health and Nutrition Examination Survey.

† Data for 1488 eligible non-Hispanic white persons who were 35 to 74 years of age and had no vascular disease in their medical history. There were 10 507 non-Hispanic white persons in the NHANES III sample (out of 33 199 for all ethnicities). Persons <35 years of age (n = 4825), persons >74 years of age (n = 1658), those who fasted less than 9 hours (n = 1841), those with a history of vascular disease (n = 262), and those with missing risk factor data (n = 433) were excluded.

individuals at risk for CHD from step 3 to calculate the numbers of adults with incident CHD over a 10-year period for each risk factor combination in each baseline age stratum. We have previously reported that Framingham Study risk functions yield reasonable estimates of absolute CHD risk in samples of white persons in the United States (24).

6. We determined the fractions of estimated CHD events in each risk factor combination within each baseline age stratum (and overall) by dividing the number of estimated CHD events in that risk factor combination by the total number of estimated CHD events in an age stratum (and overall). Bar graphs were constructed to facilitate interpretation of these fractions (30).

7. The numbers obtained from step 5 were summed across all risk factor categories to estimate the fractions of CHD events in white persons in the United States that arise from each risk factor combination.

Role of the Funding Source

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RESULTS

Risk Factor Profiles in the Framingham Study and NHANES III

Table 1 shows the prevalence of individual CHD risk factors and risk factor combinations in the Framingham Study and NHANES III samples. Generally, the risk factor distributions were similar. Individuals in the Framingham Study sample had a higher prevalence of high blood pressure and smoking, and a greater proportion of women in the Framingham Study had elevated levels of low-density lipoprotein cholesterol. Optimal levels of all 5 risk factors were distinctly rare in both samples. Twenty-six percent of men and 41% of women in the NHANES III sample had 1 or more borderline risk factor but no elevated risk factors (Appendix Table 2, available at www.annals.org). Approx-

Table 2. Age-Specific Prevalence of Risk Factor Groups in the Third National Health and Nutrition Examination Survey*

Risk Factor Group	Borderline Risk Factors, n	Men, %†				Women, %†			
		35–44 y (n = 15 816 000 [33.7%])	45–54 y (n = 14 669 000 [31.2%])	55–64 y (n = 9 680 000 [20.6%])	65–74 y (n = 6 836 000 [14.5%])	35–44 y (n = 15 810 000 [32.3%])	45–54 y (n = 14 900 000 [30.4%])	55–64 y (n = 10 244 000 [20.9%])	65–74 y (n = 8 059 000 [16.4%])
All optimal	0	0	0	0	0.2	8.9	3.7	0.3	0.4
Only borderline	1	3.0	2.0	1.5	0.7	15.2	10.4	7.3	4.5
	2	11.0	5.4	9.8	4.0	24.8	18.1	15.3	10.7
	3	10.2	9.1	10.2	8.0	11.3	12.4	8.8	6.5
	4 or 5	8.4	7.0	4.1	6.3	3.9	4.5	8.7	6.9
	Total	32.6	23.5	25.6	19.0	55.2	45.4	40.1	28.6
1 high	0	0.3	0	0	1.3	1.9	2.6	1.2	2.5
	1	10.6	9.9	2.1	6.5	7.2	10.8	12.8	8.6
	2	8.5	11.0	17.5	9.3	8.7	11.5	15.0	12.9
	3	13.4	15.1	12.9	11.5	4.6	6.0	6.6	9.1
	4	0.9	1.9	2.2	7.1	0.4	1.9	1.7	2.7
Total	33.7	37.9	34.7	35.7	22.8	32.8	37.3	35.8	
2 high	0	3.9	3.8	1.9	7.3	2.6	0.6	1.8	6.1
	1	9.6	11.2	7.6	13.8	5.5	9.0	5.6	12.5
	2	10.9	9.2	9.7	13.3	3.1	6.8	7.1	9.3
	3	2.0	2.7	5.6	1.3	0	0	1.3	0.9
	Total	26.4	26.9	24.8	35.7	11.2	16.4	15.8	28.8
3 high	0	2.7	3.7	2.4	1.3	0.9	0.7	0.8	1.3
	1	4.3	5.7	4.6	4.6	0.5	0.4	3.7	3.6
	2	0.3	1.1	4.3	1.5	0.5	0.6	1.5	1.0
	Total	7.3	10.5	11.3	7.4	1.9	1.7	6.0	5.9
4 high	0 or 1	0	1.2	3.6	2.0	0	0	0.5	0.5

* Data for non-Hispanic white persons who were 35 to 74 years of age and had no vascular disease in their medical history (see text for details). The Third National Health and Nutrition Examination Survey includes several million men and women when weights are applied, so the 95% CIs around the estimates do not differ greatly from the estimates themselves.

† Numbers of persons are for 2001 (based on post-census updates to the 2000 U.S. Census). Data are from reference 27. Percentages are percentages within sex.

imately 60% of the men in both samples, 60% of the women in the Framingham Study sample, and approximately 50% of the women in the NHANES III sample had 1 or 2 elevated risk factors in both samples. Few individuals in either sample had 3 or more elevated CHD risk factors.

Table 2 shows the age-specific prevalence of risk factors in the NHANES III sample. Optimal levels of all 5 CHD risk factors were distinctly rare in any age group for either sex, with the exception of women 35 to 44 years of age. Prevalence of elevated risk factors increased with age in both sexes. For any given age group, the risk factor profile was worse in men than in women. As a result, a higher proportion of women had 1 or more borderline risk factors. Two thirds of men and one third of women 35 to 44 years of age had 1 or more elevated risk factors. Three quarters of men and more than half of women older than age 55 years had 1 or more elevated CHD risk factors.

CHD Event Rates in Age and Risk Factor Strata in the Framingham Study Sample

On follow-up, 478 first hard CHD events (135 in women) occurred in the Framingham Study sample. Tables 3 and 4 show the age-adjusted and age-specific 10-year CHD event rates by sex (95% CIs around estimates of event rates are shown in Appendix Table 3, available at www.annals.org). In both sexes, event rates increased progressively from those seen in persons with only borderline risk factors to those seen in persons with increasing numbers of elevated risk factors.

In men, CHD event rates rose as the number of borderline risk factors increased when strata with all borderline risk factors or with only 1 risk factor were considered. Ten-year absolute CHD risk exceeded 10% in men older than age 45 years at baseline who had any 1 elevated risk factor and borderline levels of the other 4 risk factors, and in those who had at least 2 elevated risk factors. In men with 2 or more elevated risk factors, the presence of other borderline risk factors did not have additional incremental influence on risk.

Generally, presence of borderline risk factors increased risk further in women in whom 1 or more CHD risk factors were elevated. Absolute CHD risk exceeded 10% only in women older than age 55 years who had at least 3 elevated risk factors. An exception was the age group 65 to 74 years, in which the absolute CHD risk exceeded this threshold with 1 or 2 elevated risk factors and multiple borderline risk factors.

Estimated Population at High Global Risk in the United States

We estimated that of 47 million white men between age 35 and 74 years, 17.7 million (37.7%) would be categorized as at increased global risk (10-year absolute CHD event rates >10%) and about 6.5 million men would be categorized as at extremely high risk (10-year absolute CHD event rates >20%). Overall, 10.4 million men older than age 55 years (63%) would exceed the 10% risk threshold for hard CHD events. Of 49 million white women between age 35 and 74 years, 2.39 million (4.9%) would be deemed to be at high risk. About 2.3 million

Table 3. Hard Coronary Heart Disease Rates and Absolute Number of Events according to Risk Factor Groups in Men*

Risk Factor Group	Borderline Risk Factors, n	Age-Adjusted 10-Year Risk for Hard CHD, %†					Estimated White Men in the United States, n‡			
		All Ages	35–44 y	45–54 y	55–64 y	65–74 y	35–44 y	45–54 y	55–64 y	65–74 y
All optimal	0									13 672
Only borderline	1						474 480	293 380	145 200	47 852
	2	3.14	2.07	3.10	4.63	6.87	1 739 760	792 126	958 320	273 440
	3	3.22	2.13	3.18	4.74	7.04	1 613 232	1 349 548	987 360	546 880
	4 or 5	3.42	2.26	3.37	5.03	7.46	1 328 544	1 026 830	396 880	444 340
	Total	3.13	2.06	3.09	4.63	6.90	–	–	–	–
1 high	0						47 448			88 868
	1	2.73	1.80	2.69	4.02	5.98	1 660 680	1 452 231	203 280	444 340
	2	5.31	3.52	5.24	7.78	11.46	1 344 360	1 628 259	1 694 000	635 748
	3	8.05	5.37	7.96	11.72	17.08	2 024 448	2 215 019	1 258 400	792 976
	4	14.46	9.76	14.30	20.70	29.43	142 344	278 711	212 960	485 356
Total	6.80	4.51	6.72	9.96	14.64	–	–	–	–	
2 high	0	14.86	10.04	14.70	21.25	30.17	616 824	557 422	183 920	499 028
	1	13.82	9.31	13.66	19.81	28.24	1 518 336	1 642 928	735 680	1 011 728
	2	10.87	7.28	10.74	15.70	22.65	1 834 656	1 349 548	938 960	909 188
	3	9.60	6.42	9.49	13.92	20.17	237 240	396 063	542 080	88 868
	Total	11.72	7.84	11.59	16.96	24.44	–	–	–	–
3 high	0	16.45	11.14	16.27	23.42	33.04	427 032	542 753	232 320	88 868
	1	20.40	13.93	20.18	28.74	39.90	680 088	836 133	445 280	321 292
	2	16.61	11.25	16.43	23.64	33.33	126 528	161 359	416 240	102 540
	Total	18.83	12.80	18.62	26.71	37.43	–	–	–	–
4 high	0 or 1	27.97	19.40	27.68	38.57	51.92	0	176 028	348 480	143 556
Total	–	–	–	–	–	–	–	–	–	

* CHD = coronary heart disease.

† Age-adjusted to Third National Health and Nutrition Examination Survey midpoints in each age group (40 y, 50 y, 60 y, and 70 y).

‡ Based on applying age-specific prevalence in the Third National Health and Nutrition Examination Survey (4 age groups: 35–44 y, 45–54 y, 55–64 y, 65–74 y) to age distribution of the white non-Hispanic population in 2001 (based on post-census updates to the 2000 U.S. Census). Data are from reference 27.

§ Derived by multiplying the age-adjusted 10-year risk for hard CHD by the estimated white men in the United States and dividing by 100.

|| No events observed in group in Framingham Study sample or age-specific prevalence = 0.

women older than age 55 years (12.6%) would exceed the 10% threshold. The proportions of men and women at varying degrees of vascular risk in different age groups are shown in **Figure 1**.

Projected Burden of Hard CHD Events due to Elevated Risk Factors

We estimated that over a 10-year period, nearly 4.72 million white men and 1.09 million white women in the United States would experience a first hard CHD event (**Tables 3 and 4**). The numbers of estimated hard CHD events by sex, in different age groups, and according to borderline and elevated risk factors are displayed in **Tables 3 and 4**. During 10 years of follow-up, about 56% of CHD events in men and 70% of events in women will occur in those older than age 55 years at baseline; 29.5% of events in men and 39.6% of events in women will occur in those older than age 65 years at baseline. Of note, a significant proportion of events will occur in younger age groups. In men, 17% of events will occur in the next 10 years in those 35 to 44 years of age at baseline and 26.7% of events will occur in those 45 to 54 years of age at baseline. Corresponding figures in women are 9.7% and 20.5%, respectively.

More than 90% of CHD events will occur in persons with 1 or more elevated risk factors. About 8% of hard CHD events will occur in people with multiple borderline risk factors but without a single elevated value (**Figure 2**).

More than 25% of CHD events will occur in persons with only a single elevated CHD risk factor, and more than two thirds will occur in people with 1 or 2 elevated risk factors. The contribution of multiple borderline risk factors was marginally higher in the younger age groups, in part because of a greater prevalence (**Figure 2**).

DISCUSSION

Our principal findings are 5-fold. First, an optimal CHD risk profile is rare among U.S. adults. Consistent with other reports (1, 3, 4), we noted very few CHD events in the small group of men and women with an optimal risk factor profile. Second, about half of the men and 5% of women between the ages of 35 and 74 years would be categorized as having high global risk according to the 10% absolute event rate threshold for hard CHD events. Third, despite a high prevalence in the United States, borderline CHD risk factors alone contributed to only about one tenth of hard CHD events across the different age groups in both sexes. Fourth, as reported by others (1, 3, 4), most CHD event rates were noted in persons with 1 or more elevated CHD risk factors. Borderline risk factors contributed incrementally to CHD risk in the presence of other elevated risk factors, a finding that was more consistent in women than in men. Fifth, nearly

Table 3—Continued

Absolute Hard CHD Events among White Men in 10 Years§				
35–44 y	45–54 y	55–64 y	65–74 y	
36 013	24 556	44 370	18 785	
34 362	42 916	46 801	38 500	
30 025	34 604	19 963	33 148	
100 400	102 076	111 134	90 433	
29 892	39 065	8 172	26 572	
47 321	85 321	131 793	72 857	
108 713	176 316	147 484	135 440	
13 893	39 856	44 083	142 840	
199 819	340 557	331 532	377 709	
61 929	81 941	39 083	150 557	
141 357	224 424	145 738	285 712	
133 563	144 941	147 417	205 931	
15 231	37 586	75 458	17 925	
352 080	488 893	407 695	660 124	
47 571	88 306	54 409	29 362	
94 736	168 732	127 973	128 196	
14 234	26 511	98 399	34 177	
156 542	283 549	280 782	191 734	
0	48 725	134 409	74 534	
808 841	1 263 799	1 265 553	1 394 535	

one sixth of hard CHD events in men occur prematurely, that is, before age 55 years.

There are several reasons why borderline risk factors accounted for a smaller proportion of hard CHD events in our study than had formerly been reported. First, with the sequential lowering of thresholds defining elevated risk factors in national guidelines, what was considered average a decade ago has been reclassified as elevated today. Second, the actual contribution of borderline risk factors may be greater than observed in our study because of measurement error (regression dilution bias). A third explanation is that our analyses did not consider duration of exposure to risk factor levels because we focused on 10-year risks for CHD. It is conceivable that long-term exposure to borderline risk factors may be associated with higher risk over a longer period of follow-up. Current guidelines (7) recommend considering both short- and long-term risk for CHD associated with risk factors.

Strengths and Limitations

Several strengths of our investigation merit comment. Our CHD event rates were derived from a large community-based sample that was under continuous longitudinal surveillance for CHD events defined using standardized criteria. We estimated the prevalence of risk factor levels within age strata by using a sample representative of the U.S. adult population. However, our approach also has

Table 4. Rates of Hard CHD Events and Absolute Numbers of Events according to Risk Factor Groups in Women*

Risk Factor Group	Borderline Risk Factors, n	Age-Adjusted 10-Year Risk for Hard CHD, %†				Estimated White Women in the United States, n‡				Absolute Hard CHD Events among White Women in 10 Years§				
		All Ages	35–44 y	45–54 y	55–64 y	65–74 y	35–44 y	45–54 y	55–64 y	65–74 y	35–44 y	45–54 y	55–64 y	65–74 y
All optimal	0						1 407 624	542 753	29 040	27 344				
Only borderline	1						2 404 032	1 525 576	706 640	307 620				
	2	0.24	0.13	0.22	0.36	0.59	3 938 184	2 655 089	1 481 040	731 452	5120	5841	5332	4316
	3						1 787 208	1 818 956	851 840	444 340	0	0	0	0
	4 or 5	1.95	1.11	1.81	2.97	4.83	616 824	660 105	842 160	471 684	6847	11 948	25 012	22 782
	Total	0.26	0.15	0.25	0.39	0.62	–	–	–	–	11 967	17 789	30 344	27 098
1 high	0						300 504	381 394	116 160	170 900				
	1	1.39	0.78	1.29	2.11	3.44	1 138 752	1 584 252	1 239 040	587 896	8882	20 437	26 144	20 224
	2	1.28	0.73	1.19	1.95	3.19	1 391 808	1 686 935	1 452 000	881 844	10 160	20 075	28 314	28 131
	3	4.15	2.36	3.86	6.27	10.10	727 536	880 140	638 880	622 076	17 170	33 973	40 058	62 830
	4						63 264	278 711	164 560	184 572				
Total	1.77	1.05	1.66	2.61	4.12	–	–	–	–	36 212	74 485	94 516	111 184	
2 high	0	1.76	1.00	1.63	2.67	4.35	411 216	88 014	174 240	416 996	4112	1435	4652	18 139
	1	3.57	2.03	3.32	5.40	8.73	869 880	1 320 210	542 080	854 500	17 659	43 831	29 272	74 598
	2	6.44	3.69	6.00	9.67	15.40	490 296	997 492	696 960	635 748	18 092	59 850	67 396	97 905
	3	4.01	2.29	3.73	6.06	9.77			125 840	61 524			7626	6011
	Total	4.42	2.62	4.13	6.48	10.09	–	–	–	–	39 863	105 115	108 946	196 653
3 high	0	7.72	4.43	7.19	11.54	18.27	142 344	102 683	77 440	88 868	6306	7383	8937	16 236
	1	7.96	4.58	7.41	11.90	18.81	79 080	58 676	358 160	246 096	3622	4348	42 621	46 291
	2	4.01	9.74	15.50	24.20	36.60	79 080	88 014	145 200	68 360	7702	13 642	35 138	25 020
	Total	8.86	5.31	8.29	12.84	19.60	–	–	–	–	17 630	25 373	86 696	87 547
4 high	0/1	11.39	6.60	10.61	16.86	26.18			48 400	34 180			8160	8948
Total	–	–	–	–	–	–	–	–	–	105 672	222 762	328 662	431 430	

* CHD = coronary heart disease.
 † Age-adjusted to Third National Health and Nutrition Examination Survey midpoints in each age group (40 y, 50 y, 60 y, and 70 y).
 ‡ Based on applying age-specific prevalence in the Third National Health and Nutrition Examination Survey (4 age groups: 35–44 y, 45–54 y, 55–64 y, 65–74 y) to age distribution of white non-Hispanic population in 2001 (based on post-census updates to the 2000 U.S. Census). Data are from reference 27.
 § Derived by multiplying the age-adjusted 10-year risk for hard CHD by the estimated white women in the United States and dividing by 100.
 || No events observed in group in Framingham Study sample or age-specific prevalence = 0.

some limitations. We chose to estimate absolute CHD risk using categories of risk factors (optimal, borderline, and high) that were consistent with national guidelines. We acknowledge that the definition of what constitutes optimal or borderline may itself vary according to global CHD risk. Definitions of categories of smoking varied between the Framingham Study and NHANES III samples. On a similar note, the assessment of hypertension status was probably aided by the periodic nature of examination visits in the Framingham Study sample. This may account in part for the higher prevalence in this sample compared with the sample from NHANES III. We noted earlier that our statistical modeling had an inherent limitation that weighted the hazards associated with corresponding categories of the various risk factors equally for the sake of simplicity. This may not be appropriate for diabetes mellitus, which guidelines recommend treating as equivalent to having established CHD (global risk of $\geq 20\%$) (7). It is important to note that our use of 10-year absolute event rates may have resulted in an underestimation of the contributions of risk factors over longer periods (31). Also, our use of the outcome of hard CHD events and restriction of participants to those younger than 75 years of age may have caused us to underestimate the contribution of CHD risk factors in women. Women more frequently experience angina as a manifestation of CHD and develop CHD manifestations 10 to 15 years later than men. It is also important to note that the lifetime risk for CHD remains high, at about 1 in 3 for women, only slightly lower than the lifetime estimate of 1 in 2 for men (32). Furthermore,

we did not evaluate regression models with risk factors modeled as time-varying covariates; such models would better characterize risk associations over time by accounting for the changing levels of risk factors. Although we reported on CHD burden in white persons, similar methods can be used to determine estimates in other ethnic groups.

Public Health Implications

The quantitative estimates of the fractions of events arising from risk factor combinations are valuable data for the economic appraisal of alternative health policy strategies, such as the potential benefits of health interventions. For example, it can be argued on the basis of our data that using a “polypill” for all individuals older than age 55 years (14) may be inappropriate for several reasons, at least in the United States. First, about one sixth of the CHD events in men and one tenth of the CHD events in women occurred before age 55 years and would not be prevented by a polypill. Second, for women, the 10-year absolute CHD event rates do not cross the 10% threshold regarded as high, even when 2 CHD risk factors are elevated (29). The polypill intervention strategy (14) may merit investigation for men older than age 55 years, in whom absolute CHD rates may exceed the 10% threshold with a single elevated risk factor.

Our data indicate that isolated borderline risk factors, without elevated risk factors, account for only about one tenth of the burden of hard CHD events. Given that control of elevated blood pressure and lipid levels is suboptimal in the United States (19, 33), a focus on lowering

Figure 1. Estimated numbers of U.S. individuals at risk for hard coronary heart disease events, according to estimated 10-year absolute risk.

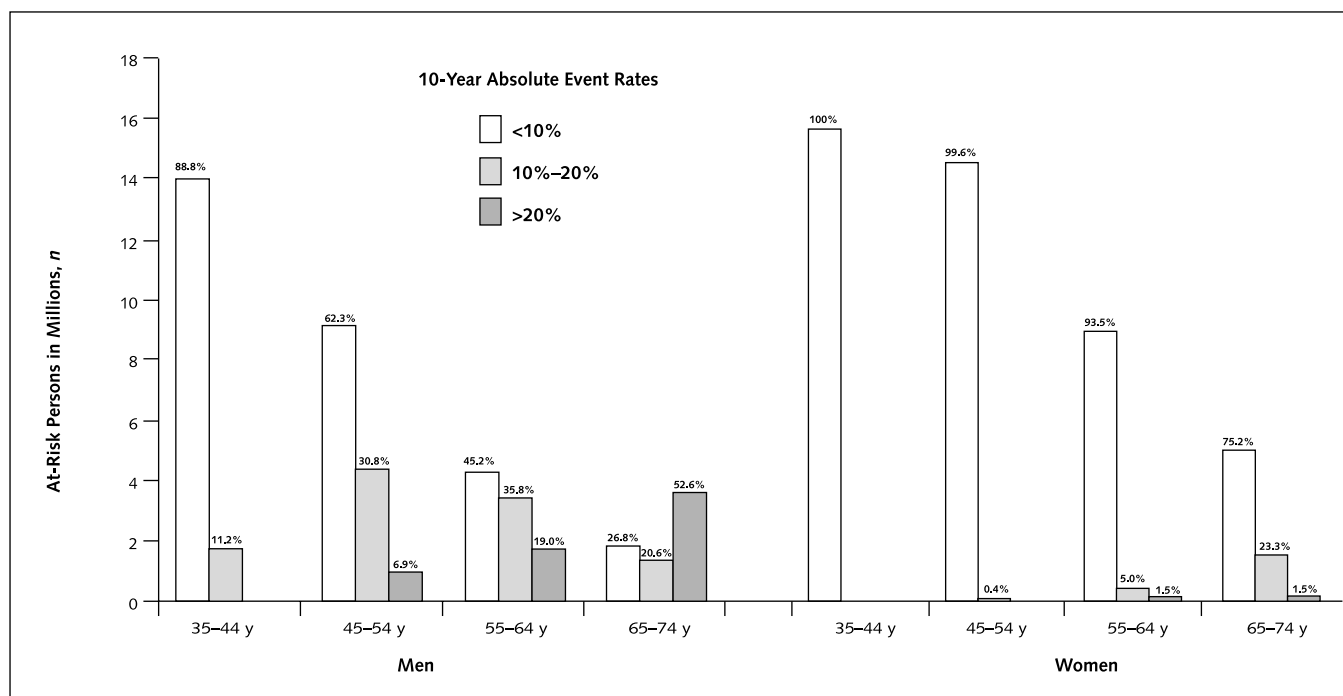
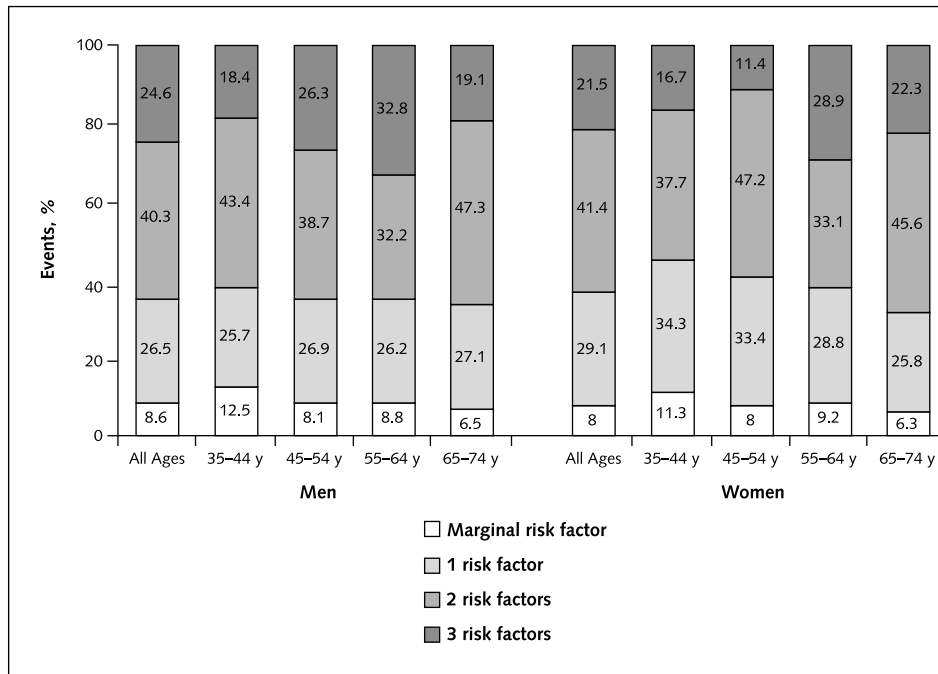


Figure 2. Estimated proportion of hard coronary heart disease (CHD) events according to numbers of borderline and elevated risk factors for all ages pooled and within age groups for men and women.



Prevalence of risk factors was as follows in men: borderline risk factors, 25.5%; 1 risk factor, 34.7%; 2 risk factors, 28.2%; ≥ 3 risk factors, 11.8%. Prevalence of risk factors was as follows in women: borderline risk factors, 41.3%; 1 risk factor, 31.1%; 2 risk factors, 17.6%; ≥ 3 risk factors, 5.8%.

borderline levels of these risk factors by pharmacologic means would seem misplaced in persons without previous CHD events. Nonpharmacologic measures to reduce borderline levels of risk factors may be more appropriate. Periodic monitoring of individuals with borderline levels of risk factors is also important because of the greater probability of further increases in risk factor levels on follow-up.

Although clinical trial data indicate that lowering borderline levels of risk factors can improve outcome, we must consider the number needed to treat for benefit (NNT_B) to prevent an outcome before advocating pharmacologic treatment. This figure is determined not only by the relative risk reduction but also by the absolute event rates observed. Thus, the 5-year NNT_B for treatments that can reduce risk by 25% varies from 80 to 160 if the global risk (absolute CHD event rate) is between 10% and 5%. Even if a treatment reduces risk dramatically, for example, by 80% (as claimed for the polypill), the 5-year NNT_B for men with only borderline risk factors (10-year absolute event rate $\leq 7.5\%$) would be 33 or higher. In women with only borderline risk factors (absolute event rate $\leq 5\%$), the 5-year NNT_B for the polypill would be 50 or higher, assuming an 80% efficacy.

Overall, our data support the current practice of assessing CHD risk by measuring several risk factors and using an appropriately calibrated risk prediction algorithm to guide interventions (6, 28). Our data are also consistent with current national guidelines noting that absolute CHD event rates are lower than 10% in individuals with 0 to 1

risk factor (7). The observation that one sixth of the CHD events in men and one tenth of the CHD events in women occurred before age 55 years should promote efforts to successfully identify the presence of elevated major risk factors before middle age and to intervene appropriately.

Our data indicate that about two thirds of men and one third of women 35 to 44 years of age have an elevated modifiable risk factor that could be targeted for intervention. Determining the effectiveness of nonpersonal health interventions (34) and therapeutic lifestyle changes (7) would be important complementary steps. The markedly low prevalence of optimal risk factors in the United States and the national trend toward a decrease in the proportion of adults with optimal risk factor profiles (35) should strengthen primary prevention efforts (36).

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APPENDIX

We estimated sex-specific Cox proportional hazards regression functions that related the various risk factor combinations to the incidence of a first hard CHD event in the Framingham Study sample. To illustrate the procedure for estimating age-adjusted rates of CHD, the model for men is given in **Appendix Table 1**. Age was modeled as a continuous variable; models with a squared term for age were also estimated to evaluate for non-linearity of age effects, but the age square term was not significant.

Using the β -coefficients, the means of the risk factors, and the average 10-year survival estimate, denoted as $S(10)$, the 10-year probability of developing a hard CHD event can be estimated as follows:

$$\text{Hard CHD Risk Estimate} = 1 - S(t)^{\exp(\Sigma\beta X - \Sigma\beta\bar{X})} \quad (1)$$

where $S(t)$ is the average survival at time t (for example, $t = 10$ years), $\Sigma\beta X$ is the sum of the product of the β -coefficients and the values of individual risk factors and $\Sigma\beta\bar{X}$ the sum of the product of the β -coefficients and the means of the risk factors.

The sum of the products of the β -coefficients and the means of the risk factors are computed as follows:

$$\begin{aligned} \Sigma\beta\bar{X} &= 0.041 \times (50.24) - 10.837 \times (0.002) - 10.996 \\ &\times (0.013) - 0.025 \times (0.049) + 0.061 \times (0.067) - 11.172 \\ &\times (0.004) - 0.168 \times (0.045) + 0.511 \times (0.136) + 0.943 \\ &\times (0.147) + 1.564 \times (0.023) + 1.593 \times (0.011) + 1.514 \\ &\times (0.093) + 1.258 \times (0.152) + 1.127 \times (0.037) + 1.704 \\ &\times (0.023) + 1.943 \times (0.074) + 1.714 \times (0.027) + 2.306 \\ &\times (0.021) = 2.759 \end{aligned} \quad (2)$$

To estimate age-adjusted 10-year risk for hard CHD for each category of risk (that is, for each combination of risk factors), we used the first equation in this appendix and substituted the mean age for the age group under consideration (for example, 50 years for the category of 45 to 54 years), a 1 for the specific risk factor category, and 0 for all others. For example, for men 45 to 54 years of age with 1 high risk factor and 2 marginal risk factors, we estimated the 10-year risk as follows:

$$\Sigma\beta\bar{X} = 0.041 \times (50) + 0.511 \times (1) = 2.561 \quad (3)$$

Hard CHD Risk Estimate =

$$\begin{aligned} 1 - S(t)^{\exp(\Sigma\beta X - \Sigma\beta\bar{X})} &= 1 - 0.937^{\exp(2.561 - 2.759)} = \\ &= 1 - 0.948 = 0.052 \end{aligned} \quad (4)$$

Note that in **Table 3**, we estimated that the 10-year CHD rate for men age 45 to 54 years with 1 high risk factor and 2 marginal risk factors would be 5.24%. The difference is due to rounding.

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Appendix Table 1. Cox Model for Men*

Risk Factor Group	Borderline Risk Factors, <i>n</i>	β -Coefficient	Proportion of Events in Risk Factor Category
All optimal	0	-10.837	0.002
Only borderline	1	-10.996	0.013
	2	-0.025	0.049
	3	Referent group†	0.077
	4 or 5	0.061	0.067
1 high	0	-11.172	0.004
	1	-0.168	0.045
	2	0.511	0.136
	3	0.943	0.147
	4	1.564	0.023
2 high	0	1.593	0.011
	1	1.514	0.093
	2	1.258	0.152
	3	1.127	0.037
3 high	0	1.704	0.023
	1	1.943	0.074
	2	1.714	0.027
4 high	0 or 1	2.306	0.021
S(10) = 0.937‡			

* For age, the β -coefficient was 0.041 and the mean was 50.24 years.

† Chosen as the referent because of adequate numbers in the cell.

‡ S(10) = survival until 10 years.

Appendix Table 2. Distribution of Risk Factor Combinations in the Framingham Study and the Third National Health and Nutrition Examination Survey*

Risk Factor Group	Borderline Risk Factors, <i>n</i>	Prevalence in the Framingham Study Sample (95% CI), %†		Prevalence in the NHANES III Sample, %‡	
		Men	Women	Men	Women
All optimal	0	0.2 (0.1-0.4)	1.4 (1.0-1.7)	0.03	4.3
Only borderline	1	1.3 (0.9-1.6)	6.5 (5.8-7.3)	2.1	9.8
	2	4.9 (4.2-5.6)	11.9 (10.9-12.9)	7.7	17.2
	3	7.7 (6.8-8.6)	9.6 (8.7-10.5)	9.0	9.0
	4 or 5	6.7 (5.8-7.5)	2.4 (1.9-2.9)	6.6	5.2
	Total	20.6 (19.4-22.1)	30.4 (28.9-31.8)	25.4	41.2
1 high	0	0.4 (0.2-0.6)	2.5 (2.1-3.0)	0.3	2.1
	1	4.5 (3.8-5.2)	11.1 (10.2-12.1)	8.0	10.2
	2	13.5 (12.4-14.7)	16.5 (15.3-17.6)	11.0	12.1
	3	14.7 (13.5-15.9)	7.1 (6.3-7.9)	13.1	5.8
	4	2.3 (1.8-2.8)	0.7 (0.4-0.9)	2.2	0.9
	Total	35.4 (23.8-27.0)	37.9 (36.4-39.5)	34.6	31.1
2 high	0	1.1 (0.8-1.5)	2.4 (1.9-2.8)	3.2	2.8
	1	9.3 (8.3-10.3)	11.1 (10.1-12.0)	9.8	7.7
	2	15.2 (14.0-16.4)	8.0 (7.1-8.8)	11.4	6.0
	3	3.7 (3.1-4.3)	1.0 (0.7-1.3)	3.8	1.1
	Total	29.3 (27.8-30.9)	22.5 (21.1-23.7)	28.2	17.6
3 high	0	2.3 (1.8-2.8)	1.7 (1.3-2.1)	2.4	1.6
	1	7.4 (6.5-8.2)	4.1 (3.5-4.7)	5.2	3.0
	2	2.7 (2.1-3.2)	0.6 (0.4-0.8)	2.4	0.5
	Total	12.4 (11.3-13.5)	6.4 (5.7-7.2)	10.0	5.1
4 high	0 or 1	2.1 (1.6-2.6)	1.4 (1.1-1.8)	1.8	0.7

* NHANES III = Third National Health and Nutrition Examination Survey.

† Age-adjusted to NHANES III sex-specific mean ages (men, 50.3 y; women, 51.5 y).

‡ NHANES III includes several million men and women when weights are applied, so the 95% CIs around the estimates for NHANES III do not differ greatly from the estimates.

Appendix Table 3. Rates of Hard Coronary Heart Disease Events according to Risk Factor Groups*

Risk Factor Group	Borderline Risk Factors, <i>n</i>	Age-Adjusted 10-Year Risk for Hard CHD (95% CI), %†				
		Men				
		All Ages	35–44 y	45–54 y	55–64 y	65–74 y
All optimal	0	‡	‡	‡	‡	‡
Only borderline	1	‡	‡	‡	‡	‡
	2	3.14 (0.1–5.9)	2.07 (0.1–4.0)	3.10 (0.5–5.3)	4.63 (1.5–7.8)	6.87 (2.1–11.7)
	3	3.22 (0.1–6.2)	2.13 (0.1–3.7)	3.18 (0.1–6.0)	4.74 (0.2–8.9)	7.04 (0.2–13.3)
	4 or 5	3.42 (1.1–5.8)	2.26 (0.1–3.8)	3.37 (1.0–5.6)	5.03 (1.6–8.2)	7.46 (2.3–12.4)
	Total	3.13 (1.8–4.3)	2.06 (1.1–3.0)	3.09 (1.7–4.4)	4.63 (2.6–6.7)	6.90 (3.7–10.1)
1 high	0	‡	‡	‡	‡	‡
	1	2.73 (0.1–5.4)	1.80 (0.1–3.5)	2.69 (0.1–5.2)	4.02 (0.1–7.7)	5.98 (0.2–11.6)
	2	5.31 (3.2–7.4)	3.52 (2.0–4.9)	5.24 (3.1–7.2)	7.78 (4.6–10.6)	11.46 (6.6–15.9)
	3	8.05 (5.7–10.4)	5.37 (3.5–7.0)	7.96 (5.5–10.1)	11.72 (8.2–14.8)	17.08 (11.5–22.0)
	Total	6.80 (5.6–8.0)	4.51 (3.3–5.7)	6.72 (5.3–8.2)	9.96 (7.8–12.2)	14.64 (10.8–18.5)
2 high	0	14.86 (3.8–25.9)	10.04 (2.0–17.5)	14.70 (3.7–25.2)	21.25 (6.0–35.8)	30.17 (9.4–50.0)
	1	13.82 (9.9–17.7)	9.31 (6.2–12.0)	13.66 (9.6–17.2)	19.81 (14.1–24.8)	28.24 (19.6–35.9)
	2	10.87 (8.2–13.5)	7.28 (5.0–9.3)	10.74 (7.9–13.1)	15.70 (11.8–19.0)	22.65 (16.5–28.0)
	3	9.60 (4.6–14.6)	6.42 (2.9–9.7)	9.49 (4.5–14.2)	13.92 (6.6–20.7)	20.17 (9.5–30.0)
	Total	11.72 (9.6–12.7)	7.84 (6.0–9.7)	11.59 (9.5–13.7)	16.96 (14.0–19.9)	24.44 (19.2–29.7)
3 high	0	16.45 (8.2–24.7)	11.14 (5.1–16.8)	16.27 (8.0–24.0)	23.42 (11.9–34.1)	33.04 (17.2–47.8)
	1	20.40 (15.5–25.3)	13.93 (9.7–17.7)	20.18 (15.0–24.7)	28.74 (21.8–34.7)	39.90 (30.0–48.7)
	2	16.61 (9.5–23.7)	11.25 (5.8–16.2)	16.43 (9.2–23.0)	23.64 (13.7–32.7)	33.33 (19.6–45.9)
	Total	18.83 (14.8–21.9)	12.80 (9.5–16.0)	18.62 (14.9–22.4)	26.71 (21.6–31.8)	37.43 (29.4–45.5)
4 high	0/1	27.97 (17.9–38.0)	19.40 (11.4–27.2)	27.68 (17.7–37.6)	38.57 (25.9–51.4)	51.92 (36.2–68.0)

* CHD = coronary heart disease.

† Age-adjusted to Third National Health and Nutrition Examination Survey midpoints in each age group (40 y, 50 y, 60 y, and 70 y).

‡ No events observed in group in Framingham Study sample or age-specific prevalence = 0.

Appendix Table 3—Continued

Age-Adjusted 10-Year Risk for Hard CHD (95% CI), %†				
Women				
All Ages	35–44 y	45–54 y	55–64 y	65–74 y
‡	‡	‡	‡	‡
‡	‡	‡	‡	‡
0.24 (0–0.7)	0.13 (0–0.4)	0.22 (0–0.6)	0.36 (0–1.0)	0.59 (0–0.2)
‡	‡	‡	‡	‡
1.95 (0–4.6)	1.11 (0–2.6)	1.81 (0–4.2)	2.97 (0–6.8)	4.83 (0–11.2)
0.26 (0–0.4)	0.15 (0–0.33)	0.25 (0–0.52)	0.39 (0–0.83)	0.62 (0–1.3)
‡	‡	‡	‡	‡
1.39 (0.4–2.4)	0.78 (0.2–1.3)	1.29 (0–4.2)	2.11 (0.6–3.5)	3.44 (0.9–5.8)
1.28 (0.5–2.1)	0.73 (0.2–1.2)	1.19 (0.4–2.1)	1.95 (0.8–3.0)	3.19 (1.1–5.1)
4.15 (1.9–6.4)	2.36 (0.1–3.7)	3.86 (1.7–5.8)	6.27 (2.9–9.3)	10.10 (4.3–15.4)
‡	‡	‡	‡	‡
1.77 (1.8–2.2)	1.05 (0.5–1.5)	1.66 (1.0–2.3)	2.61 (1.7–3.6)	4.12 (2.4–5.9)
1.76 (0–3.8)	1.00 (0–2.1)	1.63 (0.5–1.9)	2.67 (0–5.5)	4.35 (0–9.0)
3.57 (2.0–5.1)	2.03 (0.1–3.1)	3.32 (1.8–4.7)	5.40 (3.2–7.3)	8.73 (4.9–12.1)
6.44 (3.9–9.0)	3.69 (0.2–5.4)	6.00 (3.5–8.2)	9.67 (6.0–12.9)	15.40 (8.9–21.2)
4.01 (0–9.5)	2.29 (0–5.4)	3.73 (0–8.6)	6.06 (0–13.9)	9.77 (0–22.4)
4.42 (3.1–5.3)	2.62 (1.5–3.8)	4.13 (2.8–5.5)	6.48 (4.7–8.2)	10.09 (6.8–13.4)
7.72 (2.1–13.3)	4.43 (0.1–7.8)	7.19 (1.8–12.2)	11.54 (3.3–19.2)	18.27 (5.4–30.4)
7.96 (4.3–11.6)	4.58 (1.9–7.0)	7.41 (3.8–10.7)	11.90 (6.7–16.6)	18.81 (10.3–26.5)
16.60 (3.2–30.0)	9.74 (1.2–17.9)	15.50 (2.8–27.5)	24.20 (5.4–42.0)	36.60 (9.5–62.3)
8.86 (4.3–11.6)	5.31 (2.7–7.9)	8.29 (5.1–11.4)	12.84 (8.5–17.2)	19.60 (12.3–26.9)
11.39 (4.1–18.7)	6.60 (1.9–12.3)	10.61 (3.9–18.2)	16.86 (6.7–27.1)	26.18 (10.4–40.6)