Low Risk-Factor Profile and Long-term Cardiovascular and Noncardiovascular Mortality and Life Expectancy

Findings for 5 Large Cohorts of Young Adult and Middle-Aged Men and Women

Jeremiah Stamler, MD
Rose Stamler, MA†
James D. Neaton, PhD
Deborah Wentworth, MA
Martha L. Daviglus, MD, PhD
Dan Garside, MA
Alan R. Dyer, PhD
Kiang Liu, PhD
Philip Greenland, MD

Context Three major coronary risk factors—serum cholesterol level, blood pressure, and smoking—increase incidence of coronary heart disease (CHD) and related end points. In previous investigations, risks for low-risk reference groups were estimated statistically because samples contained too few such people to measure risk.

Objective To measure long-term mortality rates for individuals with favorable levels for all 3 major risk factors, compared with others.

Design Two prospective studies, involving 5 cohorts based on age and sex, that enrolled persons with a range of risk factors. Low risk was defined as serum cholesterol level less than 5.17 mmol/L (<200 mg/dL), blood pressure less than or equal to120/80 mm Hg, and no current cigarette smoking. All persons with a history of diabetes, myocardial infarction (MI), or, in 3 of 5 cohorts, electrocardiogram (ECG) abnormalities, were excluded.

Setting and Participants In 18 US cities, a total of 72 144 men aged 35 through 39 years and 270 671 men aged 40 through 57 years screened (1973-1975) for the Multiple Risk Factor Intervention Trial (MRFIT); in Chicago, a total of 10 025 men aged 18 through 39 years, 7490 men aged 40 through 59 years, and 6229 women aged 40 through 59 years screened (1967-1973) for the Chicago Heart Association Detection Project in Industry (CHA) (N = 366 559).

Main Outcome Measures Cause-specific mortality during 16 (MRFIT) and 22 (CHA) years, relative risks (RRs) of death, and estimated greater life expectancy, comparing low-risk subcohorts vs others by age strata.

Results Low-risk persons comprised only 4.8% to 9.9% of the cohorts. All 5 low-risk groups experienced significantly and markedly lower CHD and cardiovascular disease death rates than those who had elevated cholesterol level, or blood pressure, or smoked. For example, age-adjusted RRs of CHD mortality ranged from 0.08 for CHA men aged 18 to 39 years to 0.23 for CHA men aged 40 through 59 years. The age-adjusted relative risks (RRs) for all cardiovascular disease mortality ranged from 0.15 for MRFIT men aged 35 through 39 years to 0.28 for CHA men aged 40 through 59 years. The age-adjusted RR for all-cause mortality rate ranged from 0.42 for CHA men aged 40 through 59 years to 0.60 for CHA women aged 40 through 59 years. Estimated greater life expectancy for low-risk groups ranged from 5.8 years for CHA women aged 40 through 59 years to 9.5 years for CHA men aged 18 through 39 years.

Conclusions Based on these very large cohort studies, for individuals with favorable levels of cholesterol and blood pressure who do not smoke and do not have diabetes, MI, or ECG abnormalities, long-term mortality is much lower and longevity is much greater. A substantial increase in the proportion of the population at lifetime low risk could contribute decisively to ending the CHD epidemic.

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LONG-TERM, POPULATION-BASED, prospective studies have amassed extensive data on relationships of major coronary-cardiovascular risk factors—particularly serum cholesterol level, blood pressure, and cigarette smoking—with incidence of coronary heart disease (CHD), stroke, and cardiovascular disease (CVD), to mortality from these causes and all causes and longevity.[1-7] These relationships have been well summarized as " . . . strong, continuous, graded, consistent, independent, predictive, and etiologically significant for those with and without coronary heart disease."[7] The judgment on etiologic significance is based on the consistent results of many epidemiological studies and on concordant findings from clinical and postmortem investigations and animal experimentation. This judgment is reinforced by data from randomized controlled trials demonstrating that sustained lowering of high blood pres-

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Author Affiliations, Corresponding Author, and Reprint information available at the end of this article.

sure or elevated serum cholesterol level produces sizable reductions in CHD-CVD incidence and in cause-specific and all-cause mortality.[7-14] These positive results have been obtained repeatedly, even though trials have been undertaken in middle-aged and older people after decades of exposure to these adverse traits. Extensive data also document that smoking cessation has similar favorable effects.[15,16]

Most epidemiologic research on the impact of major risk factors deals with the predictive value of higher levels of such factors. In assessments of their combined impact, risks of those with favorable status for all 3 major risk factors have been estimated statistically, for example, by extrapolation down multiple logistic smoothed curves.[3] This was necessary because in the population samples studied, numbering in the hundreds or thousands, too few people had low levels of all major risk factors—hence too few CVD events—to permit direct measurement of risk.

Large, long-term studies permit measured estimates based on actual observed mortality. In this article, we use data on 5 cohorts from 2 studies, the Multiple Risk Factor Intervention Trial (MRFIT) and the Chicago Heart Association Detection Project in Industry (CHA): 2 cohorts of young adult men, 2 cohorts of middle-aged men, and 1 cohort of middle-aged women—366 559 people all together.

METHODS

Published reports on the MRFIT and CHA cohorts detail their baseline screening methods.[5,6,17-19] We provide a summary of these here.

Multiple Risk Factor Intervention Trial

All together, 361 662 men aged 35 through 57 years were screened in 1973-1975 at 22 centers in 18 US cities for recruitment for MRFIT. The 342 815 men with complete baseline risk factor data are the focus here, stratified into 2 cohorts: those aged 35 through 39 years (n = 72 144) and 40 through 57 years (n = 270 671). Trial eligibility was based on a man's major risk factor profile; therefore, initial screening included measurements only of blood pressure and serum cholesterol level; current smoking (by questionnaire), including number of cigarettes per day; and conditions for exclusion, ie, drug treatment for diabetes and previous hospitalization for myocardial infarction (MI). Blood pressure was measured according to a standardized protocol by trained certified staff, using a mercury sphygmomanometer, with the man seated. Diastolic blood pressure (DBP) was measured at the fifth Korotkoff sound. Three readings per individual were taken; the average of the second and third systolic blood pressure (SBP) measurements was used for analyses. Serum total cholesterol level was determined, in 15 standardized local laboratories, by the Lieberman-Burchard color reaction and use of serum calibrators to yield values equivalent to Abell-Kendall reference values.[17-19]

Vital status of the men is ascertained periodically through the US National Death Index. Prior to 1979, Social Security Administration records were used. With a mean follow-up of 16 years, 38 265 deaths have been identified; cause of death is known for 98.9% of decedents. Underlying cause of death was coded by a nosologist using the *International Classification of Diseases, Ninth Revision* (*ICD-9*).[20]

Chicago Heart Association Detection Project in Industry

Employees of 84 Chicago-area companies and organizations, about 75 000 people, were invited to participate. The response rate was 55%. Screening was done by 2 trained and standardized 4-person field teams who collected demographic information, medical history, and medical treatment data; information on past and present smoking status; 1 measurement of height, weight, heart rate, and supine blood pressure; resting electrocardiogram (ECG); and venipuncture for blood chemistry measurements. Serum total cholesterol level was determined by the Levine and Zak method.[6,17] The criteria of the Pooling Project[3] were used to code ECG abnormalities. Three cohorts are the focus here: men aged 18 through 39 years, men aged 40 through 59 years, and women aged 40 through 59 years.

Methods of follow-up to ascertain vital status include local procedures and use of Social Security Administration and National Death Index records. With a mean follow-up of 22 years, vital status has been determined for more than 99% of the cohorts. For each decedent, underlying cause of death was coded by a trained staff professional, using the *International Classification of Diseases, Eighth Revision* (*ICD-8*).[21]

Low-Risk Criteria

Criteria for defining a person as low risk were all of the following at baseline: serum cholesterol level less than 5.17 mmol/L (<200 mg/dL), SBP/DBP of 120/80 mm Hg or lower; not a current smoker; no history of diabetes or MI; and, for the 3 CHA cohorts, no ECG abnormalities.

Deaths from all CHDs were defined for MRFIT cohorts as *ICD-9* codes 410 through 414 and 429.9, for CHA cohorts as *ICD-8* codes 410 through 414; MI, code 410; stroke, codes 430 through 438; all CVD, codes 390 through 459; all cancers, codes 140 through 209; violence, for MRFIT cohorts *ICD-9* codes 800 through 999, for CHA cohorts *ICD-8* codes E800 through E999 exclusive of codes E930 through E936. Coders were blinded to baseline data.

Statistical Methods

To focus on risk for persons with favorable levels of serum cholesterol, blood pressure, and no tobacco use (all 3 combined), compared with persons with adverse levels of 1 or more of these, persons with histories of diabetes or MI were excluded (all 5 cohorts), as were persons with ECG abnormalities (the 3 CHA cohorts). Mortality rates for low-risk and other persons were age-adjusted by the direct method to the age distribution of all persons in an age stratum. Cox proportional hazards regression was used to calculate age-adjusted relative risks (RRs) and their 95% confidence intervals (CIs) for low-risk compared with other persons.

Cox multivariate proportional hazards regression was used to calculate coefficients for the relation of baseline major risk factors to all-cause mortality for each cohort. Coefficients were used to estimate number of years of greater life expectancy for each low-risk subcohort compared with other persons of the same cohort.[17] Thus, the coefficient for the relationship of SBP to all-cause mortality in the Cox multivariate analyses for CHA men aged 18 through 39 years is 0.0116. Average SBP for the 942 low-risk men was 116.0 mm Hg; for the 9083 other men, 136.0 mm Hg; by exponentiation, estimated RR of death is $e^{-0.0116\times20} = e^{-0.232} = 0.793$. To estimate impact of this lower SBP on life expectancy, we used the concomitant Cox coefficient for the relationship of age to all-cause mortality, 0.0703. The product for SBP exponentiation, $0.0116 \times 20 = 0.232$, is also obtained when the coefficient for age, 0.0703, is multiplied by 3.3, which indicates that SBP of 116 mm Hg vs 136 mm Hg is equivalent to being, on average, 3.3 years younger: eg, age 26.7 years rather than age 30 years. From US life tables,[22] male expectation of life at age 30 years is 44.1 years; at age 26.7 years, 47.2 years: ie, 3.1 years estimated greater life expectancy is attributable to SBP 116 mm Hg vs SBP 136 mm Hg. Similar calculations yield data on impact on life expectancy of favorable status of the low-risk subcohort for serum cholesterol level and smoking compared with the other subcohort. These 3 estimates are summed to give the overall estimate presented here.

RESULTS

Baseline Findings: Low-Risk Subcohorts vs Others

The proportion of persons meeting low-risk criteria was small: for young adult men, 9.9% (MRFIT) and 9.4% (CHA); for middle-aged men, 6.0% (MRFIT) and 4.8% (CHA); and for middle-aged women, 6.8% (CHA) (TABLES 1 and 2). In accordance with low-risk criteria, average blood pressure and serum cholesterol levels were much lower for low-risk subcohorts compared with other persons. Body mass index was lower for CHA low-risk subcohorts compared with others (Table 2).

Table 1. Baseline Descriptive Statistics: MRFIT Low-Risk Subcohorts and Other Men Aged 35-39 and 40-57 Years*

Variable	Age 35-39 y		Age 40-57 y	
	Low-Risk Subcohort	Others	Low-Risk Subcohort	Others
No.	7163	64 981	16 302	254 369
Age, y†	36.9 (1.4)	37.0 (1.4)	47.2 (5.0)	48.3 (5.0)
Systolic BP, mm Hg†	112.5 (5.9)	128.0 (13.0)	112.3 (6.1)	132.0 (16.0)
Diastolic BP, mm Hg†	72.5 (5.8)	82.7 (10.0)	73.0 (5.5)	85.0 (10.4)
Serum cholesterol†				
mmol/L	4.44 (0.49)	5.42 (1.00)	4.54 (0.46)	5.66 (1.00)
mg/dL	171.8 (19.0)	209.5 (38.6)	175.7 (17.8)	218.9 (38.5)
Cigarette smokers, %	0.0	44.4	0.0	37.7
Cigarette/d, overall†	0.0	11.3 (15.4)	0.0	9.8 (15.0)
Cigarette/d, smokers†	0.0	25.4 (13.2)	0.0	25.9 (13.3)
Annual income, $†‡	24 635 (6472)	24 406 (6239)	25 384 (6499)	24 271 (6354)
Ethnicity, %				
White	91.1	88.2	92.7	90.4
African American	4.1	7.2	3.8	6.4
Asian	2.1	1.6	1.3	1.1
Hispanic	2.0	2.3	1.6	1.8
Other	0.9	0.8	0.6	0.4

*Low risk is defined as baseline serum cholesterol <5.17 mmol/L (<200 mg/dL), systolic BP/diastolic BP ≤120/≤80 mm Hg, nonsmoker, no history of drug treatment for diabetes, no history of hospitalization for 2 weeks or longer for myocardial infarction; other, all other men, not low risk, excluding those with history of treated diabetes or hospitalization for myocardial infarction. MRFIT indicates the Multiple Risk Factor Intervention Trial; BP, blood pressure.
†Data are mean (SD).
‡Data are based on mean income of ZIP code of residence according to 1980 US census.

Mortality by Cause, Low-Risk Subcohorts vs Others

Coronary Heart Disease. The CHD mortality rate was much lower for low-risk subcohorts than for others, by 86% to 92% for low-risk young adult men (<40 years) and 77% to 79% for low-risk middle-aged subcohorts (TABLE 3). Findings were similar for death attributed to acute MI.

For low-risk subcohorts, CHD death accounted for a much smaller proportion of all death than for others (Table 3). This finding was especially prominent for low-risk young adult men, with CHD mortality only 6% to 8% of all mortality vs 25% to 29% for others.

All CVDs. All CVD mortality was much lower for low-risk subcohorts than for others by 72% to 85% (Table 3).

Stroke, All Cancers, Violence, and All Other Mortality. There were no stroke deaths in the 2 young adult low-risk subcohorts. For the 2 middle-aged, male low-risk subcohorts, stroke mortality was lower than for others by 52% to 76%. Mortality from cancers was consistently lower for low-risk subcohorts compared with others: by 44% to 56% for the 4 male low-risk subcohorts and 17% for the female low-risk subcohort. No results significantly supported the hypothesis that low serum cholesterol level is associated with greater risk of violent death. For the 2 young adult cohorts, mortality from all other causes was similar for low-risk men and others. For the 3 middle-aged cohorts, RR was lower for low-risk groups than others by 36% to 86%(TABLE 4).

All-Cause Mortality. Mortality from all causes was consistently and markedly lower for low-risk groups vs others: by 50% to 58% for men and 40% for women (TABLE 5). Estimated greater life expectancy for low-risk subcohorts vs others ranged from 5.8 years to 9.5 years.

COMMENT

Large sample sizes and long follow-up of the 5 MRFIT and CHA cohorts en-

Table 2. Baseline Descriptive Statistics: Low-Risk Subcohorts and Other Men Aged 18-39 and 40-59 Years, Low-Risk Subcohorts and Other Women Aged 40-59 Years, CHA Study*

	Men Aged 18-39 Years		Men Aged 40-59 Years		Women Aged 40-59 Years	
Variable	Low-Risk Subcohort	Others	Low-Risk Subcohort	Others	Low-Risk Subcohort	Others
No.	942	9083	358	7132	421	5808
Age, y	28.7 (5.3)	29.7 (5.5)	47.2 (5.2)	48.4 (5.5)	46.3 (4.7)	49.5 (5.4)
BMI, kg/m^2	24.6 (3.0)	26.1 (3.7)	25.5 (3.0)	27.2 (3.5)	23.6 (3.3)	25.1 (4.4)
Systolic BP, mm Hg	116.0 (5.4)	136.0 (14.5)	115.7 (5.5)	141.1 (18.3)	114.7 (6.3)	136.3 (18.9)
Diastolic BP, mm Hg	69.8 (7.3)	78.8 (10.3)	71.9 (6.6)	83.9 (11.2)	70.2 (7.3)	80.2 (11.2)
Serum cholesterol						
mmol/L	4.28 (0.53)	4.97 (0.94)	4.54 (0.45)	5.52 (0.92)	4.55 (0.43)	5.72 (1.03)
mg/dL	165.5 (20.5)	192.0 (36.2)	175.4 (17.3)	213.4 (35.7)	175.8 (16.8)	221.1 (39.7)
Smokers, %	0.0	51.8	0.0	42.7	0.0	39.2
Cigarettes/d, overall	0.0	10.9 (13.0)	0.0	10.2 (13.9)	0.0	7.0 (10.4)
Cigarettes/d, smokers	0.0	21.1 (10.5)	0.0	23.8 (11.3)	0.0	17.7 (9.1)
Education, y	14.7 (2.5)	13.8 (2.6)	14.0 (2.7)	12.9 (2.8)	12.6 (2.4)	11.9 (2.2)
African American, %	5.9	7.9	3.9	4.8	5.9	5.4

*Low risk is defined as all of the following at baseline: serum cholesterol <5.17 mmol/L (<200 mg/dL); systolic BP ≤120 mm Hg; diastolic BP ≤80 mm Hg; not current smoker; no history of diagnosed diabetes, diagnosed myocardial infarction, or diagnosed coronary heart disease, and no codable electrocardiographic (ECG) abnormality; and other, all others, not low risk, with exclusion of persons with a history of diabetes, myocardial infarction, other coronary heart disease, or any ECG abnormality at baseline. CHA indicates Chicago Heart Association Detection Project in Industry; BMI, body mass index; and BP, blood pressure. Data are mean (SD) unless otherwise indicated.

abled measurement of actual cause-specific and all-cause mortality experience of adults assessed to be low risk at baseline. Results were consistent qualitatively and quantitatively for all 5 cohorts, young adult and middle-aged, male and female, free at baseline of a history of diabetes and MI, and of ECG abnormalities (CHA cohorts). Only a small minority (<10%) met all criteria for low risk—serum cholesterol level under 5.17 mmol/L (<200 mg/dL), SBP/DBP of 120/80 mm Hg or less, and no cigarette smoking. During long-term follow-up, low-risk subcohorts, compared with others, consistently experienced significantly and markedly lower CHD death rates by 77% to 92%, and CHD mortality was a much smaller proportion of all-cause mortality. Findings for stroke and for all CVD paralleled those for CHD. There was no evidence of significant countervailing non-CVD mortality for low-risk subcohorts; rather, their cancer mortality was consistently lower. Consequently, compared with others, all-cause mortality was markedly lower for low-risk persons (by 40% to 58%), and their estimated longevity was much greater (by 5.8 to 9.5 years).

Table 3. Mortality From Coronary Heart Disease and All Cardiovascular Diseases for Low-Risk Subcohorts and Others*

Cohort†	No.	Low-Risk Subcohort	Others	Age-Adjusted RR (95% CI), Low-Risk Subcohorts vs Others
Coronary Heart Disease Mortality‡				
MRFIT men aged 35-39 y	72 144	11 (0.2)	735 (1.5)	0.14 (0.08-0.25)
CHA men aged 18-39 y	10 025	1 (0.6)	126 (5.9)	0.08 (0.01-0.61)
MRFIT men aged 40-57 y	270 671	126 (4.4)	9578 (19.9)	0.22 (0.18-0.26)
CHA men aged 40-59 y	7490	6 (8.8)	516 (38.1)	0.23 (0.10-0.51)
CHA women aged 40-59 y	6229	2 (3.5)	181 (14.5)	0.21 (0.05-0.84)
All Cardiovascular Disease Mortality‡				
MRFIT men aged 35-39 y	72 144	16 (0.3)	1022 (2.1)	0.15 (0.09-0.24)
CHA men aged 18-39 y	10 025	3 (1.4)	163 (7.7)	0.20 (0.06-0.62)
MRFIT men aged 40-57 y	270 671	190 (6.7)	13 247 (27.5)	0.24 (0.21-0.28)
CHA men aged 40-59 y	7490	10 (15.8)	714 (53.1)	0.28 (0.15-0.52)
CHA women aged 40-59 y	6229	4 (5.3)	281 (22.6)	0.27 (0.10-0.72)

*MRFIT indicates the Multiple Risk Factor Intervention Trial; CHA, Chicago Heart Association Detection Project in Industry; RR, relative risk; and CI, confidence interval. For definitions of "low risk" and "others," see footnotes to Tables 1 and 2.
†Ages are baseline ages; follow-up averaged 16 years in the MRFIT study and 22 years in the CHA study.
‡Data presented as No. of deaths (age-adjusted mortality rate per 10 000 person-years).

These findings directly confirm earlier statistical estimates of the benefits of low-risk status. For example, in the national cooperative Pooling Project, risk of a first major coronary event was estimated by multiple logistic regression to be lower by 70% for middle-aged men in the lowest quintile of risk, compared with all other men.[3] Concordantly, recent data from the Framingham Study estimate CHD risk to be considerably reduced for low-risk men and women compared with all men and women.[23] Results for the 5 MRFIT and CHA cohorts go beyond such estimates in several respects: (1) they are actual observations, not extrapolations from regression analyses; (2) they are not only for middle-aged men and women, but also young adult men; (3) they demonstrate the favorable impact of low-risk status not only on CHD incidence, but

Table 4. Mortality From Stroke, Cancer, Violence, and Other Causes for Low-Risk Subcohorts and Others*

Cohort†	No.	Low-Risk Subcohort‡	Others‡	Age-Adjusted RR (95% CI), Low-Risk Subcohorts vs Others
Stroke Mortality				
MRFIT men aged 35-39 y	72 144	0 (0.0)	86 (0.2)	. . .
CHA men aged 18-39 y	10 025	NA§	NA§	. . .
MRFIT men aged 40-57 y	270 671	15 (0.6)	1054 (2.2)	0.24 (0.14-0.40)
CHA men aged 40-59 y	7490	2 (8.3)	89 (13.5)	0.48 (0.12-1.94)
CHA women aged 40-59 y	6229	1 (1.9)	54 (9.0)	0.36 (0.05-2.58)
Cancer				
MRFIT men aged 35-39 y	72 144	36 (0.7)	758 (1.5)	0.44 (0.32-0.62)
CHA men aged 18-39 y	10 025	7 (7.9)	140 (13.7)	0.56 (0.26-1.19)
MRFIT men aged 40-57 y	270 671	393 (13.5)	11 579 (24.0)	0.56 (0.51-0.62)
CHA men aged 40-59 y	7490	16 (50.7)	653 (95.6)	0.48 (0.29-0.79)
CHA women aged 40-59 y	6229	22 (45.8)	409 (69.2)	0.83 (0.54-1.28)
Violence				
MRFIT men aged 35-39 y	72 144	45 (0.8)	394 (0.8)	1.04 (0.76-1.42)
CHA men aged 18-39 y	10 025	1 (1.2)	100 (11.5)	0.10 (0.01-0.68)
MRFIT men aged 40-57 y	270 671	93 (3.1)	1777 (3.7)	0.81 (0.65-0.99)
CHA men aged 40-59 y	7490	3 (8.8)	65 (9.1)	0.86 (0.27-2.75)
CHA women aged 40-59 y	6229	3 (12.5)	24 (4.1)	1.94 (0.57-6.58)
Other Causes				
MRFIT men aged 35-39 y	72 144	42 (0.8)	400 (0.8)	0.96 (0.70-1.32)
CHA men aged 18-39 y	10 025	9 (9.7)	76 (8.2)	1.15 (0.57-2.29)
MRFIT men aged 40-57 y	270 671	172 (6.0)	4431 (9.2)	0.64 (0.55-0.74)
CHA men aged 40-59 y	7490	7 (23.1)	252 (37.3)	0.55 (0.26-1.17)
CHA women aged 40-59 y	6229	1 (6.9)	129 (21.7)	0.14 (0.02-1.03)

*Other causes are other than cardiovascular disease, cancer, and violence. MRFIT indicates the Multiple Risk Factor Intervention Trial; CHA, Chicago Heart Association Detection Project in Industry; RR, relative risk; CI, confidence interval; and ellipses, not applicable. For definitions of "low risk" and "others," see footnotes to Tables 1 and 2.
†Ages are baseline ages; follow-up averaged 16 years in the MRFIT study and 22 years in the CHA study.
‡Data presented as No. of deaths (age-adjusted rate per 10 000 person-years).
§NA indicates not analyzed; only 10 stroke deaths occurred, all in the other substratum.

Table 5. Mortality From All Causes, Low-Risk Subcohorts and Others, and Estimated Greater Life Expectancy for Low-Risk Subcohort Compared With Others*

Cohort†	No.	Low-Risk Subcohort‡	Others‡	Age-Adjusted RR (95% CI), Low-Risk Subcohorts vs Others	Estimated Greater Life Expectancy, Low-Risk Subcohorts vs Others, y§
MRFIT men aged 35-39 y	72 144	139 (2.5)	2574 (5.2)	0.50 (0.42-0.59)	6.3
CHA men aged 18-39 y	10 025	20 (10.2)	479 (23.5)	0.43 (0.28-0.68)	9.5
MRFIT men aged 40-57 y	270 671	848 (29.2)	31 034 (64.4)	0.45 (0.42-0.48)	5.9
CHA men aged 40-59 y	7490	36 (54.6)	1684 (124.9)	0.42 (0.30-0.58)	6.0
CHA women aged 40-59 y	6229	30 (36.1)	843 (68.4)	0.60 (0.42-0.87)	5.8

*MRFIT indicates the Multiple Risk Factor Intervention Trial; CHA, Chicago Heart Association Detection Project in Industry; RR, relative risk; and CI, confidence interval. For definitions of "low risk" and "others," see footnotes to Tables 1 and 2.
†Ages are baseline ages; follow-up averaged 16 years in the MRFIT study and 22 years in the CHA study.
‡Data presented as No. of deaths (age-adjusted mortality rate per 10 000 person-years).
§Coefficients from the multiple proportional hazards regression (Cox) analyses on all-cause death, used to estimate greater life expectancy for low-risk subcohorts, were, for each of the cohorts, age, 0.095237, 0.070310, 0.088974, 0.087617, 0.081819; serum cholesterol, 0.004108, 0.007514, 0.001890, 0.001317, −0.000123; systolic blood pressure, 0.015329, 0.011641, 0.015168, 0.011213, 0.011565; and cigarettes per day, 0.024274, 0.026640, 0.024504, 0.027344, 0.037216. All *P* values for these coefficients were <.001 except for serum cholesterol for CHA men aged 40-59 years (T-score = 1.941) and for CHA women aged 40-59 years (T-score = −0.142). Other variables in these Cox multivariate analyses were for the 2 MRFIT cohorts, ethnicity (African American, yes/no) and for the 3 CHA cohorts, body mass index (BMI), BMI^2, education (y), former smoker (yes/no), and ethnicity (African American, yes/no).

also CHD mortality, risk of fatal stroke, all CVD, all cancers, and all causes, without any significant evidence of countervailing mortality risks; (4) they indicate that low-risk status is associated with greater life expectancy by several years; and (5) additional analyses (reported previously) on the CHA cohorts show further that low risk in middle age is associated with lower average annual costs for medical care in older age.[24]

These data on the benefits of low risk are almost certainly underestimates due to both misclassification of individuals with a single measurement of the 3 major risk factors[25] and lack of data on the fourth independent major risk factor, adverse dietary pattern.[1,2,5,6,8,17,19,26] Data on participant exercise habits were also missing. In this regard, the 2 diet-dependent major risk factors (serum cholesterol level and blood pressure) may be viewed not only as etiologically significant traits, but also as markers of other lifestyle characteristics contributing to favorable outcomes for low-risk subcohorts. This inference is supported by the CHA data showing lower average body mass index for low-risk individuals vs others.

The data here challenge the view that the major risk factors " . . . explain at most half of all myocardial infarctions." [27] Despite underestimation, favorable status for all 3 major risk factors consistently predicted long-term CHD and MI mortality rates that are lower by much more than 50%: by 86% to 92% for young adult men and 77% to 79% for middle-aged persons compared with others. Consequently, for low-risk subcohorts, in contrast to others, MI and CHD mortality rates were not at epidemic levels, were not main causes of death, and did not account for a large proportion of all deaths. Available data indicate that this favorable status for low-risk persons holds for both African Americans and whites, and for those of lower and higher socioeconomic status.[28]

These findings are relevant for the national effort to end the CHD-CVD epidemic. They lend strong support to the

concept[2] that a strategy based on identifying, evaluating, and treating people with risk factors is not enough. A population-wide strategy is critical to prevent and reduce the magnitude of all the major risk factors, first and foremost by safe nutritional-hygienic means, so that a substantial increase is achieved in the proportion of people in the population who, throughout life, have favorable levels for all the major risk factors and so are at low risk. For upcoming generations, this means encouraging favorable behaviors beginning in early childhood in regard to eating, drinking, exercising, and smoking. For others (particularly older children, teenagers, and young adults), this strategy emphasizes efforts to preserve favorable risk factor status for those who still have none of the major risk factors.

Genetic makeup undoubtedly influenced propensity to fall into low-risk categories. However, as shown by multiple data sets on groups such as American Seventh Day Adventists, Chinese, Greeks, Italians, Japanese, and South Africans, adult population average serum cholesterol level lower than 5.17 mmol/L (<200 mg/dL) is widely prevalent.[1,2] For the US population as a whole in the 1990s, mean serum cholesterol level has fallen almost to the national health goal for the year 2000 of no more than 5.17 mmol/L (200 mg/dL).[29] Similarly, extensive data are available on isolated populations around the world with average adult SBP/DBP of 120/80 mm Hg or less, with little or no blood pressure rise during adulthood, and with little or no hypertension[30]: favorable blood pressure patterns that are not due to unusual genetic makeup, since with migration and adoption of modern lifestyles these populations too develop adverse blood pressure levels.

Therefore, lifestyle also clearly influences who will fall into the low risk-factor group. Since the 1960s, nutritional recommendations have been available for prevention of dyslipidemia in the form of advice to decrease intake of dietary total fat, saturated fat, cholesterol; partially replace saturated fat with monounsaturated and polyunsaturated fat; increase intake of dietary fiber, especially water-soluble fiber; and prevent or reduce overweight.[1,2,8,19,26,29,31] Average serum cholesterol levels of the adult population have decreased from approximately 6.21 mmol/L (240 mg/dL) to less than 5.30 mmol/L (205 mg/dL).[29] More recently, lifestyle recommendations have been set down for prevention of adverse blood pressure levels. These initially involved avoidance of high salt intake, inadequate potassium intake, excess alcohol use, overweight, and sedentary habits,[30-32] and have been expanded to include high intake of fruits and vegetables, fat-free and low-fat protein sources, and low intake of lipid-rich foods (ie, reduced dietary total fat, saturated fat, and cholesterol).[7,33,34] National survey data indicate that average blood pressure levels of Americans and rates of high blood pressure are lower as a result of improved lifestyles, independent of effects of antihypertensive drug treatment.[35] All these data support the concept that lifestyles, particularly nutritional habits, interdigitate with polygenic propensities (widespread in the population) to influence average serum lipid and blood pressure levels of both individuals and the overall population. Adverse levels are not fixed consequences of the genome; they are widely amenable to prevention by safe nutritional-hygienic means, with resultant sizable increases in the proportion of the population at low risk.

In summary, data from large, population-based, prospective studies indicate that lifetime favorable status in regard to all 3 major CHD-CVD risk factors (serum cholesterol level, blood pressure, and smoking) leads to low mortality rates from CHD, CVD, and all causes and increased life expectancy. The extensive findings support a strategic emphasis on population-wide primary prevention of all major risk factors as a key component of the effort to end the CHD-CVD epidemic. Research advances have supplied the scientific information to make implementation of this strategic component widely feasible. The challenge is to mobilize the societal will and resources to realize these goals in all population strata to help end the CHD-CVD epidemic early in the next century.

Author Affiliations: Department of Preventive Medicine, Northwestern University Medical School, Chicago, Ill (Drs Stamler, Daviglus, Dyer, Liu, and Greenland, Ms Stamler, and Mr Garside); and Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis (Dr Neaton and Ms Wentworth).
†Ms Stamler died February 28, 1998.
Corresponding Author and Reprints: Jeremiah Stamler, MD, Department of Preventive Medicine, Northwestern University Medical School, 680 N Lake Shore Dr, Suite 1102 (D335), Chicago, IL 60611.
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REFERENCES

1. Stamler J. *Lectures on Preventive Cardiology*. New York, NY: Grune & Stratton; 1967.
2. Inter-Society Commission for Heart Disease Resources, Atherosclerosis Study Group, and Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. *Circulation*. 1970;42:A55-A95.
3. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *J Chronic Dis*. 1978;31:201-306.
4. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA, for the Bogalusa Heart Study. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N Engl J Med*. 1998;338:1650-1656.
5. Stamler J, Greenland P, Neaton JD. The established major risk factors underlying epidemic coronary and cardiovascular disease. *CVD Prevention*. 1998;1:82-97.
6. Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Arch Intern Med*. 1998; 158:2007-2014.
7. National High Blood Pressure Education Program.

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med*. 1997;157:2413-2446.
8. Stamler J, Stamler R, Brown WV, et al. Serum cholesterol: doing the right thing. *Circulation*. 1993;88:1954-1960.
9. Watts GF, Lewis B, Brunt JN, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St. Thomas' Atherosclerosis Regression Study (STARS). *Lancet*. 1992;339:563-569.
10. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
11. Shepard J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
12. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.
13. Downs JR, Clearfield M, Weis S, et al, for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA*. 1998;279:1615-1622.
14. The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357.
15. Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Rockville, Md: US Dept of Health and Human Services, Public Health Service; 1990:628.
16. Rose G, Colwell L. Randomized controlled trial of anti-smoking advice: final (20 year) results. *J Epidemiol Community Health*. 1992;46:75-77.
17. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology*. 1993;82:191-222.
18. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA*. 1982;248:1465-1477.
19. Stamler J, Caggiula AW, Cutler JA, et al. Dietary and nutritional methods and findings: the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Clin Nutr*. 1997;65(suppl):183S-402S.
20. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977.
21. World Health Organization. *International Classification of Diseases, Eighth Revision (ICD-8)*. Geneva, Switzerland: World Health Organization; 1967.
22. National Center for Health Statistics. *Vital Statistics of the United States, 1990*. Vol 2. Washington, DC: Public Health Service; 1994:12.
23. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-1847.
24. Daviglus ML, Liu K, Greenland P, et al. Benefit of a favorable cardiovascular risk-factor profile in middle age with respect to Medicare costs. *N Engl J Med*. 1998;339:1112-1129.
25. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease, I: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765-774.
26. Stamler J, Shekelle R. Dietary cholesterol and human coronary heart disease: the epidemiologic evidence. *Arch Pathol Lab Med*. 1988;112:1032-1040.
27. Wilmshurst P. Temperature and cardiovascular mortality [editorial]. *BMJ*. 1994;309:1029-1030.
28. Stamler J, Stamler R, Garside D, et al. Socioeconomic status, cardiovascular risk factors, and cardiovascular disease: findings on U.S. working populations. In: Stamler J, Hayerda HP, eds. *Report of the Conference on Socioeconomic Status and Cardiovascular Health and Disease, November 6-7, 1995*. Bethesda, Md: National Heart, Lung, and Blood Institute; 1996:109-118.
29. Ernst ND, Sempos CT, Briefel RR, Clark MB. Consistency between US dietary fat intake and serum total cholesterol concentrations: the National Health and Nutrition Examination Surveys. *Am J Clin Nutr*. 1997;66(suppl 4):965S-972S.
30. Stamler J. The INTERSALT Study: background, methods, findings, and implications. *Am J Clin Nutr*. 1997;65(suppl):626S-642S.
31. National Research Council Committee on Diet and Health. *Diet and Health: Implications for Reducing Chronic Disease Risk*. Washington, DC: National Academy Press; 1989.
32. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. *Arch Intern Med*. 1993;153:186-208.
33. Stamler J. Setting the TONE for ending the hypertension epidemic [editorial]. *JAMA*. 1998;279:878-879.
34. Appel LJ, Moore TJ, Obarzanek E, et al, for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336:1117-1124.
35. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1960-1991. *Hypertension*. 1995;303:305-313.

Language is the dress of thought.
—Samuel Johnson (1709-1784)