Favorable Cardiovascular Risk Profile in Young Women and Long-term Risk of Cardiovascular and All-Cause Mortality

Martha L. Daviglus, MD, PhD
Jeremiah Stamler, MD
Amber Pirzada, MD
Lijing L. Yan, PhD, MPH
Daniel B. Garside, BS
Kiang Liu, PhD
Renwei Wang, MD, MS
Alan R. Dyer, PhD
Donald M. Lloyd-Jones, MD, ScM
Philip Greenland, MD

Context For women, impact of cardiovascular risk factors measured in young adulthood, particularly favorable (low-risk) profile, on mortality has been difficult to assess due to low short-term death rates.

Objective To assess the relationship of baseline coronary risk factor status to mortality from coronary heart disease (CHD), cardiovascular diseases (CVDs), and all causes in young women.

Design Prospective cohort study.

Setting and Participants A total of 7302 women aged 18 to 39 years without prior CHD or major electrocardiographic abnormalities screened between 1967 and 1973 for the Chicago Heart Association Detection Project in Industry. Risk groups were defined using national guidelines for values of systolic and diastolic blood pressure, serum cholesterol level, body mass index, presence of diabetes, and smoking status. Participants were divided into 4 groups: low risk, 0 risk factors high but 1 or more unfavorable, 1 only risk factor high, and 2 or more risk factors high.

Main Outcome Measures All-cause mortality, CHD mortality, and CVD mortality; hazard ratio of outcome measures comparing low-risk group with other groups.

Results Only 20% met low-risk criteria; 59% had high levels of 1 or more risk factors. During an average follow-up of 31 years, there were 47 CHD deaths, 94 CVD deaths, and 469 deaths from all causes. The age-adjusted CVD death rate per 10000 person-years was lowest for low-risk women and increased with the number of risk factors, ie, 1.5, 1.7, 5.0, and 9.1 for low-risk; 0, 1, and 2 or more risk factors high, respectively. Multivariate-adjusted CVD mortality hazard ratio for low-risk women was 0.19 (95% confidence interval, 0.08-0.45) compared with women with 2 or more risk factors high. Similar patterns were observed for CHD and all-cause mortality and for both blacks and whites.

Conclusion For women with favorable levels for all 5 major risk factors at younger ages, CHD and CVD are rare; long-term and all-cause mortality are much lower compared with others.

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YOUNG ADULT MEN AND MIDDLE-aged men and women with favorable levels of all major cardiovascular risk factors, ie, low-risk status, have much lower age-specific risks for cardiovascular disease (CVD) and all-cause mortality than those with adverse levels of 1 or more risk factors.[1] However, the impact of a favorable cardiovascular risk profile in young women on subsequent mortality has only been estimated statistically using coronary heart disease (CHD) risk prediction models.[2] In this study, we examined the relationship of low CHD/CVD risk and individual risk factors in young women to long-term CHD, CVD, and all-cause mortality.

METHODS

From 1967 to 1973, the Chicago Heart Association (CHA) Detection Project in Industry Study screened 39522 employed Chicago-area men and women aged 18 years and older. Standardized examination methods, follow-up procedures, and death certificate coding were used.[3-7] Vital status was ascertained through 2001, with an average (SD) follow-up of 31 (1.3) years. Informed consent was obtained from each study participant. The study has been periodically approved by the Northwestern University Institutional Review Board.

Author Affiliations: Department of Preventive Medicine (Drs Daviglus, Stamler, Pirzada, Yan, Liu, Wang, Dyer, Lloyd-Jones, and Greenland and Mr Garside); Department of Medicine, Division of Geriatrics (Drs Daviglus and Liu); and Department of Medicine, Division of Cardiology (Drs Greenland and Lloyd-Jones), Northwestern University, Feinberg School of Medicine, Chicago, Ill.
Corresponding Author: Martha L. Daviglus, MD, PhD, Department of Preventive Medicine, Northwestern University, Feinberg School of Medicine, 680 N Lake Shore Dr, Suite 1102, Chicago, IL 60611 (daviglus@northwestern.edu).

Of 7748 women (baseline ages 18-39 years), 446 were excluded for the following reasons: baseline CHD (n=7); major electrocardiographic (ECG) abnormality (n=403); missing data on smoking, blood pressure (BP), serum cholesterol level, body mass index (BMI), diabetes, or education (n=36).

Eligible women (n=7302) were classified into 4 risk groups according to baseline CVD risk status. Low-risk status was defined as favorable levels of all the following: systolic BP (SBP) 120 mm Hg or less and diastolic BP (DBP) 80 mm Hg or less and not taking antihypertensive medication, serum cholesterol level less than 200 mg/dL (<5.17 mmol/L) and not taking cholesterol-lowering medication, BMI less than 25.0, no diabetes, and not smoking. Participants not at low risk were classified as having 0 risk factors high but 1 or more unfavorable, any 1 only, or 2 or more of the following: SBP 140 mm Hg or higher or DBP 90 mm Hg or higher or taking antihypertensive medication, serum cholesterol level 240 mg/dL or higher (≥6.21 mmol/L) or taking cholesterol-lowering medication, BMI 30.0 or higher, diabetes, and cigarette smoking. Unfavorable levels are defined as SBP 121 to 139 mm Hg and DBP 81 to 89 mm Hg and not taking antihypertensive medication, serum cholesterol level 200 to 239 mg/dL (5.17-6.18 mmol/L) and not taking cholesterol-lowering medication, and BMI 25.0 to 29.9. Race/ethnicity was assessed by interviewers to clarify reasons for the higher CVD rates in blacks than whites, a major US problem requiring additional research then and now.

Age-adjusted CHD, CVD, and all-cause mortality rates per 10000 person-years of follow-up were computed by risk category. Cox proportional hazards regression was used to calculate mortality hazard ratios (HRs) and 95% confidence intervals (CIs) by baseline risk category, adjusted for baseline age only and for other risk factors. Tests of the proportional hazards assumption showed no violation. Models were computed to estimate the HR and 95% CI ($P<.05$) for individual risk factors and for the low-risk group compared with other strata. Kaplan-Meier cumulative mortality curves were also plotted for the 4 risk categories. All analyses were conducted with SAS statistical software version 8.02 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 7302 young women, 1469 (20.1%) were classified as low risk; a majority (58.5%) of the cohort had 1

Table 1. Baseline Characteristics (1967-1973) of 7302 Women Aged 18 to 39 Years According to Risk Categories and Mortality Experience at Follow-up, Chicago Heart Association Detection Project in Industry Study*

	Baseline Risk Category†				Follow-up Vital Status‡			
Variable	Low Risk (n = 1469)	No Risk Factors High But ≥1 Unfavorable (n = 1558)	1 Only Risk Factor High (n = 3217)	≥2 Risk Factors High (n = 1058)	Survivors (n = 6833)	CHD Death (n = 47)	CVD Death (n = 94)	All Deaths (n = 469)
Age, y	25.4 (5.5)	26.8 (6.1)	26.7 (6.1)	28.8 (6.4)§	26.6 (6.0)	31.1 (5.8)§	30.4 (6.0)§	29.8 (6.5)§
Black race, %	19.6	22.1	26.6	26.0§	24.0	29.8	34.0§	26.9
Education, y	13.5 (2.1)	13.1 (2.1)	12.8 (1.9)	12.5 (2.0)§	13.0 (2.0)	12.3 (2.0)§	12.4 (1.9)§	12.6 (2.2)§
Minor ECG abnormality, %	2.6	1.9	3.8	5.1§	3.3	4.3	5.3	3.6
Current smoker, %	0	0	73.7	85.3	43.6	72.3§	68.1§	63.1§
Cigarettes per day, No.	0	0	12.1 (10.8)	15.5 (11.6)	7.2 (10.4)	12.8 (11.6)§	12.6 (11.8)§	12.5 (12.7)§
Blood pressure, mm Hg								
Systolic	113.2 (6.6)	123.2 (9.2)	123.0 (12.9)	138.0 (14.7)	123.1 (13.5)	127.7 (15.0)§	127.6 (14.3)§	125.9 (14.0)§
Diastolic	67.7 (8.1)	72.2 (8.0)	72.3 (10.1)	81.7 (11.2)	72.6 (10.3)	75.8 (11.5)§	76.2 (10.5)§	74.6 (10.7)§
Hypertension medication, %	0	0	0.4	3.8	0.8	0.0	1.1	0.4
Serum cholesterol, mg/dL‖	163.5 (20.8)	185.6 (29.4)	180.0 (32.7)	198.9 (42.3)	180.3 (33.3)	194.8 (34.0)§	191.2 (31.9)§	185.9 (32.9)§
Diabetes, %	0	0	0.7	4.1	0.9	0.0	2.1	1.3
BMI	20.9 (2.1)	22.9 (3.1)	22.4 (3.5)	26.5 (6.1)	22.7 (4.0)	25.6 (5.7)§	24.9 (5.1)§	23.7 (4.9)§

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram.
SI conversion factor: to convert cholesterol levels from mg/dL to mmol/L, multiply by 0.0259.
*Data are expressed as mean (SD) unless otherwise noted.
†With exclusion of persons with history or ECG evidence of CHD and major electrocardiographic abnormalities, low risk is defined as all of the following: baseline serum cholesterol level less than 200 mg/dL (<5.17 mmol/L) and not currently taking cholesterol-lowering medication; systolic blood pressure 120 mm Hg or less, diastolic blood pressure 80 mm Hg or less, not currently taking antihypertensive medication; not currently smoking; no diabetes; and BMI less than 25.0. Persons who were not low risk were further classified into 3 groups as having 0 but 1 or more unfavorable, any 1 only, or 2 or more of the following 5 risk factors: cholesterol 240 mg/dL or higher (≥6.21 mmol/L) or taking cholesterol-lowering medication, systolic blood pressure 140 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher or currently taking antihypertensive medication, current smoking, diabetes, and BMI greater than 30.0.
‡Coronary heart disease mortality was defined as *International Classification of Diseases 8th Revision* (*ICD-8*)/*International Classification of Diseases Ninth Revision* (*ICD-9*) codes 410.0-414.9 and *International Classification of Diseases 10th Revision* (*ICD-10*) codes 120.0-125.9; CVD mortality was defined as *ICD-8*/*ICD-9* codes 390.0-458.9 and *ICD-10* codes 100.0-199.9.
§$P<.05$ for overall group differences across 4 risk strata, for the comparison of mortality groups with survivor group for all categorical (from χ^2 tests) and continuous (from F tests) variables. No tests were performed for all other factors because they were included in the definition of baseline risk status.
‖Only 1 woman was taking cholesterol-lowering medication.

or more high-risk factors (TABLE 1). Low-risk women tended to be younger, white, and better educated. During 31 years of follow-up, there were 47 CHD deaths, 94 CVD deaths, and 469 deaths from all causes (Table 1).

Table 2. Age-Adjusted and Multivariate-Adjusted Hazard Ratios of Baseline Risk Factors for Coronary Heart Disease, Cardiovascular Disease, and All-Cause Mortality*

Risk Factor	Age-Adjusted Hazard Ratio (95% CI)	Multivariate-Adjusted Hazard Ratio (95% CI)
Coronary Heart Disease Mortality		
Smoking (per 10 cigarettes per day)†	1.43 (1.14-1.79)‡	1.40 (1.13-1.72)‡
BMI (per 4 units)†	1.48 (1.21-1.80)‡	1.41 (1.13-1.76)‡
SBP (per 15 mm Hg)†	1.25 (0.97-1.60)	1.05 (0.80-1.39)
Cholesterol (per 30 mg/dL)†	1.26 (0.96-1.64)	1.16 (0.91-1.48)
Diabetes (no vs yes)§	. . .	. . .
Minor ECG abnormalities (no vs yes)	1.14 (0.28-4.71)	0.93 (0.23-3.86)
Race (nonblack vs black)	1.42 (0.76-2.65)	1.38 (0.73-2.62)
Cardiovascular Disease Mortality		
Smoking (per 10 cigarettes per day)	1.42 (1.21-1.67)‡	1.41 (1.22-1.65)‡
BMI (per 4 units)	1.37 (1.18-1.60)‡	1.29 (1.09-1.52)‡
Systolic blood pressure (per 15 mm Hg)	1.26 (1.05-1.50)‡	1.10 (0.91-1.34)
Cholesterol (per 30 mg/dL)	1.18 (0.97-1.43)	1.10 (0.92-1.31)
Diabetes (no vs yes)	2.06 (0.51-8.37)	2.19 (0.54-8.90)
Minor ECG abnormalities (no vs yes)	1.46 (0.59-3.60)	1.22 (0.49-3.00)
Race (nonblack vs black)	1.70 (1.10-2.61)‡	1.72 (1.12-2.67)‡
All-Cause Mortality		
Smoking (per 10 cigarettes per day)	1.42 (1.32-1.52)‡	1.40 (1.30-1.50)‡
BMI (per 4 units)	1.12 (1.03-1.23)‡	1.08 (0.99-1.18)
SBP (per 15 mm Hg)	1.14 (1.05-1.24)‡	1.09 (1.00-1.20)
Cholesterol (per 30 mg/dL)	1.03 (0.94-1.13)	1.00 (0.92-1.09)
Diabetes (no vs yes)	1.23 (0.55-2.76)	1.28 (0.57-2.86)
Minor ECG abnormalities (no vs yes)	0.97 (0.60-1.58)	0.86 (0.53-1.40)
Race (nonblack vs black)	1.21 (0.98-1.48)	1.29 (1.05-1.59)‡

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CI, confidence interval; ECG, electrocardiogram; SBP, systolic blood pressure.
SI conversion factor: to convert cholesterol levels from mg/dL to mmol/L, multiply by 0.0259.
*Variables included in the model were age, cigarette smoking, BMI, SBP, serum cholesterol, diabetes, minor ECG abnormalities, and race.
†Difference (delta) is approximately 1 SD.
‡$P<.05$.
§No CHD deaths occurred in the 64 diabetic women.

All risk factors considered individually were related to CHD and CVD death with cigarette smoking and BMI, significantly so in multivariate analyses (TABLE 2).

Age-adjusted CHD mortality rates were similar for low-risk women and those with 0 risk factors high but 1 or more unfavorable and were much lower than for women with 1 only risk factor or 2 or more risk factors high. Women with 2 or more risk factors high had the highest CHD mortality rates (TABLE 3). Findings were similar for CVD and all-cause mortality, eg, CVD mortality rate per 10 000 person-years for women with 2 or more risk factors high was 9.1, about 6 times that of low-risk women (1.5). With adjustment for age, race, and minor ECG abnormalities, HRs for 31-year all-cause mortality were lowest for low-risk women and increased with the number of risk factors. Results stratified by race were similar (data not shown). Kaplan-Meier cumulative mortality curves depict similar results (FIGURE).

COMMENT

Among young women without baseline major ECG abnormalities or prevalent CHD at baseline, 31-year risks of CHD, CVD, and all-cause mortality were markedly lower for those who were low-risk compared with others. The presence of high levels of major risk factors was associated with much higher mortality risk.

Table 3. Age-Adjusted 31-Year Mortality Rates and Hazard Ratios From Coronary Heart Disease, Cardiovascular Diseases, and All Causes by Baseline Risk Category*

	Coronary Heart Disease Mortality				Cardiovascular Disease Mortality				All-Cause Mortality			
	Low Risk	No Risk Factors High But ≥1 Unfavorable	1 Only Risk Factor High	≥2 Risk Factors High	Low Risk	No Risk Factors High But ≥1 Unfavorable	1 Only Risk Factor High	≥2 Risk Factors High	Low Risk	No Risk Factors High But ≥1 Unfavorable	1 Only Risk Factor High	≥2 Risk Factors High
No. of women	1469	1558	3217	1058	1469	1558	3217	1058	1469	1558	3217	1058
Person-years of follow-up	43168	46036	94115	30803	43168	46036	94115	30803	43168	46036	94115	30803
No. of deaths	2	3	23	19	6	8	47	33	51	57	251	110
Rate per 10000 person-years	0.7	0.7	2.4	5.4	1.5	1.7	5.0	9.1	12.8	12.4	26.7	30.6
Hazard ratio (95% confidence interval)												
Age-adjusted	0.10 (0.02-0.45)	0.12 (0.04-0.42)	0.47 (0.26-0.87)	1.00	0.17 (0.07-0.41)	0.18 (0.09-0.40)	0.54 (0.35-0.85)	1.00	0.42 (0.30-0.59)	0.39 (0.28-0.54)	0.85 (0.68-1.07)	1.00
Multivariate-adjusted†	0.12 (0.03-0.50)	0.13 (0.04-0.45)	0.49 (0.26-0.90)	1.00	0.19 (0.08-0.45)	0.20 (0.09-0.43)	0.56 (0.36-0.88)	1.00	0.44 (0.32-0.62)	0.40 (0.29-0.56)	0.87 (0.69-1.09)	1.00

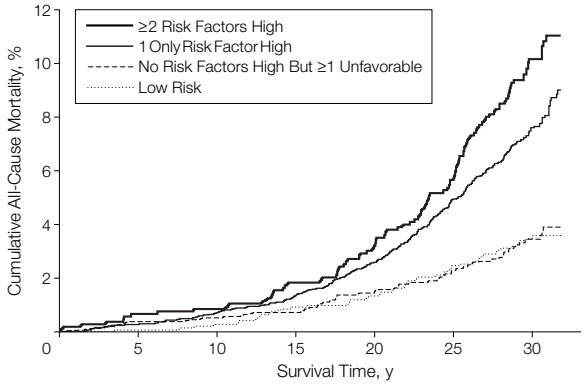
*For definition of risk categories, see footnotes to Table 1.
†Adjusted for age, race, minor electrocardiographic abnormalities, and education.

Prospective population-based research involving large cohorts with long-term follow-up into older age has delineated multiple favorable consequences of baseline low-risk status. For the small percentage of young men and middle-aged men and women who were low-risk at baseline compared with all others, CHD/CVD is rare (endemic) not epidemic; CHD, CVD, and all-cause mortality rates are remarkably lower.[1,8] Persons at low risk earlier in life experience higher quality of life, lower medication use and prevalence of clinical diseases,[9,10] less subclinical coronary atherosclerosis,[11] and also substantially lower average annual health care costs in older age[12] compared with others.

To our knowledge, the relationship of low-risk status to subsequent mortality has not been previously assessed in young women. The few reports on women have presented estimates from statistical extrapolation,[2] have defined low risk alternatively,[13] or did not include younger women.[1] A report describing CHD risk prediction models derived from Framingham data estimated that 10-year incidence of fatal and nonfatal CHD was 1% or less for women ages 30 to 39 years who were low risk (ie, no diagnosed diabetes, nonsmoker, with optimal BP and cholesterol levels).[2] In the Nurses' Health Study, low-risk status was defined as nonsmoking, moderate/vigorous exercise 30 minutes or more per day, BMI less than 25, moderate alcohol consumption, and a diet score in the top 2 quintiles. Low-risk women (only 3% of 84 129 women, baseline ages 30-55 years) had an 83% lower 14-year risk of fatal and nonfatal coronary events compared with others.[13]

In a previous report among middle-aged women (baseline ages 40-59 years) from the CHA study, CHD and CVD mortality rates for those at low risk were lower by 79% and 73%, respectively, and all-cause mortality was lower by 40% compared with those with adverse levels of 1 or more risk factors.[1] With over 3 decades of follow-up, our results now reveal the importance of a low-risk profile in young women. Of note, our study incorporates BMI in the low-risk definition since overweight/obesity is a major independent CVD risk factor that is increasingly prevalent among Americans.[14-16]

Figure. Kaplan-Meier Cumulative Mortality Curve for All-Cause Mortality by Baseline Risk Category for 7302 Women Aged 18 to 39 Years at Baseline (1967-1973), Followed Through 2001



No. at Risk

≥2 Risk Factors High	1469	1468	1465	1456	1450	1434	1420
1 Only Risk Factor High	1558	1552	1550	1547	1536	1523	1506
No Risk Factors High But ≥1 Unfavorable	3217	3208	3195	3175	3136	3064	2983
Low Risk	1058	1051	1049	1039	1026	999	955

For definition of risk categories, see footnotes to Table 1.

Limitations of this study include measurement of risk factors once only at baseline, which would likely lead to underestimation of the impact of risk status, ie, regression dilution bias toward the null. Furthermore, information on dietary habits and physical activity was not collected. Also, the use of death certificates for ascertaining cause of death may result in overestimation of CHD mortality.[17] Nevertheless, it is unlikely that this would differ systematically across risk strata.

Our findings show that for young women, a low cardiovascular risk profile is associated with lower long-term CHD, CVD, and all-cause mortality—results in concert with previous findings on young men and middle-aged men and women.[1] They demonstrate that among persons at low risk earlier in life, CHD and CVD cease to occur at epidemic rates. These data underscore the importance of a national public policy priority emphasizing prevention and control of all major CVD risk factors by lifestyle approaches from conception, weaning, childhood, and youth on to increase proportions of the population at low CVD risk.

Author Contributions: Dr Daviglus had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Daviglus, Stamler, Liu, Dyer, Greenland.
Acquisition of data: Stamler, Garside, Greenland.
Analysis and interpretation of data: Daviglus, Stamler, Pirzada, Yan, Wang, Dyer, Lloyd-Jones, Greenland.
Drafting of the manuscript: Daviglus, Stamler, Pirzada, Yan.
Critical revision of the manuscript for important intellectual content: Daviglus, Stamler, Yan, Garside, Wang, Dyer, Lloyd-Jones, Greenland.
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