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

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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 39,522 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.

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 7,302 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.

Analysis

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 10,000 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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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 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
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).

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 10000 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 2. Age-Adjusted and Multivariate-Adjusted Hazard Ratios of Baseline Risk Factors for Coronary Heart Disease, Cardiovascular Disease, and All-Cause Mortality

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coronary Heart Disease Mortality</th>
<th>Cardiovascular Disease Mortality</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (per 10 cigarettes per day)</td>
<td>1.43 (1.14-1.79)†</td>
<td>1.40 (1.13-1.72)‡</td>
<td>1.41 (1.13-1.76)‡</td>
</tr>
<tr>
<td>BMI (per 4 units)‡</td>
<td>1.48 (1.21-1.80)‡</td>
<td>1.41 (1.13-1.76)‡</td>
<td>. . .</td>
</tr>
<tr>
<td>SBP (per 15 mm Hg)†</td>
<td>1.25 (0.97-1.60)</td>
<td>1.05 (0.80-1.39)</td>
<td>. . .</td>
</tr>
<tr>
<td>Cholesterol (per 30 mg/dL)†</td>
<td>1.26 (0.96-1.64)</td>
<td>1.16 (0.91-1.48)</td>
<td>. . .</td>
</tr>
<tr>
<td>Diabetes (no vs yes)§</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Minor ECG abnormalities (no vs yes)</td>
<td>1.14 (0.28-4.71)</td>
<td>0.93 (0.23-3.86)</td>
<td>. . .</td>
</tr>
<tr>
<td>Race (nonblack vs black)</td>
<td>1.42 (0.76-2.65)</td>
<td>1.38 (0.73-2.62)</td>
<td>. . .</td>
</tr>
</tbody>
</table>

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

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</tr>
<tr>
<td>BMI (per 4 units)‡</td>
<td>1.12 (1.03-1.23)§</td>
<td>1.08 (0.99-1.18)</td>
</tr>
<tr>
<td>SBP (per 15 mm Hg)†</td>
<td>1.14 (1.05-1.24)‡</td>
<td>1.00 (0.92-1.10)</td>
</tr>
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<td>Cholesterol (per 30 mg/dL)†</td>
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<tr>
<td>Diabetes (no vs yes)§</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Minor ECG abnormalities (no vs yes)</td>
<td>0.97 (0.60-1.58)</td>
<td>0.86 (0.53-1.40)</td>
</tr>
<tr>
<td>Race (nonblack vs black)</td>
<td>1.21 (0.98-1.48)</td>
<td>1.29 (1.05-1.59)†</td>
</tr>
</tbody>
</table>

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.
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 diseases9,10 less subclinical coronary atherosclerosis,11 and also substantially lower average annual health care costs in older age12 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 CHD compared with others.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

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, Liu, Dyer, Lloyd-Jones, Greenland. Statistical analysis: Stamler, Garside, Liu, Wang. Obtained funding: Stamler, Dyer, Greenland. Administrative, technical, or material support: Stamler, Pirzada, Greenland. Study supervision: Daviglus, Stamler.

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REFERENCES


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