Combined Effects of Cardiorespiratory Fitness, Not Smoking, and Normal Waist Girth on Morbidity and Mortality in Men

Chong-Do Lee, EdD; Xuemei Sui, MD; Steven N. Blair, PED

Background: Physical inactivity, cigarette smoking, and abdominal obesity are key modifiable risk factors for coronary heart disease (CHD). We investigated the combined effects of not having these risk factors on CHD events and cardiovascular disease (CVD) and all-cause mortality in men.

Methods: We followed up 23,657 men, aged 30 to 79 years, who completed a medical evaluation including a maximal treadmill exercise test and self-reported health habits. A low-risk profile was defined as not smoking, moderate or high fitness, and normal waist girth. There were 482 CHD events (nonfatal myocardial infarction or fatal CHD) and 1034 deaths (306 CVD, 387 cancers, and 341 others) during a mean 14.7 years of follow-up (348,811 man-years).

Results: After adjustment for age, examination year, and multiple baseline risk factors, there was an inverse association between a greater number of low-risk factors and CHD events, and CVD and all-cause mortality in men (P value for trend, < .001 for all). Men with a normal waist girth and who were physically fit and not smoking had a 59% lower risk of CHD events (95% confidence interval [CI], 39%-72%), a 77% lower risk of CVD mortality (95% CI, 65%-85%), and a 69% lower risk of all-cause mortality (95% CI, 60%-76%) compared with men with none of these low-risk factors. Men with 0 compared with 3 low-risk factors had a shorter life expectancy by 14.2 years (95% CI, 12.2-15.9 years).

Conclusion: Being physically fit, not smoking, and maintaining a normal waist girth is associated with lower risk of CHD events, and CVD and all-cause mortality in men.

Arch Intern Med. 2009;169(22):2096-2101

See Invited Commentary on page 2124

See also page 2102, 2109, and 2116

Author Affiliations:
Department of Exercise and Wellness, Arizona State University, Mesa (Dr Lee); and Departments of Exercise Sciences (Dr Sui and Dr Blair) and Epidemiology and Biostatistics (Dr Blair), University of South Carolina, Columbia.
MEASUREMENTS

The study protocol was reviewed and approved annually by the institutional review board at The Cooper Institute. All participants gave their informed written consent for the medical evaluation and subsequent registration in the follow-up study. The medical evaluation, performed after an overnight fast of at least 12 hours, included a physical examination, anthropometric analyses, electrocardiogram, blood chemistry analyses, blood pressure assessment, a maximal exercise treadmill test, self-report of health habits, and demographic characteristics. Body weight and height were measured with a standard physician’s scale and stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the level of the umbilicus with a plastic tape measure. A normal waist girth was defined as waist girth less than 94 cm.19 Resting blood pressure was measured in a seated position by auscultatory methods with a mercury sphygmomanometer. Serum, plasma, and whole blood samples were drawn from an antecubital vein and were analyzed by automated bioassays at the Cooper Clinic Laboratory, which meets quality control standards of the US Centers for Disease Control and Prevention Lipid Standardization Program. Details of the clinical evaluation procedures have been previously published.17 Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher or a history of physician-diagnosed hypertension. Diabetes mellitus was defined as a fasting plasma glucose level of 126 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555) or a history of physician-diagnosed diabetes mellitus. High serum cholesterol level was defined as a serum total cholesterol level of 240 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0259).

Cardiorespiratory fitness was measured by a maximal treadmill exercise test as described previously.16,17 All participants achieved at least 85% of their age-predicted maximal heart rate (220-age in years) during the treadmill test. Total treadmill endurance time (in minutes) was used as an index of aerobic power, with time on treadmill in this protocol correlated highly \( r = 0.92 \) with maximal oxygen uptake \( (V\dot{O}_2 \text{ max}) \).20 All participants were classified into low, moderate, or high physical fitness groups based on age-specific treadmill time percentiles of the entire ACLS cohort (low, least-fit 20%; moderate, next 40%; and high, most-fit 40%) to maintain consistency in our study methods and because a widely accepted clinical categorization of physical fitness does not exist. The detailed cutoff points have been published previously.21 Age-specific distributions of treadmill exercise duration were created within the following age groups: 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 years or older.

Smoking habits, alcohol use, and parental history of CHD (either parent died of CHD) were assessed with a self-report on a medical history questionnaire. Smoking status was classified as never smoked, former smoker, or current smoker. Current smokers were further classified as smoking fewer than 20, 20 to fewer than 40, and 40 or more cigarettes per day. Alcohol consumption was classified as a continuous variable (ethanol intake, g/d) and further categorized as moderate (14 to <30 g/d) or nonmoderate alcohol intake.

We defined a low-risk profile as not smoking, moderate or high fitness, and normal waist girth. We combined these low-risk factors and categorized them as 0, 1, 2, or 3 combined low-risk factors.

ASSERMENT OF MORBIDITY AND MORTALITY

We observed all participants from the baseline examination to the date of a CHD event or death or December 31, 2003, for survivors. We defined CHD events as nonfatal myocardial infarction or coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention) or definite fatal CHD. The incidence of nonfatal myocardial infarction or coronary revascularization was ascertained from responses to mail-back health surveys in 1982, 1986, 1990, 1995, 1999, and 2004. The cumulative response rate across all survey periods in the ACLS was approximately 65%21,22 Nonresponse bias is a concern in epidemiologic surveillance, and this issue has been investigated in the ACLS cohort.23 Although health histories, clinical measures, and mortality rates between responders and nonresponders were similar,21 it is impossible to completely rule out potential response bias. Deaths were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes before 1999 and International Statistical Classification of Diseases, 10th Revision (ICD-10) codes during 1999 to 2004 (in brackets) (CHD, 410-414 [I20-I25]; CVD, 390-449.9 [I00-I78]; and cancer, 140-208 [C00-C97]).

STATISTICAL ANALYSIS

General linear models were used to test mean differences across number of low-risk factors after adjustment for age. A \( \chi^2 \) test was used to compare frequency differences across number of low-risk factors. Cox proportional hazards regression was used to examine the associations of single and combined number of low-risk factors with CHD events and CVD and all-cause mortality.24 Relative risks and 95% confidence intervals (CIs) for incidence or mortality were estimated after adjustment for age and examination year, and further adjustment for alcohol intake, hypertension, diabetes mellitus, high cholesterol level, and family history of CHD. Men with zero low-risk factors constituted the reference category. Inspection of empirical cumulative hazard plots [log–log(survival function) vs log(time)] across number of low-risk factors indicated that the proportional hazards assumption was justified. Kaplan-Meier survival curves also were constructed to compare probability of CHD events and CVD and all-cause mortality across number of low-risk factors. Population attributable risks were estimated for low cardiorespiratory fitness, current smoking, and abdominal obesity (action level I).19,21 Survival differences between 0 compared with 3 combined low-risk factors were estimated using the risk advancement period approach.26 All statistical analyses were performed by Statistical Analysis Systems software (SAS Institute Inc, Cary, North Carolina) and STATA statistical software (Stata Corp, College Station, Texas).

RESULTS

As Table 1 indicates, the prevalences of current smoking, hypertension, diabetes mellitus, and family history of CHD were progressively lower with increasing number of low-risk factors (all \( P < 0.001 \)). The mean scores of BMI, waist girth, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol level, total

©2009 American Medical Association. All rights reserved.
Table 1. Characteristics of the Study Participants Across Low-Risk Profiles at Baseline: the ACLS (1971-2003)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0 (n = 668)</th>
<th>1 (n = 3445)</th>
<th>2 (n = 9319)</th>
<th>3 (n = 10 225)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>43.3</td>
<td>44.2</td>
<td>45.3</td>
<td>43.1</td>
<td></td>
</tr>
<tr>
<td>Mean levelsb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>30.6</td>
<td>29.9</td>
<td>27.6</td>
<td>24.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Metabolic equivalents, METs c</td>
<td>9.5</td>
<td>10.5</td>
<td>12.2</td>
<td>13.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist girth, cm</td>
<td>106.3</td>
<td>103.8</td>
<td>97.1</td>
<td>83.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>122.1</td>
<td>122.8</td>
<td>121.7</td>
<td>118.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>223.4</td>
<td>218.8</td>
<td>214.4</td>
<td>202.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>207.9</td>
<td>188.8</td>
<td>150.6</td>
<td>108.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>106.6</td>
<td>104.5</td>
<td>101.4</td>
<td>98.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ethanol intake, g/d</td>
<td>28.4</td>
<td>22.3</td>
<td>21.3</td>
<td>17.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frequency, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>100</td>
<td>49.8</td>
<td>17.7</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41.0</td>
<td>41.2</td>
<td>34.4</td>
<td>21.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9.3</td>
<td>6.9</td>
<td>4.1</td>
<td>2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>29.2</td>
<td>24.1</td>
<td>23.7</td>
<td>21.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ACLS, Aerobics Center Longitudinal Study; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; METs, metabolic equivalent tasks.

c Adjusted for age, examination year, alcohol intake, hypertension, diabetes mellitus, high cholesterol, and family history of CHD.

Table 2. Relative Risks (RRs) of CHD Events and CVD and All-Cause Mortality by the Combination of Moderate to High Cardiorespiratory Fitness, Not Smoking, and Normal Waist Girth in Men: the ACLS (1971-2003)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0 (n = 482)</th>
<th>1 (n = 10 225)</th>
<th>2 (n = 9319)</th>
<th>3 (n = 3445)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1 [Reference]</td>
<td>0.59 (0.40-0.89)</td>
<td>0.43 (0.29-0.63)</td>
<td>0.32 (0.22-0.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)c</td>
<td>1 [Reference]</td>
<td>0.65 (0.43-0.98)</td>
<td>0.50 (0.34-0.73)</td>
<td>0.41 (0.28-0.61)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1 [Reference]</td>
<td>0.47 (0.31-0.71)</td>
<td>0.26 (0.18-0.39)</td>
<td>0.16 (0.10-0.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1 [Reference]</td>
<td>0.55 (0.36-0.83)</td>
<td>0.33 (0.22-0.49)</td>
<td>0.23 (0.15-0.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>All-cause mortality (n = 10 534)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1 [Reference]</td>
<td>0.56 (0.44-0.72)</td>
<td>0.33 (0.26-0.42)</td>
<td>0.27 (0.21-0.34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)c</td>
<td>1 [Reference]</td>
<td>0.59 (0.46-0.76)</td>
<td>0.36 (0.28-0.46)</td>
<td>0.31 (0.24-0.40)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ACLS, Aerobics Center Longitudinal Study; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease.

a A low-risk profile was classified as not smoking, moderate or high fitness, and normal waist girth and further categorized as 0, 1, 2, and 3 combined low-risk factors.

b Adjusted for age (single year).

c Adjusted for age, examination year, alcohol intake, hypertension, diabetes mellitus, and family history of CHD.

We also estimated relative risks of CHD incidence or mortality in men. After adjustment for age and examination year, the relative risks (95% confidence intervals [CI]) of CHD events for not smoking, moderate or high fitness, and normal waist girth were 0.74 (0.60-0.90), 0.69 (0.54-0.87), and 0.70 (0.58-0.85), respectively (all \( P < .05 \)). These low-risk factors also remain significant after further adjustment for alcohol intake, hypertension, diabetes mellitus, high cholesterol, and family history of CHD (all \( P < .05 \)). We observed similar findings in CVD mortality with or without adjustment for multiple risk factors (all \( P < .05 \). Table 2 shows the association between the number of low-risk factors and CHD incidence or mortality in men. After adjustment for age and examination year, there was an inverse association between the number of low-risk factors and CHD events and CVD and all-cause mortality (\( P \) for trend, all \( < .001 \)). Associations persisted after fur-
ther adjustment for multiple risk factors. Men who were physically fit, not smoking, and with a normal waist girth had a 59% lower risk of CHD events (95% CI, 39%-72%), a 77% lower risk of CVD mortality (95% CI, 65%-85%), and a 69% lower risk of all-cause mortality (95% CI, 60%-76%) compared with men with zero low-risk factors. The Kaplan-Meier survival curves also indicate that men with 3 combined low-risk factors had greater CHD event-free time compared with men with 0 low-risk factors (Figure). We observed similar findings in CVD and all-cause mortality (Figure).

The CHD events, CVD mortality, and all-cause mortality in this population might have been reduced by 31% (95% CI, 17%-44%), 45% (95% CI, 27%-59%), and 29% (95% CI, 19%-39%), respectively, if the men had been physically fit, not smoking, and had a normal waist girth (Table 3). Men with 0 compared with 3 low-risk factors had 2.4 times the risk of CHD events (95% CI, 1.63-3.58), which was equivalent to an earlier development of CHD of 10.6 years (95% CI, 6.7-13.8 years) (Table 3). Men with 0 vs 3 low-risk factors also had 4.4 times the risk of CVD mortality (95% CI, 2.85-6.67) and 3.2 times the risk of all-cause mortality (95% CI, 2.52-4.12), which was equivalent to a shorter life expectancy by CVD and all-cause mortality of 16.3 years (95% CI, 13.4-18.4 years) and 14.2 years (95% CI, 12.2-15.9 years), respectively.

**COMMENT**

The combined health benefits of cardiorespiratory fitness, not smoking, and normal waist girth on morbidity and mortality remain less explored. Our major finding was that men who were physically fit, not smoking, and with a normal waist girth had a 59% lower risk of CHD events, a 77% lower risk of CVD mortality, and a 69% lower risk of all-cause mortality over 15 years, compared with men with none of these low-risk factors. This finding is consistent in direction with the Health Professionals Follow-up Study and the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. According to the Health Professionals Follow-up Study, men who exercised regularly (>30 min/d of moderate to vigorous activity), did not smoke, had a prudent diet (top 40% of a healthy diet), had a moderate alcohol consumption (5-30 g/d), and maintained a normal body weight (BMI <25) had a 87% lower risk of CHD events compared with men without these lifestyle factors. The EPIC Study also showed that men and women who maintained a healthy lifestyle (ie, physically active, not smoking, moderate alcohol intake, and fruit and vegetable intake) had an 80% lower risk of CVD mortality compared with their counterparts who did not maintain these behaviors. Another European study in elderly participants also showed that men and women who involved in healthy lifestyle choices (ie, Mediterranean diet, moderate alcohol use, physically active, nonsmoking) had a 73% lower risk of CHD mortality compared with men and women without these lifestyle choices.

Our findings indicate a dose-response relationship between number of low-risk factors and morbidity and mortality risks. Men with 1, 2, or 3 combined low-risk factors had a 35% (95% CI, 2%-57%), a 50% (95% CI, 27%-66%), or a 59% (95% CI, 39%-72%) lower risk of CHD events,
respectively, compared with men with 0 low-risk factors. There are several plausible ways by which increasing number of low-risk factors might reduce atherosclerotic vascular disease risk. For instance, we observed a direct relationship between number of low-risk factors and clinical CHD risk profiles (Table 1). Men with 2 or 3 combined low-risk factors had lower blood lipid levels (total cholesterol, low-density lipoprotein cholesterol, and triglycerides), blood pressures (systolic and diastolic), fasting glucose levels, and lower frequencies of diabetes and cigarette smoking, all of which may contribute to slowing the progression of early atherosclerosis. Further studies are needed to determine whether lifestyle factors are related to inflammatory markers or early atherosclerotic vascular disease across age and sex groups.

In our study, approximately 31% of CHD events might have been avoided if the patients had been physically fit, were not smoking, and had a normal waist girth. Approximately 51% (95% CI, 29%-69%) of CHD events might have been reduced if the patients additionally had lipid levels and blood pressure at target levels without diabetes (data not shown). The Health Professionals Follow-up Study also showed that about 62% of CHD events might have been avoided if the patients had adhered to 5 low-risk lifestyles. Even in the elderly population, the CHD events might have been reduced by 64% if the patients had adhered to 4 healthy lifestyle choices (ie, healthy diet, moderate alcohol intake, exercise regularly, not smoke). The INTERHEART Study also documented that about 80% of myocardial infarctions might have been avoided if the patients had not been smoking, were not obese, and had controlled blood lipid levels, hypertension, and diabetes.26

Our findings indicate that men with 3 low-risk factors had a 14.2-year longer life expectancy (all-cause mortality) compared with men with none of these low-risk factors. The EPIC Study also showed that men and women who adhered to 4 healthy lifestyles had a 14-year longer life expectancy (all-cause) compared with their counterparts without healthy behaviors. Stamler et al27 showed that persons who maintained a total cholesterol level lower than 200 mg/dL, blood pressure of 120/80 mm Hg, and did not smoke had a 5- to 10-year longer life expectancy (all cause) compared with their counterparts. Because there is a causal pathway between these low-risk factors and clinical CHD risk profiles, clinicians should emphasize the importance of evaluating dietary, physical activity, and smoking habits as routinely as assessing dyslipidemia, hypertension, and diabetes mellitus.

A strength of this study is the large, well-characterized cohort of men who had received an extensive clinical examination at baseline that provided objective laboratory data on several exposures and confounders. Our study used standardized maximal exercise testing to quantify an objective measurement of fitness. Although most previous studies have used physical activity questionnaires to assess physical activity, which tends to be imprecise and have large measurement errors, the health benefits of physical fitness used in our study were consistent with previous studies used in physical activity questionnaires. To our knowledge, our study is the first study to estimate the combined health benefits of cardiorespiratory fitness, not smoking, and normal waist girth on morbidity and mortality, population attributable risk, and longevity. One of limitations of our study is that we were not able to adjust for C-reactive protein level due to insufficient data, which is a specific marker of inflammation that is also associated with CHD. Our study is also limited to white men in the middle and upper socioeconomic levels. Finally, we were unable to detect changes in the exposure measures during follow-up, which may underestimate the true relative risk. Further studies are needed to confirm our findings reported here with adjustment for nontraditional CHD risk factors in other populations.

In conclusion, to address health promotion and disease prevention strategies, it is important to increase healthy low-risk populations, which is a key to CHD prevention. We found that being fit, not smoking, and having a normal waist girth is associated with lower risk of CHD events and CVD and all-cause mortality in men. The magnitude of having the 3 low-risk factors is impressive for both population attributable risk and for longevity and indicates the clinical and public health importance of these characteristics.

Accepted for Publication: August 24, 2009.

Correspondence: Chong-Do Lee, EdD, Department of Exercise and Wellness, Arizona State University, 7350 E Unity Ave, Mesa, AZ 85212 (Chong.Lee@asu.edu).

Author Contributions: Study concept and design: Lee. Acquisition of data: Blair. Analysis and interpretation of data: Lee, Sui, and Blair. Drafting of the manuscript: Lee. Critical revision of the manuscript for important intellectual content: Lee, Sui, and Blair. Statistical analysis: Lee and Sui.

Table 3. Relative Risks (RRs), Population Attributable Risks (PARs), and Estimated Decreased Life Expectancy by 0 vs 3 Combined Low-Risk Factors in Men: The ACLS (1971-2003)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Cases, No.</th>
<th>RR (95% CI)</th>
<th>PAR (95% CI)</th>
<th>Decreased Life Expectancy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>482</td>
<td>2.42 (1.63-3.58)</td>
<td>31 (17-44)</td>
<td>10.6 (6.7-13.8)</td>
</tr>
<tr>
<td>DVD mortality</td>
<td>306</td>
<td>4.36 (2.85-6.67)</td>
<td>45 (27-59)</td>
<td>16.3 (13.4-18.4)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1034</td>
<td>3.22 (2.52-4.12)</td>
<td>29 (19-39)</td>
<td>14.2 (12.2-15.9)</td>
</tr>
</tbody>
</table>

Abbreviations: ACLS, Aerobics Center Longitudinal Study; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease.

* Adjusted for age, examination year, alcohol intake, hypertension, diabetes, high cholesterol level, and family history of CHD.

+ Estimated PAR for low cardiorespiratory fitness, cigarette smoking, and abdominal obesity.

+ Compared β coefficients for incidence or mortality associated with each year of age with the β coefficients difference in incidence or mortality for 0 vs 3 combined low-risk factors after adjustment for age, examination year, and multiple risk factors.
Obtained funding: Blair. Administrative, technical, and material support: Lee. Study supervision: Lee and Blair.

Financial Disclosure: None reported

Funding/Support: This study was supported by National Institutes of Health grants AG06945 and HL62508.

Additional Contributions: Cooper Clinic physicians and technicians collected the baseline data, and staff at the Cooper Institute assisted in data entry and data management.

REFERENCES