Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age

Donald M. Lloyd-Jones, MD, ScM; Eric P. Leip, PhD; Martin G. Larson, ScD; Ralph B. D’Agostino, PhD; Alexa Beiser, PhD; Peter W.F. Wilson, MD; Philip A. Wolf, MD; Daniel Levy, MD

Background—Lifetime risk for atherosclerotic cardiovascular disease (CVD) has not previously been estimated, and the effect of risk factor burden on lifetime risk is unknown.

Methods and Results—We included all Framingham Heart Study participants who were free of CVD (myocardial infarction, coronary insufficiency, angina, stroke, claudication) at 50 years of age. Lifetime risks to 95 years of age were estimated for men and women, with death free of CVD as a competing event. We followed up 3564 men and 4362 women for 111 777 person-years; 1757 had CVD events and 1641 died free of CVD. At 50 years of age, lifetime risks were 51.7% (95% CI, 49.3 to 54.2) for men and 39.2% (95% CI, 37.0 to 41.4) for women, with median survivals of 30 and 36 years, respectively. With more adverse levels of single risk factors, lifetime risks increased and median survivals decreased. Compared with participants with ≥2 major risk factors, those with optimal levels had substantially lower lifetime risks (5.2% versus 68.9% in men, 8.2% versus 50.2% in women) and markedly longer median survivals (>39 versus 28 years in men, >39 versus 31 years in women).

Conclusions—The absence of established risk factors at 50 years of age is associated with very low lifetime risk for CVD and markedly longer survival. These results should promote efforts aimed at preventing development of risk factors in young individuals. Given the high lifetime risks and lower survival in those with intermediate or high risk factor burden at 50 years of age, these data may be useful in communicating risks and supporting intensive preventive therapy. (Circulation. 2006;113:791-798.)

Key Words: cardiovascular disease ■ epidemiology ■ risk factors ■ survival

Despite 4 decades of declining mortality from cardiovascular disease (CVD) in the United States, CVD remains by far the leading cause of morbidity and mortality, and it is soon to be the leading cause of morbidity and mortality in the developing world. Recent data suggest disturbing increases in the prevalence of CVD risk factors such as diabetes, obesity, and the metabolic syndrome, which may reverse downward trends in CVD mortality. In the face of the enormous public health burden imposed by CVD, renewed efforts are needed to promote prevention.

Clinical Perspective p 798

One tool that may be useful in public health education is an understanding of the lifetime risk for CVD, which has not been estimated in any population to date. Given that lifetime risk estimates provide an absolute risk assessment, they may be more easily understood by clinicians and patients than relative risks, and they may help to motivate beneficial changes in lifestyle or health behaviors. The best example of lifetime risk data being used effectively to change behavior is the widespread dissemination of data on lifetime risk for breast cancer (1 in 8 for women at 40 years of age), which appears to have contributed to markedly increased rates of screening for breast cancer in the early 1990s.

The Framingham Heart Study, with its well-defined cohorts, long-term follow-up, and careful documentation of risk factors and events, provides a unique opportunity to examine factors that may modify remaining lifetime risk for CVD in the context of overall survival. Factors that increase short-term risk for CVD are well known. However, the effect of risk factors on long-term and lifetime risk may be unpredictable because some risk factors also increase risk for non-CVD death, resulting in competing risks. We sought to estimate the lifetime risk for CVD and to examine overall survival in the presence and absence of established risk factors.
Methods

Study Sample
Study design and entry criteria for the Framingham Heart Study cohorts have been detailed elsewhere.9,10 All study protocols and procedures have been approved by the Institutional Review Board of Boston Medical Center. For the present analysis, to reflect more contemporary experience, we included all participants who were free of CVD before their earliest examination between 1971 and 2002, provided that they were examined at least once between 50 and 94 years of age and they had follow-up after their earliest eligible examination. Participants who were <50 years of age at the beginning of the study period entered the sample on attainment of 50 years of age. Only 32 participants (0.4%) were lost to follow-up during the study period.

Risk Factor Measurement
During routine examinations at the Heart Study, participants underwent standardized anthropometric measurements to determine height and weight, from which body mass index (BMI) was calculated. Current smoking was defined as self-report of active smoking within the last year before the examination. Blood pressure was determined from the average of 2 separate readings taken by a physician at least 5 minutes apart, as described previously.10 Blood, drawn in ethylene diaminetetracetic acid plasma for all cholesterol measurements, was measured as described previously.11 Diabetes was defined as the use of insulin or hypoglycemic agents, a fasting blood glucose >6.88 mmol/L (≥125 mg/dL) in offspring participants, or a casual blood glucose ≥11 mmol/L (≥200 mg/dL) in original cohort participants.

Case Ascertainment
Events during follow-up were ascertained from review of interim medical records of those who appeared and those who failed to appear for scheduled examinations. Atherosclerotic CVD events were defined by the occurrence of myocardial infarction, coronary insufficiency, death resulting from coronary heart disease, angina pectoris, atherothrombotic stroke, intermittent claudication, or other cardiovascular death. We did not include congestive heart failure events (for which the lifetime risk has previously been published12) because they often are not mediated by atherosclerosis13,14; we also did not include revascularization procedures occurring in isolation without a preceding clinical event because those typically were initiated by knowledge of the presence of risk factors rather than clinically overt disease. All deaths and suspected cardiovascular events were reviewed by a panel of 3 physicians who applied established criteria for such events.14

Statistical Analysis
All statistical analyses were performed with SAS statistical software.15 To calculate lifetime risk, a modified technique of survival analysis was used, as described previously.16 In this type of analysis, participants contributed information on the incidences of CVD and death free of CVD for each age they attained during follow-up. Participants could enter the sample at ≥50 years of age and contribute person-time to follow-up if they were still free of CVD (and therefore were free of CVD at 50 years of age) and if risk factor data had been measured at 50 years of age. Age-specific hazards, incidence rates, cumulative incidence, and survival probabilities were calculated as in a Kaplan-Meier analysis.17 Because the Kaplan-Meier cumulative incidence does not reflect the competing risk for death from other causes before the development of CVD, adjustment was made for this competing risk to yield a true remaining lifetime risk for CVD.18 Each subject in the study sample was followed up from entry through 2002 until the occurrence of a first CVD event, death, attainment of 95 years of age, or the last clinic examination or medical contact for which follow-up data were available. Lifetime risk estimates for CVD were calculated for men and women beginning at 50 years of age and extended only to 95 years of age because few participants survived past 94 years of age. We repeated the analyses, ignoring angina and claudication as first events and counting only “hard” CVD events.

We grouped participants according to risk factor levels as measured at the examination most closely preceding and up to 5 years before 50 years of age. Lifetime risks for CVD and Kaplan-Meier overall survival were then calculated as above for men and women in each risk factor stratum. Separate analyses indicated no substantial difference when we included and excluded participants receiving antihypertensive therapy, so they were included and defined as being hypertensive. Rates of cholesterol-lowering therapy were low until near the end of the study period, so we ignored treatment status in assigning cholesterol strata. Because HDL cholesterol levels were measured only from 1971 on, we did not have follow-up to 94 years of age by strata of HDL cholesterol; we also used HDL cholesterol levels measured up to 10 years before 50 years of age to increase the sample size for those analyses. For the analysis examining lifetime risk among diabetics, lifetime risk was calculated to 75 years of age because of limited follow-up among diabetics >75 years of age. Finally, we stratified participants a priori into mutually exclusive categories based on whether they had all optimal risk factor levels, ≥1 low risk factors, ≥1 intermediate risk factors, 1 major risk factor only, or ≥2 major risk factors (see Table 1 footnote for definitions). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics
We followed up 3564 men and 4362 women for a total of 111 777 person-years. Baseline characteristics for participants at 50 years of age are shown in Table 1. During follow-up, 1757 participants suffered an incident CVD event, and 1641 died free of overt CVD.

Lifetime Risk for CVD and Median Survival at 50 Years of Age
Among men free of CVD at 50 years of age, the lifetime risk to 95 years of age for developing CVD was 51.7% (95% CI, 49.3 to 54.2). Median overall survival in men was 30 years. Among women, lifetime risk to 95 years of age was 39.2% (95% CI, 37.0 to 41.4), with median overall survival of 36 years. Lifetime risks for hard CVD to 95 years of age were 41.2% (95% CI, 38.8 to 43.7) in men and 28.8% (95% CI, 26.6 to 30.8) in women.

Effect of Individual Risk Factors
As shown in Table 2 and Figure 1, increasing blood pressure and total cholesterol were associated with increased lifetime risk for CVD and with shorter median survival in both men and women. The presence of diabetes at 50 years of age conferred the highest lifetime risk for CVD of any single risk factor, at 67.1% for diabetic men and 57.3% for diabetic women through 75 years of age. Median survival was substantially lower among diabetic compared with nondiabetic men. Overweight and obesity were associated with modest increases in lifetime risk and reductions in survival compared with normal weight.

Lifetime risk for CVD was similar for smokers and nonsmokers (Table 2 and Figure 1). Smokers had CVD events much earlier than nonsmokers; eg, through 70 years of age, smokers had almost twice the adjusted cumulative incidence of CVD as nonsmokers. However, the competing risk of death from other smoking-related causes shortened the observed incidence.
median survival by 5 years and limited lifetime risk for CVD among smokers.

As shown in Table 2, the relative effect of some risk factors on lifetime risks for CVD differed through 75 years of age compared with effects through 95 years of age. For example, smoking and elevated blood pressure at 50 years of age were associated with greater relative increases in lifetime risk for CVD through 75 years of age than through 95 years of age. Conversely, elevated cholesterol was associated with a fairly constant relative effect on lifetime risk for CVD. Lifetime risk estimates through 75 years of age in effect assume that the last individual in the cohort would die at this age. However, the preponderance of mortality occurred after 75 years of age (median survival was 33 years at 50 years of age). Because smoking and elevated blood pressure increase risk for nonatherosclerotic and non-CVD death but cholesterol does not, the different effects of these risk factors on short-term and lifetime risks for CVD become evident with longer follow-up.

**Effect of Overall Risk Profile**

When we stratified participants by their burden of risk factors at 50 years of age, the magnitude of lifetime risk rose steeply from those with optimal risk factor levels to those with ≥2 major risk factors, whereas median survival declined substantially. As shown in Table 3 and Figure 2, compared with participants with ≥2 major risk factors, participants with optimal levels had substantially lower lifetime risks (5.2% versus 68.9% in men, 8.2% versus 50.2% in women) and markedly longer median survival (by >11 years in men, >8 years in women). For both men and women >50 years of age, the adjusted cumulative incidence curves across aggregate risk strata (Figure 2) separated early and continued to diverge throughout the remaining lifespan.

When low HDL cholesterol (<1.03 mmol/L [<40 mg/dL] in men, <1.29 mmol/L [<50 mg/dL] in women) and obesity (BMI ≥30 kg/m²) were included as major risk factors, lifetime risks for CVD were similar to those shown in Table 3 and Figure 2, indicating that low HDL cholesterol and obesity were equivalent to major risk factors. There were too few participants with otherwise optimal risk factor profiles and high HDL cholesterol or normal BMI (≤25 kg/m²) to provide meaningful estimates of lifetime risk in this stratum.

**Discussion**

**Principal Findings**

These results represent the first estimates of the lifetime risk for developing CVD; for people free of CVD at 50 years of age, more than half of men and nearly 40% of women will develop CVD during their remaining lifespan. Diabetes at 50 years of age confers the highest lifetime risk for CVD of any single risk factor. Participants with optimal risk factor levels at 50 years of age (only 3.2% of men and 4.5% of women in our sample) have very low remaining lifetime risk for CVD and markedly longer survival, whereas participants with ≥2 major risk factors (20.2% of men and 17.1% of women) have very high lifetime risk even in the face of substantially shorter survival.

**Clinical and Public Health Implications**

The lifetime risks for CVD are among the highest published for any disease to date. Compared with the present results, the lifetime risks for cancers are substantially lower. At 50 years of age, the most common types are breast cancer in women, with a lifetime risk of 12.5%, and prostate cancer in men, with a lifetime risk of 19%.¹⁹ Lifetime risks for lung cancer are 8% and 6% in men and women, respectively, and for colorectal cancer are 6% and 6%, respectively.¹⁹
Despite the fact that the risks of developing and dying from CVD are substantially higher than for cancer,1,19 surveys continue to indicate that most Americans perceive that their risk of cancer is higher. In a 2003 survey of a nationally representative sample of women, fewer than half correctly identified CVD as the leading cause of death among women in the United States. Furthermore, only 13% identified CVD as their greatest personal health risk, whereas 51% identified cancer as their greatest health risk.20 Thus, a substantial deficit in awareness of CVD risk exists, and there is a paradoxical gap between perceived and actual personal risk.20 Greater media coverage of cancer risks (especially breast cancer risks) during the 1990s has been well documented21 and may have perpetuated some of the knowledge gap among women. The American Heart Association and National Heart, Lung, and Blood Institute have recently initiated national programs attempting to improve women’s awareness of CVD, and there are now specific guidelines published for CVD prevention in women.22 It is hoped that the current data can help galvanize media and public interest in preventing CVD in both women and men.

Clearly, prevention efforts need to begin decades before 50 years of age because even the presence of a single major risk factor at 50 years of age is associated with substantially increased lifetime risk for CVD and markedly shorter survival. Lifestyle measures focused on diet and exercise in young adulthood and middle age could prevent the development of obesity, diabetes, hypertension, and dyslipidemia in large numbers of individuals,23 but few segments of the population have been successful in implementing them. Among individuals who already have intermediate or major risk factors at 50 years of age, our data suggest that aggressive global risk factor modification should be considered, given the associated high lifetime risks for CVD. Special attention should be paid to diabetics, who have the highest lifetime risk and shortest median survival.

Lifetime risk estimates represent an average experience derived from large cohorts, so applying them to an individual patient should be done with caution. Each patient has unique risk for developing CVD, depending on his or her levels of risk factors and genetic predisposition, that should be considered in determining the need for primary prevention strategies. In addition, patients have differing risks for death from non-CVD causes. Nonetheless, the absolute risks and median survivals provided here may be extremely useful for guiding clinicians and patients in decisions about how intensively to focus on prevention and modification of risk factors.

Our findings support the concept of estimating global risk rather than focusing on single risk factors to make treatment decisions.
decisions because we observed better discrimination of lifelong risk with aggregate risk factor burden than with any single risk factor alone. The current European guidelines\textsuperscript{24} and National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) guidelines\textsuperscript{25} recommend estimation of global 10-year risk for fatal CVD or major CHD events in determining the need for preventive therapy. However, relying solely on estimates of short-term absolute risk is problematic. Any single risk factor can produce cumulative damage and high risk if left untreated for many years.\textsuperscript{11,26–28} Long-term risk assessment is particularly relevant for younger patients, in whom exclusive attention to low short-term risk may discourage initiation of or adherence to lifestyle modification and treatment. Hence, there is a need to consider lifetime risk in addition to short-term risk, as recommended in the NCEP-ATP III guidelines.\textsuperscript{25}

These lifetime risk data, in conjunction with the median survival data, could provide a useful adjunct to short-term risk estimation in the clinical setting. For example, using the ATP-III online risk estimator (http://hin.nhlbi.nih.gov/atpiii/riskcalc.htm) indicates that a 50-year-old nonsmoking, non-diabetic man with total cholesterol of 6.47 mmol/L (250 mg/dL), HDL cholesterol of 1.55 mmol/L (60 mg/dL), and untreated systolic blood pressure of 160 mm Hg has an estimated 10-year risk for hard CHD of 7%. In contrast, his average lifetime risk for CVD is nearly 70%, and his median survival is >11 years shorter than that for a man at the same age with optimal risk factors. A woman at 50 years of age with identical risk factor levels has an estimated 10-year risk...
of only 2% compared with a lifetime risk for CVD of 50% and >8-years-shorter median survival compared with a woman at the same age with optimal risk factors. These data, placed in the clinical context, may be much more useful in motivating therapeutic lifestyle changes and promoting adherence to therapy.

**Effect of Risk Factors**

The most striking findings in the present analysis were the enormous differences in lifetime risk and survival between participants with optimal risk factor levels and those with ≥2 major risk factors. Increasing interest is being focused on participants with optimal or low levels of traditional risk factors. In addition to substantially lower risks for CVD, cardiovascular death, and total mortality,29–31 individuals with low risk factor levels also appear to age more successfully.

Daviglus et al32 recently reported that individuals with favorable risk profiles in middle age had better health-related quality of life after ~25 years of follow-up compared with those who had intermediate or major risk factors. These data underscore the importance of preventing the development of traditional risk factors at younger ages to increase healthy longevity in older adults. However, national survey data indicate that between 1991 and 2001, the percentage of American adults with no known major risk factors declined from 42% to 36%,3 a trend driven by increases in the prevalence of high cholesterol, hypertension, diabetes, and especially obesity.3,4

Our data should not be interpreted as indicating that smoking has no overall effect on CVD or health in general. To the contrary, consistent with the overwhelming weight of epidemiological evidence, smoking was associated with a

### Table 3. Lifetime Risk for CVD and Median Survival for Men and Women by Aggregate Risk Factor Status at 50 Years of Age

<table>
<thead>
<tr>
<th>Risk Stratum*</th>
<th>To 75 y</th>
<th>To 95 y</th>
<th>Median Survival (IQR), y</th>
<th>To 75 y</th>
<th>To 95 y</th>
<th>Median Survival (IQR), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>35.0 (32.9–37.2)</td>
<td>51.7 (49.3–54.2)</td>
<td>30 (22–37)</td>
<td>19.2 (17.5–20.8)</td>
<td>39.2 (37.0–41.4)</td>
<td>36 (28–42)</td>
</tr>
<tr>
<td>All optimal risk factors</td>
<td>5.2 (0–12.2)</td>
<td>5.2 (0–12.2)</td>
<td>&gt;39 (32–&gt;45)</td>
<td>8.2 (0–22.3)</td>
<td>8.2 (0–22.3)</td>
<td>&gt;39 (28–&gt;45)</td>
</tr>
<tr>
<td>≥1 Not optimal risk factor</td>
<td>17.6 (10.9–24.4)</td>
<td>36.4 (23.1–49.6)</td>
<td>36 (29–42)</td>
<td>6.9 (3.3–10.5)</td>
<td>26.9 (18.4–35.5)</td>
<td>39 (33–43)</td>
</tr>
<tr>
<td>≥1 Elevated risk factor</td>
<td>26.0 (21.0–31.0)</td>
<td>45.5 (38.0–53.1)</td>
<td>35 (26–42)</td>
<td>14.6 (11.2–17.9)</td>
<td>39.1 (33.0–45.1)</td>
<td>39 (32–44)</td>
</tr>
<tr>
<td>1 Major risk factor</td>
<td>37.6 (33.8–41.5)</td>
<td>50.4 (46.2–54.5)</td>
<td>30 (23–36)</td>
<td>18.0 (15.3–20.7)</td>
<td>38.8 (35.0–42.6)</td>
<td>35 (28–42)</td>
</tr>
<tr>
<td>≥2 Major risk factors</td>
<td>53.2 (47.1–59.3)</td>
<td>68.9 (61.7–73.2)</td>
<td>28 (18–35)</td>
<td>37.7 (32.5–43.0)</td>
<td>50.2 (44.7–55.7)</td>
<td>31 (23–38)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

*Risk factor levels defined as for Table 1.
substantially higher short-term risk for CVD and with shortened survival (by 5 years in men and women). However, in the context of the competing risk for death over the longer term, the force of mortality from noncardiovascular causes associated with smoking (ie, cancers, lung diseases) had the effect of constraining lifetime risk for CVD among smokers. Conversely, nonsmokers lived longer and had CVD events later in life. In addition, participants who subsequently ceased smoking may have lowered their risk for CVD and thereby lowered the lifetime risk estimate for smokers as a group. One-time assignment of risk factor status at the index age without updating for later crossover may appear to be a limitation of the current methods, but it best represents the data available to clinicians and patients in the office for prediction of future risk. To the best of our knowledge, these are the first data to examine lifetime risks for CVD according to BMI status. Of note, higher BMI at 50 years of age was associated with increased lifetime risk for CVD and with reduced median survival (by 3 to 4 years).

**Potential Study Limitations**

The Framingham cohorts, which are exclusively white, have consistently had risk factor levels, treatment rates, and disease incidence rates that are quite similar to US whites as a group. Blacks tend to have a heavier burden of some CVD risk factors compared with whites, but Framingham risk equations have been shown to be broadly applicable in ordering risk, although absolute risk estimates may differ. Data from another cohort suggest that lifetime risks for CVD death are similar among blacks and whites. Whereas blacks have somewhat higher age-specific incidences for CVD, they also have substantially higher competing risks for non-CVD mortality at all ages, limiting the lifetime risks for CVD. Application of these absolute lifetime risk estimates results to other race/ethnic groups is uncertain.

The high prevalence of smoking among study participants at 50 years of age, which likely reflects several decades of exposure, was associated with increased intermediate-term incidence of CVD, as observed in the lifetime risk estimates through 75 years of age (ie, 25-year follow-up). However, this increased risk is constrained when lifetime CVD risk is extended through 95 years of age, probably because of the substantial competing risk for non-CVD death associated with smoking (eg, chronic lung disease and cancer) and the preponderance of mortality from these causes occurring after 75 years of age. Lifetime risk estimates may be subject to birth cohort effects, particularly when disease incidence rates are changing rapidly. Individuals born in different decades may experience diverse risks for CVD based on temporal changes in environment and exposure to risk factors. Given the decline in CVD mortality rates in the United States over the last 4 decades, there may have been changes in lifetime risk also. Nonetheless, these lifetime risk estimates represent an important adjunct to understanding population risks that can add to short-term risk estimates.

**Acknowledgments**

Dr Lloyd-Jones is supported by grant K23 HL04253 from the National Heart, Lung, and Blood Institute. The Framingham Heart Study is supported by NIH/NHLBI contract N01-HC-25195.

**Disclosures**

None.

**References**


Current practice in primary prevention of CVD involves estimation of short-term (typically 10-year) risks for developing CVD to identify individuals at high risk who may benefit most immediately from the institution of drug therapy. However, focusing solely on short-term risk results in treatment only for older individuals with substantial risk factor burden. Younger and middle-age individuals with moderate or clearly adverse risk factor levels may have low short-term but substantial lifetime risks for development of CVD. Here, we estimated the lifetime risks for CVD and median survivals (5.2% versus 68.9% in men, 8.2% versus 50.2% in women) and markedly longer median survivals (39 versus 28 years in men, >39 versus 31 years in women). It is hoped that these findings will galvanize public health and clinical efforts to prevent the development of risk factors, to increase awareness of the dangers of cardiovascular risk factors in the long term, to improve risk communication, and to promote efforts at primary prevention. We suggest that lifetime risk estimation should be used as an adjunct to 10-year risk estimation to improve patient understanding of cardiovascular risk, to identify new segments of the population who may merit preventive therapy, and to motivate lifestyle changes and adherence to therapy.
Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age

Donald M. Lloyd-Jones, Eric P. Leip, Martin G. Larson, Ralph B. D'Agostino, Alexa Beiser, Peter W.F. Wilson, Philip A. Wolf and Daniel Levy

_Circulation_. 2006;113:791-798; originally published online February 6, 2006;
doi: 10.1161/CIRCULATIONAHA.105.548206

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/6/791

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/