Relation Between Modifiable Lifestyle Factors and Lifetime Risk of Heart Failure

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With an annual incidence of 550,000, heart failure remains a major public health issue and is the leading cause of hospitalization among older adults in the United States. Despite improved medical and surgical management, mortality after onset of heart failure remains high, ranging from 20% to 50%. A large proportion of heart failure cases is accounted for by antecedent coronary heart disease and hypertension, suggesting that predictors of coronary heart disease and hypertension might influence the risk of heart failure. The concept of lifetime risk is important in public health practice and is defined as cumulative incidence adjusted for mortality or, more simply, the risk of ever developing a disease during one's remaining lifetime before dying from other causes. It is estimated that 1 in every 5 adults aged 40 years will develop heart failure during their remaining lifetime. Thus, it remains important to focus on the primary prevention of heart failure. Several predictors of heart failure can be influenced by modifiable lifestyle factors. For example, maintaining healthy weight, not smoking, engaging in regular exercise, and maintaining a healthy diet have been shown to favorably influence heart failure risk factors including coronary artery disease, diabetes mellitus, and hypertension. However, it is unclear whether adherence to the healthy lifestyle factors could further lead to the reduction in lifetime risk of heart failure. A demonstration of beneficial influence of healthy lifestyle habits on lifetime risk has potential clinical and public health implications.

With its careful prospective collection of lifestyle factors and health outcomes and more than 20 years of follow-up, the Physicians' Health Study (PHS) offers a unique opportunity to address these important questions. Therefore, the current study sought to prospectively assess the association between modifiable lifestyle factors and the remaining lifetime risk of heart failure in a large cohort of men.

Context The lifetime risk of heart failure at age 40 years is approximately 1 in 5 in the general population; however, little is known about the association between modifiable lifestyle factors and the remaining lifetime risk of heart failure.

Objective To examine the association between modifiable lifestyle factors and the lifetime risk of heart failure in a large cohort of men.

Design, Setting, and Participants Prospective cohort study using data from 20,900 men (mean age at baseline, 53.6 years) from the Physicians' Health Study I (1982-2008) who were apparently healthy at baseline. Six modifiable lifestyle factors were assessed: body weight, smoking, exercise, alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables.

Main Outcome Measure Lifetime risk of heart failure.

Results During a mean follow-up of 22.4 years, 1200 men developed heart failure. Overall, the lifetime risk of heart failure was 13.8% (95% confidence interval [CI], 12.9%-14.7%) at age 40 years. Lifetime risk remained constant in men who survived free of heart failure through age 70 years and reached 10.6% (95% CI, 9.4%-11.7%) at age 80 years. Lifetime risk of heart failure was higher in men with hypertension than in those without hypertension. Healthy lifestyle habits (normal body weight, not smoking, regular exercise, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) were individually and jointly associated with a lower lifetime risk of heart failure, with the highest risk in men adhering to none of the 6 lifestyle factors (21.2%; 95% CI, 16.8%-25.6%) and the lowest risk in men adhering to 4 or more desirable factors (10.1%; 95% CI, 7.9%-12.3%).

Conclusion In this cohort of apparently healthy men, adherence to healthy lifestyle factors is associated with a lower lifetime risk of heart failure.

See also pp 401 and 437.
METHODS

Study Population
Participants in these analyses are members of the PHS I, a completed randomized, double-blind, placebo-controlled trial designed to study low-dose aspirin and beta carotene for the primary prevention of cardiovascular disease and cancer. A detailed description of the PHS I has been published. Of the total 22,071 participants, we excluded 1145 with missing information on lifestyle factors (body mass index [BMI], smoking, exercise, alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables), 25 with prevalent heart failure at baseline, and 1 with heart failure that occurred after age 100 years. Thus, a final sample of 20,900 participants was used for the current analyses. Each participant provided written informed consent, and the institutional review board at Brigham and Women’s Hospital approved the study protocol.

Ascertainment of Incident Heart Failure in the PHS
Ascertainment of end points including heart failure in the PHS has been achieved using follow-up questionnaires. A questionnaire was mailed to each participant every 6 months during the first year and annually thereafter to obtain information on compliance with the intervention and the occurrence of new outcomes, including heart failure. Detailed description of heart failure validation in the PHS using self-reported information and the Framingham criteria has been published elsewhere.

Furthermore, we conducted an additional validation of self-reported heart failure using a review of medical records. In the PHS, a systematic request of medical records is available for only the trial primary end points (myocardial infarction, stroke, cancer, pulmonary embolus, and death). We selected all participants who reported a diagnosis of heart failure on a yearly questionnaire and had a subsequent diagnosis of one of the trial primary end points within 30 days after reported heart failure. The rationale for selecting these conditions was that medical records for a cardiovascular event are more likely to contain pertinent information on cardiovascular signs, symptoms, treatments, and diagnostic workup including echocardiography, cardiac catheterization, and other cardiac imaging techniques. In contrast, cancer diagnoses are frequently confirmed by histologic reports.

Two physicians (a general internist and a cardiologist) independently reviewed 55 charts that met the above criteria. A diagnosis of heart failure was made if there was sufficient evidence in the chart defined as 1 of the following: (1) diagnosis of heart failure on the discharge summary prior to the current stroke or myocardial infarction, (2) major signs and symptoms from the Framingham criteria for heart failure diagnosis (2 major criteria or 1 major criterion plus 2 minor criteria for diagnosis), (3) evidence of congestive heart failure on chest radiograph, echocardiography, or other left ventricular imaging techniques, or (4) minor signs and symptoms with concomitant treatment for heart failure (use of diuretics, digoxin in the absence of atrial fibrillation, angiotensin-converting enzyme inhibitors, angiotensinogen receptor blockers, and β-blockers).

Using these criteria, heart failure was confirmed in 50 of 55 cases (91%). For 5 study participants, we did not find sufficient evidence in the chart to confirm the diagnosis of heart failure. Interrater agreement between the 2 examiners was excellent (κ = 92.3%). For the present analyses, we used heart failure and death cases ascertained through February 2008.

Assessment of Lifestyle Factors and Other Factors
We focused on modifiable lifestyle factors that have been shown to influence the risk of cardiovascular disease. These included adiposity, smoking, physical activity, alcohol intake, and dietary habits. At baseline, each study participant provided information on smoking (never, former, and current smoker), exercise (how often do you exercise vigorously enough to work up sweat? Possible answers in-
Table 2. Lifetime Risk of Heart Failure According to Age Attained Free of Heart Failure and Prevalent Hypertension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lifetime Risk (95% CI), %a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>No.</td>
<td>20,900</td>
</tr>
<tr>
<td>Total deaths, No.</td>
<td>5673</td>
</tr>
<tr>
<td>Heart failure, No.</td>
<td>1200</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>13.8 (12.9-14.7)</td>
</tr>
<tr>
<td>50</td>
<td>13.8 (12.8-14.8)</td>
</tr>
<tr>
<td>60</td>
<td>13.8 (12.8-14.8)</td>
</tr>
<tr>
<td>70</td>
<td>13.1 (12.1-14.1)</td>
</tr>
<tr>
<td>80</td>
<td>10.6 (9.4-11.7)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Table 3. Lifetime Risk of Heart Failure at Age 40 Years According to Lifestyle Factors

<table>
<thead>
<tr>
<th>Lifestyle Factors</th>
<th>No.</th>
<th>Total Deaths, No.</th>
<th>Heart Failure, No.</th>
<th>Lifetime Risk (95% CI), %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index &lt; 25</td>
<td>12,007</td>
<td>3021</td>
<td>517</td>
<td>11.3 (10.2-12.5)</td>
</tr>
<tr>
<td>Body mass index ≥ 25</td>
<td>8,809</td>
<td>2652</td>
<td>683</td>
<td>16.9 (15.4-18.4)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10,360</td>
<td>227</td>
<td>473</td>
<td>13.2 (11.7-14.7)</td>
</tr>
<tr>
<td>Ever</td>
<td>10,540</td>
<td>3399</td>
<td>727</td>
<td>14.4 (13.1-15.6)</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5 times/wk</td>
<td>3,380</td>
<td>930</td>
<td>161</td>
<td>11.4 (9.4-13.5)</td>
</tr>
<tr>
<td>&lt; 5 times/wk</td>
<td>17,520</td>
<td>4743</td>
<td>1039</td>
<td>14.3 (13.2-15.4)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-14 drinks/wk</td>
<td>7,807</td>
<td>2431</td>
<td>460</td>
<td>13.1 (11.7-14.5)</td>
</tr>
<tr>
<td>&lt; 5 drinks/wk</td>
<td>13,093</td>
<td>3242</td>
<td>740</td>
<td>14.2 (13.0-15.5)</td>
</tr>
<tr>
<td>Breakfast cereal consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 serving/wk</td>
<td>11,393</td>
<td>3094</td>
<td>620</td>
<td>12.9 (11.7-14.1)</td>
</tr>
<tr>
<td>&lt; 1 serving/wk</td>
<td>9,507</td>
<td>2579</td>
<td>580</td>
<td>15.0 (13.5-16.5)</td>
</tr>
<tr>
<td>Fruit and vegetable consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4 servings/d</td>
<td>1,485</td>
<td>546</td>
<td>97</td>
<td>11.9 (9.5-14.4)</td>
</tr>
<tr>
<td>&lt; 4 servings/d</td>
<td>19,415</td>
<td>5127</td>
<td>1103</td>
<td>14.0 (13.0-15.1)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Definition of Lifestyle Groups
To investigate the association between healthy lifestyle factors and the lifetime risk of heart failure, each lifestyle risk factor was dichotomized: normal weight (BMI < 25) vs overweight/obese (BMI ≥ 25); never smoker vs ever smoker; regular exercise (≥ 5 times/wk) vs infrequent/no exercise (< 5 times/wk); moderate drinking (≥ 5 drinks/wk) vs < 5 drinks/wk); consumption of breakfast cereal (≥ 1 servings/wk) vs none; and consumption of fruits and vegetables (≥ 4 servings/d vs < 4 servings/d). Of note is that a small proportion (3%) of the total sample reported consuming more than 2 alcoholic drinks per day. These cut points were chosen based on prior associations between individual lifestyle factors and heart failure risk in this cohort or on public health recommendations.

Each person could have a minimum of 0 and a maximum of 6 healthy lifestyle factors. Since only 397 (1.9%) and 32 (0.2%) men were in the categories with 5 and 6 healthy lifestyle factors, re-
respectively, we collapsed the upper 3 categories to obtain stable estimates (subsequently referred to as the ≥4 group). Thus, study participants were categorized according to the number of desirable lifestyle factors (0, 1, 2, 3, and ≥4).

**Statistical Analyses**

Means and percentages of baseline characteristics of the study participants are presented according to the number of healthy lifestyle factors. To calculate the lifetime risk of heart failure, a modified technique of survival analysis was used, as described previously. Because few men survived past age 98 years, lifetime risk estimates were calculated only through age 98. Each person in the study sample was followed from baseline until either the year of a first heart failure event, the year of death, or attainment of age 98 years. The lifetime risk was calculated separately for each index age of 40, 50, 60, 70, and 80 years. Risk estimates were produced using the Practical Incidence Estimators Macro, which has been described in detail.

Calculation of lifetime risks was stratified by individual lifestyle factors and number of healthy lifestyle factors as described above. In addition, stratification by prevalent hypertension was completed. Because alcohol consumption may increase blood pressure levels and heavy drinking has been associated with cardiomyopathy, and because we lacked complete dietary information to fully assess the role of diet, we repeated our analyses restricted to the 3 remaining lifestyle factors (adiposity, smoking, and exercise). In a sensitivity analysis, we repeated our analysis restricted to heart failure with and without antecedent coronary disease (angina, myocardial infarction, revascularization, or bypass) or with antecedent myocardial infarction, type 2 diabetes, and hypertension.

In addition, we repeated analyses accounting for possible changes in BMI, smoking, exercise, and dietary factors where available. Specifically, for continuous variables, we used a cumulative average from baseline to censoring date or development of heart failure to classify participants. For smoking, a never smoker was required to remain a never smoker throughout all smoking variables assessed prior to heart failure occurrence or censoring date. A similar approach was used for exercise and dietary factors.

All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina), and the α level was set at .05. All P values were 2-sided.

**RESULTS**

**Characteristics**

During a mean follow-up of 22.4 years, 1200 new cases of heart failure (5.7%) and 4999 confirmed deaths (23.9%) occurred in the study. Baseline characteristics according to the number of healthy lifestyle factors are presented in Table 1. Compared with participants adhering to no healthy lifestyle factors, those adhering to 4 or more factors tended to be older and had a lower prevalence of hypertension and diabetes mellitus.

**Lifetime Risk of Heart Failure**

Overall, the lifetime risk of heart failure was 13.8% (95% confidence interval [CI], 12.9%-14.7%) at age 40 years and remained constant through age 70; at age 80 years, the lifetime risk for heart failure was 10.6% (95% CI, 9.4%-11.7%) (Table 2). As expected, the remaining lifetime risk of heart failure was approximately 2% to 4% higher in men with hypertension than in those without hypertension (Table 2). For men with heart failure but without antecedent myocardial infarction, the lifetime risk was about 1 in 9, or 11.5% (95% CI, 10.6%-12.4%) at age 40 years, 11.5% (95% CI, 10.6%-13.3%) at age 50, 11.5% (95% CI, 10.6%-12.4%) at age 60, 10.9% (95% CI, 10.0%-11.8%) at age 70, and 8.7% (95% CI, 7.6%-9.7%) at age 80.

**Lifestyle Factors and Lifetime Risk of Heart Failure**

Normal body weight, never smoking, regular exercise, moderate alcohol intake, and consumption of breakfast cereal and fruits and vegetables were individually associated with a lower lifetime risk of heart failure compared to the corresponding undesirable behavior (Table 3). There was an inverse and graded association between the number of healthy lifestyle factors and lifetime risk of heart failure (Figure 1). For example, the lifetime risk for heart failure was approximately 1 in 5 (21.2%; 95% CI, 16.8%-25.6%) in men adhering to none of the desirable lifestyle factors, compared to 1 in 10 (10.1%; 95% CI, 7.9%-12.3%) in those adhering to 4 or more healthy factors accounting for change over time in body mass index, smoking, exercise, breakfast cereal consumption, and fruit and vegetable consumption.
of heart failure persisted in the overall population (Figure 3) as well as in men with and without hypertension (Figure 4). We also observed a similar association between healthy lifestyle factors and the lifetime risk of heart failure with antecedent myocardial infarction, type 2 diabetes mellitus, or hypertension (Figure 5).

**COMMENT**

In this cohort of apparently healthy male physicians, we observed that the remaining lifetime risk of heart failure was approximately 1 in 7 at age 40, 50, 60, and 70 years. Despite the homogeneity in educational attainment and socioeconomic status in this cohort, we noted that adherence to healthy lifestyle factors was associated with the remaining lifetime risk of heart failure. As expected, the lifetime risk of heart failure was higher in men with hypertension than in those without hypertension. We observed a similar relation between heart failure with antecedent myocardial infarction, type 2 diabetes mellitus, or hypertension.

Few studies have examined the remaining lifetime risk of this condition. In the Framingham Heart Study, Lloyd-Jones et al. found that the lifetime risk of heart failure in 3757 men at age 40 years was 21.0%. In the Rotterdam Study, a lower risk was observed only in men aged 80 years. Such lower risk in the oldest age group could be attributable to the shorter remaining time at risk as well as the depletion of susceptible individuals, decreased disease ascertainment or reporting with very advanced age, or both. Although the lifetime risk of heart failure in our study (approximately 1 in 7) was high, it was lower than the 1 in 5 observed in the Framingham heart study or the 1 in 3 observed in the Rotterdam study in men of similar ages. What factors could account for the discrepancy?

First, we acknowledge the difficulty of direct comparison of lifetime risk across populations in the absence of comparable mortality rates. A high mortality rate from other causes can lead to lower lifetime risks of heart failure, owing to a shorter period at risk. In contrast, longevity can lead to a higher lifetime risk than expected, particularly if the disease is prevalent at advanced ages. At age 40 years, PHS I participants have a life expectancy of 49.3 additional years—12 years longer than that of 40-year-old men in the general US population. It is notable that even though our cohort was longer lived (and thus had a longer period at risk for heart failure) than the cohorts in the Framingham or Rotterdam studies, we observed substantially lower lifetime risks of heart failure. This may be attributable to the healthy lifestyle factors in our population leading to a decreased incidence of heart failure.

Second, the study period may be a possible contributing source for the variability in estimates of lifetime risk of heart failure across studies. Although there was limited overlap between the Framingham study period (1971 to 1996) and that of the PHS I...
(1982 to 2008), the Rotterdam study period (1989 to 2000) was completely included in the PHS study period. A reduction in annual incidence over time (attributable to better treatment) would partially explain the lower lifetime risk of heart failure in the most recent study. However, published data on secular trends in heart failure incidence suggest no substantial change in rate over time.

Third, it is possible that the variability in diagnosis criteria for heart failure could have led to heterogeneity in cases across studies. Fourth, the PHS I population consisted of adult male physicians recruited for a primary prevention trial, and it is possible that physicians may have lower risk of heart failure, given their medical knowledge, their access to state-of-the-art treatment, and their early recognition of signs and symptoms leading to the detection of milder cases of heart failure that may have been missed in the Framingham or Rotterdam studies. However, early detection of heart failure in the PHS I would have led to increased rate of heart failure and would not explain the observed lower lifetime risk of heart failure compared with the Framingham and Rotterdam studies. Lastly, the healthy volunteer effect could have contributed to the lower lifetime risk of heart failure in this cohort.

Our finding for heart failure without antecedent coronary disease was similar to the Framingham data in men. As expected, men with hypertension had a higher lifetime risk of heart failure than those without hypertension.

In this cohort, we noted that normal body weight, not smoking, regular exercise, moderate alcohol intake, consumption of breakfast cereal, and consumption of fruits and vegetables were individually and jointly associated with a lower lifetime risk of heart failure. The lowest risk was observed in men with 4 or more healthy lifestyle factors. Our data were robust in that restriction to 3 common lifestyle factors (adiposity, smoking, and exercise) yielded similar results, and these results were further strengthened after accounting for change in lifestyle factors over time.

To the best of our knowledge, this is the first study to examine the influence of modifiable lifestyle factors on the remaining lifetime risk of heart failure in a large cohort. Of note is that the lifetime risk was 22% in men adhering to none of the desirable healthy lifestyle factors. This is about the same risk observed among men in the Framingham Heart Study who were the same age (40 years) and suggests that education alone without adherence to healthy lifestyle factors may not be adequate to lower the lifetime risk of heart failure. To the contrary, our data suggest that maintenance of healthy habits known to lower the risk of cardiovascular disease remains critical to lowering the risk of heart failure.

The large number of participants, more than 22 years of follow-up, and standardized methods of end-points ascertainment are major strengths of this study. On the other hand, all participants were male physicians, most of whom white, which limits the generalizability of the current findings. In addition, we were unable to examine the lifetime risk of systolic heart failure vs diastolic heart failure, and we did not have data on the etiology of heart failure. Although the ascertainment of heart failure in this study was self-reported, the high confirmation rates of diagnosis using Framingham criteria and review of medical records on 2 subsamples is reassuring that we had a reasonable case ascertainment. Nevertheless, we cannot exclude misclassification of some cases. It is possible that change in lifestyle factors before incident heart failure may have led to an underestimation of the effect measure. However, findings accounting for change in lifestyle factors over time yielded similar conclusions, suggesting that such bias may not completely explain our findings. Furthermore, we had reasonable Pearson correlation coefficients or levels of agreement across repeated measures. We were unable to account for early lifestyle factors for men who entered the study at an older age (ie, >75 years), despite the 22 years of follow-up. Lastly, in the absence of randomization of studied lifestyle factors, we cannot exclude unmeasured or residual confounding as partial or complete explanation of these findings.

Our data provide further evidence supporting a high burden of heart failure, even among individuals with a higher educational attainment. Our estimate of lifetime risk of heart failure could help public health officials allocate resources for the prevention and management of this condition. Our findings of a low lifetime risk in men who adhere to modifiable lifestyle factors emphasize the need for incorporation of these behaviors in prevention strategies against heart failure at both the individual and the population level.

CONCLUSIONS

In this cohort of apparently healthy men, our findings suggest that adherence to healthy lifestyle factors is associated with a lower lifetime risk of heart failure as compared with the general population. Confirmation of the influence of modifiable lifestyle factors on the lifetime risk of heart failure in other populations is warranted.

Author Contributions: Drs Djousse and Gaziano had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Djousse, Driver.

Acquisition of data: Gaziano.

Analysis and interpretation of data: Djousse, Driver.

Drafting of the manuscript: Djousse.

Critical revision of the manuscript for important intellectual content: Djousse, Driver, Gaziano.

Statistical analysis: Djousse, Driver.

Obtained funding: Gaziano.

Administrative, technical, or material support: Djousse, Gaziano.

Study supervision: Gaziano.

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MODIFIABLE LIFESTYLE FACTORS AND LIFETIME RISK OF HEART FAILURE

REFERENCES


