Association Between a 20-Year Cardiovascular Disease Risk Score Based on Modifiable Lifestyles and Total and Cause-Specific Mortality Among US Men and Women

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Background—The previously validated Healthy Heart Score effectively predicted the 20-year risk of cardiovascular disease (CVD). We examine whether the Healthy Heart Score may extend to an association with total and cause-specific mortality.

Methods and results—The prospective cohort study investigated 58 319 women (mean age 50.2 years) in the Nurses' Health Study (1984–2010) and 29 854 in men (mean age 52.7 years) in the Health Professionals' Follow-up Study (1986–2010) free of cancer and CVD at baseline. The Healthy Heart Score included baseline current smoking; high body mass index; low physical activity; no or excessive alcohol intake; low intake of fruits and vegetables, cereal fiber, or nuts; and high intake of sugar-sweetened beverages or red/processed meats. There were 19 122 total deaths. Compared with participants in the first quintile of the Healthy Heart Score (lowest CVD risk), participants in the fifth quintile (highest CVD risk) had a pooled hazard ratio of 2.26 (95% confidence interval [CI], 1.53–3.33) for total mortality; 2.85 (95 % CI, 1.92–4.23) for CVD mortality, and 2.14 (95% CI, 1.56–2.95) for cancer mortality. Participants in the fifth versus the first quintile also had significantly greater risk of death due to coronary heart disease (3.37; 95% CI, 2.16–5.25), stroke (1.75; 95% CI, 1.02–2.99), lung cancer (6.04; 95% CI, 2.78–13.13), breast cancer (1.45; 95% CI, 1.14–1.86), and colon cancer (1.51; 95% CI, 1.18–1.93).

Conclusions—The Healthy Heart Score, composed of 9 self-reported, modifiable lifestyle predictors of CVD, is a potentially useful tool for the counseling of healthy lifestyles that was strongly associated with greater risk of all-cause, CVD, and cancer mortality. (*J Am Heart Assoc*. 2018;7:e010052. DOI: 10.1161/JAHA.118.010052.)

Key Words: cohort study • lifestyle • mortality • prevention • risk score

Despite the decline in cardiovascular disease (CVD) mortality in the United States, it remains the leading cause of death.[1] Several well-established clinical risk factors for CVD, including high blood pressure, diabetes mellitus, and hypercholesterolemia, are viewed as major risk factors for management and control of subsequent CVD risk.[2] The primary prevention of CVD has largely focused on pharmacological treatment plus lifestyle counseling, mostly addressing high-risk adults identified by risk prediction tools that include in their assessment clinical risk factors (eg, high blood pressure or high cholesterol). Additionally, in the 1990s, dietary guidelines focused on low-fat diets for prevention of CVD based on little evidence. However, evidence from controlled feeding trials with risk factors as outcome, long-term epidemiologic studies, and older small randomized trials indicated that the health effects of dietary fats are heavily dependent on the replacement macronutrien.[3,4] Another strategy for CVD prevention is through the primordial prevention of CVD risk factors through lifestyle modification, rather than the treatment or modification of risk factors once

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Clinical Perspective

What Is New?

- This is a large prospective cohort that extends the association of the Healthy Heart Score, which is composed of 9 self-reported, modifiable lifestyle predictors of cardiovascular disease, to mortality risk.
- Participants in the fifth quintile with a higher predictive cardiovascular disease risk based on the Healthy Heart Score had a 2.2-fold higher risk of total mortality, 2.9-fold higher risk of cardiovascular disease mortality, and 2.1-fold higher risk of cancer mortality over 26 years (women) or 24 years (men).

What Are the Clinical Implications?

- The Healthy Heart Score is a potentially useful tool for the counseling of healthy lifestyles that was strongly associated with greater risk of all-cause, cardiovascular disease, and cancer mortality.
- A lifestyle-only risk score could be used to assess and motivate a larger audience in clinical and population-wide settings.

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they become elevated. Data from epidemiological studies have shown that healthy dietary choices, physical activity, weight maintenance, and not smoking each play an important role in primordial prevention[5,6] and the maintenance of cardiovascular health.[7]

A primordial prevention strategy may also extend to a lower risk in major cause-specific deaths and greater longevity. For example, following a healthy lifestyle pattern may prevent more than 50% of deaths due to ischemic strokes,[8] 80% of sudden cardiac deaths,[9] and 75% of all deaths due to CVD.[10] Recent data suggest that a 60% lower risk of premature mortality was found in individuals with a body mass index (BMI) <22.4 kg/m^2 and with a high score on the Alternate Healthy Eating Index, high level of physical activity, and nonsmoking.[11]

The previously validated Healthy Heart Score predicted the 20-year risk of CVD in mid-adulthood based on modifiable health behaviors (diet, physical activity, alcohol intake, smoking, and body weight) to address both primordial and primary prevention.[12] Previously, women in the fifth quintile, with higher predicted CVD risk based on the Healthy Heart Score, had 18, 5, and 3-fold higher risk of diabetes mellitus, hypertension, and hypercholesterolemia, respectively.[13] In addition, the Healthy Heart Score recently showed moderately good performance (C statistic, 0.71; 95% confidence interval [CI], 0.66–0.76) in younger people.[14]

It remains unclear how well the Healthy Heart Score, a tool that can be potentially translated to a clinical setting, may extend to lower mortality risk. The support that the Healthy

Heart Score may be associated with a broad range of outcomes is important clinically because an individual can adopt a set of behaviors to prevent different outcomes. Thus, we assessed the association between the Healthy Heart Score and total and cause-specific mortality in NHS (Nurses' Health Study) and HPFS (Health Professionals' Follow-up Study).

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Channing Division of Network Medicine at nhsaccess@channing.harvard.edu.

Study Participants

We conducted analyses in NHS, a prospective cohort of 121 700 female nurses aged 30–55 years at baseline in 1976[15] and in HPFS, a cohort of 51 529 US male health professionals, aged 40 to 75 years, in 1986.[16] Participants in both cohorts provided information on medical history, lifestyle factors, and newly diagnosed diseases on self-reported questionnaires throughout follow-up every 2 to 4 years. In the current investigation, 1984 was used as baseline for NHS and 1986 for HPFS, when we first obtained detailed information on diet and lifestyle, to calculate the 20-year CVD risk score. We excluded participants with a history of CVD (myocardial infarction, angina, stroke, transient ischemic attack, and coronary revascularization) or cancer, or who were missing information on alcohol, physical activity, BMI, or smoking at baseline, and those who were outside of the predefined limits of energy intake levels (<800 or >4200 kcal/d for men and <500 or >3500 kcal/d for women) at baseline. The final study population consisted of 58 319 women in NHS (1984–2010) (mean age 50.2 years in 1984) and 29 854 in men in HPFS (1986–2010) (mean age 52.7 years in 1986). The institutional review boards at the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital approved the study protocols and return of the questionnaire implied informed consent.

Assessment of Healthy Lifestyle

The Healthy Heart Score is a CVD risk prediction model that estimates the 20-year risk of CVD (nonfatal MI, fatal coronary heart disease [CHD], and ischemic stroke) based on lifestyle factors and was developed among a random two thirds of participants separately within 2 cohorts (HPFS and NHS)[15,16] free of CVD, diabetes mellitus, and cancer at baseline.[12] The sex-specific risk scores were validated in the remaining one

third of participants in each cohort and demonstrated good discrimination (Harrell C Index: 0.72; 95% CI, 0.71–0.74 [women]; 0.77; 95% CI, 0.76–0.79 [men]), fit, and calibration. While numerous lifestyle predictors of CVD were considered, the final parsimonious model included the 9 factors that best estimated CVD risk: current smoking; higher BMI; low physical activity; no or excessive alcohol consumption; low intake of fruits, vegetables, cereal fiber, or nuts; and high intake of sugar-sweetened beverages or red/processed meats (Figure S1). A higher Healthy Heart Score reflected a higher risk of CVD.[12] In addition, we set age as a constant (age=50) in the prediction model for this analysis because we were interested in the modifiable components of the Healthy Heart Score. Additionally, age is predictive of all disease, and specifically mortality. Because it is the strongest component of the score, it would have driven any observed association with mortality. We also adjusted for age separately by including it as a covariate in our Cox models. In sensitivity analysis we also conducted the analysis with the original equation.

Smoking status was self-reported and categorized as "never," "past," or "current." BMI (kg/m^2) was calculated from self-reported height and weight, which was highly correlated with previously directly measured weight ($r=0.96$).[17] For physical activity, we used a previously validated physical activity questionnaire[18,19] to estimate the average hours per week spent in moderate- or vigorous-intensity activity (≥ 3 metabolic equivalent task). For each food item, participants were asked how often on average a specified portion was consumed during the past year.[20] Cereal fiber and alcohol intake was calculated by multiplying the nutrient content of each food item (from the Harvard University Food Composition Database) by the frequency of intake and summed across all food items. We used the residual method to adjust cereal fiber for total energy.[21] We calculated average grams per day of alcohol intake, assuming 12.8 g of alcohol in 12 oz of beer, 11.0 g of alcohol in 4 oz of wine, and 14.0 g of alcohol in 1.5 oz of liquor.

Data were obtained on family history of myocardial infarction, cancer, or diabetes mellitus; aspirin use; vitamin supplement use; new physician-diagnosed hypertension, hypercholesterolemia, or diabetes mellitus; and menopausal status and postmenopausal hormone therapy and oral contraceptives use (in women).

Ascertainment of Mortality

Deaths through 2010 from any cause were the primary outcome of this analysis. Deaths were identified from the state vital statistics records and the National Death Index, or reported by families and the postal system.[22] Using these methods, 98% of deaths in each cohort were able to be ascertained.[22] For all deaths, we sought death certificates and, when appropriate, requested permission from the next of kin to review medical records. The underlying cause of death was assigned by a physician who was unaware of the data on diet quality after reviewing death certificates and medical records according to the *International Classification of Diseases, Eighth Revision (ICD-8)*.

Statistical Analysis

Person-years were calculated from the date of return of the baseline questionnaire to the date of diagnosis of death or the end of follow-up (January 31, 2010, for HPFS and June 30, 2010, for NHS), whichever occurred first. We categorized the Healthy Heart Score into quintiles based on the distribution in each study population.

The hazard ratios (HRs) and 95% CIs for all-cause and cause-specific mortality according to quintiles of the Healthy Heart Score were estimated using Cox proportional hazards models using calendar year as the underlying time scale, and adjusting for age, race (white versus others), family history of myocardial infarction, aspirin use, multivitamin use, menopausal status and hormone use in women, total energy, and last time of physical checkup examination (first multivariable model). Since diagnoses of some conditions may encourage a participant to change their diet or other lifestyles, we additionally adjusted for history of hypertension, hypercholesterolemia, or type 2 diabetes mellitus (yes versus no) in a separate model. As the inclusion of these covariates did not change the HRs, we reported only the age-adjusted and first multivariable model above.

We conducted a test for linear trend across quintiles of the Healthy Heart Score by assigning the median value to each quintile and modeling this as a continuous variable.[23]

We tested for interaction by age (<median versus $\geq$median), BMI status (<25 versus $\geq$25 kg/m^2, ie, normal versus overweight/obesity), smoking status (never smoker versus ever smoker), alcohol intake (nondrinker, moderate drinker, heavy drinker), physical activity (<150 minutes versus $\geq$150 minutes), and diet score (above and below the median). For each potential modifier, we created a cross-product term between the modifier and quintiles of the Healthy Heart Score. We used the quintile cut points established in the combined NHS and HPFS population to maintain consistency in the distribution of the Healthy Heart Score across categories of each modifier. We used likelihood ratio tests to compare models with and without the cross-product terms to test formally for an interaction. All analyses were performed separately in each cohort and then pooled using an inverse, variance-weighted meta-analysis with fixed-effects model. All analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc).

Table 1. Age-Adjusted Baseline Characteristics According to Quintiles of the Healthy Heart Score

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Nurses' Health Study					
Healthy Heart Score (20-y risk)*	2.1 (0.2)	2.6 (0.1)	3.1 (0.2)	4.2 (0.6)	7.3 (3.0)
Healthy Heart Score components					
Age, y	50.0 (7.3)	50.1 (7.3)	50.4 (7.2)	50.7 (7.0)	50.0 (6.9)
BMI, kg/m^2	21.5 (1.8)	23.3 (2.2)	25.3 (2.6)	27.4 (5.1)	27.0 (6.4)
Current smoker, %	0	0	0.1	27.1	86.0
Fruits and vegetables, servings per d	5.9 (2.6)	5.5 (2.5)	5.2 (2.6)	5.2 (2.6)	4.5 (2.5)
Sugar-sweetened beverages, servings per d	0.2 (0.3)	0.2 (0.4)	0.3 (0.5)	0.3 (0.6)	0.4 (0.8)
Red and processed meats, servings per d	0.9 (0.5)	1.1 (0.6)	1.2 (0.7)	1.3 (0.7)	1.3 (0.8)
Cereal fiber, g/d	5.2 (2.8)	4.5 (2.4)	4.0 (2.0)	3.8 (2.0)	3.4 (1.8)
Nuts, servings per d	0.2 (0.3)	0.1 (0.3)	0.1 (0.2)	0.1 (0.3)	0.1 (0.2)
Alcohol intake, g/d	8.6 (9.3)	6.0 (8.8)	4.7 (8.6)	6.7 (11.4)	8.5 (15.7)
Physical activity, MET-h/wk	4.3 (2.2)	3.2 (2.1)	2.7 (1.9)	2.9 (2.1)	2.6 (1.9)
Energy intake, kcal	1736 (489)	1735 (511)	1747 (531)	1765 (544)	1754 (554)
Baseline diabetes mellitus, %	1.2	1.6	2.5	4.5	3.9
Baseline hypertension, %	13.1	15.9	21.6	27.9	25.3
Baseline hypercholesterolemia, %	6.3	7.3	8.4	9.5	8.6
Family history of MI, %	17.0	17.7	19.7	20.7	20.5
Family history of cancer, %	15.9	15.4	15.3	15.5	14.1
Family history of diabetes mellitus, %	24.7	27.4	31.7	32.8	31.9
Aspirin use (yes), %	71.5	72.6	71.6	71.0	70.1
Multivitamin use,%	44.2	39.8	36.6	35.3	31.7
Underwent physical examination for screening purposes	63.3	61.5	59.5	56.9	53.9
Health Professionals' Follow-up Study					
Healthy Heart Score (20-y risk)†	2.7 (0.3)	3.3 (0.1)	3.8 (0.2)	4.5 (0.2)	6.6 (3.1)
Healthy Heart Score components					
Age, y	53.1 (9.8)	52.5 (9.6)	52.7 (9.5)	52.8 (9.3)	52.2 (8.9)
BMI, kg/m^2	22.5 (1.6)	24.0 (1.4)	25.1 (1.5)	26.4 (1.9)	29.2 (4.1)
Current smoker, %	0.4	0.9	2.8	9.6	32.7
Fruits and vegetables, servings per d	5.4 (2.8)	4.9 (2.5)	4.6 (2.4)	4.4 (2.4)	4.2 (2.4)
Sugar-sweetened beverages, servings per d	0.2 (0.3)	0.3 (0.4)	0.3 (0.5)	0.4 (0.6)	0.6 (0.8)
Red and processed meats, servings per d	0.8 (0.6)	1.0 (0.7)	1.2 (0.7)	1.3 (0.8)	1.6 (0.9)
Cereal fiber, g/d	7.4 (3.6)	6.2 (3.2)	5.6 (2.9)	5.1 (2.6)	4.5 (2.3)
Nuts, servings per d	0.8 (0.9)	0.6 (0.7)	0.6 (0.7)	0.6 (0.7)	0.5 (0.6)
Alcohol intake, g/d	14.0 (14.7)	12.1 (14.1)	11.0 (14.1)	10.4 (14.6)	10.0 (15.2)
Physical activity, MET-h/wk	5.7 (6.1)	3.2 (3.7)	2.4 (3.0)	1.8 (2.6)	1.3 (2.2)
Energy intake, kcal	2076 (587)	2037 (593)	2044 (617)	2065 (628)	2145 (668)
Baseline diabetes mellitus, %	2.0	2.2	2.2	2.3	3.2
Baseline hypertension, %	13.9	16.3	17.8	21.0	26.0
Baseline hypercholesterolemia, %	11.2	9.6	10.0	9.7	11.0
Family history of MI, %	32.5	31.5	31.7	31.6	32.0

Table 1. Continued

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Family history of cancer, %	36.3	34.1	34.9	34.4	32.8
Family history of diabetes mellitus, %	17.8	17.6	19.0	20.1	21.6
Aspirin use (yes), %	25.4	25.6	27.1	27.0	29.7
Currently uses multivitamins, %	50.2	45.5	41.4	39.4	36.9
Underwent physical examination for screening purposes	53.3	51.9	50.9	49.8	42.6

MET indicates metabolic equivalent; MI, myocardial infarction.

Continuous variables are presented as means (SDs) and categorical values as percentages.

*The formula to estimate the 20-year risk of cardiovascular disease (percentage) based on lifestyle predictors derived includes age as a constant (50 years) and includes smoking, body mass index (BMI), physical activity, alcohol, and a composite diet score (fruits and vegetables, sugar-sweetened beverages, red/processed meats, cereal fiber, nuts) (Figure S1).

Results

During 7 789 315 participant-years of follow-up, we documented 19 122 total deaths, including 11 403 in women and 7719 in men.

Baseline and lifestyle characteristics by quintiles of the Healthy Heart Score are shown in Table 1. In both cohorts, participants with the higher predictive CVD risk (top quintile) were more likely to have a higher BMI, be a current smoker, have higher energy intake, have a higher prevalence of diabetes mellitus or hypertension, and have a family history of diabetes mellitus. In addition, participants with the highest quintile had lower diet score, physical activity, and multivitamin use, and were less likely to undergo physical checkup examinations.

Both age- and multivariable-adjusted analyses showed a significant association across quintiles of the Healthy Heart Score and total mortality, as well as cause-specific mortality for CVD or cancer in both men and women (all *P* trend<0.05), across quintiles, and per 5% increase in the 20-year risk of CVD (Table 2). The pooled HR comparing participants in the highest quintile (median, 6.6 in Healthy Heart Score) versus participants in the lowest quintile (median, 2.1) was 2.26 (95% CI, 1.53–3.33) for total mortality, 2.85 (95% CI, 1.92–4.23) for CVD mortality, and 2.14 (95% CI, 1.56–2.95) for cancer mortality. Those results were stronger for women than men especially in the fourth and fifth quintiles (Table 2).

In addition, we evaluated specific causes of CVD, cancer, and non-CVD and noncancer deaths. Participants in the top quintile versus the first quintile of the Healthy Heart Score had significantly higher risk of death due to CHD (pooled HR, 3.37; 95% CI, 2.16–5.25), stroke (pooled HR, 1.75; 95% CI, 1.02–2.99), lung cancer (pooled HR, 6.04; 95% CI, 2.78–13.13), breast cancer (pooled HR, 1.45; 95% CI, 1.14–1.86), and colon cancer (pooled HR, 1.51; 95% CI, 1.18–1.93) (Table 3).

In analyses stratified by dichotomous categories of risk factors of the Healthy Heart Score, the association between quintiles of the Healthy Heart Score and total mortality was significantly higher for participants in the top quintile for each category studied, for both cohorts (Table 4).

However, the association was greatest among participants who were younger (below the median [50 years for women and 52 years for men]), were ever smokers, had an alcohol consumption higher than the recommendations (5–14 g for women, 10–25 g for men), and had a diet score below the median (1.83 for women and 0.71 for men) (Table 4).

Discussion

In this large prospective cohort of women and men, participants in higher quintiles of the Healthy Heart Score, composed of 9 self-reported, modifiable lifestyle predictors of CVD (higher BMI, current smoking, low physical activity, lack of moderate alcohol consumption, low composite diet score), had a significantly increased risk of total and cause-specific mortality. Specifically, participants in the fifth quintile with a higher predictive CVD risk based on the Healthy Heart Score had a 2.2-fold higher risk of total mortality, 2.9-fold higher risk of CVD mortality, and 2.1-fold higher risk of cancer mortality over 26 years (women) or 24 years (men). Further, a higher predictive CVD risk was associated with greater risk of death due to specific types of CVD (CHD, stroke) and several site-specific cancers (lung, breast, and colon). The association appeared to be more pronounced among participants who were younger, had optimal weight, were ever smokers, had alcohol consumption higher than recommended, or had a diet score below the median.

The findings in the current study are consistent with the scientific literature that an excess of adiposity,[11,24] insufficient physical activity,[25] cigarette smoking,[26] and poor diet[27] are independently associated with a greater risk of mortality. Studies analyzing a set of different lifestyles are difficult to compare because the estimates vary according to the lifestyle definition and the lifestyle factors selected.[28–30] For example, prior studies in the NHS and the HPFS cohorts compared 5

Table 2. Total, Cardiovascular, and Cancer Mortality According to Quintiles of the Healthy Heart Score*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P Trend	Per 5% Increase in the Score
Total mortality							
NHS							
Baseline median	2.1	2.6	3.0	4.1	6.6		
Cases	1494	1604	1821	2752	3732		
Person-years	284 421	284 321	284 031	283 160	282 278		
Age-adjusted model	1 [Reference]	1.08 (1.00–1.15)	1.21 (1.13–1.30)	1.92 (1.80–2.04)	2.99 (2.81–3.17)	<0.0001	3.42 (3.25–3.60)
MV-adjusted model	1 [Reference]	1.06 (0.99–1.14)	1.15 (1.08–1.23)	1.74 (1.63–1.85)	2.75 (2.59–2.92)	<0.0001	3.17 (3.01–3.34)
HPFS							
Baseline median	2.8	3.3	3.8	4.5	5.9		
Cases	1362	1350	1453	1576	1978		
Person-years	132 506	132 475	132 282	132 063	131 594		
Age-adjusted model	1 [Reference]	1.07 (0.99–1.15)	1.17 (1.08–1.26)	1.32 (1.3–1.42)	1.99 (1.86–2.13)	<0.0001	3.07 (2.77–3.39)
MV-adjusted model	1 [Reference]	1.06 (0.98–1.14)	1.14 (1.06–1.23)	1.28 (1.19–1.37)	1.86 (1.73–2.00)	<0.0001	2.75 (2.48–3.05)
Pooled							
Age-adjusted model	1 [Reference]	1.08 (1.02–1.14)	1.19 (1.13–1.25)	1.59 (1.11–2.29)	2.43 (1.63–3.64)	<0.0001	3.27 (2.94–3.63)
MV-adjusted model	1 [Reference]	1.06 (1.01–1.12)	1.15 (1.09–1.21)	1.48 (1.09–2.02)	2.26 (1.53–3.33)	<0.0001	2.97 (2.59–3.41)
Cardiovascular mortality							
NHS							
Cases	238	314	393	611	821		
Age-adjusted model	1 [Reference]	1.32 (1.11–1.56)	1.63 (1.39–1.92)	2.67 (2.30–3.11)	4.23 (3.66–4.89)	<0.0001	4.23 (3.78–4.73)
MV-adjusted model	1 [Reference]	1.25 (1.06–1.48)	1.42 (1.20–1.66)	2.09 (1.79–2.43)	3.49 (3.01–4.04)	<0.0001	3.63 (3.23–4.08)
HPFS							
Cases	374	390	410	503	683		
Age-adjusted model	1 [Reference]	1.14 (0.99–1.32)	1.22 (1.06–1.40)	1.58 (1.38–1.81)	2.65 (2.33–3.01)	<0.0001	4.95 (4.13–5.94)
MV-adjusted model	1 [Reference]	1.11 (0.97–1.28)	1.17 (1.01–1.34)	1.47 (1.28–1.68)	2.33 (2.05–2.65)	<0.0001	4.05 (3.37–4.87)
Pooled							
Age-adjusted model	1 [Reference]	1.23 (1.09–1.38)	1.41 (1.06–1.87)	2.06 (1.23–3.43)	3.34 (2.11–5.29)	<0.0001	4.50 (3.87–5.24)
MV-adjusted model	1 [Reference]	1.18 (1.06–1.32)	1.28 (1.06–1.55)	1.75 (1.25–2.46)	2.85 (1.92–4.23)	<0.0001	3.75 (3.39–4.13)
Cancer mortality							
NHS							
Cases	658	649	761	1087	1563		
Age-adjusted model	1 [Reference]	0.99 (0.89–1.10)	1.14 (1.03–1.27)	1.67 (1.51–1.84)	2.62 (2.39–2.87)	<0.0001	3.08 (2.84–3.34)
MV-adjusted model	1 [Reference]	0.99 (0.88–1.10)	1.13 (1.01–1.25)	1.62 (1.47–1.79)	2.52 (2.29–2.76)	<0.0001	2.95 (2.72–3.20)
HPFS							
Cases	444	467	479	565	668		
Age-adjusted model	1 [Reference]	1.11 (0.98–1.27)	1.15 (1.01–1.31)	1.38 (1.21–1.56)	1.87 (1.65–2.10)	<0.0001	2.74 (2.30–3.25)
MV-adjusted model	1 [Reference]	1.11 (0.97–1.26)	1.14 (1.00–1.30)	1.37 (1.21–1.55)	1.82 (1.61–2.06)	<0.0001	2.63 (2.20–3.12)

Table 2. Continued

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P Trend	Per 5% Increase in the Score
Pooled							
Age-adjusted model	1 [Reference]	1.05 (0.93–1.18)	1.14 (1.06–1.24)	1.51 (1.24–1.85)	2.21 (1.59–3.09)	<0.0001	2.98 (2.68–3.31)
MV-adjusted model	1 [Reference]	1.04 (0.93–1.17)	1.13 (1.04–1.23)	1.49 (1.25–1.77)	2.14 (1.56–2.95)	<0.0001	2.86 (2.58–3.17)

Values are expressed as hazard ratios (95% confidence intervals).
Multivariable model, adjusted for age, race, marital status, baseline postmenopausal hormone use(women only), family history of diabetes mellitus, myocardial infarction and cancer, and baseline history of diabetes mellitus, hypertension, hypercholesterolemia, multivitamin use, aspirin use, energy intake, and physical examination.
HPFS indicates Health Professionals' Follow-up Study; MV, multivariable; NHS, Nurses' Health Study.
*The formula to estimate the 20-year risk of cardiovascular disease (percentage) based on lifestyle predictors derived include age as a constant (50 years) and includes smoking, body mass index, physical activity, alcohol, and a composite diet score (fruits and vegetables, sugar-sweetened beverages, red/processed meats, cereal fiber, and nuts) (Figure S1).

versus 0 lifestyle risk factors (cigarette smoking, lack of physical activity, low diet quality, alcohol intake of 0 or ≥15 g/d, and overweight) and reported significant relative risks of 3.26, 8.17, and 4.31 for cancer, cardiovascular, and total mortality, respectively.[10] In a Dutch study, the relative risks of total mortality for the least versus the most healthy lifestyle score were 4.07 for women and 2.61 for men.[30]

In our study that comprised the 9 most predictive modifiable lifestyle factors for CVD risk, the observed estimates were higher when we included age in the risk

Table 3. Cause-Specific Mortality Based on Quintiles of the Healthy Heart Score*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P Trend
Coronary heart disease						
Cases	413	485	572	848	1200	
MV-adjusted model	1 [Reference]	1.20 (1.06–1.37)	1.35 (1.19–1.53)	2.00 (1.37–2.91)	3.37 (2.16–5.25)	<0.0001
Stroke						
Cases	197	222	230	265	305	
MV-adjusted model	1 [Reference]	1.13 (0.93–1.37)	1.06 (0.55–2.04)	1.26 (0.80–1.97)	1.75 (1.02–2.99)	<0.0001
Lung cancer						
Cases	132	158	174	359	792	
MV-adjusted model	1 [Reference]	1.26 (0.89–1.79)	1.38 (1.10–1.73)	2.84 (2.16–3.75)	6.04 (2.78–13.13)	<0.0001
Breast cancer (women)						
Cases	79	98	133	182	219	
MV-adjusted model	1 [Reference]	1.14 (0.89–1.47)	1.13 (0.88–1.46)	1.53 (1.21–1.95)	1.45 (1.14–1.86)	0.0009
Prostate cancer (men)						
Cases	84	82	80	72	69	
MV-adjusted model	1 [Reference]	1.10 (0.81–1.49)	1.08 (0.79–1.47)	0.99 (0.72–1.37)	1.13 (0.82–1.57)	0.64
Colon cancer						
Cases	109	104	143	168	160	
MV-adjusted model	1 [Reference]	0.95 (0.72–1.24)	1.26 (0.98–1.63)	1.48 (1.16–1.89)	1.51 (1.18–1.93)	0.005
Other deaths						
Cases	706	897	923	1558	2543	
MV-adjusted model	1 [Reference]	1.01 (0.91–1.13)	1.09 (1.00–1.18)	1.29 (0.75–2.22)	1.92 (1.02–3.60)	0.006

Values are expressed as pooled hazard ratios (95% confidence intervals).
Multivariable model, adjusted for age, race, marital status, baseline postmenopausal hormone use (women only), family history of diabetes mellitus, myocardial infarction and cancer, and baseline history of diabetes mellitus, hypertension, hypercholesterolemia, multivitamin use, aspirin use, energy intake, and physical examination. Pooled data from the Nurses' Health Study and Health Professionals' Follow-up Study.
*The formula to estimate the 20-year risk of cardiovascular disease (percentage) based on lifestyle predictors derived include age as a constant (50 years) and includes smoking, body mass index, physical activity, alcohol, and a composite diet score (fruits and vegetables, sugar-sweetened beverages, red/processed meats, cereal fiber, and nuts) (Figure S1).
MV indicates multivariable.

Table 4. Total Mortality Based on Each Behavioral Component of the Healthy Heart Score by Quintiles of the Healthy Heart Score

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P Trend	P for interaction
Age younger than the median*							
Cases	443	444	536	704	1341		
Person-years, NHS	140 303	140 671	134 535	131 542	145 491		
Person-years, HPFS	65979	68 955	67 785	66 214	71 837		
MV-adjusted model, NHS	1 [Reference]	1.01 (0.85–1.19)	1.16 (0.98–1.36)	1.65 (1.42–1.92)	2.84 (2.48–3.26)	<0.0001	0.083
MV-adjusted model, HPFS		0.91 (0.73–1.13)	1.20 (0.98–1.47)	1.31 (1.07–1.60)	2.19 (1.83–2.62)	<0.0001	0.002
Age older than or equal to the median							
Cases	2410	2515	2735	3620	4374		
Person-years, NHS	144 073	143 730	149 461	151 576	136 749		
Person-years, HPFS	66 527	63 520	64 497	65 849	59 757		
MV-adjusted model, NHS	1 [Reference]	1.07 (0.99–1.16)	1.15 (1.07–1.24)	1.76 (1.64–1.88)	2.73 (2.55–2.92)	<0.0001	
MV-adjusted model, HPFS		1.09 (1.01–1.18)	1.13 (1.05–1.23)	1.26 (1.17–1.37)	1.78 (1.64–1.92)	<0.0001	
BMI <25 kg/m^2							
Cases	2067	1751	1138	1455	2007		
Person-years, NHS							
Person-years, HPFS	92 744	66 143	39 413	19 721	104 412		
MV-adjusted model, NHS	1 [Reference]	1.05 (0.97–1.14)	1.12 (1.03–1.23)	2.56 (2.37–2.77)	2.80 (2.61–3.01)	<0.0001	<0.001
MV-adjusted model, HPFS	1 [Reference]	1.21 (1.08–1.36)	1.40 (1.24–1.58)	2.10 (1.84–2.39)	3.34 (2.88–3.86)	<0.0001	0.07
BMI ≥25 kg/m^2							
Cases	162	584	1466	2149	2806		
Person-years, NHS	274 811	227 442	132 590	92 408	141 142		
Person-years, HPFS	18 481	44 129	70 497	87 758	93 902		
MV-adjusted model, NHS	1 [Reference]	1.02 (0.79–1.30)	1.08 (0.85–1.37)	1.31 (1.03–1.66)	2.51 (1.98–3.18)	<0.0001	
MV-adjusted model, HPFS	1 [Reference]	0.87 (0.67–1.12)	1.15 (0.91–1.44)	1.26 (1.00–1.58)	2.06 (1.66–2.57)	<0.0001	
Never smoker							
Cases	1777	1554	1546	1349	670		
Person-years, NHS	203 965	171 480	149 074	98 894	17 689		
Person-years, HPFS	88 898	78 604	69 681	59 849	42 990		
MV-adjusted model, NHS	1 [Reference]	1.05 (0.96–1.14)	1.16 (1.06–1.27)	1.43 (1.30–1.58)	2.37 (2.03–2.76)	<0.0001	0.007
MV-adjusted model, HPFS	1 [Reference]	1.05 (0.94–1.17)	1.12 (1.01–1.25)	1.17 (1.05–1.31)	1.56 (1.39–1.76)	<0.0001	0.11
Ever smoker							
Cases	1076	1405	1725	2975	5045		
Person-years, NHS	80 411	112 821	134 981	184 225	264 551		
Person-years, HPFS	43 608	53 871	62 601	72 214	88 605		
MV-adjusted model, NHS	1 [Reference]	1.01 (0.90–1.13)	1.04 (0.93–1.16)	1.68 (1.51–1.85)	2.41 (2.19–2.65)	<0.0001	
MV-adjusted model, HPFS	1 [Reference]	1.04 (0.93–1.16)	1.08 (0.98–1.20)	1.23 (1.11–1.37)	1.77 (1.60–1.95)	<0.0001	
Nondrinker†							
Cases	1467	1836	2240	2799	3840		
Person-years, NHS	134 666	185 892	213 637	193 055	188 171		
Person-years, HPFS	66 957	74 694	81 561	87 986	92 204		
MV-adjusted model, NHS	1 [Reference]	1.05 (0.95–1.15)	1.12 (1.02–1.23)	1.59 (1.45–1.74)	2.79 (2.56–3.04)	<0.0001	<0.001
MV-adjusted model, HPFS	1 [Reference]	1.05 (0.96–1.16)	1.05 (0.96–1.16)	1.15 (1.05–1.27)	1.68 (1.54–1.84)	<0.0001	0.04

Continued

Table 4. Continued

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P Trend	P for interaction
Moderate drinker							
Cases	920	748	675	879	1009		
Person-years, NHS	94 480	65 904	47 772	50 249	51 844		
Person-years, HPFS	47 833	42 893	38 191	32 638	27 917		
MV-adjusted model, NHS	1 [Reference]	1.11 (0.97–1.27)	1.19 (1.03–1.38)	2.10 (1.85–2.39)	2.58 (2.28–2.92)	<0.0001	
MV-adjusted model, HPFS	1 [Reference]	1.00 (0.87–1.15)	1.17 (1.01–1.34)	1.34 (1.17–1.55)	1.97 (1.71–2.26)	<0.0001	
Heavy drinker							
Cases	519	423	331	544	649		
Person-years, NHS	44 460	22 068	12 461	22 107	14 900		
Person-years, HPFS	7146	5988	4714	3880	2877		
MV-adjusted model, NHS	1 [Reference]	1.12 (0.91–1.36)	1.60 (1.29–1.99)	1.95 (1.63–2.32)	2.76 (2.29–3.32)	<0.0001	
MV-adjusted model, HPFS	1 [Reference]	1.46 (0.96–2.22)	1.28 (0.81–2.02)	1.37 (0.84–2.25)	2.80 (1.69–4.64)	0.0004	
Physical activity >150 min							
Cases	1989	1513	1283	1761	1885		
Person-years, NHS	217 459	163 657	130 670	137 792	121 665		
Person-years, HPFS	90 543	65 995	50 619	39 105	27 926		
MV-adjusted model, NHS	1 [Reference]	1.04 (0.96–1.14)	1.10 (1.01–1.21)	1.88 (1.74–2.04)	2.74 (2.53–2.97)	<0.0001	0.008
MV-adjusted model, HPFS	1 [Reference]	1.02 (0.91–1.13)	1.15 (1.02–1.28)	1.28 (1.13–1.44)	1.72 (1.51–1.95)	<0.0001	0.07
Physical activity ≤150 min							
Cases	864	1446	1988	2563	3830		
Person-years, NHS	66 917	120 644	153 326	145 327	160 575		
Person-years, HPFS	41 963	66 480	81 662	92 958	103 669		
MV-adjusted model, NHS	1 [Reference]	1.08 (0.95–1.22)	1.20 (1.06–1.35)	1.61 (1.43–1.80)	2.78 (2.49–3.10)	<0.0001	
MV-adjusted model, HPFS	1 [Reference]	1.06 (0.94–1.18)	1.07 (0.96–1.19)	1.17 (1.05–1.30)	1.73 (1.56–1.91)	<0.0001	
Diet score above the median‡							
Cases	1131	1632	1379	1678	1411		
Person-years, NHS	114 001	164 323	122 100	115 886	115 886		
Person-years, HPFS	90 543	65 995	50 619	39 105	27 926		
MV-adjusted model, NHS	1 [Reference]	1.05 (0.97–1.14)	1.14 (1.05–1.24)	1.81 (1.68–1.96)	2.34 (2.15–2.54)	<0.0001	<0.001
MV-adjusted model, HPFS		1.09 (0.99–1.19)	1.08 (0.98–1.19)	1.23 (1.12–1.36)	1.78 (1.61–1.98)	<0.0001	0.008
Diet score below the median							
Cases	722	1327	1892	2646	4304		
Person-years, NHS	59 375	119 978	161 895	167 232	202 255		
Person-years, HPFS	41 963	66 480	81 662	92 958	103 669		
MV-adjusted model, NHS	1 [Reference]	1.07 (0.92–1.25)	1.18 (1.02–1.36)	1.70 (1.48–1.95)	3.04 (2.66–3.47)	<0.0001	
MV-adjusted model, HPFS	1 [Reference]	0.99 (0.85–1.16)	1.13 (0.97–1.30)	1.18 (1.03–1.36)	1.71 (1.49–1.96)	<0.0001	

Values are expressed as hazard ratios (95% confidence intervals).
Multivariable model, adjusted for age, race, marital status, baseline postmenopausal hormone use (women only), family history of diabetes mellitus, myocardial infarction and cancer, and baseline history of diabetes mellitus, hypertension, hypercholesterolemia, multivitamin use, aspirin use, energy intake, physical examination.
BMI indicates body mass index; HPFS, Health Professionals' Follow-up Study; MV, multivariable; NHS, Nurses' Health Study.
*The median age was 50 years for women and 52 years for men.
†Nondrinker: 0 to 5 g/alcohol (women) and 0 to 10 g alcohol (men); moderate: 5 to 14.9 g/alcohol (women) and 10 to 25 g/alcohol (men); heavy drinker: >15 g/alcohol (women) and >25 g/alcohol (men).
‡The median of diet score was 1.83 for women and 0.72 for men.

equation, as expected. A recent study that compared the contribution of changes in modifiable risk factors versus aging in a cohort of black participants showed that aging alone accounted for 60% of the development of 10-year predicted atherosclerotic CVD risk.[31] In our study, by observing significant associations exclusive of age, we showed that modifiable risk factors have an important contribution to CVD risk and, thus, these factors should be targeted for primary and primordial prevention strategies. Although our results were stronger in women than in men in the categorical analysis, that difference was less in the continuous analysis (per 5% increment in the risk score). That might be because the range of the score was greater among women than men.

This set of lifestyle behaviors may decrease CVD risk,[12] the development of clinical risk factors,[13] and, based on the present study, total, CVD, and cancer mortality. Based on data from the National Health and Nutrition Examination Survey 1988 to 2006, individuals with 6 or 7 ideal metrics, compared with individuals with 0 metrics, had significant relative risks of 0.49 for all-cause mortality and 0.24 for CVD mortality over 14.5 years of follow-up. The Healthy Heart Score extends upon this range as a 20-year risk assessment, which uniquely focuses on risk factors for the primordial prevention of CVD. In addition, in our study, a higher predictive CVD risk was associated with cause-specific mortality, due to CHD, stroke, lung cancer, breast cancer, or colon cancer. However, no effect was found for the Healthy Heart Score on prostate cancer mortality. Prior studies in the NHS and the HPFS cohorts showed that 82% of CHD,[32] 47% of total stroke,[8] 54% of ischemic stroke,[8] and 81% of sudden cardiac death[9] could be attributed to poor adherence to a low-risk lifestyle pattern (defined as not smoking, healthy weight, daily exercise at moderate intensity, moderate alcohol intake, and prudent diet). Among men in the HPFS, 62% of CHD (79% among men younger than 65 years),[33] 35% of total stroke,[8] and 52% of ischemic stroke[8] deaths may have been prevented with adherence to a low-risk lifestyle. With regard to prostate cancer incidence, a previous meta-analysis found no association with a healthy dietary pattern; however, an association may be observed with advanced cancer rather than total prostate cancer.[34] More studies are needed to clarify these results. In our study, the associations were slightly more pronounced among participants who were younger (<50 years), had optimal weight, were ever smokers, had alcohol consumption higher than the recommendations, and had a diet score below the median. A recent study showed that adults with a BMI <22.4 kg/m^2 and unhealthy lifestyles had a significantly higher risk of mortality than overweight individuals.[11] The authors found that the lowest risk of premature mortality was in people with a BMI <22.4 kg/m^2 with a healthy diet, physical activity, moderate alcohol consumption, and who did not smoke.

Study Strengths and Limitations

Our study includes a large sample size, a long and high follow-up rate, large number of deaths, and the inclusion of overall as well as cause-specific mortality. We studied a combination of 9 key modifiable lifestyle factors previously determined to predict CVD risk,[12] which may have a stronger additive impact in behavioral lifestyle strategies and outcomes. In addition, recognizing that physicians now have less time to assess or advise patients on healthy lifestyle behaviors,[35] this evidence-based tool (web/online calculator: https://healthyheartscore.sph.harvard.edu/) can simplify the incorporation of health behavior assessment and counseling during clinical visits. Additionally, a lifestyle-only risk score could be used to assess and motivate a larger audience in clinical and population-wide settings, who may not have laboratory-based measures available because of irregular checkups or lack of healthcare resources.

Some limitations need to be considered. The study may not be generalizable to the broader population as it included mostly white, well-educated male and female health professionals, although the resulting homogeneity by socioeconomic status, education, or healthcare access helps reduce confounding. Measurement error in self-reported lifestyle variables is inevitable; however, the data were collected prospectively and this error may be independent of study outcome ascertainment and, therefore, are more likely to attenuate associations towards the null.

Conclusions

The Healthy Heart Score, composed of 9 self-reported, modifiable lifestyle predictors of CVD, is a potentially useful tool for the counseling of healthy lifestyles that was strongly associated with greater risk of all-cause, CVD, and cancer mortality.

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Disclosures

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SUPPLEMENTAL MATERIAL

Figure S1. **Formula to estimate the 20-Year Risk of CVD based on lifestyle predictors in women.**

<div>

WOMEN
20-year CVD risk (%) "Healthy Heart Score" = $[1 - 0.9660^{(exp\,[W-\,6.57301])}] \times 100\%$

where W= 0.10820 x age + 0.15285 (if **past smoker**) + 0.90138 (if **current smoker**) + 0.04676 × **BMI** – 0.01923 × **grams/d of alcohol** + 0.0004 × (grams/d of alcohol)^2– 0.029251 × **hours/week of physical activity** - 0.05113 × **diet score**[*]

[*]Diet score = (0.03626 × grams/d of cereal fiber + 0.18283 [if fruits + vegetables ≥3 servings/d] + 0.14522 [if nuts 0.1-1 servings/d + 0.2444 [if nuts >1 servings/d]- 0.14631 × servings/d of sugar-sweetened beverages - 0.15624 × servings/d of red and processed meats)*10

MEN
20-year CVD risk (%) "Healthy Heart Score" = $[1 - 0.96368^{(exp\,[W-7.2437])}] \times 100\%$

where W= 0.13580 x age- 0.0005 x (age)^2 + 0.06979 (if **past smoker**) + 0.42305 (if **current smoker**) +0.07424 × **BMI** – 0.00898 × **grams/d of alcohol** + 0.0001 × (grams/d of alcohol)^2– 0.01755 × **hours/week of physical activity** - 0.06691 × **diet score**[*]

[*]Diet score = (0.01816× grams/d of cereal fiber + 0.08819 [if fruits + vegetables ≥3 servings/d] + 0.00535 [if nuts 0.1-1 servings/d + 0.14285 [if nuts >1 servings/d]- 0.14734 × servings/d of sugar-sweetened beverages - 0.07112 × servings/d of red and processed meats)*10

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