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Association Between a Healthy Heart Score and the Development of Clinical Cardiovascular Risk Factors Among Women: A Potential Role for Primordial Prevention

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Abstract

Background—The prevailing efforts for cardiovascular disease (CVD) prevention focused on treatment of common CVD risk factors rather than primordial prevention of risk factors through health behaviors. The previously validated Healthy Heart Score effectively predicted the 20-year risk of CVD in mid-adulthood; however, it is unknown whether this risk score is associated with clinically-relevant CVD risk factors.

Methods and Results—We analyzed the association between the Healthy Heart Score and incidence of clinical CVD risk factors, including diabetes, hypertension, and hypercholesterolemia among 69,505 U.S women in the Nurses' Health Study II (1991-2011). The Healthy Heart Score estimates the 20 –year CVD risk based on 9 lifestyle factors, thus a higher score reflected a higher predictive CVD risk. Over 20 years, we documented 3,275 incident cases of diabetes, 17,420 of hypertension, and 24,385 of hypercholesterolemia. Women with higher predicted CVD risk based on the Healthy Heart Score (highest quintile vs. lowest) had significantly greater risk of each clinical risk factor individually: Hazard Ratio (HR) 18.1 (95% confidence interval (CI): 14.4-22.7) for diabetes; 5.10 (4.66, 5.57) for hypertension; and 2.57 (2.40, 2.75) for hypercholesterolemia.

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The HR for developing the high-CVD profile was 52.5 (33.6-82.1). These associations were most pronounced among women who were younger, non-smokers, or had optimal weight.

Conclusions—An absolute 20-year risk of CVD, estimated by the Healthy Heart Score, was strongly associated with the development of CVD clinically-relevant risk factors. This risk score may serve as the first step for CVD risk assessment in primordial prevention.

Keywords

lifestyle; prevention; women; epidemiology; clinical risk factors

Despite significant reductions in mortality, cardiovascular disease (CVD) remains the leading cause of death in the US.[1] Clinical risk factors such as diabetes, hypertension, and dyslipidemia are associated with substantial long-term risk of CVD.[2, 3] Current prevention strategies focus on the primary prevention of CVD through the reduction in levels of clinical risk factors, primarily through drug therapy.[4] However, successful pharmacological treatment of clinical risk factors does not eliminate the harmful effects of having developed risk factors entirely and is associated with substantial costs and side effects.[5] Alternatively, primordial prevention of CVD focuses on the prevention of the development of clinical risk factors through healthy lifestyle factors.[6] Nonetheless, the prevalence of these healthy behaviors among US adults remains low.[7, 8]

We recently derived and validated the Healthy Heart Score, a 20-year CVD risk prediction model based on modifiable lifestyle factors in middle-aged adults.[9] Such a tool may help prioritize primordial prevention strategies in clinical and community-based settings; however, whether the Healthy Heart Score is associated with intermediate clinical CVD risk factors is not known. We aimed to quantify the association between the previously derived Healthy Heart Score and incidence of clinical risk factors, including diabetes, hypertension, and hypercholesterolemia, among women in the Nurses' Health Study II (NHSII).

Methods

Study population

The NHSII was established in 1989 when 116,430 registered nurses aged 25-42 years responded to a self-administered questionnaire about detailed medical history, lifestyle and other health information. Participants first completed a validated semi-quantitative food frequency questionnaire (FFQ)[10] to assess dietary intake in 1991, which served as the baseline for the current investigation. We send follow-up questionnaires biennially to update participant information on potential risk factors and to identify newly diagnosed diseases.

We excluded women who had invalid dietary data (>70 food items blank or reported energy intake <600 kcal/d or > 3500 kcal/d) or who were missing information on alcohol, physical activity, BMI, or smoking in 1991. Additionally, we excluded women who had CVD, cancer, diabetes, hypertension, or hypercholesterolemia at baseline, leaving 69,505 women available for the current analysis. The IRB at Brigham and Women's Hospital approved the study protocol 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 based on lifestyle factors and was developed separately within 2 cohorts of men [the Health Professional Follow-up Study(HPFS)][11] and women [the Nurses' Health Study (NHS))[12] free of CVD, diabetes and cancer at baseline.[9] The Score demonstrated good discrimination, fit and calibration. We applied the Healthy Heart Score derived in the NHS to this new cohort of younger female nurses. While numerous lifestyle predictors of CVD were considered, the final parsimonious model included the 9 most critical factors that best estimated CVD risk: current smoking, higher BMI, low physical activity, lack of moderate alcohol consumption, low intakes of fruits, vegetables, cereal fiber, and nuts, and high intakes of sugar-sweetened beverages and red and processed meats (Figure 1). A higher Healthy Heart Scores reflected a higher risk of CVD.

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 directly measured weight previously (r=0.96).[13] For physical activity, we used a previously validated physical activity questionnaire[14, 15] to estimate the average hours per week spent in moderate or vigorous intensity activity (≥3 metabolic equivalent tasks [METs]). For each food item, participants were asked how often on average a specified portion was consumed during the past year.[10] Cereal fiber and alcohol intake were 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.[16] We calculated average g/day of alcohol intake, assuming 12.8g of alcohol in 12oz of beer, 11.0g of alcohol in 4oz of wine, and 14.0g of alcohol in 1.5oz of liquor. Every two years, we updated information on smoking status, weight and physical activity. Diet was updated every four years.

Data on parental history of myocardial infarction (MI), aspirin use, menopausal status, postmenopausal hormone use, parity, and oral contraceptive use were assessed on biennial self-reported questionnaires.

Assessment of clinical risk factors

The outcomes for this study included three health factors included in the American Heart Association's definition of cardiovascular health: type 2 diabetes, hypertension, and hypercholesterolemia.[7] Self-reported type 2 diabetes was confirmed by a validated supplemental questionnaire using the National Diabetes Data Group criteria[17] for cases identified before 1998 and the American Diabetes Association criteria[18] for cases identified after 1998. In a previous validation study, 98% of self-reported cases were confirmed by medical records.[19] Participants self-reported physician-diagnosed hypertension and hypercholesterolemia. We defined incident hypertension and hypercholesterolemia as the first report of either the physician diagnosis of the risk factor or the reported use of medication for lowering blood pressure or cholesterol, respectively. In validation studies, 94% of self-reported cases of hypertension and 86% of self-reported cases of hypercholesterolemia were confirmed by medical records.[20, 21] The calendar year of diagnosis was recorded and used to estimate a time-to-event month assignment for the

purposes of survival analysis, based on the month of questionnaire return.[22] We defined a high CVD risk profile as the diagnosis of all 3 clinical risk factors.

We conducted sensitivity analyses with alternative case definitions for hypercholesterolemia and hypertension to test the robustness of the association. First we defined hypertension and hypercholesterolemia based on self-reported physician diagnosis only, without considering medication use. Second, we restricted cases of incident hypertension and hypercholesterolemia to participants also reporting medication use.

Statistical Analysis

Women contributed person-time from the return of the 1991 questionnaire until the date of diagnosis of the first clinical risk factor, CVD, death, or end of follow-up (June 2011), whichever came first. For the analysis of the high CVD risk profile, we used the date of diagnosis of the final clinical risk factor. We skipped any questionnaire cycle during which a participant was pregnant, as lifestyle habits among pregnant women may not be reflective of typical habits. To obtain the best estimate of the long-term Healthy Heart Score and to reduce measurement error, we used the cumulative average of the Healthy Heart Score from repeated time-point assessments.[16] We categorized the Healthy Heart Score into quintiles based on the distribution of the study population.

We estimated the hazard ratio (HR) and 95% confidence interval (CI) for each clinical risk factor individually and the high CVD risk profile according to quintiles of the Healthy Heart Score using Cox proportional hazards models adjusting for adjusted for age (in months) calendar time, parental history of MI before 60 years, aspirin use, menopausal status, postmenopausal hormone use, parity, and oral contraceptive use. We did not have direct information on socioeconomic variables, such as household income. However, we further adjusted for current employment status, marital status, and spouse's attained education status to account for potential variation in SES in this population. All variables were modeled as time-varying covariates. When we analyzed each clinical risk factor individually, we included the other clinical risk factors in the model.

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. We examined potential deviation from linearity with a likelihood ratio test, comparing a model with the linear term with a model including the linear term plus restricted cubic spline transformations.[23] For this analysis, we excluded women with a Healthy Heart Score above the 99th percentile below the 1st percentile (2.3% of total person-years) to make the estimates more stable and meaningful.

We tested for effect modification by age (<45y vs. ≥45y), smoking status (not current vs. current), and BMI (<25 vs ≥25kg/m^2). For each potential modifier, we created a cross-product term between the modifier and the quintiles of the Healthy Heart Score. We used the quintile cutpoints established in the entire population to maintain consistency in the distribution of the Score between different categories of the effect modifiers. 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 using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, NC).

Results

Over 20 years, we documented 3,275 cases of diabetes, 17,420 of hypertension and 24,385 of hypercholesterolemia. In total, 32,505 women were diagnosed with ≥1 clinical risk factor, 2,794 women had ≥2 risk factors and 1,641 women had the high-CVD risk profile. In this population of women (mean age 36 ± 4.7 years), the mean 20-year risk of CVD at baseline, estimated by the Healthy Heart Score, was 0.83% (10^{th} percentile 0.28%, 90^{th} percentile 1.56%). Women with a higher predicted CVD risk were more likely to be older, have a higher BMI, be a current smoker, have a family history of MI, and use aspirin. In addition, women with a higher predicted CVD risk were less physical active, and had a lower alcohol intake and diet score (Table 1).

A higher Healthy Heart Score was significantly associated with each clinical risk factor and this Score was associated most strongly with risk of diabetes (Table 2). In multivariable models, women in the highest compared to lowest quintile of the Healthy Heart Score had a HR of 18.1 (95%CI: 14.4-22.7) for diabetes; 5.10 (95%CI: 4.66-5.57) for hypertension; and 2.57 (95%CI: 2.40-2.75) for hypercholesterolemia (Table 2). Further adjustment for variables that may impact SES did not appreciably alter the results (data not shown). For a 2% increment in the Healthy Heart Score, the HR was 5.94 (95%CI: 5.38-6.55) for diabetes, 2.62 (95%CI: 2.50-2.73) for hypertension, and 1.72 (1.66-1.79) for hypercholesterolemia. In a sensitivity analysis, we removed age as a covariate in our multivariate models, to understand better the magnitude of the association driven by lifestyle factors only (Supplemental Table1). The magnitude of association between the Healthy Heart Score and risk of diabetes was attenuated when age was not included the multivariable model. In contrast, the association between the Healthy Heart Score and risk of hypertension and hypercholesterolemia was not appreciably altered when we did not adjust for age. When we calculated the Healthy Heart Score at baseline only, the associations were attenuated. The HR comparing 5th vs. 1st quintile: 13.80 (95%CI: 11.51-16.54) for diabetes, 4.38 (95%CI: 4.04-4.74) for hypertension and 2.40 (95%CI: 2.25-2.56) for hypercholesterolemia. The associations were not appreciably altered when we defined hypertension and hypercholesterolemia based only on self-reported physician diagnosis or when we restricted cases of incident hypertension and hypercholesterolemia to women also reporting medication use (data not shown).

There was a strong, linear association between the Healthy Heart Score and the risk of the high CVD risk profile (p, linear trend <0.001, Figure 2). The HR for the high CVD risk profile was 52.5 (95%CI: 33.6-82.1) comparing women in the highest to lowest quintile of the Healthy Heart Score (Table 3).In addition, for a 2% increment in the predicted CVD risk based on Healthy Heart Score, the HR was 1.51 (95%CI: 1.46, 1.55) for developing ≥1 risk factor, 5.33 (95%CI: 4.86, 5.85) for developing ≥2 risk factors, and 6.01 (95%CI: 5.31-6.79) for developing the high CVD risk profile. The association between the Healthy Heart Score and the high CVD risk profile was greatest in magnitude among women who were <45 years, non-smokers, had a BMI <25 Kg/m^2 (p, interaction<0.001) (Table 4).

Discussion

In this large prospective cohort of middle-age women, a higher predicted CVD risk, estimated by the Healthy Heart Score, was associated with a greater risk of developing clinical risk factors. Specifically, women with a higher predictive CVD risk had an 18-fold higher risk of type 2 diabetes, 5-fold higher risk of hypertension, and 3-fold higher risk of hypercholesterolemia over 20-years. Further, a higher predictive CVD risk was associated with a 53-fold greater risk of developing a high CVD risk profile and this association was most pronounced among women who were younger, did not smoke, and had optimal weight.

Clinical risk factors during early and mid-adulthood are associated with elevated long-term risk of CVD.[2, 3, 24] Conversely, the maintenance of a low-risk profile, defined as blood glucose levels <120mg/dl, untreated blood pressure <120/80 mmHg, and untreated cholesterol <200mg/dl, is associated with substantially low risk of CVD.[24-26] Adults who reach age 55 with the low-risk profile have a lifetime risk of CVD of 5-8%.[24, 25] In contrast, adults who develop ≥2 risk factors have a lifetime risk of 29-50%.[4,25] Further, adults with the low-risk profile live free of CVD 14 years longer than individuals with ≥2 risk factors.[26] Yet, the prevalence of optimal risk factor status is low. Among US adults >50 years old, 38% have ideal levels of fasting glucose, 20% have ideal blood pressure, and 25% have ideal levels of total cholesterol.[1,27] It has been posited that treating clinical risk factors is not equivalent to avoiding them because even with optimal treatment, the risk of CVD remains elevated.[5, 7, 27, 28] Thus, primordial prevention strategies are needed to prevent the development of CVD risk factors and eventual CVD.

Higher predicted CVD risk based on the Healthy Heart Score was strongly associated with the risk of type 2 diabetes, in particular. The findings in the current study are consistent with prior studies that found over 90% of diabetes cases, compared with 57% of hypertension and 40% of hypercholesterolemia cases, may be attributed to poor lifestyle factors.[29] Further, several components of the Healthy Heart Score such as sugar sweetened beverages[30], red meats[31], and BMI[32] are extremely strong risk factors for diabetes. In fact, excess adiposity is the single most important lifestyle determinant of type 2 diabetes. In previous studies, 60-85% of cases of diabetes may be attributed to overweight (BMI ≥25) in women. [29, 32] Further, the magnitude of association between the Healthy Heart Score and risk of diabetes was attenuated when we did not adjust for age in our multivariable models, suggesting that the lifestyle factor components in the Score were more strongly associated with diabetes risk than age. In contrast, the association between the Score and risk of hypertension and hypercholesterolemia were similar when age was included and not included as a covariate in the multivariable model.

The Healthy Heart Score was most strongly associated with a higher CVD risk profile among women who were younger, were non-smokers, and were at a healthy weight. In other words, even among women who may be considered low-risk because they do not smoke or are at a healthy weight, other lifestyle factors that contribute to the Healthy Heart Score play an important role in the development of clinical CVD risk factors. These results highlight the need for educational strategies on CVD prevention that address many lifestyle factors

simultaneously and further support the benefits of healthy lifestyle behaviors initiated in adolescence[33] and young adulthood[6, 34].

The Healthy Heart Score is a unique, scientifically-derived lifestyle-based prediction model with important clinical and public health relevance. First, the Healthy Heart Score may identify individuals who are likely to develop clinical risk factors and ultimately CVD due to poor lifestyle habits,[29, 35] but who would not be classified at high risk by existing primary prevention risk models.[36-38] Second, many existing CVD prediction tools are based on clinical risk factors[4, 36-41] and address primary care prevention. Because many clinical risk factors may mediate the effect of lifestyle on CVD risk, the addition of lifestyle factors to established risk prediction models does not improve risk prediction.[42] Third, physicians have limited time to assess lifestyle factors, even among patients who would be classified as low risk by the Framingham Risk Score.[28] The Healthy Heart Score may be a practical tool that can initiate the communication about primordial prevention between patients and clinicians and can complement existing primary prevention models. A predictive model that includes lifestyle measures without the need for clinical measurements may be useful beyond the clinical setting, such as workplace wellness programs or community-based health fairs.

BMI is a component of the Healthy Heart Score, even though BMI is not a true lifestyle "behavior" and is determined in part by other factors in the Score. The magnitude of association between the Healthy Heart Score and clinical risk factors was greatest among women with a BMI<25 kg/m^2. Notably, the Healthy Heart Score was also significantly associated with risk among women with elevated BMI. In prior studies, healthy lifestyle factors were associated with a lower risk of coronary heart disease (CHD) among both obese and non-obese individuals.[43] The findings from the current study provide further support for the importance of weight control for the prevention of clinical risk factors, even among individuals who maintain other behaviors.

This population is well suited to explore the Healthy Heart Score due to its prospective design, large sample size of women free of clinical risk factors, long follow-up, and repeated dietary and lifestyle measurements. However, there are also limitations. First, the Healthy Heart Score prediction model includes key dietary and lifestyle factors associated with CVD. However, there are numerous emerging lifestyle factors of CVD that are not included, such as sleep[44], sedentary behaviors[45], and other dietary components.[46] The Healthy Heart Score was created as a parsimonious, rather than comprehensive, model for CVD risk prediction given that time is already limited in the clinical setting. We focused on lifestyle factors that are modifiable on an individual level although an individual's ability to choose a healthy lifestyle is facilitated and influenced by the built environment, social network and public health policies that can influence the accessibility to healthy lifestyle options.[4748, 49] Second, although some measurement error in self-reported lifestyle variables is inevitable, the data are collected prospectively. Therefore, this error is likely non-differential with respect to the risk factors and would underestimate the true relative risk.[29, 32] We relied on self-reported diagnosis of hypertension and hypercholesterolemia, rather than directly measured clinical factors. Among health care professionals, reporting of these risk factors is fairly reliable,[20] but we cannot rule out the potential for misclassification. The generalizability of our results from a population of predominantly white, well-educated

nurses to men and individuals of diverse racial/ethnic or socioeconomic compositions is limited. Finally, while we adjusted for many confounders in our analysis, residual confounding remains a potential source of bias.

Conclusion

In this large population of middle-aged women free of clinical risk factors, the predicted CVD risk estimated by the Healthy Heart Score, a lifestyle-based prediction model, was strongly associated with the development of CVD clinical risk factors. Additional research that evaluates the use of this scientifically-derived tool as a primordial prevention strategy in the clinical or community-based setting is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is Known

- The prevention of risk factor development through healthy lifestyle factors, or primordial prevention, is of paramount importance to minimize the long-term risk of CVD. However, the prevalence of these healthy behaviors among US adults remains low.
- The Healthy Heart Score, a 20-year CVD risk prediction model based on modifiable lifestyle factors, effectively predicted the 20-year risk of CVD in mid-adulthood, but whether this risk score is associated with clinically-relevant CVD risk factors is unknown.

What the Study Adds

- A higher predicted CVD risk, estimated by the Healthy Heart Score, was associated with a greater risk of developing clinical risk factors.
- The Healthy Heart Score is a patient-oriented, scientifically derived lifestyle-based prediction model that may eventually serve as the first step for risk assessment and a catalyst for communication between patients and clinicians in the primordial prevention setting.

$$\text{20-year CVD risk } (\%) = [1 - 0.9660^{(\exp[W - 6.57301])}] \times 100\%$$

where $W = 0.10820 \times \text{age} + 0.15285$ (if past smoker) $+ 0.90138$ (if current smoker) $+ 0.04676 \times \text{BMI} - 0.01923 \times \text{grams/d of alcohol} + 0.0004 \times (\text{grams/d of alcohol})^2 - 0.029251 \times \text{hours/week of physical activity} - 0.05113 \times \text{diet score}^*$

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

Figure 1.
Formula to estimate the 20-Year Risk of CVD based on lifestyle predictors in women

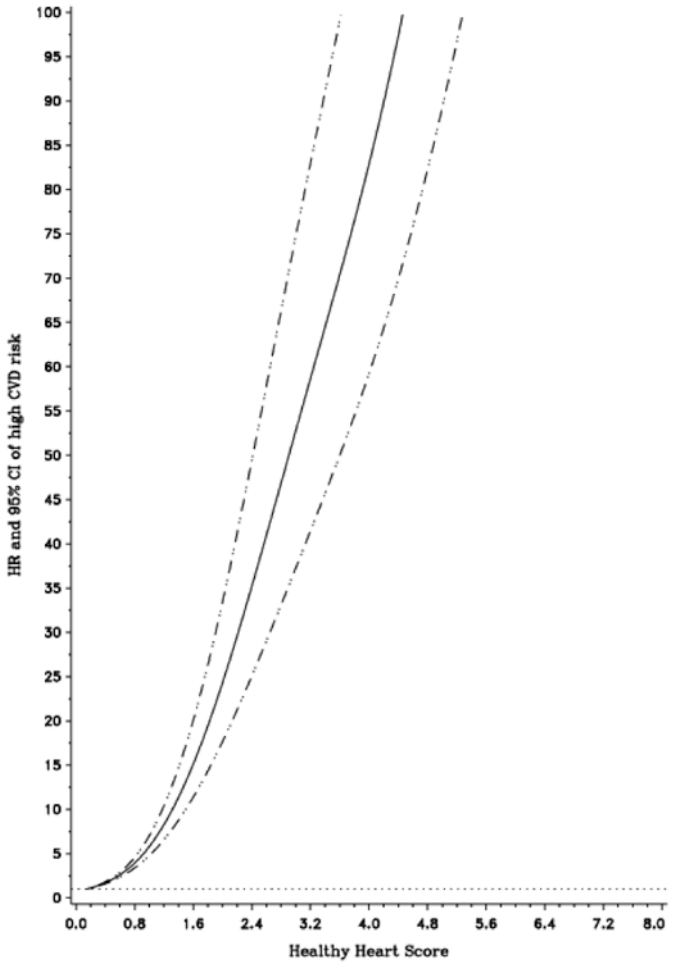

Figure 2.

Dose-Response relationship between the Healthy Heart Score and risk of developing the high CVD risk profile. Multivariable hazard ratio (95%CI) of the high CVD risk profile as a function the Healthy Heart Score updated every 4 years. Data were fitted by a restricted cubic spline Cox proportional hazards model, adjusted for age, calendar time, parental history of MI before 60 years of age, aspirin use, menopausal status, postmenopausal hormone use, parity, and oral contraceptive use. Solid line represents point estimate and dashed lines are 95%CIs. The models were based on 1419 cases after the exclusion of women with a Healthy Heart Score <0.15 (1st percentile) and >6.09 (99th percentile)

Table 1

Age-adjusted baseline characteristics according to quintiles of Healthy Heart Score

	Predictive 20-year risk of CVD (%) based on the Healthy Heart Score*				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Healthy Heart Score (20-y risk)†	0.3 (0.1)	0.5 (0.1)	0.7 (0.1)	0.9 (0.1)	1.9 (0.8)
No. of participants‡	10831	11386	11960	12462	13178
Age, y	31 (3)	34 (3)	37 (3)	39 (3)	40 (3)
BMI kg/m^2	21.6 (2.5)	22.7 (3.2)	23.4 (3.7)	24.4 (4.4)	27.2 (6.1)
Current smoker, %	0.5	2.2	5.3	10.7	39.3
Diet score (points)¥	2.5 (2.3)	2.2 (2.4)	2.0 (2.4)	1.8 (2.4)	1.0 (2.5)
Alcohol intake, g/d	3.5 (5.2)	3.2 (5.2)	3.0 (5.1)	3.1 (5.5)	2.9 (5.7)
Physical activity, MET-h/wk	5.1 (5.2)	3.5 (4.0)	3.0 (3.6)	2.5 (3.1)	1.8 (2.6)
Parental history of MI before 65y, %	13.3	17.0	20.6	23.4	27.0
Post-menopausal status, %	0.5	1.1	2.1	3.3	5.5
Postmenopausal hormone use					
never users	90.7	88.6	87.3	85.6	82.1
past users	7.3	8.5	8.5	8.9	9.4
current users	1.3	1.9	3.2	4.5	7.3
Missing	0.8	1.0	1.1	1.0	1.2
Past oral contraceptive, %	53.8	66.8	75.6	80.7	83.9
Current oral contraceptive, %	27.5	14.5	8.9	5.1	2.6
Parity	1.2 (1.2)	1.6 (1.2)	1.8 (1.2)	1.8 (1.2)	1.8 (1.2)
Aspirin use (yes), %	7.0	8.5	10.5	12.4	14.5

MI, Myocardial Infarction

*Continuous variables are presented as means (SD) and categorical values as %.

†The formula to estimate the 20-year risk of CVD based on lifestyle predictors derived including smoking, BMI, physical activity, alcohol, and a

¥composite diet score (fruit and vegetables, sugar-sweetened beverages, red/processed meats, cereal fiber, nuts)(Figure 1).

‡The quintiles were determined by the distribution of the Healthy Heart Score across the total person-time of the study

Table 2

Hazard ratios (95%CI) of the clinical risk factors(diabetes, hypertension, and hypercholesterolemia) according to quintiles of the Healthy Heart Score

	Predictive 20-year risk of CVD (%) based on the Healthy Heart Score					
Clinical risk factors	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***P*-trend**
Diabetes						
Median Healthy Heart Score (20-y risk)*	0.42	0.74	1.13	1.77	3.37	
Cases	141	277	391	714	1752	
Person-years	243373	241775	240486	238424	2343301	
Model 1	1 [Ref]	2.30 (1.84-2.87)	4.00 (3.19- 5.02)	8.46 (6.76-10.6)	25.1 (20.0-31.5)	<.0001
Model 2	1 [Ref]	2.38 (1.90-2.97)	4.15 (3.31-5.20)	8.73 (6.98-10.9)	25.2 (20.1-31.7)	<.0001
Model 3	1 [Ref]	2.26 (1.81-2.82)	3.71 (2.96-4.64)	7.26 (5.80-9.09)	18.1 (14.4-22.7)	<.0001
Hypertension						
Median Healthy Heart Score (20-y risk)*	0.40	0.70	1.06	1.62	3.02	
Cases	1182	2191	3187	4613	6247	
Person-years	219229	216967	214992	212239	208080	
Model 1	1 [Ref]	1.61 (1.48-1.75)	2.34 (2.15-2.54)	3.47 (3.19-3.78)	5.54 (5.08-6.06)	<.0001
Model 2	1 [Ref]	1.61 (1.48-1.75)	2.34 (2.15-2.55)	3.47 (3.18-3.78)	5.52 (5.05-6.04)	<.0001
Model 3	1 [Ref]	1.59 (1.46-1.73)	2.28 (2.09-2.48)	3.31 (3.03-3.60)	5.10 (4.66-5.57)	<.0001
Hypercholesterolemia						
Median Healthy Heart Score (20-y risk)*	0.39	0.68	1.02	1.56	2.93	
Cases	2435	3462	4664	6081	7743	
Person-years	201696	199607	197529	195070	191326	
Model 1	1 [Ref]	1.43 (1.35-1.52)	1.88 (1.76-2.00)	2.33 (2.19-2.49)	2.98 (2.78-3.18)	<.0001
Model 2	1 [Ref]	1.41 (1.33-1.50)	1.83 (1.72-1.95)	2.24 (2.10-2.39)	2.79 (2.61-2.98)	<.0001
Model 3	1 [Ref]	1.40 (1.32-1.48)	1.80 (1.69-1.92)	2.17 (2.03-2.31)	2.57 (2.40-2.75)	<.0001

Model 1: Adjusted for age. Model 2: Model 1 + parental history of MI before 60 years of age, aspirin use, menopausal status, postmenopausal hormone use, parity, oral contraceptive use. Model 3: Model 2 + respectively adjusted by the other clinical risk factors (i.e., model 3 with diabetes as outcome is further adjusted for hypertension and hypercholesterolemia).

*The formula to estimate the 20-year risk of CVD based on lifestyle predictors derived including smoking, BMI, physical activity, alcohol, and a composite diet score (fruit and vegetables, sugar-sweetened beverages, red/processed meats, cereal fiber, nuts)(Figure 1)

Table 3

Hazard ratios of the combination of clinical risk factors according to quintiles of the Healthy Heart Score

	Predictive 20-year risk of CVD (%) based on the Healthy Heart Score					
Combination of clinical risk factors	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***P*-trend**
At least 1						
Median Healthy Heart Score (20-y risk)[a]	0.42	0.74	1.14	1.77	3.39	
Cases	3824	5603	7254	8279	7545	
Person-years	240660	237332	234399	231404	228934	
Model 1	1 [Ref]	1.47 (1.40-1.54)	1.95 (1.86-2.05)	2.36 (2.25-2.49)	2.69 (2.54-2.85)	<.0001
Model 2	1 [Ref]	1.47 (1.40-1.54)	1.95 (1.85-2.05)	2.36 (2.24-2.48)	2.66 (2.52-2.82)	<.0001
At least 2						
Median Healthy Heart Score (20-y risk) *	0.42	0.74	1.14	1.77	3.38	
Cases	79	174	319	616	1606	
Person-years	244340	242781	241414	239410	235265	
Model 1	1 [Ref]	2.09 (1.56-2.78)	4.36 (3.28-5.79)	9.30 (7.01-12.3)	28.3 (21.3-37.6)	<.0001
Model 2	1 [Ref]	2.15 (1.61-2.87)	4.46 (3.36-5.92)	9.33 (7.04-12.4)	27.3 (20.6-36.2)	<.0001
All 3						
Median Healthy Heart Score (20-y risk) *	0.42	0.74	1.14	1.78	3.40	
Cases	28	88	182	339	1004	
Person-years	245510	244003	242672	240678	236846	
Model 1	1 [Ref]	3.27 (2.07-5.16)	8.02 (5.13-12.5)	16.9 (10.8-26.4)	58.5 (37.4-91.5)	<.0001
Model 2	1 [Ref]	3.28 (2.08-5.17)	7.88 (5.05-12.3)	16.0 (10.2-25.0)	52.5 (33.6-82.1)	<.0001

Model 1: Adjusted for age. Model 2: Model 1 + parental history of MI before 60 years of age, aspirin use, menopausal status, postmenopausal hormone use, parity, oral contraceptive use.

* The formula to estimate the 20-year risk of CVD based on lifestyle predictors derived including smoking, BMI, physical activity, alcohol, and a composite diet score (fruit and vegetables, sugar-sweetened beverages, red/processed meats, cereal fiber, nuts)(Figure 1)

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Table 4

Hazard ratios of the high CVD risk profile* stratified by age, smoker status and BMI based on quintiles of the Healthy Heart Score

	Predictive 20-year risk of CVD (%) based on the Healthy Heart Score						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p trend**	***P*- interaction**
Age							
< 45 years							
Median Healthy Heart Score (20-y risk) **	0.41	0.73	1.10	1.70	2.85		
Cases	17	54	93	86	37		
Person-years	230091	185730	105033	49018	16545		
Model 2	1 [Ref]	4.25 (2.39-7.54)	15.6 (8.94-27.2)	32.9 (18.5-58.3)	47.3 (25.0-89.5)	<.0001	
≥45 years							<.0001
Median Healthy Heart Score (20-y risk) **	0.47	0.79	1.17	1.80	3.45		
Cases	11	34	89	253	967		
Person-years	15419	58273	137639	191660	220301		
Model 2	1 [Ref]	0.93 (0.47-1.85)	1.22 (0.65-2.31)	2.80 (1.51-5.21)	10.4 (5.6-19.2)	<.0001	
Smoking status							
Non smokers							
Median Healthy Heart Score (20-y risk) **	0.42	0.74	1.14	1.77	3.32		
Cases	25	85	177	326	871		
Person-years	240548	233547	225110	212651	184538		
Model 2	1 [Ref]	4.35 (2.67-7.08)	12.6 (7.71-20.5)	30.4 (18.6-49.8)	122.4 (74.5- 201.2)	<.0001	
Current smokers							0.002
Median Healthy Heart Score (20-y risk) **	0.46	0.77	1.16	1.84	3.87		
Cases	3	3	5	13	133		
Person-years	4962	10456	17562	28027	52309		
Model 2	1 [Ref]	0.61 (0.11- 3.42)	0.51 (0.10-2.57)	0.57 (0.13-2.54)	2.32 (0.53-10.0)	<.0001	
BMI							
Median Healthy Heart Score (20-y risk) **	0.41	0.74	1.13	1.75	3.14		
< 25 kg/m^2							
Cases	6	22	50	56	111		

Predictive 20-year risk of CVD (%) based on the Healthy Heart Score							
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p trend**	***P*- interaction**
Person-years	201120	171435	147154	119590	80021		
Model 2	1 [Ref]	4.55 (1.76-11.8)	13.8 (5.36-35.5)	19.0 (7.22-49.9)	62.1 (23.4-164.5)	<.0001	0.003
BMI≥25 kg/m^2							
Median Healthy Heart Score (20-y risk) **	0.76	0.76	1.15	1.81	3.59		
Cases	22	66	132	283	893		
Person-years	44391	72568	95519	121088	156824		
Model 2	1 [Ref]	1.61 (0.96-2.69)	2.53 (1.53-4.19)	4.36 (2.63-7.22)	10.1 (6.06-16.7)	<.0001	

* High risk profile=having all 3 clinical risk factors (type 2 diabetes, hypertension, and hypercholesterolemia). Model 2: Adjusted for age, parental history of MI before 60 years of age, aspirin use, menopausal status, postmenopausal hormone use, parity, oral contraceptive use

** The formula to estimate the 20-year risk of CVD based on lifestyle predictors derived including smoking, BMI, physical activity, alcohol, and a composite diet score (fruit and vegetables, sugar-sweetened beverages, red/processed meats, cereal fiber, nuts)(Figure 1)