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Usefulness of Desirable Lifestyle Factors to Attenuate the Risk of Heart Failure Among Offspring whose Parents had Myocardial Infarction before Age 55 Years

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Abstract

Heart failure (HF) is one of the leading causes of hospitalization and death in United States and throughout Europe. While a higher risk of HF with antecedent myocardial infarction (MI) has been reported in offspring whose parents had MI before age 55, it is unclear whether adherence to healthful behaviors could mitigate that risk. The aim of the current study was therefore to prospectively examine if adherence to healthy weight, regular exercise, moderate alcohol consumption, and abstinence from smoking can attenuate such increased HF risk. The information on parental history of MI and lifestyle factors was collected using questionnaires. Subjects adhering to at least three healthy lifestyle factors were classified as having good vs. poor lifestyle score. Incident HF was assessed via yearly follow-up questionnaires and validated in a subsample. During an average follow up of 21.7 (6.5) years, 1,323 new HF cases (6.6%) of which 190 (14.4%) were preceded by MI occurred. Compared to subjects with good lifestyle score and no parental history of premature MI, multivariable adjusted hazard ratios (95% CI) for incident HF with antecedent MI was 3.21 (1.74–5.91) for people with good lifestyle score and parental history of premature MI; 1.52 (1.12–2.07) for individuals with poor lifestyle score and no parental history of premature MI; and 4.60 (2.55–8.30) for people with poor lifestyle score and parental history of premature MI. In conclusion, our data suggest that even in people at higher risk of HF due to genetic predisposition, adherence to healthful lifestyle factors may attenuate such an elevated HF risk.

Keywords

Epidemiology; Heart Failure; Myocardial Infarction; Lifestyle factors; Risk factors

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The current study was designed to examine the extent to which adherence to healthy lifestyle factors might attenuate the increased risk of heart failure (HF) with antecedent myocardial infarction (MI) in individuals with parental history of premature MI.

METHODS

The Physicians' Health Study (PHS) I is a completed randomized, double-blind, placebo-controlled trial, designed to study the effects of low-dose aspirin (ASA) and beta-carotene on cardiovascular disease and cancer among US male physicians. In 1997, a second randomized trial PHS II was started and included 7,641 physicians from original PHS I along with 7,000 new physicians. A detailed description of the PHS I and II has been published elsewhere ^{1,2}. Participants from PHS I including the 7,641 subjects who participate in PHS II are subsequently referred to as PHS. Of the 22,071 original subjects in the PHS, we excluded subjects with missing information on 12-month questionnaire (n=60), those with missing data on parental history of MI for both parents or missing parental age of MI (n=1,416), those with prevalent HF (n=25) at 12 months post-randomization, and those with missing information on covariates (n=510). Thus, a final sample of 20,060 participants was selected for current analyses. Each participant gave written informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study protocol.

During the 12 month follow-up questionnaire, information on parental history of myocardial infarction was collected using the following questions: Has your mother ever had a documented myocardial infarction? If yes, at what age? Has your father ever had a documented myocardial infarction? If yes, at what age?" Possible answers for the initial question were "No", "Yes", and "Don't know". In cases where both parent had a history of MI, we used the minimum age at diagnosis of parental MI for analyses. A parental history of premature MI was defined as having MI before 55 years of age.

Cardiovascular endpoints including HF in the PHS have been ascertained using annual follow-up questionnaires. A questionnaire was mailed to each participant every 6 months during the first year and has been mailed annually thereafter to obtain information on compliance with the intervention and the occurrence of new medical diagnoses, including HF. The validation of HF in the PHS has been previously reported ³.

Self-reported baseline weight and height were used to compute body mass index (weight in kilograms divided by height in meter squared). Each lifestyle factor was dichotomized as follows: non-current smoker vs. current smoker; normal weight (BMI <25 kg/m²) vs. overweight/obese (BMI ≥ 25 kg/m²); weekly alcohol use vs. more/less frequent alcohol use; and regular exercise (weekly) vs. infrequent/no exercise (< weekly). These cut points were chosen based on prior associations between individual lifestyle factors and HF risk in this cohort or public health recommendations ⁴. Each participant received 1 point for each of the following: BMI <25, non-current smoking, weekly alcohol use, and weekly exercise. Thus, study participants were categorized according to the number of desirable lifestyle factors (0, 1, 2, 3, and 4). A score '≥2' was defined as a 'good lifestyle score' while a score of '≤1' was defined as a 'poor lifestyle score.'

Demographic data were collected at baseline (1982–1984). Age was used as a continuous variable. Diagnosis of diabetes mellitus (DM) was made on self-reports via questionnaires mailed to each participant every 6 months during the first year and annually thereafter. Diagnosis of coronary heart disease (CHD) was initially made on self-reports via follow-up questionnaires. An Endpoint Committee reviewed medical records to confirm the diagnosis of CHD. Hypertension (HTN) was defined as anyone who self reported the diagnosis, BP >140/90 mm Hg per JNC7 guidelines or on the basis of medication list provided by the

study participants. All types of atrial fibrillation (AF) cases were assessed via follow-up questionnaires. These self-reports of AF have been validated in the same cohort using a more detailed questionnaire on the diagnosis of AF and the review of medical records in a prior study⁵.

Compared to subjects with good lifestyle score and no parental history of premature MI as reference, we classified the remaining participants into those with good lifestyle score and parental history of premature MI, poor lifestyle score and no history of parental premature MI, and poor lifestyle score and parental history of premature MI. We computed person-time of follow up from 12-month post-randomization until the first occurrence of a) HF, b) death, or c) date of receipt of last follow-up questionnaire. We used Cox proportional hazard models to compute multivariable adjusted hazard ratios with corresponding 95% confidence intervals using subjects with good lifestyle score and no parental history of premature MI as the reference group. We assessed confounding by established risk factors for HF. The initial model adjusted only for age. A second model additionally controlled for DM, HTN, AF and ASA randomization status.

Kaplan-Meier survival curves were also used to compare the HF free and MI free survival for each of the four groups considered in our analysis. Additionally, we conducted a secondary analysis stratified by each decade of age at entry to assess effect modification by age. Assumptions for proportional hazard models were tested using product terms of log (time) factor and variables of interest and were met (all p values > 0.05). All analyses were completed using SAS, version 9.3 (SAS Institute, NC). Significance level was set at 0.05.

RESULTS

Among 20,060 participants in the PHS I, the mean age at 12 months post randomization was 55 (± 9.5) years. Table 1 presents baseline characteristics of the study participants. While 94% of the subjects did not report parental history of premature MI, 6% of the participants had at least one parent who had a MI before the age of 55 y. In addition, 60% of the subjects had a good lifestyle score. Individuals with parental history of premature MI were noted to be younger than those with no parental history of premature MI. As expected, the prevalence of DM and HTN was also noted to be higher among individuals with poor lifestyle score than those with good lifestyle score.

During an average follow up of 22 years, 1,323 new cases of HF (6.6%) were documented in this cohort. Of these, 190 cases (14%) occurred in individuals with antecedent MI. Compared to subjects with good lifestyle score and no parental history of premature MI, multivariable adjusted hazard ratios (95% CI) for incident HF with antecedent MI was 3.21 (1.74–5.91) for people with good lifestyle score and parental history of premature MI, 1.52 (1.12–2.07) for individuals with poor lifestyle score and no history of parental premature MI, and 4.60 (2.55–8.30) for people with poor lifestyle score and parental history of premature MI (Table 2).

When stratified by age, the influence of healthful lifestyle factors appeared to be stronger with younger age at entry (Table 3). Kaplan-Meier survival curves comparing HF and MI free survival between different groups are as shown in Figure 1A and 1B, respectively.

DISCUSSION

Our findings demonstrate that in the presence of parental history of premature MI, adherence to healthful lifestyle factors was associated with a lower risk of HF with antecedent MI. Our data suggest that the influence of healthful lifestyle factors on above association might be stronger in younger compared to older ages.

Genetic factors have been demonstrated to play an important role in the development of HF^{6,7}. Several important HF predictors have also been shown to have a strong genetic component including HTN⁸, DM⁹, CHD¹⁰, AF¹¹, left ventricular mass (LVM)¹², and obesity¹³. Genomewide association studies have demonstrated genetic loci associated with HF risk¹⁴. However it remains critically important to identify simple and practical means to identify people with a high genetic susceptibility to HF risk and design simple, yet cost-effective strategies to mitigate such a risk.

In a prior study on the same cohort, Djoussé et al¹⁵ demonstrated a 32% higher risk of HF in the offspring of subjects with a parental history of premature MI (i.e. before age 55) in comparison to those with no parental history of premature MI. Data from the Framingham Study also demonstrated genetic susceptibility to HF onset in the offspring with ~18% of the risk attributable to parental history of HF¹⁶.

Data from this cohort⁴ has also shown beneficial effects of good lifestyle factors on the incidence of HF. Regular exercise, not smoking, moderate alcohol consumption, maintaining a normal weight, consumption of fruit and vegetables, and breakfast cereal were both individually and jointly associated with a lower lifetime risk of HF. The observed lifetime risk of HF varied from 21.20% (95% CI: 16.80%–25.60%) among those who did not follow any of the good lifestyle factors to 10.10% (95% CI: 7.90% to 12.30%) among those with 4 good lifestyle factors.

Other studies have demonstrated a beneficial effect of healthy lifestyle factors on the predictors of HF. Chiuve et al¹⁷ in their analysis of Health Professionals Follow-up Study demonstrated a beneficial effect of eating a prudent diet, regular exercise, managing weight, and abstinence from smoking to significantly reduce the risk of CHD, an important risk factor for HF, by improving lipids, blood pressure, and other risk factors. Similar beneficial effects of healthy lifestyle factors on CHD have also been demonstrated by other investigators^{18–21}.

In a recent cross sectional study²², a lack of adherence to healthy lifestyle factors (diet, exercise frequency, smoking status, and alcohol consumption) was inversely related to failure in achieving desirable blood pressure goals. A study of elderly individuals²³ demonstrated a beneficial effect of light to moderate alcohol consumption on the incidence of DM irrespective of beverage type. Kochar et al²⁴ reported an inverse association between breakfast cereals, especially whole-grain products and incident DM.

However, no prior study has directly looked into how much of the HF risk can be attenuated by adopting such healthy lifestyle factors among individuals already at a high risk with a parental history of premature MI, an indication of genetic susceptibility. The results of our study suggest that maintenance of healthy habits known to lower the HF risk remain essential even among individuals at higher risk of developing HF with antecedent MI.

Our findings have direct clinical implications in that if confirmed in other populations, a simple medical history could help identify patients at risk of HF with antecedent MI for aggressive follow up and management of co-existing risk factors. Our study has some limitations. First, parental history of MI and age at parental MI were self-reported. Inaccurate recall or misclassification could have biased our results. However, since such information was collected prior to HF occurrence, any exposure misclassification is more likely to have been non-differential and bias the results towards the null. Second, participants in this study were male mostly Caucasian physicians, thereby limiting the generalizability of our findings to other ethnic groups or in female gender. Third, in the absence of randomization, we cannot exclude chance, confounding by unmeasured factors, or residual confounding as possible explanation for our findings. Fourth, we were unable to

account for early lifestyle factors for men who entered the study at an older age (>75 y) despite the long duration of follow up. Lastly, we did not have enough subjects >80 years at entry for stratified analysis. Nevertheless, the large sample size, more than 20-years of follow up, the standardized and systematic collection and validation of endpoints in the PHS are strengths of this study.

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Figure 1A

Figure 1B

Figure 1.**1A:** Kaplan-Meier heart failure free survival curves**1B:** Kaplan-Meier myocardial infarction free survival curves

Group 1: No parental history of premature myocardial infarction and good lifestyle score

Group 2: Parental history of premature myocardial infarction and good lifestyle score

Group 3: No parental history of premature myocardial infarction and poor lifestyle score

Group 4: Parental history of premature myocardial infarction and poor lifestyle score

Table 1

Baseline characteristics of the 20,060 participants of the Physicians' Health Study

Parameter	No parental history of premature MI		Parental history of premature MI	
	Good lifestyle score	Poor lifestyle score	Good lifestyle score	Poor lifestyle score
	n=11,336	n=7,581	n=697	n=446
Age (years)	54 ± 9.5	56 ± 9.4	51 ± 7.8	53 ± 8.0
Body Mass Index (kg/m ²)	24 ± 2.3	26 ± 2.9	24 ± 2.3	26 ± 2.9
Randomized to Aspirin	50%	50%	51%	46%
Current Exercise	91%	45%	90%	47%
Never smoker	55%	42%	55%	40%
Past smoking	43%	35%	42%	32%
Current smoker	2.9%	23%	2.7%	28%
Moderate drinking (weekly)	68%	21%	69%	25%
Hypertension	20%	29%	19%	27%
Diabetes Mellitus	2.2%	4.7%	2.7%	4.0%
Atrial Fibrillation	1.8%	2.0%	0.9%	1.6%
Coronary Heart Disease	8.4%	13%	14%	19%

Abbreviation: MI – Myocardial Infarction

Incidence rates and relative risks (95% CI) of heart failure according to the parental history of myocardial infarction (age <55 y) and lifestyle score

Table 2

Parameter	No parental history of premature MI		Parental history of premature MI	
	Good lifestyle score	Poor lifestyle score	Good lifestyle score	Poor lifestyle score
Cases/person-years	79/253925	86/156559	12/16304	13/9449
Crude incidence rate (10,000 person-years)	3.1	5.5	7.4	13.8
Unadjusted Model	1.0	1.83 (1.35–2.49)	2.31 (1.26–4.25)	4.52 (2.51–8.12)
Age-adjusted Model	1.0	1.68 (1.23–2.28)	3.25 (1.76–5.98)	5.21 (2.90–9.38)
Multivariable Model	1.0	1.52 (1.12–2.07)	3.21 (1.74–5.91)	4.60 (2.55–8.30)

Multivariable Model: age, diabetes mellitus, hypertension, atrial fibrillation, and aspirin randomization

Abbreviation: MI – Myocardial Infarction

Table 3

Relative risks (95% CI) of heart failure according to the parental history of myocardial infarction (age <55 y) and lifestyle score stratified by age

Age Group (years)	No of Cases	Sample Size	No parental history of premature MI		Parental history of premature MI	
			Good lifestyle score	Poor lifestyle score	Good lifestyle score	Poor lifestyle score
40-50	27	7,571	1.0	1.46 (0.62-3.47)	3.18 (0.88-11.57)	6.93 (1.92-24.98)
50-60	69	6,891	1.0	2.97 (1.76-5.01)	0.81 (0.11-6.00)	3.08 (0.91-10.40)
60-70	61	4,101	1.0	1.07 (0.60-1.90)	8.05 (3.50-18.53)	8.00 (3.29-19.44)
70-80	31	1,335	1.0	0.70 (0.32-1.52)	2.68 (0.35-20.74)	1.87 (0.25-14.23)
80+	2	162	1.0	**	**	**

** Not enough events for stable estimates of effect

Abbreviation: MI – Myocardial Infarction