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Parental history of myocardial infarction and risk of heart failure in male physicians

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Abstract

Background—Although heart failure (HF) remains a major public health issue, limited data are available on the utility of parental information on the risk of HF in offspring.

Materials and Methods—We prospectively examined the association between parental history of myocardial infarction (MI) and incident HF among 20,187 offspring in the Physicians' Health Study I. Parental history and age at MI was assessed by a questionnaire and a Cox regression was used to estimate relative risks of HF.

Results—After an average follow up of 19.6 years, 1,036 new HF cases were documented. Overall, while a history of early parental MI (before age 55) was associated with a 32% increased risk of HF in offspring compared with subjects whose parent did not have MI, parental MI at older ages was not associated with HF risk. However, the relation between parental history of MI and HF was stronger and mainly observed for HF with antecedent MI. Compared with subjects without parental history of MI, multivariable adjusted hazard ratios (95% CI) for HF with antecedent MI were 3.44 (2.15–5.51), 2.24 (1.20–4.21), 1.26 (0.63–2.51), and 1.37 (0.92–2.03) for parental MI occurred at the age of <55, 55–59, 60–64, and 65+ y, respectively.

Conclusions—Our data suggest that parental MI at early ages is a strong and independent predictor of HF with antecedent MI among US male physicians. This information along with existing tools may help clinicians identify patients at risk of HF with antecedent MI.

Keywords

Epidemiology; heart failure; genetics

Introduction

Heart failure (HF) affects more than 5 millions Americans and is associated with higher costs and societal burden(1). Data from the Framingham Heart Study have estimated the lifetime risk for HF at 20% (1 in 5) for both men and women aged 40 years(2). While recent data suggest stable incidence rate over the past two decades(3), mortality after onset of HF remains high. Thus, making it imperative to focus on primary prevention of HF. Advanced age, hypertension,

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diabetes mellitus, obesity, valvular heart disease, and myocardial infarction have been recognized as independent predictors of HF(4,5). Because genetic factors play an important role in the development of major risk factors for HF such as hypertension, myocardial infarction (MI), diabetes, left ventricular (LV) hypertrophy, and obesity, it is possible that some of those genes may predict directly or indirectly the development of HF. Previous studies have demonstrated genetic factors play an important role in the development of hypertrophic and dilative cardiomyopathy(6,7). Data from the Strong Heart Study reported a heritability of LV mass of 27%(8). In a review article, the heritability of LV mass was estimated between 30% and 70% (9), suggesting that a substantial proportion of the LV mass variability is accounted for by genes. Animal models have identified quantitative trait loci influencing LV mass on chromosomes 7 and 17 (10,11). Song et al.(12) mapped a novel locus for cardiomyopathy to chromosome 7. Data from the Framingham Study showed that parental cardiovascular disease (CVD) was an independent predictor of CVD in middle age adults (13) and that parental history of atrial fibrillation was associated with a nearly 2-fold increase in atrial fibrillation risk among offspring(14). In addition, parental history of HF was an independent predictor of HF in offspring(15).

To our knowledge, no previous study has examined whether parental history of premature MI is an independent predictor of HF in offspring. In addition, it is not known whether such parental history of MI will predict HF with or without antecedent MI in offspring. Given the poor prognosis of HF, it is important to identify people at risk in order to prevent or delay HF onset. The current project sought to examine the association between parental history of MI and incident HF in the Physicians' Health Study (PHS) I data and to determine whether such relation differs between HF with and without antecedent MI.

Methods

Study population

The PHS I is a completed randomized, double-blind, placebo-controlled trial, designed to study the effects of low-dose aspirin and beta-carotene on cardiovascular disease and cancer among US male physicians. A description of the PHS I has been published(16). Of the 22,071 subjects in the PHS I, we excluded 1,884 subjects because of prevalent heart failure (n=27) at 12 months post-randomization when information on parental history of MI was collected, missing data a) on parental history of myocardial infarction on both mother and father or missing parental age of myocardial infarction (n=1,446), b) death by 12 months post-randomization (n=2), or c) covariates (n=409). Thus, a final sample of 20,187 participants for current analyses. Each participant gave written informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study protocol.

Assessment of parental history of myocardial infarction

During the 12th 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.

Ascertainment of HF in the PHS

Cardiovascular endpoints 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(17).

Other variables

Demographic data were collected at baseline. Information on comorbidity (i.e. atrial fibrillation, hypertension, left ventricular hypertrophy, and diabetes mellitus) has been collected through annual follow-up questionnaires as described above. Data on selected foods such as fruits and vegetables; breakfast cereals; physical activity; smoking; and alcohol consumption were obtained at baseline (1982).

Statistical analyses

Using subjects whose parent did not have a history of MI as reference, we classified the remaining participants according to their parental age at diagnosis of MI (<55, 55-59, 60-64, and 65+ y). We computed person-time of follow up from 12-month post-randomization until the first occurrence of a) HF, b) death, or c) censoring date - 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 without parental history of MI as the reference group. We assessed confounding by established risk factors for HF. The initial model adjusted only for age (<45, 45-49, 50-54, 55-59, 60-64, 65+ y). A second model also controlled for smoking (never, past, and current smokers), body mass index (<25, 25-29, 30+ kg/m²), exercise (0, ≤ 1, 2-4, 5+ times per week), alcohol consumption (<1, 1-4, 5-7, and 8+ drinks/week), breakfast cereals (≤ 1, 2-6, 7+ servings/week), and history of hypertension, diabetes, and atrial fibrillation. A third model also adjusted for aspirin, fruit and vegetable consumption (<3, 3-4, 5-6, 7-13, 14+ servings/week), and multivitamin use. We also examined the association between parental history of MI and HF with and without antecedent MI. For analyses of HF with antecedent MI, cases of HF without prior MI were recoded as non-cases and censored at the time of HF occurrence. Similarly, for analyses of HF without antecedent MI, subjects with MI prior to HF were censored at the time of MI occurrence. 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 9.1 (SAS Institute, NC). Significance level was set at 0.05.

Results

Characteristics

Among 20,187 participants in the PHS I, the mean age at 12 months post randomization was 54.6±9.4 years (range 40.7 to 87.1 years). Table 1 presents baseline characteristics of the study participants. While 69% of the subjects did not report parental history of MI, 5.7% of the participants indicated that at least one parent had a MI before age 55 y. In addition, 4.0% reported parental history of MI between age 55 and 59 y and for 16% of individuals, parental history of MI was after age 65 y. Among subjects with a parental history of MI before age 55, the onset of MI was on average 5 years earlier than in subjects without parental history of MI or those with parental history of MI at age 65+ years (Table 1).

Association between parental history of MI and HF

During an average follow up of 19.6 years, 1,036 new cases of HF (5.1%) were documented in this cohort. Of these, 167 cases (16%) occurred in individuals with antecedent MI. In multivariable Cox regression models, subjects with a parental history of MI before age 55 had a 32% increased risk of HF compared with subjects without parental history of MI (Table 2). A positive parental history of MI at an older age was not associated with an increased risk of HF in offspring (Table 2).

Parental history of MI and HF type

Parental history of MI was strongly associated with HF preceded by MI: compared with subjects without parental history of MI, multivariable adjusted hazard ratios (95% CI) for HF with antecedent MI were 3.44 (2.15-5.51), 2.24 (1.20-4.21), 1.26 (0.63-2.51), and 1.37 (0.92-2.03) for parental MI occurred at the age of <55, 55-59, 60-64, and 65+ y, respectively (Table 3). In contrast, no association was observed between parental history of MI and HF without antecedent MI in offspring (Table 4).

Contrasting early parental history of MI and other HF risk factors

In a multivariable adjusted model, the relative contribution of early parental history of MI on HF risk was modest (32% increased risk) compared with the increased risk of HF associated with other well known risk factors including hypertension (66%), atrial fibrillation (112%), current smoking (114%), type 2 diabetes (149%), and obesity (163%) (Table 5).

Discussion

In this prospective study, we demonstrated that history of premature parental MI (before age 55 y) was associated with an increased risk of HF in offspring. In addition, we showed that such association was stronger for HF with antecedent MI with a 3.4-fold increased risk of HF if a parent had an MI before the age of 55. In contrast, parental history of MI was not associated with HF without a prior MI in offspring. To the best of our knowledge, this is the first large prospective study to examine the association between parental history of MI and subsequent risk of HF in offspring.

Genetics and Cardiovascular Disease

It is well known that genetic factors play an important role in the development of HF risk factors including diabetes(18), atrial fibrillation(19), coronary artery disease(20), obesity(21), and hypertension(22,22). Despite recent advances in genetic epidemiology, the hunt for major genes for these chronic diseases had been unsuccessful, partly because these chronic conditions are more likely to be influenced by multiple genes whereby individual genes exert only a small effect on the outcome. In addition, despite the completion of human genome and the availability of high throughput assays, statistical methods to fully take advantage of available data are not fully developed. Consequently, it remains important to identify other practical means to understand the influence of genetic factors on chronic diseases such as HF. Our findings of a positive association between early parental MI and incident HF in offspring underscore the genetic influence on HF risk. This hypothesis is supported by previous reports showing a higher heritability of left ventricular mass - with 27% to 70% of the variability of left ventricular mass accounted for by genetic factors(8,9). Furthermore, data from the Framingham Study found that parental history of HF was associated with an increased risk of HF in offspring(15). Other investigators have reported genetic influence on the etiology of HF(23-25). It is more likely that early parental history of MI is driven by susceptible genes for MI and that vertical transmission of those genes then lead to early MI in offspring and subsequent HF development. The fact that offspring with early parental history of MI suffered their MI on average 5 years earlier than their counterpart without parental history or those with parental MI at age 65+ years lend support to this hypothesis. The restriction of our findings on HF with antecedent MI further supports this theory.

Limitations of the current study

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 thus bias the results towards the null. Second, participants in this study were male physicians, thereby limiting the generalizability of our findings. Third, we did not collect information on energy intake and other dietary factors to account for their influence on the studied association. Fourth, in the absence of randomization, we can not exclude chance, confounding by unmeasured factors, or residual confounding as possible explanation for our findings. Nevertheless, the large sample size, the 20-years of follow up, the standardized and systematic collection and validation of endpoints in the PHS are strengths of this study.

Conclusions

Our data indicate that parental history of early MI is an independent predictor of HF with antecedent MI in offspring. If confirmed in other studies, such information along with other risk factors could help identify patients at risk of HF for aggressive monitoring and risk factor management.

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Table 1
Baseline characteristics of the 20,187 participants according to parental age of myocardial infarction

Characteristics	No (n=13,902)	Parental history of myocardial infarction			
		< 55 y (n=1,149)	55-59 y (n=812)	60-64 y (n=1,099)	65+ y (n=3,225)
Age (y)	53.5±9.6	50.5±7.9	52.0±8.6	53.0±8.9	55.7±9.1
Age at MI onset in offspring*	69.5±10.3	64.9±10.2	66.2±9.7	65.9±10.7	70.2±9.9
Body mass index (kg/m ²)	24.8±2.8	24.8±2.9	25.0±2.9	24.9±2.8	24.7±2.6
Fruits and vegetables (servings/wk)	8.1±4.8	8.0±4.7	8.0±4.9	8.0±4.6	8.2±4.6
Hypertension (%)	23.3	23.8	24.6	23.7	26.3
Left ventricular hypertrophy (%)	0.2	0.3	0.5	0.4	0.3
Atrial fibrillation (%)	1.8	1.1	2.3	1.0	1.6
Current exercise (%)	86.3	88.2	87.7	85.7	86.8
Diabetes mellitus (%)	3.0	2.8	3.0	3.5	3.3
Current smokers (%)	10.7	12.5	12.9	13.2	10.4
Breakfast cereal consumption (%)	67.0	67.3	69.4	69.4	69.4
Current drinkers (%)	73.3	75.6	77.7	76.6	74.9

* MI=myocardial infarction; data limited on subjects with incident myocardial infarction.

Table 2

Hazard ratio (95% confidence interval) of heart failure according age of parental history of myocardial infarction

Age of parental history of Myocardial infarction	Cases	Hazard Ratio (95% CI)		
		Age-adjusted	Model 1 [*]	Model 2 [†]
No parental history	681	1.0	1.0	1.0
< 55 y	62	1.38 (1.06-1.79)	1.31 (1.01-1.71)	1.32 (1.02-1.72)
55-59 y	43	1.21 (0.89-1.65)	1.16 (0.85-1.58)	1.16 (0.85-1.58)
60-64 y	49	0.91 (0.68-1.22)	0.91 (0.68-1.22)	0.91 (0.68-1.22)
65+ y	201	1.04 (0.89-1.22)	1.07 (0.92-1.26)	1.08 (0.92-1.26)

* Adjusted for age (<45, 45-49, 50-54, 55-59, 60-64, 65+ y), smoking (never, past, and current smokers), body mass index (<25, 25-29, 30+ kg/m²), exercise (0, ≤ 1, 2-4, 5+ per week), alcohol (<1, 1-4, 5-7, and 8+ drinks/week), breakfast cereals (≤ 1, 2-6, 7+ servings/week), cereal and history of hypertension, diabetes, left ventricular hypertrophy, and atrial fibrillation.

† Additional control for aspirin, fruit and vegetable consumption (<3, 3-4, 5-6, 7-13, 14+ servings/week), and multivitamin use.

Table 3

Hazard ratio (95% confidence interval) of heart failure with antecedent myocardial infarction according to parental age of myocardial infarction

Parental age at Myocardial infarction	Cases	Hazard Ratio (95% CI)		
		Age-adjusted	Model 1 [*]	Model 2 [†]
No parental history	91	1.0	1.0	1.0
< 55 y	22	3.61 (2.26-5.77)	3.42 (2.14-5.48)	3.44 (2.15-5.51)
55-59 y	11	2.28 (1.22-4.26)	2.23 (1.19-4.17)	2.24 (1.20-4.21)
60-64 y	9	1.25 (0.63-2.48)	1.26 (0.63-2.50)	1.26 (0.63-2.51)
65+ y	34	1.32 (0.89-1.96)	1.36 (0.92-2.02)	1.37 (0.92-2.03)

* Adjusted for age (<45, 45-49, 50-54, 55-59, 60-64, 65+ y), smoking (never, past, and current smokers), body mass index (<25, 25-29, 30+ kg/m²), exercise (0, ≤ 1, 2-4, 5+ per week), alcohol (<1, 1-4, 5-7, and 8+ drinks/week), breakfast cereals (≤ 1, 2-6, 7+ servings/week), cereal and history of hypertension, diabetes, left ventricular hypertrophy, and atrial fibrillation.

† Additional control for aspirin, fruit and vegetable consumption (<3, 3-4, 5-6, 7-13, 14+ servings/week), and multivitamin use.

Table 4

Hazard ratio (95% confidence interval) of heart failure without antecedent myocardial infarction according to parental age of myocardial infarction

Parental age at Myocardial infarction	Cases	Hazard Ratio (95% CI)		
		Age-adjusted	Model 1 [*]	Model 2 [†]
No parental history	590	1.0	1.0	1.0
< 55 y	40	1.09 (0.79-1.50)	1.03 (0.75-1.43)	1.04 (0.76-1.44)
55-59 y	32	1.06 (0.74-1.51)	1.01 (0.71-1.44)	1.02 (0.71-1.45)
60-64 y	40	0.88 (0.64-1.21)	0.88 (0.64-1.21)	0.88 (0.64-1.21)
65+ y	167	1.02 (0.86-1.21)	1.06 (0.89-1.26)	1.06 (0.89-1.26)

* Sixty subjects with prevalent myocardial infarction were excluded. Adjusted for age (<45, 45-49, 50-54, 55-59, 60-64, 65+ y), smoking (never, past, and current smokers), body mass index (<25, 25-29, 30+ kg/m²), exercise (0, ≤ 1, 2-4, 5+ per week), alcohol (<1, 1-4, 5-7, and 8+ drinks/week), breakfast cereals (≤ 1, 2-6, 7+ servings/week), cereal and history of hypertension, diabetes, left ventricular hypertrophy, and atrial fibrillation.

† Additional control for aspirin, fruit and vegetable consumption (<3, 3-4, 5-6, 7-13, 14+ servings/week), and multivitamin use.

Table 5

Multivariable hazard ratios (95% confidence interval) for heart failure comparing early parental history of myocardial infarction and other risk factors

Risk factor	Hazard Ratio (95% CI)*
Parental history of myocardial infarction <55 y vs. none	1.32 (1.02-1.72)
Hypertension vs. normal blood pressure	1.66 (1.46-1.89)
Atrial fibrillation vs. normal sinus rhythm	2.12 (1.60-2.81)
Current smokers vs. never smokers	2.14 (1.78-2.58)
Past smokers vs. never smokers	1.27 (1.11-1.46)
Type 2 diabetes vs. none	2.49 (2.01-3.08)
Obese vs. normal weight	2.63 (2.07-3.35)
Overweight vs. normal weight	1.42 (1.25-1.61)

* Mutual adjustment for age (<45, 45-49, 50-54, 55-59, 60-64, 65+ y), smoking (never, past, and current smokers), body mass index (<25, 25-29, 30+ kg/m²), exercise (0, ≤ 1, 2-4, 5+ per week), alcohol (<1, 1-4, 5-7, and 8+ drinks/week), breakfast cereals (≤ 1, 2-6, 7+ servings/week), cereal and history of hypertension, diabetes, left ventricular hypertrophy, atrial fibrillation, aspirin, fruit and vegetable consumption (<3, 3-4, 5-6, 7-13, 14+ servings/week), and multivitamin use.