

Higher Fitness Is Strongly Protective in Patients with Family History of Heart Disease: The FIT Project

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ABSTRACT

BACKGROUND: Cardiorespiratory fitness protects against mortality; however, little is known about the benefits of improved fitness in individuals with a family history of coronary heart disease. We studied the association between cardiorespiratory fitness and risk of incident coronary heart disease and all-cause mortality, hypothesizing an inverse relationship similar to individuals without a family history of coronary heart disease.

METHODS: We included 57,999 patients (aged 53 ± 13 years; 49% were female; 29% were black) from the Henry Ford Exercise Testing (FIT) Project. Cardiorespiratory fitness was expressed in metabolic equivalents of task based on exercise stress testing. Family history was determined as self-reported coronary heart disease in a first-degree relative at any age. We used Cox proportional hazards models adjusted for demographics and cardiovascular disease risk factors to examine the association between cardiorespiratory fitness and risk of incident coronary heart disease and mortality over a median (interquartile range) follow-up of 5.5 (5.6) and 10.4 (6.8) years, respectively.

RESULTS: Overall, 51% reported a positive family history. Each 1-unit metabolic equivalent increase was associated with lower incident coronary heart disease and mortality risk regardless of family history status. The hazard ratio and 95% confidence interval for a negative family history and a positive family history were 0.87 (0.84-0.89) and 0.87 (0.85-0.89) for incident coronary heart disease and 0.83 (0.82-0.84) and 0.83 (0.82-0.85) for mortality, respectively. There was no significant interaction between family history and categorical cardiorespiratory fitness, sex, or age ($P > .05$ for all).

CONCLUSIONS: Higher cardiorespiratory fitness is strongly protective in all patients regardless of family history status, supporting recommendations for regular exercise in those with a family history.

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A family history of coronary heart disease is an independent risk factor for incident coronary heart disease and cardiovascular mortality.¹ Preventive efforts aimed at addressing traditional, modifiable risk factors in this group have been shown to reduce cardiovascular disease risk.²

Cardiorespiratory fitness is known to be a central determinant of survival in both healthy individuals and those with comorbidities.^{3,4} Low fitness has been proposed as a novel, modifiable marker to improve risk stratification.³ However,

the extent to which cardiorespiratory fitness can provide clinically meaningful risk stratification beyond traditional risk factors based on family history of coronary heart disease status remains to be studied.

We aimed to study the association of cardiorespiratory fitness and risk of incident coronary heart disease and all-cause mortality among individuals with and without a family history of coronary heart disease. We hypothesized that cardiorespiratory fitness is inversely associated with incident coronary heart disease and mortality independently of family history status.

MATERIALS AND METHODS

The Henry Ford Exercise Testing (FIT) Project is a retrospective cohort study consisting of 69,885 consecutive patients who underwent a physician-referred exercise stress test at Henry Ford Health System–affiliated hospitals and ambulatory cares centers in Detroit, Michigan, between 1991 and 2009. The Henry Ford Health System institutional review board approved the FIT Project, and the methods have been published.⁵

Patients with a history of coronary heart disease or heart failure ($n = 10,948$) and any missing stress test data ($n = 938$) were excluded, resulting in a final cohort of 57,999 patients. Family history was determined by self-report as the presence of coronary heart disease at any age in a first-degree relative (ie, father, mother, or sibling). Patients were stratified by family history status: those with a family history (family history positive) ($n = 29,745$) and those without (family history negative) ($n = 28,254$).

Incident coronary heart disease (including myocardial infarction and coronary revascularization) was ascertained through linkage with administrative claims files.⁵ All-cause mortality was ascertained through an algorithmic search of the Social Security Death Index Death Master File. Cardiorespiratory fitness, expressed in metabolic equivalents, was based on the workload derived from the maximal speed and grade achieved during the total treadmill time, categorized into 4 groups: <6 , 6 to 9, 10 to 11, and ≥ 12 metabolic equivalents.⁵

Baseline characteristics between the family history groups were compared using analysis of variance or chi-square test as appropriate. Incident event rates were reported per 1000 patient-years. We used Cox proportional hazards models to calculate hazard ratios (HRs) (95% confidence interval [CI]) of incident events for each family history group. The proportionality assumption was tested

using complementary log-log plots. Models were adjusted for age (years); sex; race; body mass (kilograms); cigarette smoking; hypertension; hyperlipidemia; diabetes; obesity; and medication use for chronic obstructive pulmonary disease, hyperlipidemia, hypertension, and cardiorespiratory fitness. We also tested for multiplicative interaction between family history status and each of categorical cardiorespiratory fitness, sex, and age (<60 vs ≥ 60 years) in the association with incident events.

A 2-sided P value of $<.05$ was considered statistically significant. All analyses were performed using Stata/IC version 13.1 (StataCorp LP, College Station, Tex).

RESULTS

Baseline characteristics are shown in **Table 1**. The mean (standard deviation) age was 53 (13) years (49% were female; 29% were black), and 51% ($n = 29,745$) were family history positive. Compared with family history negative, patients with a positive family history were more likely to be female, to be white, and to have dyslipidemia ($P <.001$ for all).

After a median (interquartile range) of 5.5 (5.6) years and 10.4 (6.8) years follow-up, a total of 1699 coronary heart disease events and 6600 mortality events were recorded, respectively. The unadjusted incidence rates for coronary heart disease and mortality (per 1000 person-years) were 4.74 and 10.34, respectively. Family history was not associated with outcomes in univariate analyses or in models adjusted for cardiovascular risk factors and cardiorespiratory fitness (HR, 1.01; 95% CI, 0.92-1.12 and HR, 0.97; 95% CI, 0.92-1.02 for coronary heart disease and mortality, respectively). The occurrence of incident events in the follow-up period decreased with higher metabolic equivalents in patients with and without family history (**Figure A and B**).

In fully-adjusted models, the HRs (95% CI) of events per unit metabolic equivalents increase for family history negative and family history positive were as follows: 0.87 (0.84-0.89) and 0.87 (0.85-0.89) for incident coronary heart disease and 0.83 (0.82-0.84) and 0.83 (0.82-0.85) for mortality, respectively. Similar results were obtained in categorical metabolic equivalents analyses (**Table 2**). There was no significant interaction between family history and categories of metabolic equivalents, sex, or age in the association with either event (all $P >.05$).

DISCUSSION

In this large, demographically diverse cohort free of known coronary heart disease or heart failure at baseline, we found

CLINICAL SIGNIFICANCE

- Increasing exercise capacity is protective against cardiovascular disease and mortality among those with and without a family history of coronary heart disease.
- Each metabolic equivalent increase in cardiorespiratory fitness is associated with a 13% and 17% decrease in incident coronary heart disease and all-cause mortality, respectively.
- Patients with a family history of coronary heart disease should be encouraged to engage in guideline-recommended exercise regimens to improve fitness and thus prognosis.

Table 1 Baseline Characteristics of the Study Population by Family History Status

	Total Cohort (n = 57,999)	FH- (n = 28,254)	FH+ (n = 29,745)	P Value*
Age (y)	53 (13)	54 (13)	53 (12)	<.001
Female, %	28,151 (49)	12,395 (44)	15,756 (53)	<.001
Race, %				<.001
White	37,152 (64)	16,958 (60)	20,194 (68)	
Black	16,724 (29)	9096 (32)	7628 (26)	
Other	4123 (7)	2200 (8)	1923 (6)	<.001
Weight (kg)	85 (19)	85 (19)	84 (19)	<.001
BMI, kg/m ²	29.5 (6.1)	29.6 (6.2)	29.4 (6.0)	.03
History of obesity, %	13,308 (23)	6324 (22)	6984 (23)	.002
Cigarette smoking, %	23,972 (41)	11,372 (40)	12,600 (42)	<.001
Hypertension, %	35,640 (61)	17,483 (62)	18,157 (61)	.04
Dyslipidemia, %	24,806 (43)	11,427 (40)	13,379 (45)	<.001
Diabetes mellitus, %	10,445 (18)	5514 (20)	4931 (17)	<.001
METs of task	9.2 (3.0)	9.1 (3.1)	9.3 (2.9)	<.001
<6	7626 (13)	4159 (15)	3467 (12)	
6-10	15,627 (27)	7694 (27)	7933 (27)	
10-12	21,323 (37)	10,022 (35)	11,301 (38)	
≥12	13,423 (23)	6379 (23)	7044 (24)	

Continuous variables presented as mean (standard deviation); categoric variables presented as number (percentage).

BMI = body mass index; FH = family history of any coronary heart disease; MET = metabolic equivalent.

*P value calculated using analysis of variance for continuous variables and chi-square test for categoric variables.

that higher fitness was inversely associated with incident coronary heart disease and mortality in all patients, irrespective of family history status. Each metabolic equivalent

increase in cardiorespiratory fitness was associated with a 13% and 17% reduction in incident coronary heart disease and mortality risk, respectively. Our results are consistent with the current literature on the importance of cardiorespiratory fitness, with benefits from higher fitness likely mediated through reductions in coronary heart disease risk factor burden and severity of acute cardiovascular events.⁶

The association between family history and coronary heart disease risk is well studied; however, relatively limited data are available on the association of improved fitness and hard events in individuals with a family history of coronary heart disease. Similar to prior studies, our study did not find a significant association between family history and outcomes, even after adjustment for cardiorespiratory fitness.⁷ Indeed, the presence of family history influences decision making regarding risk factor management in a positive fashion,⁸ which may balance out the risk imparted by the interaction of genetic risk factors and environmental exposures. In addition, individuals with a strong family history may die prematurely, resulting in a survivorship bias with less extreme forms of family history.⁹

Study Limitations

Data for family history were based on medical records, suggesting that the definition for family history may not have been applied consistently, introducing misclassification bias. Accurate family history assessment may be limited by reporting errors, resulting in underestimation of the true risk associated with family history.¹⁰ However, we believe our definition of family history is justified for the following reasons: (1) Family history is generally fixed (shared genetic risk factors), such that family history of any coronary heart

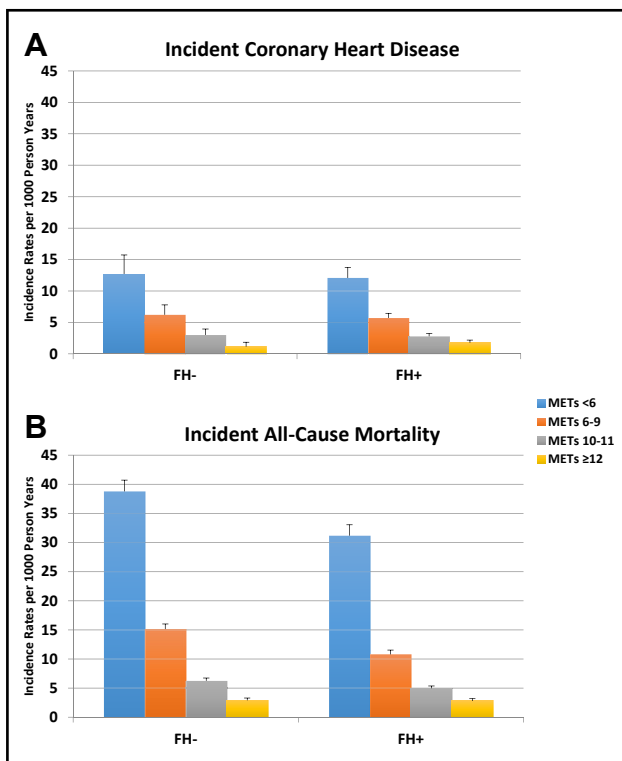


Figure (A and B) Unadjusted incidence rates for coronary heart disease and all-cause mortality stratified by family history status. family history of any coronary heart disease; MET = metabolic equivalent.

Table 2 Hazard Ratios (95% Confidence Interval) for the Association Between Metabolic Equivalents and Incident Coronary Heart Disease and All-Cause Mortality, Stratified by Baseline Family History Status

METs	FH− (n = 28,254)				FH+ (n = 29,745)			
	METs <6	METs 6-10	METs 10-12	METs ≥12	METs <6	METs 6-10	METs 10-12	METs ≥12
N	4159	7694	10,022	6379	3467	7933	11,301	7044
CHD								
Events (n)	337	305	209	65	238	263	195	87
Unadjusted IR*	14.13	6.96	3.45	1.44	12.09	5.71	2.79	1.77
Unadjusted HR	1 (ref)	0.51 (0.44-0.59)	0.25 (0.21-0.30)	0.10 (0.07-0.12)	1 (ref)	0.48 (0.41-0.58)	0.23 (0.19-0.28)	0.14 (0.11-0.18)
Model 1	1 (ref)	0.63 (0.54-0.74)	0.38 (0.31-0.46)	0.18 (0.13-0.24)	1 (ref)	0.61 (0.51-0.73)	0.35 (0.28-0.43)	0.22 (0.17-0.30)
Model 2	1 (ref)	0.64 (0.54-0.76)	0.45 (0.37-0.55)	0.24 (0.18-0.33)	1 (ref)	0.63 (0.52-0.76)	0.38 (0.30-0.47)	0.28 (0.21-0.38)
All-Cause Mortality								
Deaths (n)	1613	1207	678	223	1105	913	623	238
Crude IR*	38.78	15.14	6.23	2.90	31.17	10.80	4.96	2.79
Unadjusted HR	1 (ref)	0.40 (0.37-0.43)	0.16 (0.15-0.17)	0.07 (0.06-0.08)	1 (ref)	0.35 (0.32-0.38)	0.16 (0.14-0.17)	0.08 (0.07-0.10)
Model 1	1 (ref)	0.52 (0.48-0.57)	0.28 (0.26-0.31)	0.17 (0.14-0.20)	1 (ref)	0.48 (0.44-0.52)	0.28 (0.25-0.31)	0.17 (0.15-0.20)
Model 2	1 (ref)	0.55 (0.51-0.60)	0.30 (0.27-0.33)	0.18 (0.15-0.21)	1 (ref)	0.51 (0.46-0.56)	0.30 (0.27-0.34)	0.19 (0.16-0.23)

Model 1 adjusted for age (years), sex, and race. Model 2 adjusted for Model 1 + weight (kg), cigarette smoking, hypertension, hyperlipidemia, diabetes, history of obesity, chronic obstructive pulmonary disease medication use, statin use, and antihypertensive medication use.

CHD = coronary heart disease; CI = confidence interval; FH = family history of any coronary heart disease; HR = hazard ratio; IR = incidence rate; MET = metabolic equivalent.

*Incident rate reported per 1000 person-years.

disease in a first-degree relative is significantly associated with early- and late-onset coronary heart disease¹¹; and (2) similar rates of coronary heart disease events are seen when comparing premature family history with any family history of coronary heart disease in a first-degree relative.¹² This was a retrospective study, and analysis was based on administrative claims files; thus, some data may not have been available, and misclassification may have been introduced because of coding errors.

CONCLUSIONS

Higher cardiorespiratory fitness was associated with a lower risk for incident coronary heart disease and mortality in all patients, regardless of family history status. Family history did not modify the association between cardiorespiratory fitness and incident events. Our results add to the growing body of evidence regarding the benefits of fitness by extending it to include individuals with a family history of coronary heart disease.

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