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Original Article

Parental-Offspring Association of Age of Onset of Coronary Heart Disease or Stroke A Prospective Cohort Study of Parents and Offspring

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ABSTRACT

Objective: To investigate the effect of parental age of onset of coronary heart disease (chd) or stroke on age of onset of chd or stroke in offspring. **Design:** inception cohort study. **Method:** the association between age of onset of chd or stroke in offspring and maternal age of onset of chd or stroke and the association between age of onset of chd or stroke in offspring and paternal age of onset of chd or stroke were assessed using the cox proportional hazard model after conditionally imputing the censored parents (i.E. Parents who did not experience chd or stroke during the study). **Results:** parental age of onset of chd was predictive of offspring age of onset of chd for both maternal age of onset of chd (p<0.0001 N=1378) and for paternal age of onset of chd (p=0.0005 N=1194). A negative estimate of the coefficient of interest signifies that late onset of coronary heart disease in parents is protective of onset of chd in offspring. Beer intake and hdl were important confounding variables associated with parental and offspring age of onset chd. **Conclusions:** using cox proportional hazard model, we found that late onset of chd or stroke in parents is cardioprotective for offspring. Parental age of onset of chd or stroke is associated with offspring age of onset of chd, and this relationship is described for each unit increase or decrease of age of onset using these statistical methods. This relationship suggests that data on parental history can be useful in the clinical setting in the determination of risk among those at intermediate levels of predicted risk using existing risk calculators.

Key words: Cardiovascular Disease, Risk Factor, Coronary Heart Disease, Stroke, Cerebrovascular Accident, Onset of Cardiovascular Disease

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality both in the United States and worldwide.[1] The major types of CVD are coronary heart disease, cerebrovascular disease or stroke, peripheral artery disease, congenital heart disease, heart valve complications, arrhythmias, and myocardial infarctions.[1] Of the 17.5 million deaths globally due to CVD in 2012, coronary heart disease (CHD) accounted for 7.4 million (42.3%) deaths and strokes accounted for 6.7 million (38.3%) deaths.[1] Several risk factors have been identified as major contributors to the increased incidence of coronary disease and stroke, including elevated serum lipids, obesity/overweight, tobacco use, physiologic stress, estrogen levels, and family history.[1-14]

In addition to the established risk factors, multiple prospective studies have identified a positive correlation between onset of cardiovascular disease in parents and their incidence in offspring.[6,7,8,9,11] Studies suggest that multiple factors contribute to the correlation between parental and offspring onset of cardiovascular disease, including genetic components,[6-15] age of onset in parents,[6,8,11] parental gender[8] number of first degree relatives effected,[9] and, in more recent studies, parental degree of coronary artery calcification as detected by computed tomography.[13] However, using established risk factors, the Framingham study established a multivariate algorithm for estimating 10 year CVD risk, called the Framingham Risk Score (FRS),[7,14-15] that does not incorporate a positive parental history of CVD into the estimation. Other guidelines, including ATP-IV[16] and JNC 8[17] recommend consideration of a positive family history in cardiovascular risk estimation; however, the magnitude of independent risk conferred by the presence of parental cardiovascular disease is not well described. In our study, we present the importance of parental age of onset of CHD or stroke, which was excluded from the FRS, and its significance as an independent predictive variable for risk assessment.

In our investigation, by using the survival model for analysis, we sought to determine both the maternal-offspring and paternal-offspring association of age of onset of CHD or stroke. Our approach differs from previous studies in that we use a time-to-event predictor of parental age of onset of CHD or stroke and

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the time-to-event outcome, offspring age of onset of CHD or stroke, while controlling for offspring modifiable risk factors. This analysis enables us to interpret results in a unit scale rather than using the thresholding approach, in which the distinction of "premature" cardiovascular disease is determined using a cutoff age of 55 for males and 65 for females.[14] The thresholding approach dichotomizes the independent variable (family history of CHD or stroke) in to a "yes" or "no" binary outcome, which oversimplifies and reduces the power of the relationship between the two variables. Identifying the precise age of onset of these cardiovascular diseases in parents and characterizing the effect on risk of CHD or stroke development in offspring has the potential to aid clinicians in risk stratification and management plans for patients determined to be at intermediate risk after traditional risk factors are accounted. This detailed characterization can also establish a more appropriate time for the initiation of primary prevention and risk factor modification in offspring to prevent or delay the onset of CHD or stroke.

MATERIALS AND METHOD

For this analysis, we used The Framingham Heart Study (FHS) database. The FHS is a well-known, longitudinal prospective cohort study that is a premier database for the study of cardiovascular disease and other chronic diseases. The study started in 1948, when FHS scientists and participants embarked on an ambitious project to identify risk factors for heart disease. The FHS Original Cohort consists of 5209 respondents (55% females). All 5209 participants, aged 28–62 years with mean age 44 years, were present for the first medical examination, administered beginning in 1948. Nearly all of the initial subjects were Caucasians. The Offspring Cohort (FHSO) was launched in 1971 with 5,124 participants (52% females), with a mean age of 36 years and range 5-70 years. Our analysis used values collected during the FHS Original Cohort (1971 – 1974, n = 3,261) Exam 12 and the FHSO Exam 1 (1971 – 1975, n = 5124). There was a total of 2572 linked parent-offspring pairs. Participants were included only if they had not yet developed overt symptoms of coronary heart disease or stroke and excluded if they had missing data. The deterministic linkage of the two datasets was possible, thanks to the Framingham Executive Committee that provided anonymous patient IDs and specific family codes.

In our study, in order to evaluate the relationship between age of onset CHD or stroke in parents and age of onset CHD or stroke in offspring, we controlled for offspring modifiable risk factors including cigarette smoking, beer intake, BMI, SBP, diabetes mellitus, HDL, and total cholesterol. Similar to the thresholding approach that allocates different risks for CHD or stroke depending on the sex of the first-degree relative, separate analyses were performed for each parent, male and female.

STATISTICAL ANALYSIS

We used Cox's proportional hazards model[18] to examine the relationship between offspring age of onset of CHD or stroke and parental age of onset of CHD or stroke. As an illustration for our paper, we are interested in estimating the parameters of the Cox proportional hazards model of the relationship between parent age of onset of coronary disease or stroke as a primary predictor while controlling for the offspring's risk factors such, smoking status, beer intake, diabetes status, HDL, and SBP. Age of onset of CHD or stroke in offspring participants was the outcome of interest.

SAS statistical software version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis. Basic descriptive statistics to describe the median, twenty-fifth, and seventy-fifth percentiles of the primary predictor of interest (parent age of onset of CHD or stroke) can be found in Table 2. The proportional hazard regression calibration approach employed in this paper for analyzing offspring time to CHD or stroke and censored predictor is similar to the proportional hazards regression model for survival data with measurement error.[20,21] This Cox regression calibration approach was extended by Atem and Matsouaka[22] for the association of a random censored predictor and a random censored dependent variable. Unlike binary variable thresholding approaches that have shown increased risk of CHD or stroke if a first-degree blood relative has had coronary heart disease or a stroke before the age of 55 years (for a male) or 65 years (for a female), we can compute a hazard ratio for each unit increase or decrease of parent age of onset of CHD or stroke on offspring age of disease onset.

The conditional imputation approach employed in this paper combined the non-modifiable risk factors, age of onset of CHD or stroke in mother or father, and parental history by defining parental onset of CHD or stroke as the instantaneous risk of the cardiovascular event, given that the event has not previously occurred. This leads to a relatively stable estimate and avoids bias estimates, as shown by the thresholding approach described by Rigobon & Stocker[23] and Austin & Hoch.[24] Similar to the thresholding approach, our approach also controls for modifiable risk factors of CHD and stroke, such as cigarette smoking, beer intake, BMI, SBP, diabetes mellitus, HDL, and hypercholesterolemia. Basic statistics were performed and describe the distribution of frequency, mean value, and range of the confounding variables (Table 3A and 3B).

The age of onset of CHD or stroke is defined as the age at which either parent or offspring was diagnosed with CHD or stroke by a medically-trained professional. The dependent variable, age of onset of CHD or stroke in offspring, is potentially right-censored. That is, offspring that truly had CHD or stroke but were not diagnosed with CHD or stroke by a medical professional during this study are considered censored. Similarly, for the primary predictor variable, age of onset of CHD or stroke in parents, those that truly had CHD or stroke but went undiagnosed during the observation period are considered censored. In order to consider censored parents in the Cox model for age of onset of CHD or stroke in offspring, we employed the conditional mean imputation technique.[22,23,24] A 2-tailed P value less than .05 was defined as statistically significant.

RESULTS

Our primary variable of interest is parental age of onset of CHD or stroke, which is potentially right-censored. The outcome, offspring age of onset of CHD or stroke, is survival data. Separate analyses were performed for each parent, and the data was separated into two groups. The baseline

Table 1A: Baseline Characteristics of Offspring Based on Maternal and Offspring Associations

Variable		Mean (SD)	N (%)
CHD Status	No		3000 (59.1)
	Yes		2079 (40.9)
CHD in Offspring	No Event		1080 (78.4)
	Event		298 (21.6)
CHD in Mother	No Event		805 (58.4)
	Event		573 (41.6)
Smoke	No		747 (54.2)
	Yes		631 (45.8)
Beer Intake	No		568 (66.5)
	Yes		286 (33.5)
Diabetes	No		1314 (98.6)
	Yes		19 (1.4)
BMI		25.77 (4.5)	
HDL		50.67 (14.5)	
SBP		129.15 (17.2)	

characteristics for the men and women in the sample are shown in Table 1A and Table 1B, respectively. The study sample included 2572 subjects in total, consisting of 1378 mothers and 1194 fathers. Out of 1378 mothers, 45.79% of their offspring smoked, 33.49% consumed beer, and 1.43% were diabetic. Maternal mean BMI, HDL, and SBP values were 25.77, 50.67, and 129.15, respectively. Of the 1,194 fathers, 42.21% of their offspring smoked, 36.32% consumed beer, and 1.37% were diabetic. The fathers' mean BMI, HDL, and SBP values were 25.36, 50.69, and 128.10, respectively.

Table 1B: Baseline Characteristics of Offspring Based on Paternal and Offspring Associations (original)

Variable		Mean (SD)	N (%)
CHD Status	No		3000 (59.1)
	Yes		2079 (40.9)
CHD in Offspring	No Event		979 (81.9)
	Event		215 (18.0)
CHD in Father	No Event		807 (67.6)
	Event		387 (32.4)
Smoke	No		690 (57.8)
	Yes		504 (42.2)
Beer Intake	No		491 (63.7)
	Yes		280 (36.3)
Diabetes	No		1154 (98.6)
	Yes		16 (1.4)
BMI		25.36 (4.4)	
HDL		50.69 (14.2)	
SBP		128.10 (17.3)	

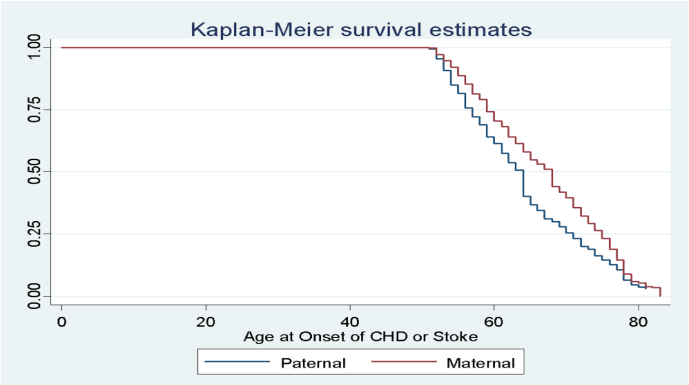

Figure 1: Parent-Offspring Kaplan-Meier Survival Estimates

Table 2: Median Percentile Distribution of Parental Onset of CHD or Stroke (original)

Parent	N	25%	50%	75%
BMI	1194	57	64	71
HDL	1378	59	68	75
SBP	2572	58	64	73

The median age of onset of CHD or stroke was 68 years and 64 years for mothers and fathers, respectively (Figure 1). The 25th and 75th percentiles were 59 and 75 years for mothers, respectively, and 57 years and 71 years for fathers, respectively (Table 2). The overall median age of onset of CHD or stroke in parents was 64 years. The primary variables of interest, paternal and maternal age of onset of CHD or stroke, were imputed using the single imputation for a random censored covariate. Values for the variables BMI, SBP, total cholesterol and HDL, were entered as continuous variables while diabetes status, smoking status and drinking status were entered as categorical variables. Non-diabetics, non-smokers, and non-drinkers, respectively, were the designated reference groups for the categorical variables. Some confounders had missing data. We analyzed the data using SAS 9.4, and assumed that the data is missing is at random.

FThe Cox proportional hazard (Cox PH) models were used to analyze the relationship between offspring age of onset of CHD or stroke and parental age of onset of CHD or stroke. We presented a separate analysis for

Table 3A: Survival Analysis for the Association between Maternal Age of Onset of CHD and Offspring Age of Onset of CHD (original)

Parameter	Estimate (SE)	Adjusted Hazard Ratio (95%C.I)	p-value
Maternal Age of onset of CHD	- -0.041(0.009)()	0.96(0.94-0.98)	<.0001
Smoke	0.547(0.157)	1.73(1.27-2.35)	0.0005
BMI	0.448(0.539)	1.57(0.54-4.51)	0.4059
Diabetes	-0.790(1.034)	0.45(0.06-3.44)	0.4449
SBP	-0.132(0.164)	0.88(0.63-1.21)	0.4180
HDL	-0.670(0.283)	0.51(0.29-0.89)	0.0181
Total Cholesterol	-0.838(0.431)	0.43(0.19-1.01	0.0521
Beer Intake	0 0.519(0.171)	1.68(1.20-2.35)	0.0024

Table 3B: Survival Analysis for the Association Between Paternal Age of Onset of CHD and Offspring Age of Onset of CHD (original)

Parameter	Estimate (SE)	Adjusted Hazard Ratio(95% C.I)	p-value
Paternal Age of onset of CHD	- -0.027(0.011)	0.97(0.95-0.99)	0.0133
Smoke	0.390(0.181)	1.48(1.04-2.11)	0.0313
BMI	0.277(0.576)	1.32(0.43-4.08)	0.6300
Diabetes	0.599(0.776)	1.82(0.40-8.34)	0.4401
SBP	-0.048(0.203)	0.95(0.64-1.42)	0.8146
HDL	-0.965(0.329)	0.38(0.20-0.73)	0.0033
Total Cholesterol	-0.700(0.530)	0.50(0.18-1.40)	0.1863
Beer Intake	0.607(0.200)	1.83(1.24-2.71)	0.0023

the association between offspring and maternal age of onset of CHD or stroke and offspring and paternal age of onset of CHD or stroke and controlled for the risk factor covariates: beer drinking status, diabetes status, smoking status, BMI, HDL, SBP, and total cholesterol (Table 3A and 3B).

The primary variables of interest, maternal and paternal age of onset of CHD or stroke, are statistically significantly related to age of onset of CHD or stroke in offspring with adjusted hazard ratios of 0.96 and 0.97, respectively. The negative estimates of the coefficients of interest, maternal and paternal age of onset of CHD or stroke, are -0.041 and -0.027, respectively. This signifies that late onset of CHD or stroke events in mothers and fathers is protective of CHD or stroke occurrence in offspring. Significant confounders for offspring age of onset of CHD or stroke were beer intake (maternal P=0.0024 and paternal P=0.0023), HDL (maternal

P=0.0181 and paternal P=0.0033), and smoking (maternal P=0.0005 and paternal P=0.0313).

DISCUSSION

In the present study, hazard ratios are used to assess parental-offspring associations of CHD or stroke, enabling us to determine that late onset of CHD or stroke in parents is cardioprotective for offspring. The effects of both maternal and paternal age of onset of CHD or stroke on offspring age of onset of CHD or stroke were statistically significant. The main confounding variables were offspring HDL levels, beer intake, and smoking (maternal relationship only). Previous studies suggest that onset of CHD or strokes in parents could be used as an independent variable to predict the onset of CHD or stroke in offspring[8,20] however, the independent variable, parental age of onset of CHD or stroke, was presented using binary thresholding variables of 55 years for a father and 65 years for a mother, resulting in a relationship with relatively low predictive power and poor precision in the determination of the age of onset in offspring.

Our method differs by using continuous variables and regression models that enables us to present the median percentile distribution of offspring onset of CHD or stroke and to identify a hazard ratio for each unit increase or decrease of parental age of onset of CHD or stroke. This study is the first to present a time-to-event predictor of parental age of onset and time-to-event outcome of offspring age of onset of CHD or stroke while controlling for modifiable risk factors. This association will enable us to interpret results in a unit scale rather than using an oversimplified dichotomous variable that obscures the detail of the relationship between the two variables.

The Framingham Risk Score (FRS) uses a multivariate approach to determine 10-year cardiovascular risk[7] but excludes family history and age of onset as predictive variables, which has been determined through this survival analysis to have a significant association. The addition of multiple risk factors, including family history of CHD, can improve the accuracy of risk estimation for patients at intermediate risk for development of cardiovascular diseases [15]. Furthermore, premature parental CVD has been previously shown to discriminate risk best among offspring with intermediate levels of cardiovascular risk as predicted by current multivariable risk equations.[18] While recent studies have confirmed that traditional modifiable risk factors account for the majority of the risk in patients who develop CVD,[25,26] data on parental history can be useful in the clinical setting in the determination of risk among those at intermediate levels of predicted risk (using existing calculators). These methods of risk assessment may alter treatment for the primary prevention of cardiovascular disease in those at borderline risk.

Prior to the Framingham Cohort Study, there was a paucity of large, prospective cohort studies that ascertained and validated parental events independent of and prior to offspring events. As a prospective cohort study, the advantages of using the database provided by the Framingham Study are present in its ability to provide a moderated longitudinal analysis and concurrent follow-up assessments every two to four years of subjects, providing a reliable source of data from which to draw conclusions. This study design allows for a significant reduction in offspring recall bias that may be present in alternative study designs. Also, the provision of a large cohort and cross generational analysis enabled us to assess the parental-offspring associations of CHD and stroke and their risk factors. Limitations of the study include the homogeneity of the study sample; subjects were almost exclusively white, middle class Americans, which may limit the generalizability of the research findings to people of varying ethnic backgrounds in the general population.

Future research can aid in strengthening the specificity of the parental-offspring association of CHD or stroke. Studies analyzing the effect of family history on cardiovascular risk using more diverse populations, including ethnic minorities and individuals from other geographic regions, have the potential to produce more generalizable results.

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CONFLICT OF INTEREST

None

ABBREVIATIONS USED

CVD: cardiovascular disease; CHD: congestive heart disease; FHS: Framingham Heart Study; HDL: high-density lipoprotein; SBP: systolic blood pressure BMI: body mass index.

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