Original Article

Predictive Value of Cardiovascular Risk Factors for Risk Assessment in Cohort of Shiraz Heart Study

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Background: Risk assessment for fast growing burden of cardiovascular diseases is very important and difficult. As a response to this challenge, in particular, genetic risk factors which potentially modify risk, we conducted a survey of primary data registry of Shiraz Heart Study on integration and application of family history data in prevention of cardiovascular disorders.
Method: This study is a longitudinal cohort project to be extended from subpopulations of different job groups to the community.
Results: Parental family history of MI, diabetes mellitus (DM), hyperlipidemia (HPL), hypertension (HTN) was reported more frequently among females than males. Histories of MI, DM, HPL, and HTN in both parents were respectively positive in 2.6%, 2%, 4.6%, and 7.9 % of the participants. Odd ratios (OR) for risk of MI from family history of MI were 2.7; risk of DM from family history of DM 4.5; risk of HPL from family history of HPL 2.04; and risk of HTN from family history HTN 4.7. Also, family history of MI modifies risk of HPL (OR=1.7, P<0.0001); and family history of DM modifies risk of HPL (OR=2.04, P<0.0001).
Conclusion: Our primary result shows potent application of family history data in risk assessment of cardiovascular outcome. In particular, HTN appears as a silent and leading risk modifier. In regard to the course of continuing Shiraz Heart Study integration of family history of risk factors crucial in public health we suggest to adopt a network of electronic health records from the "Health House" to the "Heart House".

Keywords: Myocardial Infarction, Family History, Risk Assessment, Cohort Study

Introduction

During the past two decades there has been tremendous amount of released data in the field of public, medicine and social sciences. These have happened mostly because of revolution of information technology (IT) and genomic sciences after completion of Human Genome Project.[1] In the light of putting daily affairs to computers as a result of reducing physical activity and life style changes, cardiovascular diseases have shown an increasing trend. The global burden of atherosclerosis is going to rise to rates in which developing countries will lose much healthy lives compared to what they have lost so far.[2]

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Most of these increases in cardiovascular mortalities and morbidities are due to growing prevalence of risk factors, which among them the most prominent are sedentary lifestyle, high caloric nutrition and stress of job market and workplace. To complete this list and to highlight the role of novel risks, genetic profiles of individual, family and population should be considered carefully.

The leading process to control and prevent cardiovascular diseases at first stage, i.e. primary prevention, is to identify population specific risk factors and the way of their spread in different strata of the community. For special knowledge of genetics in this field, the best tool that is easily available is family history of risk factors.[3] Assemblage of family history data in the community in the form of national and/or cohort studies will improve not only basic tools for prevention, but also can apply for efficient risk modification.

Cohort of Shiraz Heart Study is a local prevention design that aims both identification of population specific traditional risk factors and novel risks such as candidate genes and biomarkers. This project has two dimensions; one is a community organization which is known as “Shiraz Heart House” and the other is longitudinal cohort which is performed in three separate phases including. screening of risk factors, monitoring of the risks and intervention of cardiovascular outcomes and the to evaluate and apply efficient preventive measures.

The first stage of this study explores the health records and family history of cardiovascular risk factors of 2161 high school teachers.

Patients and Methods

Shiraz Heart Study as a communitywide project has started since 2009 and aims at effective prevention in various career classes and general population of Fars Province. According to the last nationwide census (2004) (1385, Solar Hegira) the capital of province, Shiraz, had a population of 1’711’186 (males=877’862). The primary design was focused on different job groups, in order to screen risk factors and to assign risk and high risk patients to proper intervention clinics. Simultaneously, a charitable organization known as Shiraz Heart House was established to coordinate the partnership of the heart study. This center included seven preventive clinics which were diabetes, lipid, obesity, nutrition, hypertension (HTN), and stress, exercise/physical activity. In the first round of the screening, Provincial branch of the Ministry of Education contracted participation of their teachers in the study of “Healthy Heart”. For each participant a general questionnaire was filled which contained demographic data, insurance status, job (first and second; to calculate working hours per day), also family size as a measure of stress, smoking, physical activity, ethnicity, systolic and diastolic blood pressures, BMI, hip ratio, lipid profile and health records especially those of cardiovascular risks and outcomes such as ischemia of heart, HTN, cerebral vascular events (CVA), diabetes, and other history of diagnosed conditions.

For pattern of nutrition, food frequency questionnaire (FFQ) and album of food are applied. Three generation pedigrees are drawn, parental consanguinity and family history of risk factors involving Myocardial Infarction (MI), diabetes (DM), hyperlipidemia (HPL), HTN, obesity, CVA, smoking and other diagnosed genetic and acquired conditions. Usage of any drug and medication was also recorded.

In addition to blood specimen for LDL, HDL, TG, cholesterol and FBS, 4ml blood was collected from each subject to extract DNA and saved in DNA Bank of study for the subsequent genetic associa-

Table 1. Anthropometric Data From 2161 Subjects, Shiraz Heart Study

	Age	BMI	Waist-hip ratio	Blood pressure		LDL	HDL	TG	Cholesterol	FBS
	(Mean ± SD)			Systolic	Diastolic	(Mean ± SD)				
Male (1303)	43.3±6.5	25.±3.7	0.908±0.067	122.2±17.97	80.02±12.01	108.6±27.32	38.8±9.42	182.4±110.1	195.5±38.31	93.3±28.50
Female (851)	41.9±6.3	26.4±3.98	0.88±0.073	116.7±15.76	75.9±11.98	105.9±28.64	43.4±9.40	121.8±68.49	191.2±38.37	91.7±27.83
Total (2154)	42.4±6.4	25.9±3.9	0.892±0.072	118.9±16.88	77.5±12.16	107.0±28.13	41.6±9.70	145.7±92.23	192.9±38.33	92.3±28.05

(n): number, BMI = (kg/m²), SD: standard deviation, BMI: body mass index, FBS: fasting blood sugar

Table 2. Parental Family History Of MI and Risk Factors, Shiraz Heart Study

	Father							Mother						
	MI	Diabetes	Hyperlipidemia	Hypertension	Obesity	CVA	Smoking	MI	Diabetes	Hyperlipidemia	Hypertension	Obesity	CVA	Smoking
Male (%)	122 (14)	39 (4.5)	62 (7)	129 (15.2)	34 (4)	73 (8.6)	106 (12.5)	70 (8.2)	87 (10.2)	165 (19.5)	256 (30)	76 (9)	35 (4)	13 (1.5)
Female (%)	234 (18)	133 (10)	153 (12)	227 (17.5)	77 (6)	121 (9.3)	156 (11.9)	115 8.8)	218 (16.7)	346 (26.6)	475 (36.5)	160 (12)	62 (4.8)	23 (1.8)
P value	0.027*	<0.0001*	0.001*	.092[a]	0.049*	0.57	0.73	0.62	<0.0001*	<0.0001*	0.002*	0.014*	0.45	0.67

* significant,

tion and linkage investigations.

Primary data set from 2161 participants were analyzed for family history of cardiovascular risk factors in first degree relatives (FDR) and potential application of this information to health record and prevention. Nonparametric statistics was applied for categorical variable such as family history and analysis of variance for continuous variables, e.g. blood pressure, LDL and so on. Also, logistic regression was used to calculate odd ratio (OR) and to evaluate effect of family history of risk factors on risk assessment of MI, HTN, DM and HPL.

Results

Total entries until February 2010 included 2161 subjects whose primary data were transmitted into local software. Table 1 shows the anthropometric and metabolites information. Parental consanguinity for study population and for those with positive family history of MI in both parents were 24.5%.and 21.8%, respectively, which do not differ significantly (P>0.05). Analysis of parental consanguinity using personal health records, i.e. ischemia of heart, HTN, CVA, DM and HPL did not show any significant relationship.

In regard to male and female participants, family history of MI and risk factors in both parents are presented in Table 2 of which 2.65% had history of MI in both parents, 2% diabetes, 4.6% hyperlipidemia, 7.9% HTN, 13.5% obesity, 1% CVA and 0.75% smoking. Except for history of HTN, CVA and smoking in father, and MI, CVA and smoking in mother, self report of family history were higher among women than that of men (Table 2, P<0.05). Also, number of women who self reported history of risk factors in the rest of FDR members were more than men (P<0.05). Siblings' family history of MI and risk factors were different among men and women for some of those factors but not all. Tables 3 and 4 display these data for first and second sis-

Table 3. Sister Family History Of MI and Risk Factors, Shiraz Heart Study

	1st							2nd						
Risk factors	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Male (%)	6 (0.7)	24 (2.8)	31 (3.6)	34 (4)	27 (3.2)	9 (0.5)	3 (0.4)	3	7	19	12	15	3	1
Female (%)	14 (1)	63 (4.8)	82 (6.3)	84 (6.5)	61 (4.7)	7 (1)	2 (0.2)	3	20	36	30	31	1	1
P value	0.38	0.02*	0.007*	0.014*	0.051	0. 17	0.39	0.45[a]	0.14	0.44	0.093	0.33	0.17	0.76

* significant, 1: MI, 2: Diabetes, 3: Hyperlipidemia, 4: Hypertension, 5: Obesity, 6: CVA, 7: Smoking

Table 4. Brother Family History Of MI and Risk Factors, Shiraz Heart Study

	1st							2nd						
Risk factors	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Male	17	17	30	29	10	4	36	4	3	9	9	6	1	11
Female	33	52	71	51	28	7	52	10	12	24	12	11	4	21
P value	0.42	0.01*	0.039*	0.54	0.063	0.54	0.79	0.41	0.096	0.15	0.75	0.72	0.34	0.55

* significant, 1: MI, 2: Diabetes, 3: Hyperlipidemia, 4: Hypertension, 5: Obesity, 6: CVA, 7: Smoking

ters and brothers.

Logistic regression analysis is shown in Table 5, in which family history of MI modifies risk of MI and diabetes; but HTN just modify risk of HTN. Family history of DM modifies risk of both DM and HPL.

From participants 972 out of 2150 (45%) had positive family history of HTN. Subjects who had not FDR history of HTN, 52% had systolic blood pressure out of normal range (i.e. 90-119) and 54% diastolic pressure out of 60-79. Those with FDR history of HTN, near one third had systolic and diastolic pressure more than normal range. Higher systolic and diastolic pressures were found in subjects with history of HTN in father than those without fathers' history of HTN (P<0.0001).

Table 5. Odds Ratio for Risk of Ischemia, HTN, Diabetes, and Hyperlipidemia from Positive Family History

Family History	Risk of	P value	Odd Ratio
MI	MI	0.029*	**2.7**
	HTN	0.144	1.2
	Diabetes	0.016*	1.8
	Hyperlipidemia	<0.001*	1.7
HTN	MI	0.531	1.4
	HTN	<0.001*	**4.7**
	Diabetes	0.75	1.1
	hyperlipidemia	0.77	1
Diabetes	MI	0.45	1
	HTN	0.36	1.23
	Diabetes	<0.001*	**4.5**
	Hyperlipidemia	<0.001*	**2.04**
Hyperlipidemia	MI	0.089	1
	HTN	0.14	1
	Diabetes	0.095	1
	Hyperlipidemia	<0.001*	**2.04**

* Significant

Discussion

Shiraz Heart Study as a longitudinal cohort investigation has been conducted in order to reach the best preventive measures based on population specific risk modification. This study consists of risk screening and intervention. Cohort studies in national health program play a pivotal role and countries with more cohort studies especially those dealing with diseases with social burden are more powerful in health management and preventive purposes.[4] Also cohort study can act as a source of reliable data for other subpopulation health programs.

Many candidate genes have been introduced to account for genetics of atherosclerosis[5-9] But none of them is predicting risk so that it can be integrated in reliable risk assessment. In this connection, collecting family history data is crucial. Family history is the best tool we have at the moment, which represents familial risk and shows both genetic and environmental factors that family members have in common.[10]

The perception of the participant of different risk factors is different. In this regard HTN as a less visible risk may be dismissed by responder compared with smoking. Also, obesity can have different concept for interviewee, as obesity in pear- and apple- shaped have different risk of heart disease.[11] Although in this primary survey, female responders have larger number. In this regard, significantly increasing report of family history of risk factors can reflect either their concerns for family members' health or higher tendency to participate in a preventive study while having some affected family members or history of risk factors (Table 2-4). This difference demands an inevitable training for collection of family history and its sensitivity in risk assessment.

Table 6. Family History Of Hypertension (HTN) versus Personal History Of Ischemia and HTN

Family History of HTN	Personal History					
	Ischemia			Hypertension		
	Yes (20)	No (2059)	Unknown (71)	Yes (117)	No (1965)	Unknown (68)
Yes (972)	10	952	10	91	870	8
No (1178)	10	1107	61	26	1095	61

Logistic regression analysis of risk factors and risk of MI, HTN, HPL and DM (Table 5) demonstrates highly important insight of family history for interpretation of risk assessment. This primary survey suggests not only the importance of family history of each of aforementioned factors' modifying risk and their prevalence in the family but also risk in relation to each other For example, family history of MI increase risk of HPL 1.7 times (P<0.001). Furthermore, diabetes is not only a prevalent metabolic disorder but also it is a critical risk factor for hyperlipidemia (OR=2.04, P<0.001). These results also prove one risk factor may be more effective than the others for population specific risk modification and subsequent prevention.

Parental history of HTN is higher than that of HPL and DM. In this regard among subjects without history of HTN, 44.3% (870/1965) were considered at risk merely based on positive family history of HTN. Also, 46.2% (952/2059) of subjects were at risk MI, although they did not have any history of ischemia (Table 6). In this primary survey hypertension appears to be a leading and also silent risk of cardiovascular mortality and morbidity.

About 75% of coronary heart disease risk is explained by conventional risk factors. For the remaining risk, family history of risk factors represented genetics and other molecular biomarkers.[12] Conventional risk factors have been integrated in risk calculation; but due attention has not yet been paid to risk of family history. Therefore, for improvement of public health, health records should adopt not only a network of electronic health record (EHR) but also incorporate family history data as a marker of genetic risk.

Genetics modify risk of heart diseases and atherosclerosis through influence of genes responsible in lipid and glucose metabolism, regulation of blood pressure, biology of wall arteries and inflammatory responses.[13] In another word, risk factors of cardiovascular diseases are genetically determined traits; but they are not completely heritable and can be modified by environmental risk and lifestyle.

There is still need to know more about the prevalence of conventional and novel risk factors in different strata of population in different countries in particular countries with lower resources. This could shed light on how the addition of novel genetic and biomarker risks on risk assessment can be more effective both for prevention at population level and at clinical situations. In this way, what we had in hand economically for population prevention and clinical intervention is family history of risk factors assembled in "electronic health record" (EHR) network by adopting information technology(IT) which has revolutionized medical care. In the arena of genomic sciences, tremendous amount of data released by the day, both for monogenic and polygenic or complex disorders such as cancers and cardiovascular diseases. Management of this information is as crucial as its generation. In this perspective importance of IT is more visible than ever. Assemblage of information of family history especially those of risk factors are more applicable when it organized in cohort and national projects. The value of such assemblage is increased if organized in the network and by HER. Collecting family history data while seems very simple can be a very complicated process, in particular when we aim this collection for preventive and intervention purposes. Moreover, collection of family history data in national and cohort studies needs a network of digital environment.

Our primary result shows potent application of family history data in risk assessment of cardiovascular outcome. In particular, HTN appears as a silent and leading risk modifier. Therefore, in the line to reach the most effective preventive measures and for subsequent genetic analysis Shiraz Heart Study should first adopt a network of electronic health records from the "Health House" to the "Heart House and second in addition of traditional risk factors it should pay due attention to integration of family history of risk factors in health records.

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