Journal of Biostatistics and Epidemiology

J Biostat Epidemiol. 2022;8(2):160-169

Original Article

Factors Associated with The Incidence of Coronary Heart Disease in The Mashad: A Cohort Study

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ARTICLE INFO

Received 22.10.2021
Revised 19.12.2021
Accepted 24.02.2022
Published 15.07.2022

Key words:
MASHAD;
Cohort study;
Incidence;
Coronary disease;
Multiple analysis

ABSTRACT

Introduction: Coronary heart disease (CHD) is the leading cause of morbidity and mortality globally, and specially in Iran. An accurate assessment of the incidence of coronary heart disease (CHD) is very important for public health. In current study we aimed to investigate the incidence of CHD and importance of several classical modifiable and un-modifiable risk factors for CHD among an urban population in eastern Iran after 6 years follow-up.

Methods: The population of MASHAD cohort study were followed up for 6 years, every 3 years initially by phone and those who reported symptoms of cardiovascular disease (CVD) were asked to attend for a cardiac examination. An estimate of the incidence of CHD was determined with 95% confidence interval (95% CI) and multiple logistic regression analysis was performed to assess the association of several baseline characteristics with the incidence of a CHD event. Evaluation of goodness-of-fit was undertaken using ROC analysis. CHD cases were divided into four different categories: stable angina, unstable angina pectoris, myocardial infarction and sudden cardiac death.

Results: In the six years of follow-up of the Mashhad study participants, the incidence density of CHD events in men and women in 1000 person-year with 95% confidence intervals were 19.20 (8.10-30.30) and 11.60 (7.30-15.90), respectively. The areas under ROC curve (AUC), based on multiple logistic regression model of CHD outcome, was determined to be 0.783.

Conclusion: Our findings indicated that the incidence rate of coronary heart diseases in MASHAD cohort study increases with age, and our final model was able to predict approximately 78% of CHD events in this Iranian population.

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Introduction

Coronary heart disease (CHD) is the leading cause of death and disability in developed countries,[1] accounting for approximately one-third of all deaths over the age of 35 years. However, there has been a sustained reduction in CHD mortality rates over recent years, in major part due to improvements in its clinical management.[2, 3]

CHD is usually due to partial or complete occlusion of one or more coronary arteries. This is often a consequence of atheroma, consisting of lipid-laden cells, extracellular matrix and extracellular lipid, accumulating in the artery wall. Complete occlusion leads to a myocardial infarction, and is often preceded by inflammation and rupture of an atheromatous plaque and the formation of an occlusive thrombus. Partial occlusion may lead to angina.[4]

CHD risk factors may be broadly categorized as modifiable and non-modifiable. The latter include: age, sex, and genetic factors such as familial hypercholesterolemia that are associated with a family history of premature CHD. Modifiable risk factors include: hypertension, cigarette smoking, dyslipidemia (raised serum low density lipoprotein and triglycerides, or low high density lipoprotein), impaired glucose tolerance including diabetes mellitus (DM), physical inactivity, and obesity[5-7] Several independent risk factors for CHD have been identified.[8] The IN TERHEART study suggests that a large proportion of the risk of a first MI is related to 9 potentially modifiable risk factors (smoking, dyslipidemia, hypertension (HTN), DM, abdominal obesity, inadequate physical activity, insufficient daily consumption of fruit and vegetable, excess alcohol consumption and the psychosocial factors), and these appear to be consistent in both sex, across geographic regions, and by ethnic group.[9, 10]

There is a high prevalence of CHD risk factors among Iranian adults,[10] and CHD remains an important public health burden in Iran, with a high prevalence and attributable mortality rate.[11] There are few reports regarding the incidence rate of cardiovascular diseases (CVD) in Middle Eastern countries, while most studies have just reported its prevalence.[12] Only two studies have been carried out in Tehran and Isfahan to determine the incidence rate of CVD in Iran, and no other study has been found in eastern Iran so far.[12-14]

Obtaining information about epidemiology of CHD is essential to inform and improve policy making for its prevention. In this study we aimed to investigate the importance of several classical, modifiable and un-modifiable risk factors for CHD in the Mashhad stroke and heart atherosclerotic disorder study (MASHAD cohort study), recruited from an Iranian population from northeastern Iran, assessed after 6 years follow-up.

Materials and Methods

Baseline assessment follow-up and identification of incident CHD

Study design

The MASHAD study is a prospective population-based cohort study.[15] The study recruitment began in 2007 and individuals were followed up every 3 years. The study concluded in 2020. Several CHD risk factors were assessed at baseline as determined from medical history, physical examination, questionnaires and laboratory tests to evaluate notable risk factors.

Participants

A stratified (age, sex, municipality) cluster

random sample of men and women were drawn from three different regions in Mashhad. Mashhad is religious city and the second most populous and large city in Iran, located in Khorasan Razavi province. A total of 9704 subjects, aged between 35 and 65 were enrolled. The subjects who had CHD, stroke and peripheral arterial disease, were excluded from project at baseline. Written informed consent was obtained from all subjects. The project was approved by the MUMS Ethics Committee.

Setting

All the participants were assessed at least twice at follow up in 2011 and 2014 by phone at a pre-agreed time and date. Data collection was performed using cardiovascular standard questionnaires. Subsequently the participants who claimed to have a CHD event, or had a history of hospitalization for CHD, were invited for further investigation in 2015. They were instructed to attend an arranged medical follow-up with a cardiologist and provide all their related medical documents.

Variables and measurement

During the follow-up session, blood samples were obtained between 8 and 10 a.m. after 12-hour overnight fast and serum harvested for the measurement of, serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG) and high sensitivity C-reactive protein (Hs-CRP) concentrations. The mentioned biochemical parameters were measured by routine methods using an auto-analyzer (BT3000), and routine enzymatic methods, using Pars Azmoon kits (mg/ dl).

Blood pressure measurement were undertaken using the right arm after a 10-min rest with subjects in a seated position using a mercury sphygmomanometer; blood pressure was measured twice, separated by a 3-minute interval; the mean of 2 separated recordings was recorded. Anthropometric parameters for all participants including height, weight, waist circumference and hip circumference were measured according to standard protocol which described, recently. The body mass index (BMI) was calculated by dividing weight to height squared (m^2).[15] Afterwards, a 12-lead electrocardiogram (ECG) was undertaken for each participant reported to have CHD then examined by a cardiologist. Possible cardiovascular disease was diagnosed using ECG, clinical findings, and medical history. If necessary, additional medical examinations were performed for the subjects and also tests such as stress echocardiography, radioisotope, angiography, computed tomography (CT) angiography and exercise tolerance test (ETT) and review of available medical records were performed. Finally, cases with a possible CHD event were reviewed by a panel of specialists who agreed a definite diagnosis. Patients with established CHD were divided into four categories: stable angina, unstable angina pectoris, myocardial infarction, and sudden cardiac death, confirmed by death registration system of the Mashhad health center and registered according to the International Classification of Diseases-10 (ICD-10, versions 2010).[16]

Statistical methods

Stata software, (Stata 14, 2015, StataCorp LP, TX, USA) and SPSS version 16 were

used for all statistical analyses. Variables that were normally distributed were expressed as means ± SD, median and data that were not normally distributed were expressed as median and interquartile range respectively. Continuous variables were compared by t-test for parametric variables (and Mann-Whithney for non-parametric variables) and chi-squared test was used to compare categorical variables. The incidence density of CHD events with 95% confidence interval (95% CI) were determined by gender, and expressed in terms of per 1000 person-year. Subjects who did not participate in follow up were excluded from incidence calculations.

Multiple logistic regression model was performed in order to assess the association of some demographic, anthropometric and biochemical characteristic with CHD event. For determining the final model, using univariate analysis, the association of each of the above-mentioned variables with CHD was assessed and then variables with P-value <0.25[17] were entered into the final model. Prediction model for incident of CHD were appraised using information of MASHAD prospective study. Predictivity of incident CHD was estimated by using the area under ROC curves, resulting from adding some demographic and biochemical risk factors especially traditional risk factors.

Evaluation of goodness-of-fit was done using receiver operating characteristic (ROC) analysis by comparing the predicted probabilities calculated based on the multiple logistic regression model with the observed CHD: discriminative power of the model as a measure of model performance is assessed by the C-stat. The level of statistical significance was $p<0.05$.

Results

Univariate and Multivariate analysis

There were significant differences in some baseline characteristics as showed in Table 1, including age, body mass index (BMI), waist and hip circumference, diastolic blood pressure, TGs, TC, HDL-C, LDL-C, Hs-CRP, smoking habit, and the presence of hypertension between men and women ($p<0.001$). There was no significant difference in FBG and CHD between the two sexes ($p= 0.064$ and $p=0.48$ respectively).

The findings differed using univariate and multiple models. According to univariate regression, age, systolic blood pressure (SBP), waist to hip ratio (WHR), FBG, TG ($p<0.001$), BMI ($p=0.001$), HDL-C ($p=0.002$) and LDL-C levels (0.021) were associated with CHD. However, after multiple logistic regression these associations were not significant except for age, SBP, FBG ($p<0.001$), BMI ($p=0.033$), HDL-C ($p=0.006$) and smoking status ($p=0.050$). The final model and evaluation of goodness-of-fit with ROC analysis was then accomplished.

ROC analysis

As shown in Figure 1, the area under ROC curve, based on multiple logistic regression model of CHD outcome, was 0.7825. Generally, ROC analysis and the area under the curve (AUC) indicates that this final model was able to predict approximately 78% of CHD events in this population.

Incidence density of CHD events

Our study showed that, 2.69% (n=235) CHD cases were confirmed in MASHAD study

Table 1. Baseline characteristics of 9818 men and women and total population.

Variable	Male (3878)	Female (5826)	p value	Total (n = 9704)
age (year)	48.83±8.43	47.55±8.09	<0.001	48.07±8.25
BMI (kg/m2)	26.35±4.14	28.92±4.83	<0.001	27.89±4.74
Waist circumference (cm)	93.68±11.03	96.24±12.55	<0.001	95.22±12.04
Hip circumference (cm)	101.06±7.95	105.50±9.75	<0.001	103.72±18.52
Systolic blood pressure (mm Hg)	122.35±17.15	121.49±20.29	0.025	121.80±18.52
Diastolic blood pressure (mm Hg)	80.04±10.64	78.56±12.45	<0.001	79.11±1.24
Triglycerides (mg/dl)	124(86-179)a	117(83-167)a	<0.001	120(85-172)a
Cholesterol (mg/dl)	186.79±37.81	194.36±39.72	<0.001	191.35±39.14
HDL-C (mg/dl)	39.84±9.25	44.87±9.89	<0.001	42.86±9.94
LDL-C (mg/dl)	113.50±34.49	118.53±35.68	<0.001	116.52±35.30
FBG (mg/dl)	91.74±37.37	93.22±40.38	0.064	92.70±39.32
Hs-CRP (mg/dl)	1.42 (0.90-2.90)a	1.82 (1.06-3.90)a	<0.001	1.63(0.99-3.53)a
Smoking, %				
Never	57.3%	76.0%	<0.001	68.5%
Past	15.3%	6.3%		9.9%
Current	27.4%	17.6%		21.6%
Diabetes, %	13.7%	14.7%	0.167	14.4%
Hypertension, %	29.7%	32.8%	0.001	31.6%
Coronary heart disease%	3%	2.4%	0.48	2.7%

BMI, Body mass index; FBG, Fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; Hs-CRP, High sensitivity C-reactive protein
aMedian (interquartile range) because of skewed distribution.

Table 2. Incidence density of CHD events in men in 100000 person- year with 95% confidence interval

	N (%)	Crude	Age adjusted
SAP	24 (0.66)	667 (427-993)	240 (140-340)
UAP	57 (1.58)	1585 (1201-2054)	1380 (280-2480)
MI	18 (0.50)	500 (296-791)	180 (100-270)
SCD	11 (0.31)	306 (152-547)	110 (50-180)
Total	110 (3.01)	3060 (2515-3688)	1920 (810-3030)

SAP, Stable angina pectoris; UAP, Unstable angina pectoris; MI, myocardial infarction; SCD, Sudden cardiac death; CHD, Coronary heart disease.

Table 3. Incidence density of CHD events in women in 100000 person- year with 95% confidence interval

		Crude	Age adjusted
Stable Angina	39 (0.76)	762 (542-1042)	490 (80-900)
UAP	61 (1.19)	1193 (912-1532)	480 (360-600)
MI	9 (0.17)	176 (80-334)	70 (20-110)
SCD	16 (0.31)	312 (178-508)	120 (60-180)
Total	125 (2.42)	2444 (2034-2912)	1160 (730-1590)

SAP, Stable angina pectoris; UAP, Unstable angina pectoris; MI, myocardial infarction; SCD, Sudden cardiac death; CHD, Coronary heart disease.

Table 4. Associated factors with CHD outcome among study participants using logistic regression model

Predictors	Univariable			Multivariable		
	OR	(95% CI)	P value	OR	(95% CI)	P value
Age	1.102	1.085-1.119	<0.001	1.078	1.062- 1.095	<0.001
Sex	0.782	0.592-1.033	0.081	0.903	0.681-1.197	0.462
SBP (mmHg)	1.029	1.023-1.036	<0.001	1.015	1.008-1.023	<0.001
BMI (kg/m^2)	1.049	1.027-1.072	0.001	1.031	1.002-1.061	0.033
WHR	1.515	1.250-1.836	<0.001	1.129	0.913-1.397	0. 245
FBG (mg/dL)	1.009	1.008-1.011	<0.001	1.007	1.006-1.009	<0.001
Triglyceride (mg/dL)	1.002	1.001-1.003	<0.001	1.000	0.999-1.001	0. 715
HDL-C (mg/dL)	0.970	0.953-0.987	0.002	0.969	0.949-0.990	0. 006
LDL-C (mg/dL)	1.004	1.000-1.009	0.021	1.003	0.998-1.007	0. 146
Smoking status	1.153	0.988-1.346	0.067	1.170	1.001-1.370	0. 050
Educational level	0.738	0.483-1.128	0.152	0.905	0.778-1.054	0. 190

SBP systolic blood pressure, BMI body mass index, WHR waist to hip ratio, FBG fasting blood glucose, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol

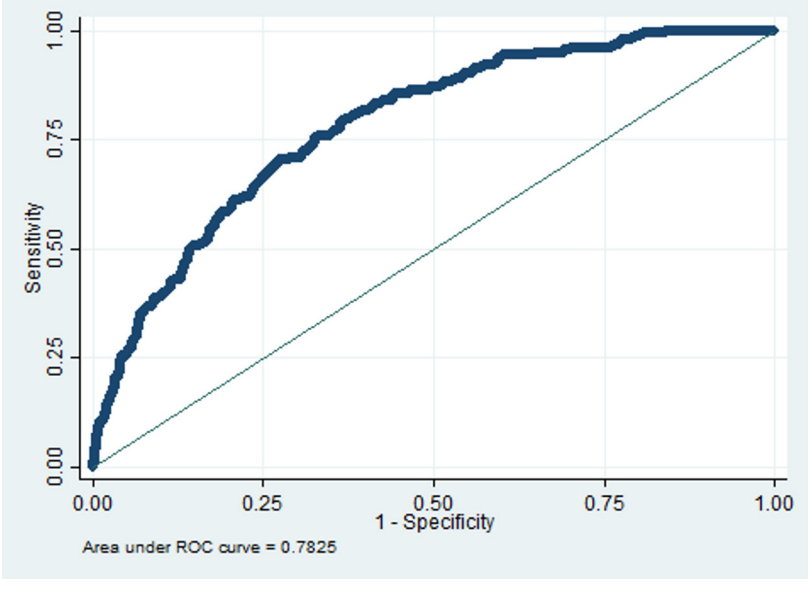

Figure 1. Receiver operating characteristic curves for prediction of CHD in MASHAD cohort study based on multiple logistic regression model.

population. In the six years' follow-up of Mashhad study, the incidence density of all CHD event in men and women in 1000 person-year with 95% confidence intervals were 19.20 (8.10-30.30) and 11.60 (7.30-15.90), respectively. The age adjusted incidence of stable angina pectoris, unstable angina pectoris, myocardial infarction, sudden cardiac death in men in 1000 person-year with 95% CI were 2.40(1.40-3.40), 13.80(2.80-24.80), 1.80(1.00-2.70) and 1.10(5.00-1.80) respectively (table 2).

Discussion

Coronary heart disease (CHD) is the cause of 13.3% of all death worldwide; it remains among the leading causes of death and disability in developed countries, and accounts for one third of deaths above age 35 in western countries.[18-20] The rate of CHD is increasing in Iran[21] and in the Middle East and Latin America.[19]

The results of the present study show that the age-adjusted incidence density of CHD was 19.20 (8.10-30.30) and 11.60 (15.90-7.30) per 1000 person-year, in men and women, respectively during the six-year follow-up study. Several studies in America have shown that the incident rate of CHD is lower than those reported in our study.[22] Given the significant statistical difference in many of anthropometric and biochemical characteristics of men and women in the Mashhad study including age, diastolic blood pressure, body mass index, waist circumference, hip circumference, serum triglycerides, total cholesterol, HDL-C, LDL-C, hs-CRP, positive smoking habit ($P<0.001$) and systolic blood pressure ($P=0.001$), the incidence density of CHD in Mashhad was compared in men to women but it was not significantly different ($P=0.48$).

In a study carried out in England, sex- and age-adjusted incidence rate of CHD in 2012-2016 and its risk factors have been reported to be 221 (225-218) per 100,000 person-year with 95% confidence level which is much lower than those observed in Mashhad study, and thus it is statistically considered a significant difference.[22]

Moreover, high blood pressure was associated with the highest rate of incidence among CHD risk factors in the mentioned follow-up study in England. In Japan, the incidence rate of fatal coronary heart disease in 1996-2003 has been reported to be 120 and 80 in men and women, respectively per 100,000 person-year which indicates the higher rate of incidence in women compared to men. Findings indicate higher incidence density of CHD in Mashhad compared to Japan.[23]

Studies carried out in neighboring countries such as Pakistan, Turkey, Afghanistan, and Iraq have estimated the prevalence of CHD in these regions, and there is no study determining the incidence rate. According to the information provided by World Health Organization (WHO), the prevalence of death due to CHD has been high in these countries. The proportion of death due to CHD in Turkey, Saudi Arabia, Pakistan, and Iran in 2016 has been 34, 37, 29, and 43 percent, respectively. CHD account for 60, 45, and 43 percent of total deaths in Lebanon, Syria and Jordon, an Egypt, respectively.[24]

In a follow-up study of blood glucose and lipids in Tehran between 1999 -2010, age-standardized incidence rate of CHD based on Iranian population has been 1050 (930-1160) and 610 (530-690) per 100,000 person-year for men and women, respectively with 95% confidence level. There was no statistical difference between Tehran and Mashhad in CHD rate of incidence in men; while incidence density in women was significantly higher in Mashhad study. High incidence of coronary diseases among women population in Iran may be the result of the high prevalence of metabolic syndrome in women compared to men (40.8% vs. 27.9% and $P<0.001$). In addition, physical activity level is lower and hence obesity is more common among women. In a cohort study carried out in Isfahan, age-adjusted rate of incidence of CHD has been estimated to be 1168 (1341-996) and 887 (738-1037) per 100,000 person-year in men and women, respectively with 95% confidence level.

However, there was no statistical difference in rate of incidence between Mashhad and Isfahan populations.[12]

In the present study, the incidence density of CHD had been determined in a six-year follow-up, it was found that CHD risk factors including age, waist circumference, blood pressure, FBG, cholesterol, uric acid, TG, hs-CRP, smoking, BMI, and LDL-C in patients with CHD were higher compared to those not reporting CHD. In addition, physical activity level and HDL-C concentration was lower in patients with CHD compared to those without. These results are consistent with those found in previous studies.[13]

The use of predictive models is increasing day by day in medicine and cardiology.[25] In our study ROC analysis and the AUC value of 78% indicates that our model has good discriminatory power. Voss et al assessed prediction of CHD in men population of PROCAM study using logistic regression, 8.4% of participants were categorized as high risk, which contained 45.8% of all CHD seen.[26] Youlian et al conducted to predict CHD risk by assessing different CHD risk factors in two cohort populations including white and black races. They found The AUC were 0.77 for white men and 0.84 for white women as well as 0.76 and 0.82 for black men and women, respectively,[27] which is in agreement with our study.

Increased rates of CHD incidence and prevalence in developing countries is likely to be the result of changes in lifestyle, urbanization, high consumption of processed foods and foods with saturated fat, low fruits and vegetables intake, and low micronutrients intake in Iranian eating style, low levels of physical activity along with high prevalence of obesity and diabetes type 2.

Conclusion

The results of the present study indicate that the incidence density of coronary heart diseases in MASHAD cohort study increases with age. As well as our final model designed in our study, was able to predict approximately 78% of CHD events in Iranian population.

Study limitations

These findings need to be tested over a longer time period for CHD follow up and other populations that have different environmental and genetic backgrounds, so that stratified data can be obtained by gender and socioeconomic group.

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