

Do Cardiometabolic Risk Factors Relative Risks Differ for the Occurrence of Ischemic Heart Disease and Stroke?

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Background: The effects of the risk factors of ischemic heart disease (IHD) and stroke on the occurrence of these diseases differ between different populations.

Objectives: To study the difference in the effects of different cardiovascular (CVD) risk factors on the incidence of IHD and stroke in an Iranian adult population.

Patients and Methods: The Isfahan Cohort Study (ICS) is a longitudinal study that followed up 6323 subjects older than 35 years with no history of CVD since 2001. Of the original sample, only 5431 participants were contacted and followed up until 2011. The end points were the occurrence of IHD (defined as fatal and non-fatal myocardial infarction, unstable angina, and sudden cardiac death) and stroke. After 10 years of follow-up, 564 new cases of IHD and 141 new cases of stroke were detected. The relative risks (RRs) of cardiometabolic risk factors such as hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, high low-density lipoprotein cholesterol (LDL-C) level, low high-density lipoprotein cholesterol (HDL-C) level, current smoking, obesity, high waist-to-hip ratio, family history of CVD, and metabolic syndrome were compared between IHD and stroke patients. The ratio of relative risks (RRR) was calculated for comparing two RRs and estimated adjusted RRR was calculated by using generalized linear regression with a log link and binomial distribution.

Results: The RRs of the occurrence of IHD and stroke in diabetic patients were 1.94 and 3.26, respectively, and the difference was statistically different ($P=0.016$). The RR of high LDL-C was significantly higher for IHD than for stroke ($P=0.045$), while all the other risk factors showed similar RRs for IHD and stroke, with no significant difference in their RRR, including hypertension. Diabetes and hypertension had the highest RRs for IHD, followed by diabetes, metabolic syndrome, and hypertension for stroke.

Conclusions: The effect of diabetes mellitus on stroke was more significant than on IHD, and the effect of high LDL-C level was more significant on IHD than on stroke, other risk factors, including hypertension, have similar RRs for IHD and stroke. Health care professionals need more training regarding the RRs of these risk factors in the Iranian society, and health decision makers should consider it in their future policies.

Keywords: Cardiovascular Diseases; Risk Factors; Stroke; Myocardial Ischemia; Cohort Studies

1. Background

The increasing prevalence of chronic metabolic diseases in the world, especially in developing countries, poses increasing threats at a global level. The World Health Organization views cardiovascular diseases (CVD) as an important cause of death in low- and middle-income countries (1), according to which about 76% of 25,000,000 deaths in developing countries by 2020 are caused by CVD. In the Middle Eastern countries, especially in the 2 recent decades, an outbreak of chronic diseases that cause high morbidity and mortality, including diabetes mellitus, hypertension, CVD, and stroke occurred (2-4). In recent years, Iran faced an increasing prevalence of CVD and metabolic diseases due to economic growth, improvement in health care, and a subsequent decrease in infectious diseases, aging, and changes in lifestyle (5).

Although the risk factors of ischemic heart disease

(IHD) and stroke are common in some properties, their effects on the occurrence of these diseases differ. For instance, hypertension exerts a significant effect on stroke (6), while dyslipidemia exerts a significant effect on IHD (7, 8). In addition, their effects differ between different populations. Metabolic risk factors such as diabetes mellitus, dyslipidemia, and hypertension, along with other factors such as age, sex, smoking, and obesity (body mass index [BMI] and proportion of waist to hip) are interrelated with heart diseases and stroke (9-14).

A large number of studies have concentrated on the risk factors of heart diseases and stroke. However, they could not completely cover and evaluate the relative risk (RR) of each factor on the incidence of IHD and stroke within a prospectively long-term follow-up in the Middle Eastern countries, including Iran. Generally, a small number

of studies examined the strength of the relationship between metabolic risk factors and CVD and stroke altogether. Discussions over their differences can contribute to a proper understanding of the baseline mechanisms of these diseases and highlight the effect of certain interventions on long-term outcomes of risk factors to make proper treatment strategies (15-17). Meanwhile, these risk factors affect different races and populations differently.

2. Objectives

The present study aimed to evaluate and compare between the RRs of cardiometabolic risk factors of the incidence of IHD and stroke in an Iranian adult population who participated in the Isfahan Cohort Study (ICS) (18).

3. Patients and Methods

ICS is a prospective cohort study started in January 2001 and is still ongoing in urban and rural areas of Isfahan, Najafabad, and Arak in Central Iran (18). The population, initially 6504, consisted of subjects older than 35 years constituted the baseline sample of the Isfahan Healthy Heart Program (19). From this study, 181 subjects with a history of myocardial infarction (MI) stroke or any other CVD were excluded. Finally, the study evaluated 6323 participants who were recruited in 2001 in the ICS, of whom 5431 participants had at least one follow-up visit until 2011. The whole design, methods, and sampling were reported elsewhere (18). Briefly, demographic variables such as sex, age, education, history of smoking, diabetes, hypertension, and dyslipidemia were determined. Cardiometabolic variables such as fasting blood glucose (FBG) and 2-hour postprandial (2 hpp) total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels; systolic and diastolic blood pressure; BMI; and waist circumference were measured and recorded in 2001. Then, in 5-year intervals, blood sampling, and physical examination were repeated, while in 2-year intervals, the data of the occurrence of fatal and non-fatal CVDs or hospitalization were recorded by a trained nurse by phone calls. With regard to hospital stay or death, the medical documents of the patients were analyzed in the respective hospital by a general physician, and the occurrence of CVDs, such as fatal and non-fatal IHD, and fatal and non-fatal stroke were recorded. Although the in-hospital diagnoses by the physicians were taken into account, the final diagnosis was confirmed by 3 cardiologists and 1 neurologist. IHD definition includes fatal and non-fatal acute MI, unstable angina, and sudden cardiac death. Acute MI was defined as the presence of at least two of the following criteria (18): typical chest pain lasting more than 30 minutes of more than 0.1 MW of ST elevation in at least two contiguous leads and positive cardiac biomarkers, including troponin I or T or creatine kinase-MB fraction. Unstable angina was defined as typical chest pain or chest discomfort at rest or at low level activity, which lasts at least 20 minutes, representing a change in the usual pattern of angina, or as pain causing a frank pain along with new or dynamic

ST-T changes in two adjacent electrocardiographic leads.

Sudden cardiac death was described as an unpredictable death outside the hospital that happens in less than 1 hour after symptoms arise. Death without existence of any data regarding symptoms is categorized as death of unknown cause.

Stroke is clinically defined as a neurological focal deficit with sudden onset, lasting at least 24 hours, and is probably caused by vascular parameters. Metabolic syndrome was defined according to the national cholesterol education programme adult treatment panel III (20) and existence of three or more of the following criteria: fasting TG level ≥ 150 mg/dL; HDL-C level < 40 mg/dL in men and < 50 in women; fasting glucose level ≥ 110 mg/dL; blood pressure $\geq 130/85$ mmHg or receiving antihypertensive medications; and a waist circumference > 102 cm in men and > 88 cm in women.

LDL-C level ≥ 130 mg/dL or total cholesterol level ≥ 200 mg/dL, or TG level ≥ 150 mg/dL or HDL-C < 40 mg/dL in men or < 50 mg/dL in women were classified as dyslipidemia. Diabetes mellitus was defined if FBG level ≥ 126 mg/dL or 2 hpp ≥ 200 , or if the patient was receiving antidiabetic agents. Obesity was as a BMI ≥ 30 kg/m². Waist-to-hip ratio (WHR) ≥ 0.95 in men and ≥ 0.8 in women was considered as a high WHR. Those who had blood pressures $\geq 140/90$ mmHg or patients receiving antihypertensive drugs were considered as hypertensive. A family history of premature CVD in first-degree relatives was defined as the occurrence of cardiovascular diseases before the age of 55 years for men and 65 years for women. Smoking means current smoking.

3.1. Statistical Analysis

All the collected data of the patients were managed and analyzed by using the Stata IC 11.0 software (Stata Corp LP, TX, USA). Data are expressed as mean \pm SD for continuous variables and number (percentage) for categorical variables. The chi-square test was used for the comparison of proportions and categorical variables, and analysis of variance was used for the comparison of quantitative variables. The incidence rate was the number of new cases during the study period divided by the sum of the person-time of the at-risk population. Ratio of relative risks (RRR) was calculated for comparing two RRs (21). Adjusted RR was calculated by using generalized linear regression with a log link and binomial distribution (22). A $P < 0.05$ was considered statistically significant.

4. Results

Among the original 6323 participants in the ICS, 5431 had at least one follow-up visit between 2001 and 2011. In this period, 705 CVD events occurred, including 564 IHD and 141 strokes. The mean ages of the IHD and stroke patients were respectively 57 and 59 years ($P = 0.09$). As a cohort study, we used the person-year indicator for calculating the incidence of CVD events. The incidence of IHD and stroke increased with the increasing age of the

participants. Table 1 shows the incidence rates of IHD and stroke according to age groups. Accordingly, the incidence of IHD and stroke in the subjects aged 35 - 44 years were 481.4 (95% CI, 397.9 - 582.4) and 98.6 per 100,000 person-years (95% CI, 64.9 - 149.7), respectively. Table 1 showed an increase of 57.7% in IHD incidence and 57.9% in stroke incidence in the 45- to 54-year age group, in comparison with the 35- to 44-year age group. The incidences of IHD and stroke based on the patients' age range show that stroke follows a slighter slope relative to IHD.

We calculated the cumulative percent of CVD events based on age group among all the patients who devel-

oped the disease during the 10-year follow-up. It was 27.4% in the patients aged less than 55 years and 53.2% in those aged less than 65 years. Differences in the frequency of CVD risk factors in those who developed IHD or stroke were significant in terms of FBG level, diabetes, and serum levels of total cholesterol and LDL-C (Table 2).

Table 3 shows the adjusted RRs of the CVD risk factors for the occurrence of IHD and stroke, and the difference between them presented as RRR. Accordingly, IHD and stroke had RRs of 1.90 (95% CI, 1.59 - 2.26) and 1.76 (95% CI, 1.11 - 2.81) in the patients with hypertension, but RR did not significantly different between them ($P = 0.76$).

Table 1. The Incidence of Ischemic Heart Disease and Stroke by Different Age Groups (Per 100,000)^a

Age, y	IHD			Stroke		
	Person-Years	Rate	95% CI	Person-Years	Rate	95% CI
35 - 44	22016	481.4	397.9 - 582.4	22309	98.6	64.93 - 149.76
45 - 54	12819	1138.8	968.3 - 1339.4	13254	233.8	164.48 - 332.57
55 - 64	8689	1714.6	1460.2 - 2013.1	9064	408.1	295.75 - 563.37
65 - 74	5366	2534.3	2142.2 - 2998.1	5672	669.9	487.46 - 920.67
≥ 75	1109	2342.7	1595.1 - 3440.8	1148	1131.4	656.98 - 1948.67
Total	50002	1125.9	1036.6 - 1222.9	51449	274	232.35 - 323.23

^a Abbreviation: IHD, ischemic heart disease.

Table 2. Comparison of the Frequency of the Baseline Risk Factors in the Patients with Ischemic Heart Disease and Stroke^{a,b}

Variables	Group		P Value
	IHD	Stroke	
Total number	564	141	-
Age, y	57 ± 11.5	59 ± 11.9	0.09
Sex			
Male	311 (55)	68 (48)	0.14
Female	253 (45)	73 (52)	
Systolic blood pressure, mmHg	133 ± 23.8	133 ± 24.9	0.81
Diastolic blood pressure, mmHg	82 ± 12.3	84 ± 14.5	0.19
Hypertension	287 (50)	74 (52)	0.73
FBG, mg/dl	98 ± 44	109 ± 58.4	0.01
2 hpp BS, mg/dl	101 ± 27.9	104 ± 29	0.36
Diabetes	123 (21)	46 (32)	0.007
Total cholesterol, mg/dl	230 ± 55.1	219 ± 56.1	0.03
Hypercholesterolemia	391 (69)	89 (63)	0.15
Total TG, mg/dl	218 ± 113.6	203 ± 113.2	0.15
Hypertriglyceridemia	396 (70)	91 (64)	0.19
HDL cholesterol, mg/dl	46 ± 10.3	48 ± 10.5	0.14
Low HDL-cholesterol	254 (45)	63 (44)	0.94
LDL cholesterol, mg/dl	140 ± 46.1	131 ± 45	0.03
High LDL-cholesterol	325 (57)	70 (49)	0.08
Smoking	147 (26)	30 (21)	0.23
BMI, kg/m²	27 ± 4.4	27 ± 5.6	0.15
WHR	0.95 ± 0.07	0.95 ± 0.08	0.92
Family history of CVD	40 (7)	9 (6)	0.76
Metabolic syndrome	292 (51)	80 (56)	0.29

^a Data are expressed as mean ± SD for continuous variables and number (percentage) for categorical variables.

^b Abbreviation: CVD, cardiovascular disease; FBG, fasting blood glucose; IHD, ischemic heart disease; TG, triglyceride; WHR, waist-to-hip ratio.

Table 3. Comparison of the Relative Risk of Each Risk Factor for the Occurrence of Coronary Heart Disease and Stroke ^a

Risk Factors	Group				P Value ^b
	IHD		Stroke		
	Adjusted ^b RR	95% CI	Adjusted ^c RR	95% CI	
Hypertension	1.90	1.59 - 2.26	1.76	1.11 - 2.81	0.762
Diabetes	1.94	1.61 - 2.35	3.26	2.23 - 4.76	0.016
Hypercholesterolemia	1.47	1.22 - 1.77	1.03	0.72 - 1.56	0.104
Hypertriglyceridemia	1.63	1.36 - 1.96	1.36	0.91 - 2.03	0.420
Low HDL-cholesterol	1.24	1.03 - 1.48	1.23	0.76 - 1.97	0.975
High LDL-cholesterol	1.40	1.19 - 1.65	0.92	0.63 - 1.34	0.045
Current smoking	1.17	0.94 - 1.44	0.80	0.42 - 1.51	0.269
Obesity	1.15	0.94 - 1.41	1.23	0.82 - 1.88	0.775
High WHR	1.68	1.35 - 2.09	1.52	0.91 - 2.54	0.725
Family history of CVD	1.64	1.22 - 2.21	1.46	0.69 - 3.08	0.777
Metabolic syndrome	1.88	1.58 - 2.24	2.25	1.49 - 3.40	0.431

^a Abbreviation: CVD, cardiovascular disease; IHD, ischemic heart disease; WHR, waist-to-hip ratio.

^b Ratio of relative risks was calculated for comparing two relative risks.

^c Adjusted based on sex and age.

In contrast, the RRs for IHD and stroke in the patients with diabetes were statistically different (1.94 and 3.26, respectively; $P = 0.016$). Furthermore, the RR of high LDL-C was significantly higher for IHD than for stroke (1.40 vs. 0.92, $P = 0.045$).

The RRs of the other factors, including hypercholesterolemia, hypertriglyceridemia, low HDL-C, smoking, obesity, waist circumference, family history, and metabolic syndrome were not significantly different between the study groups.

5. Discussion

This study presents a comparison between the RRs of cardiometabolic risk factors of CVDs, mainly IHD and stroke. According to the results, hypertension and diabetes mellitus were the most effective risk factors of IHD. Similarly, diabetes mellitus, metabolic syndrome, and hypertension were the most effective risk factors of stroke, but the effect of diabetes mellitus on stroke was more significant than that on IHD. Furthermore, the risk of developing stroke among the diabetes patients was relatively twice as high as that among IHD patients. Another finding was that the RR of high LDL-C was significantly higher for IHD than for stroke.

Another interesting result in the present study is that hypertension has equal RRs for the occurrence of both IHD and stroke. Previous reports indicated that hypertension (as a modifiable risk factor) has more potent association with the risk of stroke rather than IHD. However, according to our findings, hypertension has a strong association with the risk of IHD as well (RR = 1.90; 95% CI, 1.59-2.26). These findings are similar to those of

our previous study (18) and those of other studies such as the Honolulu Heart Program that showed that systolic blood pressure and smoking were the most important risk factors of IHD, rather than other risk factors, including high cholesterol level (23). In Iran, the prevalence of hypertension is high, with an increasing trend in recent years (24). Unfortunately, its control level among treated patients remains low (25-27). This may be one explanation of the high prevalences of IHD and stroke, and their occurrences among younger patients in Iran. The RRs of the other factors such as smoking, obesity, and metabolic syndrome were not significantly different between the two groups of patients.

A study conducted in the United States in 2005 among 18,662 men revealed that the increase in the incidence of stroke related to hypertension was similar to IHD. The RRs of hypertension for IHD and stroke were 1.74 and 1.90, respectively, with no significant difference ($P = 0.36$), as in our results. Diabetes has the highest RR for both IHD and stroke, but the difference in RR was not significant (2.31 vs. 2.64, $P = 0.44$). Furthermore, it showed that the incidences of stroke and coronary heart disease (CHD) increase 28 and 13 times, respectively, with increasing age (28). However, in our study, we observed a lower outbreak of stroke with increasing age, as compared with cardiovascular disease.

Other studies showed that cigarette smoking is the most important modifiable risk factor of CHD (29), and the continuous smoking hazard ratio for CHD is 2.9 (95% CI, 2.7 - 3.1). However, this was not the case in our study, which may be due to higher prevalence of cigarette smoking in Western communities than in nations such

as Iran (19% vs. 9.9% in 2011) (29, 30).

Some studies considered a major role for hypercholesterolemia in CHD (17), and LDL-C has the best established link with the incidence of MI and cardiovascular death (26). This is different from our results that showed that diabetes mellitus and hypertension had the highest RR for IHD. The reason may be related to the dietary habits and lifestyle of our study population. Our previous studies showed that the Iranian lipid profile differs from that of Western populations, mostly in regard to lower mean levels of total cholesterol and LDL-C but higher TG levels and more prevalent low HDL-C level (31).

A prospective study in Japan in 2007 revealed that metabolic syndrome is interrelated with a higher IHD risk. In addition, IHD patients have an older mean age and hypertension, hypercholesterolemia, hypertriglyceridemia, smoking, and lower HDL-C level than the healthy people. These factors were identical between the males and females. Stroke patients have an older mean age and higher hypertension than the control group. High level of smoking and low level of HDL-C were observed more frequently among the men. This study demonstrated that all components of metabolic syndrome, except for glucose disturbance, can increase the risk of IHD two times more among males. However, among females, they were not significantly interrelated with hypertension and obesity. In addition, stroke risk increases 3 or 4 times by hypertension and 1.5–2 times by other components of metabolic syndrome in men. This relationship was observed in females as well, except for HDL-C level. Moreover, this study showed a direct relationship between stroke and IHD risk, and the number of metabolic syndrome components (32). Other report from Japan showed that metabolic syndrome was related with two-fold higher risks of IHD and stroke, and total CVD (33).

In 2002, a prospective study from the Copenhagen City Heart study of 12,000 men and women aged 30–79 years reported a higher RR of diabetes mellitus for IHD than for other risk factors (RR of 1.69 for men and 2.74 for women), as shown in our study. The RR of hypertension for IHD was 1.46 for men and 1.42 for women (34). In addition, a number of Asian studies showed that hypertriglyceridemia and hypertension, and low HDL-C are important risk factors of IHD and diabetes mellitus, and that hypertension and low HDL-C level are the main risk factors of stroke (35–39). Perhaps the difference in RR of cardiovascular risk factors may be related to different prevalence in different populations. The interference of other factors such as genetics, difference in age groups, and other factors not considered in these studies should be considered before any conclusion.

According to our results, approximately one third (27%) of all CVD events occurred among patients younger than 55 years, which highlights the high frequency of premature CVD in Iran. When the cutoff age was considered as 65 years or younger, more than half of the events were within this definition. We consider this to

be among our important secondary findings that need more attention by health authorities. The younger patients have different risk factor profiles and prognoses from those of older patients. Therefore, health policies should consider these findings in CVD screening, diagnosis, and treatment strategies, and should intensify modifying the population lifestyle toward a healthy one starting from childhood in order to reduce cardiometabolic risk factors.

The strength of our study is its large sample size, including participants from urban and rural areas from central Iran; our standard measurement of variables; and confirming the CVD events by an expert panel of 3 cardiologists and 1 neurologist. While the limitations include non-coverage of the information of other parts of Iran and an inherent selection bias because of the observational nature of the study design.

In conclusion, according to our study findings, the RR of diabetes for stroke was significantly higher than the RR for IHD, and the RR of high LDL-C for IHD was significantly higher than the RR for stroke. Meanwhile, the RR of hypertension did not differ between IHD and stroke. Other cardiometabolic factors have no significant differences and have the same effect on both diseases. Thus, patients with diabetes mellitus and high LDL-C should be treated accurately and intensively evaluated for other risk factors of stroke and IHD. The great effect of hypertension on the occurrence of IHD and stroke should be taken seriously by health decision makers, as the prevalence of hypertension and the frequency of uncontrolled hypertension is high in our country.

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Authors' Contributions

Study concept and design: Sarrafzadegan and Sadeghi. Analysis and interpretation of data: Sarrafzadegan and Talaei. Drafting of the manuscript: Aalami Harandi. Critical revision of the manuscript for important intellectual content: Sarrafzadegan. Statistical analysis: Dianatkhah. Administrative, technical, and material support: Aalami Harandi, Pourmoghaddas, Salehi, and Sedighifard. Study supervision: Sarrafzadegan.

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