

The influence of gender and place of residence on cardiovascular diseases and their risk factors

The Isfahan cohort study

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ABSTRACT

الأهداف: تحديد تأثير الجنس ومكان الإقامة على حدوث أمراض الجهاز القلبي الوعائي، وظهور عوامل الخطر المرتبطة بهذه الأمراض.

الطريقة: أُجريت هذه الدراسة الاستطلاعية في مركز أبحاث أمراض الجهاز القلبي الوعائي التابع لجامعة أصفهان للعلوم الطبية، أصفهان، إيران. وقامت الدراسة بمتابعة 6323 مشارك غير مُصاب بأمراض الجهاز القلبي الوعائي (3255 أنثى) والذين تزيد أعمارهم عن 35 عاماً من 3 مدن (أصفهان، ناجافاباد، أراك) والمناطق الريفية في وسط إيران خلال الفترة من 2001م إلى 2007م. لقد قمنا بتعريف نقاط النهاية كالتالي: احتشاء عضلة القلب المميت - وغير المميت، والموت المفاجئ جراء مرض في القلب، والذبحة الغير مستقرة، والسكتة الدماغية التي تشكل أمراض الجهاز القلبي الوعائي.

النتائج: أشارت نتائج الدراسة إلى أن معلومات عوامل الخطر المرتبطة بأمراض الجهاز القلبي الوعائي لدى المشاركين في المناطق الريفية كانت أفضل بشكل واضح من الناحية الإحصائية مقارنةً بغيرهم في كلي الجنسين، غير أنها مرتبطة بعلاقة عكسية مع الكوليسترول منخفض الكثافة في الجنسين، وبالتدخين لدى الذكور. لقد كانت معلومات عوامل الخطر المرتبطة بأمراض الجهاز القلبي الوعائي أفضل لدى الذكور منها لدى النساء وذلك باستثناء عامل التدخين. بالإضافة إلى ذلك فقد كانت نتائج نسبة الخطر المعدلة المرتبطة بالعمر وعوامل الخطر كالتالي: 0.71 لدى الذكور (95% CI: 0.51-0.99)، و0.63 لدى الإناث (95% CI: 0.44-0.91). ولقد كان العمر الذي تحدث فيه أمراض الجهاز القلبي الوعائي متقارباً بين الذكور والإناث، وبين المشاركين في المناطق الحضرية والمناطق الريفية. وكان ارتفاع ضغط الدم من أقوى العوامل المؤدية إلى أمراض الجهاز القلبي الوعائي، باستثناء المشاركين في المناطق الريفية حيث كانت زيادة مستويات الكوليسترول المرتفع الكثافة من أقوى العوامل المسببة لهذه الأمراض.

خاتمة: أظهرت الدراسة الاختلافات في عوامل الخطر المرتبطة بحدوث أمراض الجهاز القلبي الوعائي وذلك اعتماداً على العمر ومكان الإقامة، ومثل هذه الفروق يجب أن تؤخذ بعين الاعتبار عند وضع الاستراتيجيات الوقائية ضد أمراض الجهاز القلبي الوعائي في الصحة العامة.

Objectives: To determine the impact of gender and place of residence on cardiovascular disease (CVD) events and related risk factors.

Methods: In a prospective cohort study, 6323 participants free of CVD (3255 women), with age of more than 35 years from 3 cities (Isfahan, Najafabad, and Arak) and their rural districts in central Iran

were followed-up from 2001 to 2007. This study was carried out at the Cardiovascular Research Institute of Isfahan University of Medical Sciences, Isfahan, Iran. Endpoints were defined as fatal- and nonfatal myocardial infarction, sudden cardiac death, unstable angina and stroke that constituted CVD events.

Results: Subjects in the rural area had significantly better risk factor profile in terms of most CVD risk factors in both genders, but it was reverse for low density lipoprotein (LDL)-cholesterol in both genders, and smoking in men. Except for smoking, men had an overall better risk factor profile compared to women. The age and risk factors adjusted hazard ratio of living in rural area was 0.71 (95% confidence interval [CI]: 0.51-0.99) for men, and 0.63 (95% CI: 0.44-0.91) for women. The age of CVD occurrence was similar in men and women, and in rural and urban areas. Hypertension was the strongest predictor of these events except for rural men showing that high LDL-cholesterol was the strongest risk factor.

Conclusion: The findings in this study documented differences in CVD risk factors affecting the occurrence of CVD events according to gender and place of residence. Such differences should be taken into account in future preventive public health strategies for CVD prevention.

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Non-communicable diseases (NCDs), notably cardiovascular diseases (CVD) are the leading causes of mortality and morbidity worldwide, with a rapid increase in prevalence being experienced in developing countries.^{1,2} The origins of most NCDs are in early life with complex interactions between lifestyle, social and environmental characteristics, and underlying genetic and ethnic predispositions.³ The major risk factors of NCDs and their synergistic effects are well established.⁴ However, global inequalities in access to health care,⁵⁻⁸ and disparities in cardiovascular health between males and females suggest that it may be useful to study the impact of social and environmental characteristics on CVD, and its risk factors in different geographical regions.⁹⁻¹¹ Despite bearing the highest burden of CVD in low and middle-income countries,¹ there are few longitudinal studies describing the cumulative effects of individual risk factors, or their combinations on CVD events in these regions. In particular, there are few studies based on gender or area of residence. Developing countries are experiencing various stages of epidemiologic transition with a rapid increase in urbanization and adoption of modern lifestyles.⁴ Of special concern in this context is the situation in the Middle Eastern countries, which have higher incomes and trade surpluses than most developing countries,¹ and a very high prevalence of obesity.¹² Similar to other countries in this region, Iran is facing a rapid epidemiologic transition,¹³ notably a nutrition transition.¹⁴ There is a very high prevalence of CVD risk factors even in rural areas,^{14,15} with abdominal obesity and metabolic syndrome emerging as major health problems for Iranian population particularly for women.¹⁶ This study aimed to determine the variation on the impact of gender and place of residence on CVD risk factors and events in the Isfahan Cohort Study (ICS).

Methods. This study was performed based on a population-based prospective cohort study. Details of methodology and design of the study have been published previously,¹⁷ and are presented here in brief.

Disclosure. This baseline survey as a part of Isfahan Healthy Heart Program (IHHP) was supported by a grant (No. 31309304) from the Iranian Budget and Planning Organization and the Ministry of Health. The biannual follow-ups were supported by the Isfahan Cardiovascular Research Centre affiliated to Isfahan University of Medical Sciences, Isfahan, Iran.

This study was conducted at Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran. Participants were samples of the baseline survey of a large interventional study named Isfahan Healthy Heart Program (IHHP).^{18,19} In this program, all adults aged 19 and over, living in urban and rural areas of Isfahan, Najafabad, and Arak were selected using multistage cluster random sampling, considering the age, and gender distribution of the population. Subjects were excluded if they were pregnant, physically or mentally unable to participate, or did not have Iranian nationality. All participants of IHHP aged 35 and over were enrolled into the ICS. The study started in 2001, with telephone follow-ups performed every 2 years. Subjects were recruited from January 2 to September 28, 2001. Written informed consents were obtained from all participants and the study was approved by the Ethics Committee of the Isfahan Cardiovascular Research Center. The study was carried out according to principles of Helsinki Declaration.

Baseline study. Demographic characteristics and information on smoking, diet, physical activity, and contraceptive use among females were collected. Trained health professionals measured height, weight, waist, and hip circumferences, as well as blood pressure (BP) under standard protocols.²⁰ Venous blood was collected after overnight fasting for 12 hours to measure fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C) and quantitative C-reactive protein (CRP) using enzymatic method and apolipoproteins A (apo-A) and B (apo-B) using turbidimetric method, all determined by autoanalyzer using standard kits. All blood samples were assayed at the central laboratory of ICRI that complies with the external national and international quality control standards. Low density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald equation in subjects with TG <400 mg/dl, and used standard kits in other cases. A 75 g oral glucose tolerance test was performed to determine the 2-hour post-load plasma glucose levels (2-hpp) in all participants other than the known cases of diabetes mellitus. Details of laboratory methods were described previously.¹⁷

Definition of cardiometabolic risk factors. In accordance with the American Diabetes Association criteria, participants were considered to have diabetes if their FPG level was ≥ 126 mg/dl, or 2-hpp glucose ≥ 200 mg/dl, or they were taking glucose-lowering medications.²¹ Hypertension was defined in accordance with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) as systolic BP ≥ 140 mm

Hg, or diastolic BP ≥ 90 mm Hg, or if the participant reported current use of antihypertensive medication.²² Abnormal serum lipid profiles were defined based on the appropriate risk-based threshold established by the National Cholesterol Education Panel (NCEP) Adult Treatment Panel III (ATP III) (that is, TC >240 mg/dl; TG >200 mg/dl; HDL-C <40 mg/dl for males and <50 mg/dl for females; and LDL-C >160 mg/dl).²³ Body mass index (BMI) values from ≥ 25 - 30 kg/m² were classified as overweight, and BMI ≥ 30 kg/m² were classified as obese.²⁴ According to International Diabetes Federation (IDF) cut points, waist circumference (WC) ≥ 94 cm in men or ≥ 80 cm in women were defined as abdominal obesity.²⁵

Endpoint determination. Endpoints of the study were defined as fatal and nonfatal myocardial infarction (MI), fatal and nonfatal stroke, sudden cardiac death, and unstable angina. A final decision regarding outcome events was made after a review of all patients' documents in 2 separate specialist panels consisting of 4 cardiologists and neurologists. Diagnosis of acute MI and unstable angina was based on ACC guidelines.²⁶ Sudden cardiac death was defined as death within one hour of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by more than one hour of symptoms.²⁶ The World Health Organization (WHO) stroke definition was used for a diagnosis of stroke.²

Statistical analysis. Data entry was carried out using EPI info™. All data were analyzed using the Statistical

Package for Social Sciences for Windows software version 15.0 (SPSS Inc., Chicago, IL, USA). Numerical values were presented as mean \pm standard deviation (SD). Student's t-test was used to compare means of independent groups, and the chi-square test for the comparison of categorical variables. Kaplan-Meier curves were plotted to compare urban and rural residents in each gender using the log rank test. Cox proportional hazards modeling was used with time to outcome as the dependent variable, and the presence of defined risk factors as independent dichotomous variables for the calculation of hazard ratios (HR) and 95% confidence intervals (CI). Individuals were censored at the first cardiovascular event or last successful interview. For all analyses, statistical significance was assessed at a level of 0.05 (2-tailed).

Results. Among the 6323 subjects free of CVD history, 3255 (51.5%) were women and 4572 (72.3%) lived in urban areas. Baseline characteristics of participants are presented in Table 1 and 2. Subjects in rural area had significantly lower obesity indexes, TG, and C-reactive protein and higher HDL-C in both men and women. Consequently, overweight, obesity, abdominal obesity, and hypertriglyceridemia were significantly lower in the rural area. Conversely, high LDL-C was significantly lower in urban area in both men and women, but hypercholesterolemia was lower only in urban men. While smoking rate in women

Table 1 - Characteristics of study participants.

Characteristics	Women		<i>P</i> -value	Men		<i>P</i> -value
	Urban	Rural		Urban	Rural	
	Mean \pm SD			Mean \pm SD		
Age, years	50.3 \pm 11.4**	50.3 \pm 11.2*	0.913	51.0 \pm 11.8	51.3 \pm 12.2	0.554
Systolic blood pressure, mm Hg	121 \pm 21.2	123 \pm 22.5**	0.136	120 \pm 19.8	120 \pm 20.9	0.929
Diastolic blood pressure, mm Hg	78.5 \pm 12.1**	79.2 \pm 11.9	0.140	77.7 \pm 10.6	78.9 \pm 11.3	0.006
Fasting plasma glucose, mg/dl	89.3 \pm 33.0	88.1 \pm 30.3**	0.294	88.8 \pm 34.0	84.6 \pm 25.1	<0.001
Body mass index, kg/m ²	28.1 \pm 4.6†	26.6 \pm 4.6†	<0.001	25.8 \pm 3.7	24.3 \pm 4.0	<0.001
Waist circumference, cm	98.4 \pm 12.0†	91.2 \pm 13.2†	<0.001	94.0 \pm 10.9	87.7 \pm 11.6	<0.001
Waist to hip ratio	0.935 \pm 0.08*	0.919 \pm 0.08	<0.001	0.932 \pm 0.06	0.914 \pm 0.07	<0.001
Triglycerides, mg/dl	190 \pm 101**	182 \pm 96.8	0.025	199 \pm 109	181 \pm 103	<0.001
Total cholesterol, mg/dl	218 \pm 52.1†	222 \pm 53.2†	0.111	206 \pm 51.8	211 \pm 50.0	0.007
HDL-cholesterol, mg/dl	48.0 \pm 10.5†	49.0 \pm 10.4†	0.016	44.9 \pm 10.1	46.0 \pm 9.7	0.006
LDL-cholesterol, mg/dl	132 \pm 42.7†	136 \pm 44.2†	0.017	121 \pm 43.0	129 \pm 41.2	<0.001
Total/HDL-cholesterol	4.72 \pm 1.38	4.69 \pm 1.34	0.518	4.76 \pm 1.47	4.75 \pm 1.40	0.832
C-reactive protein, mg/dl	3.47 \pm 1.75	3.06 \pm 1.39	<0.001	3.48 \pm 1.31	3.17 \pm 1.18	<0.001
Apo-B/apo-A ratio†	0.79 \pm 0.22§	0.89 \pm 0.32	0.182	0.84 \pm 0.22	0.91 \pm 0.19	0.113

HDL - high density lipoprotein, LDL - low density lipoprotein, Apo - apolipoprotein.

Comparison between men and women in urban or rural area: * $p<0.1$, ** $p<0.05$, † $p<0.01$, ‡ $p<0.001$. §Measured in a subsample of 962 participants

Table 2 - Prevalence of risk factors among participants with or without cardiovascular events according to gender and place of residence (N=6323).

Variables	Women				P-value	Men				P-value
	Urban N=2350	Rural N=905		n (%)		Urban N=2222	Rural N=846		n (%)	
Current smoking	64 (2.7) [†]	10 (1.1) [†]			0.006	680 (30.6)	294 (34.7)			0.025
Diabetes	267 (11.4) ^{**}	86 (9.5) ^{**}			0.126	211 (9.5)	53 (6.3)			0.004
Impaired glucose tolerance	199 (9.0) [§]	136 (15.9) [†]			<0.001	138 (6.5)	55 (6.5)			0.864
Hypertension	713 (30.3) [†]	284 (31.4) ^{**}			0.564	531 (23.9)	226 (26.7)			0.106
High waist circumference	2200 (93.6) [†]	730 (80.7) [†]			<0.001	1186 (53.4)	277 (32.7)			<0.001
High waist-to-hip ratio	2226 (94.7) [†]	851 (94.0) [†]			0.438	898 (40.4)	280 (33.1)			<0.001
Overweight	956 (40.7) [†]	356 (39.3) [†]			<0.001	925 (42.8)	271 (32.0)			<0.001
Obesity	788 (33.5) [†]	203 (22.4) [†]				312 (14.0)	74 (8.7)			
Hypertriglyceridemia	1396 (59.4) [*]	499 (55.1) [*]			0.027	1379 (62.1)	432 (51.1)			<0.001
Hypercholesterolemia	1448 (61.6) [†]	577 (63.8) ^{**}			0.259	1134 (51.0)	490 (57.9)			0.001
Low HDL-C	1387 (59.0) [†]	508 (56.1) [†]			0.134	734 (33.0)	236 (27.9)			0.006
High LDL-C	1182 (50.3) [†]	493 (54.5) ^{**}			0.033	879 (39.6)	418 (49.4)			<0.001
High total/HDL-C	852 (50.1%)	335 (52.2)			0.686	847 (49.9)	307 (47.8)			0.350
High Apo-B/apo-A [‡]	170 (33.9) [§]	9 (47.4)			0.226	100 (23.8)	8 (38.1)			0.135

Comparison between men and women in urban or rural area: * $p < 0.1$, ** $p < 0.05$, § $p < 0.01$, † $p < 0.001$. ‡Measured in a subsample of 962 participants. diastolic blood pressure ≥ 90 mm Hg, or current treatment for hypertension; hypertriglyceridemia - triglyceride ≥ 150 mg/dl; hypercholesterolemia - total cholesterol ≥ 200 mg/dl; LDL-C - low-density lipoprotein cholesterol; HDL-C - high-density lipoprotein cholesterol; high TC/HDL: ≥ 5 ; high Apo-B/A: ≥ 0.97 in men, ≥ 0.86 in women

Table 3 - Crude and adjusted hazard ratio (95% confidence interval)* of risk factors for cardiovascular events according to place of residence in women.

Variables	Urban						Rural					
	Crude	P-value	Adjusted [†]	P-value	Adjusted [§]	P-value	Crude	P-value	Adjusted [†]	P-value	Adjusted [§]	P-value
Diabetes	2.29 (1.57-3.33)	<0.001	1.90 (1.30-2.77)	0.001	1.85 (1.27-2.70)	0.001	1.15 (0.41-3.26)	0.787	1.03 (0.36-2.93)	0.955	1.03 (0.36-2.94)	0.955
Hypertension	3.56 (2.59-4.89)	<0.001	2.56 (1.82-3.62)	<0.001	2.52 (1.79-3.57)	<0.001	6.07 (2.92-12.6)	<0.001	4.39 (2.07-9.34)	<0.001	4.64 (2.17-9.90)	<0.001
Overweight	1.13 (0.73-1.74)	0.568	1.21 (0.79-1.87)	0.370	1.25 (0.80-1.94)	0.314	1.23 (0.56-2.69)	0.594	1.18 (0.54-2.58)	0.673	1.16 (0.53-2.56)	0.697
Obesity	1.53 (1.00-2.35)	0.049	1.76 (1.14-2.71)	0.010	1.81 (1.17-2.81)	0.008	1.51 (0.64-3.55)	0.345	2.03 (0.84-4.86)	0.112	2.03 (0.84-4.87)	0.111
Central obesity	3.10 (1.12-10.98)	0.032	3.10 (0.99-9.71)	0.052	2.99 (0.95-9.40)	0.060	0.80 (0.37-1.76)	0.583	0.64 (0.29-1.43)	0.279	0.65 (0.29-1.44)	0.293
HTG	3.07 (2.05-4.59)	<0.001	2.52 (1.68-3.78)	<0.001	2.34 (1.58-3.46)	<0.001	1.44 (0.73-2.85)	0.293	1.16 (0.58-2.31)	0.668	1.16 (0.58-2.32)	0.681
HC	2.25 (1.53-3.30)	<0.001	1.68 (1.13-4.48)	0.010	1.62 (1.10-2.41)	0.015	1.94 (0.88-4.26)	0.098	1.36 (0.61-3.04)	0.447	1.35 (0.60-3.02)	0.464
High LDL-C	2.03 (1.45-2.85)	<0.001	1.57 (1.11-2.22)	0.011	1.57 (1.11-2.22)	0.012	1.83 (0.90-3.71)	0.096	1.30 (0.63-2.69)	0.475	1.30 (0.63-2.70)	0.480
Low HDL-C	1.27 (0.91-1.77)	0.154	1.40 (1.00-1.96)	0.046	1.40 (1.00-1.95)	0.048	0.96 (0.50-1.86)	0.915	1.02 (0.53-1.96)	0.960	1.02 (0.53-1.98)	0.954
High TC/ HDL-C	1.53 (1.12-2.10)	0.007	1.39 (1.01-1.91)	0.040	1.39 (1.01-1.91)	0.041	1.15 (0.58-2.24)	0.683	0.92 (0.46-1.82)	0.818	0.92 (0.46-1.81)	0.812

*adjusted for age and smoking; †adjusted for age, smoking, menopause, and number of pregnancies; hypertriglyceridemia (HTG) - triglyceride ≥ 150 mg/dl; HC - hypercholesterolemia; HDL-C - high-density lipoprotein cholesterol, high total cholesterol (TC)/HDL - ≥ 5

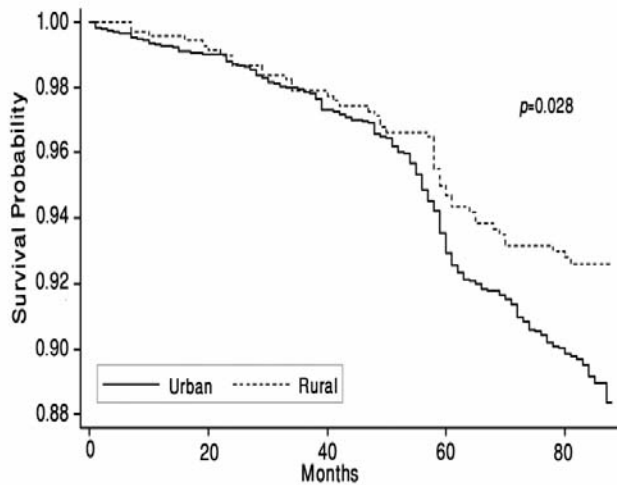


Figure 1 - Kaplan-Meier curve for cardiovascular events in men.

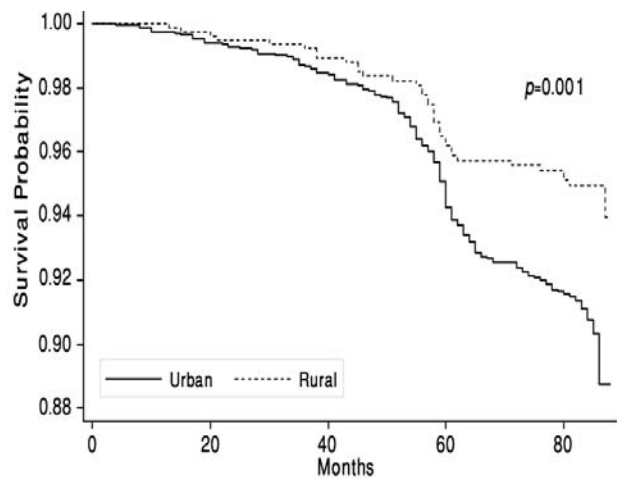


Figure 2 - Kaplan-Meier curve for cardiovascular events in women.

was significantly lower in rural than the urban area, it was higher in rural men. Diabetes did not show any significant differences between urban and rural women, but it was less prevalent in rural men compared to urban men. Conversely, impaired glucose tolerance was significantly lower in urban women with no significant differences in men. Except for smoking, men had an overall better risk factor profile compared to women in both urban and rural area. However, although hypertriglyceridemia did not differ in men and women, TG level in urban area was significantly lower in women compared to men. The WHR did not show significant difference when comparing men and women, but in concordance with other obesity indexes, high WHR was significantly lower in men in both areas. After a median follow up of 6.7 years, the data of 32893 person-years

were available. Out of 427 incident CVD events, 198 cases in females (161 in urban and 37 in rural areas) and 229 cases in males (182 in urban and 47 in rural areas) were documented (Figure 1 and Figure 2). The CVD incidence rate in men was 15.5 (13.4-18.0) in the urban, and 11.0 (8.2-14.6) per 1000 person-year in rural areas. In women, the corresponding rate was 13.3 (11.4-15.5) in the urban, and 7.5 (5.5-10.4) in rural areas. During follow-up period, 1807 (28.6%) subjects were lost to follow-up. There was no significant difference between available participants and loss-to-follow-up group in terms of hypercholesterolemia, metabolic syndrome and its component, except for central obesity (51% available subjects versus 48% lost-to-follow-up, $p=0.023$). While there was no statistically significant differences between urban and rural females (29.5% versus 27.2%, $p=0.185$), rural men were lost-to-follow-up slightly more than urban men (27.1% versus 31.2%, $p=0.028$). Comparing residents of urban areas with rural areas, CVD events occurred at the age of 62.1 ± 10.4 and 63.0 ± 12.7 years in women ($p=0.650$), and 61.9 ± 11.9 and 62.1 ± 11.7 years in men ($p=0.924$). There was also no statistically significant difference in age at event between men and women in urban ($p=0.861$) and rural ($p=0.728$) areas. Living in rural areas decreased risk of CVD events by 42% in women (HR = 0.58; 95% CI: 0.41-0.84; $p=0.004$) and 31% in men (HR = 0.69; 95% CI: 0.50-0.96; $p=0.029$) when the association was adjusted for age. The beneficial effect of living in rural areas remained statistically significant with slight decrease in both women (HR = 0.63; 95% CI: 0.44-0.91, $p=0.014$), and men (HR = 0.71; 95% CI: 0.51-0.99; $p=0.047$) when the association was adjusted for traditional CVD risk factors including age, hypertension, diabetes, hypercholesterolemia, smoking, overweight and obesity. Gender showed significant association with CVD events neither in urban population (HR = 1.15; 95% CI: 0.93-1.42; $p=0.197$) nor in rural population (HR = 1.44; 95% CI: 0.94-2.22; $p=0.094$). The HRs for the incidence of CVD events are presented in Table 3 and Table 4. In women, hypertension was the strongest predictor of CVD events in urban population and the only predictor in rural population (Table 3). In the urban setting, diabetes, high TG, high TC, and LDL-C, low HDL-C, and obesity were also significantly associated with CVD events when it was adjusted for age and smoking. Among urban men, hypertension was also the strongest risk factor for CVD events. Diabetes, overweight, obesity, central obesity, high TG, high TC, low HDL-C and high TC/HDL-C ratio were significantly associated with these events in rural men.

Table 4 - Crude and adjusted hazard ratio (95% confidence interval)* of risk factors for cardiovascular events according to place of residence in men.

Variables	Urban				Rural			
	Crude	P-value	Adjusted [*]	P-value	Crude	P-value	Adjusted [*]	P-value
Diabetes	2.51 (1.75-3.61)	<0.001	1.88 (1.30-2.73)	<0.001	1.19 (0.37-3.84)	0.769	1.07 (0.33-3.48)	0.905
Hypertension	3.15 (2.35-4.22)	<0.001	2.30 (1.66-3.18)	<0.001	1.98 (1.10-3.56)	0.022	1.54 (0.84-2.83)	0.160
Overweight	1.40 (1.01-1.94)	0.044	1.53 (1.10-2.13)	0.012	0.94 (0.50-1.74)	0.847	1.09 (0.58-2.05)	0.773
Obesity	1.70 (1.11-2.60)	0.013	1.79 (1.17-2.75)	0.007	0.44 (0.10-1.84)	0.262	0.55 (0.13-2.33)	0.419
Central obesity	1.56 (1.15-2.11)	0.004	1.36 (1.00-1.85)	0.051	1.42 (0.79-2.55)	0.235	1.50 (0.83-2.71)	0.168
Hypertriglyceridemia	1.33 (0.97-1.83)	0.077	1.43 (1.04-1.97)	0.026	1.18 (0.66-2.12)	0.575	1.42 (0.78-2.58)	0.245
Hypercholesterolemia	1.49 (1.10-2.01)	0.010	1.40 (1.03-1.89)	0.029	2.11 (1.09-4.08)	0.026	2.10 (1.09-4.06)	0.027
High LDL-C	1.34 (1.00-1.80)	0.047	1.27 (0.95-1.70)	0.106	2.98 (1.54-5.76)	0.001	2.94 (1.52-5.68)	0.001
Low HDL-C	1.32 (0.98-1.78)	0.064	1.44 (1.07-1.94)	0.017	1.08 (0.59-1.99)	0.795	1.14 (0.62-2.09)	0.679
High TC/HDL-C	1.68 (1.26-2.26)	<0.001	1.70 (1.27-2.28)	<0.001	2.73(1.51-4.94)	0.001	3.09 (1.70-5.62)	<0.001

*adjusted model including - adjusted for age and smoking; LDL-C - low-density lipoprotein cholesterol; HDL-C - high-density lipoprotein cholesterol; high total cholesterol (TC)/HDL - ≥ 5

However, high total and LDL cholesterol, as well as high TC/HDL-C ratio were the only risk factors that were detrimentally associated with CVD events in rural men when it was adjusted for age and smoking (Table 4). In rural men, although hypertension increased the CVD risk approximately 2 times, it was not significantly associated with CVD events when age and smoking was included in the model.

Discussion. This longitudinal study showed that fewer cases of CVD events occurred in rural males and females compared to urban males and females during the 7 years follow up. Hypertension was the strongest predictor of CVD events in both men and women except for rural males. The rural population tends to have lower prevalence of most CVD risk factors, except for high LDL-C in both genders, impaired glucose tolerance in females and smoking in males. There have been limited longitudinal studies examining the impact of place of residence on CVD events.²⁷ In cross-sectional studies, CVD event rates have been reported to be lower in rural settings than in equivalent urban populations. Cross-sectional data from Nigeria, India, and China all indicated that the urban population has higher obesity, lipids, and often blood pressure indices than their rural counterparts.²⁸⁻³⁰

In the current study, similar lower incident of CVD cases and lower levels of risk factors were also identified. Lifestyle differences including increased levels of physical activity due to more manual works, and the less availability of processed or fast foods are likely to account for a substantial proportion of these differences. Of importance to note is the role of

cholesterol, particularly LDL-C in rural population especially in rural men. Considering the active life style of rural residents, it probably is rooted in nutrition. As the most prevalent and strongest risk factor in the subgroup of rural men, hypercholesterolemia deserves particular public health action. However, despite a better CVD risk factor profile, the mean age at first event in our population-representative sample was similar for the urban and rural populations. This suggests that additional negative pressure must be present to counter the observed risk factor benefits. Differences in health access and availability of health services, insurance coverage, lifestyle, environmental health hazards, educational level, and socioeconomic status may have a role in explaining the differences in CVD risk factors among urban and rural residents.^{1,4} Such disparities in CVD health have been reported to be among the most important public health problems even in developed countries.⁷ This is also the case in Iran and may be offsetting those benefits. Particularly, dietary high salt intake may be a strong risk factor of hypertension and CVD. Therefore, information regarding probable differences in dietary salt intake in terms of gender and place of residence should be provided in future studies.

Studies in other settings have also documented gender differences in CVD events with men having a higher burden of CVD disease relative to women.¹⁰ Variations in short-term mortality between men and women are suggested to be due to differences in age, hormonal situation, and perhaps differences in treatment regimen during acute coronary events.¹¹ In the Framingham study, morbidity and mortality was double in men than in women. Women had a relative 10-year delay in

CVD events occurrence compared with men. However, our results did not confirm this difference in either the urban or the rural areas, and suggested a similar age of first event in this sample. Higher levels of risk factors like hypertension, obesity, and metabolic syndrome in women may explain the lack of this difference, and the premature occurrence of CVD in Iranian women.¹⁶ Likewise, longitudinal data from Italy showed that total cholesterol, which was higher in women was associated with CVD mortality, in contrast, 2-hour post-load glucose was the major determinant of CVD in men.²⁷ An additional explanation for the difference in age of CVD occurrence among men and women might be due to the differences in disease manifestations and higher rates of unrecognized MI in women than in men, which may be the case in the current study.

Study limitations. The same as most cohort studies, there was a considerable loss-to-follow-up. However, the significance of differences was not at the level that could severely affect the internal validity of the study. Although some villages were considerably far from corresponding cities in this study, rural areas were in administrative divisions related to big cities. Therefore, risk factor patterns might be different in rural areas adjacent to small cities and particularly remote villages.

In conclusion, in this study, we documented differences in CVD risk factors affecting the occurrence of CVD events according to gender and the place of residence. This study in the Eastern Mediterranean region benefited from participants representing urban and rural communities in 2 big provinces in Iran. Such differences should be taken into account in future preventive public health strategies for CVD prevention, and future studies are suggested to investigate the determinants of ischemic CVD occurrence at a younger age among Iranian women.

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