Original Article

Incidence of Cardiovascular Diseases in an Iranian Population: The Isfahan Cohort Study

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Abstract

Introduction: Accurate estimates of the incidence of cardiovascular diseases (CVD) comprising of acute myocardial infarction (AMI), unstable angina pectoris (UAP), sudden cardiac death (SCD), and stroke are very important for public health. However, such information is scarce, especially for middle- and low-income countries.

Methods: The Isfahan Cohort Study (ICS) prospectively followed up 6504 individuals, 51.8% women, aged 35 years and over, 6323 initially free of CVD, from urban and rural areas in three districts in central Iran including Isfahan, Najafabad, and Arak. A panel of specialists in cardiology and neurology decided on the diagnosis of the occurred events based on patients' hospital records, verbal autopsy, and death certificates.

Results: After 32893 person-years of follow-up, 427 new cases of CVD events (229 in men) were registered. Confirmed cases of AMI, stroke, UAP, and SCD were 57, 43, 93, and 36 in men and 32, 48, 100, and 18 in women, respectively. The corresponding crude incidence rates were 352, 265, 352, and 220 per 100000 person-years in men and 186, 279, 584, and 104 in women, respectively. No significant differences were found in age at the time of events occurrence between men and women and between different event types except for SCD and stroke in women that in average the former occurred nine years later. CVD mortality rate was 331 per 100000 person-years in men and 203 in women.

Conclusion: We found substantially high incidence rates for almost all CVDs and mortality. These findings need urgent consideration by health policy makers specifically for women.

Keywords: Cardiovascular disease, incidence, Iran, ischemic heart disease, stroke

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Introduction

Atherosclerosis is known to be a major health problem around the world. Coronary heart disease (CHD) and stroke are the first and second leading causes of death in middle-income countries[1] and have been projected to keep this ranking until 2030.[2] The incidence of cardiovascular disease (CVD) varies from country to country, and culture to culture. The Middle East and parts of Eastern Europe probably have the highest cardiovascular death rates in the world.[3] Ischemic heart disease (IHD) has been ranked first within the leading causes of mortality in the Middle East.[4] Iran possibly has a higher burden than other countries in this region.[4]

Prevalence and especially incidence estimates are crucially important to the planning of public health measures. In primary and secondary prevention, developing and maintaining public health strategies are based on disease incidence and mortality. Additionally, such information is of international interest because of highlighting disease trends and the regional differences, which are rich sources of new hypotheses that further help understanding of the disease etiology.

Data on the incidence of acute myocardial infarction (AMI) are usually derived from local primary care registries or specifically developed registries, such as the MONICA registries, cohort studies, and from linkage of regional registries,[5] all lacking in most middle- and low- income countries. However, for most countries reliable data are scarce.[4] A lack of necessary information infrastructure as well as considerable costs prohibits most countries from having these basic statistics. There are few reports concerning CVD incidence in Middle Eastern countries and most studies have only reported prevalence. In spite of the significant impact of CVD in Iran, to our knowledge, there is no report describing CVD incidence in the medical literature except for stroke in Mashhad, a city in North East[6] and a hospital-based report from Isfahan.[7] The population-based Isfahan Cohort Study (ICS) has ascertained and validated all fatal and nonfatal incident cases of IHD and stroke. This report aimed to obviate the scientific and public health need of epidemiological data in terms of incidence of CVD in Iran.

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Methods

The Isfahan Cohort Study (ICS) is a population-based, ongoing longitudinal study of adults aged 35 years old or more, living in urban and rural areas of three districts in central Iran, who had participated in the baseline survey of a community trial for CVD prevention and control, entitled the Isfahan Healthy Heart Program (IHHP).[8,9] The participants were recruited from January 2 through September 28, 2001.

Baseline Survey

The baseline survey was conducted in a representative population of adults who were living in urban and rural areas of Isfahan, Najafabad, and Arak. Isfahan is the third largest city in Iran with 1986542 individuals living in this city and its surrounding villages. In Arak and Najafabad, the population was 555975 and 282430 in 2006, respectively.[10] The participants were selected by multistage random sampling and were recruited to reflect the age, sex, and urban/rural distribution of the community. Details of the sampling method were described in a former publication.[11] Ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Center (ICRC), a WHO collaborating center.

After obtaining informed written consent, a medical interview and physical examination was conducted. Measurement of blood pressure, anthropometric parameters as well as fasting blood was carried out following standard protocols and using calibrated instruments as has been described previously.[11]

Follow-up Surveys

Follow-up surveys were carried out almost every two years and this paper is based on the seventh year of follow-up. Multiple sources were used to find events of interest. All participants were followed by telephone call interview using standard questionnaires. In the case of any report of relevant events or hospital admissions by participants or their close relatives, a group of trained nurses tried to find reliable documents describing the events such as registry or medical records and death certificates and carried out secondary interviews or verbal autopsies. Two separate outcome adjudication panels of specialists consisting of four cardiologists and a neurologist reviewed all relevant patient documents and decided on the outcomes. CVD was defined as either CHD (fatal and nonfatal MI, sudden cardiac death [SCD], and unstable angina [UA]) or stroke.

The criteria for IHD were modified from those of the World Health Organization (WHO) Expert Committee. The diagnosis of AMI was based on the presence of at least two of the following criteria: 1) typical chest pain lasting more than 30 min, 2) ST elevation > 0.1 mV in at least two adjacent electrocardiograph (ECG) leads, and 3) an increase in serum levels of cardiac biomarkers including cardiac troponin, and creatine kinase (CK) and CK-MB.[12] Unstable angina pectoris (UAP) was defined on the basis of typical chest discomfort lasting more than 20 minutes occurring at rest or with minimal exertion, new onset, or representing a change in the usual pattern of angina or pain, with a crescendo pattern, and described as severe or a frank pain.[13] The diagnosis of UAP was established in case of dynamic ST-interval or T-wave changes in at least two contiguous ECG leads. SCD was labeled to an unexpected death occurred out-of-hospital within 24 hours of the first symptom if no other obvious cause of death such as other serious life-threatening disease was proposed. Those found dead without any available relevant information about circumstances were labeled as unknown death. The diagnosis of incident stroke was made based on the clinical criteria. It was defined as a rapid-onset focal neurological disorder persisting for at least 24 hours and had a probable vascular origin. Although the in-hospital diagnoses of clinicians were taken into account, the final decisions of the outcome adjudication panel were made independently. Detailed explanation for follow-up process is available elsewhere.[11]

Statistical Analysis

The incidence rates of patients with first AMI, UAP, SCD, and stroke with 95% confidence interval (95% CI) were calculated by age and gender. Person-time was utilized as denominator for calculating the incidence rates and they were expressed in terms of per 100000 person-years. Subjects who had reported a positive history of CVD at the baseline were excluded from incidence calculations. Direct standardization was conducted to adjust the

Table 1. Characteristics of the study participants

	Men (n = 3168)	Women (n = 3336)	Total (n = 6504)
Age (year)	51.5 ± 12.0	50.6 ± 11.4	51.0 ± 11.7
Waist circumference (cm)	92.3 ± 11.5	96.5 ± 12.8	94.5 ± 12.4
Central obesity*	1943 (61.3%)	1716 (51.4%)	3659 (56.3%)
Body mass index (kg/m²)	25.5 ± 3.9	27.8 ± 4.7	26.6 ± 4.5
Obesity**	399 (12.6%)	1018 (40.3%)	1417 (21.8%)
Overweight	1267 (40.0%)	1345 (30.5%)	2612 (40.2%)
Triglycerides (mg/dL)	195 ± 108	190 ± 102	192 ± 105
Hypertriglyceridemia†	1910(60.3%)	1996 (59.8%)	3906 (60.1%)
LDL-cholesterol (mg/dL)	124 ± 43	134 ± 43	129 ± 43
High LDL-cholesterol††	1409 (44.4%)	1838 (55.1%)	3247 (49.9%)
HDL-cholesterol (mg/dL)	45.3 ± 10.1	48.4 ± 10.5	46.9 ± 10.4
Low HDL-cholesterol‡	1051 (33.2%)	2026 (60.7%)	3077 (47.3%)
Fasting plasma glucose (mg/dL)	88.2 ± 33	89.2 ± 32.5	88.7 ± 32.7
Diabetes mellitus‡‡	283 (8.9%)	373 (11.2%)	656 (10.1%)
Systolic blood pressure (mmHg)	121 ± 20	123 ± 22	122 ± 21
Diastolic blood pressure (mmHg)	78.2 ± 11.0	78.9 ± 12.1	78.5 ± 11.6
Hypertension§	800 (25.3%)	1055 (31.6%)	1855 (28.5%)
Ever smoking	1298 (41.0%)	99 (2.97%)	1397 (21.5٪)

The numerical values are presented as mean ± SD and categorical data as n (%); * Waist circumference ≥ 97cm for women and ≥ 90 cm for men (based on ICS recommendation[39]); ** Obesity: BMI ≥ 30, Overweight: BMI ≥ 25; †Triglycerides ≥ 150 mg/dL or on anti-lipid agents; ††LDL-C ≥ 130 or on antilipid agents; ‡ HDL-C < 40 for men <50 for women or on antilipid agents; ‡‡ FPG ≥ 126 mg/dL or two-hour post prandial glucose ≥ 200 mg/dL or on antidiabetic agents; § SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or on antihypertensive agents.

Table 2. Age specific incidence rates of CVD events by subtype in men in 100000 person-years with 95% confidence interval

	Age (years)					Total	
	35–44	45–54	55–64	65–74	≥ 75	Crude	Age adjusted
n	1120	614	479	324	92	2629	
CHD	551 (401–757)	1166 (870–1562)	1543 (1152–2067)	2530 (1906–3357)	2042 (1099–3796)	1158 (1003–1337)	1168 (996–1341)
AMI	159 (88–286)	308 (175–542)	441 (256–759)	936 (590–1485)	607 (196–1884)	352 (271–456)	351 (257–445)
UAP	332 (221–500)	692 (475–1009)	645 (411–1011)	1039 (670–1611)	808 (303–2153)	574 (469–704)	582 (461–704)
SCD	57 (21–153)	152 (68–339)	436 (253–751)	513 (276–953)	601 (194–1863)	220 (159–306)	221 (145–296)
CHD mortality	72 (30–173)	152 (68–339)	503 (303–835)	820 (502–1339)	801 (301–2135)	282 (211–376)	280 (196–366)
Stroke	101 (48–212)	127 (53–306)	442 (256–760)	776 (468–1288)	608 (196–1885)	265 (196–357)	260 (179–341)
Stroke mortality	0	0	33 (5–238)	308 (138–685)	200 (28–1422)	49 (24–98)	49 (13–85)
CVD	655 (489–877)	1304 (988–1720)	2017 (1559–2609)	3354 (2620–4294)	2684 (1559–4623)	1436 (1261–1635)	1445 (1253–1637)
CVD mortality	72 (30–173)	152 (68–339)	537 (329–876)	1128 (743–1713)	1002 (417–2406)	331 (253–432)	330 (238–422)
All cause mortality	215 (130–357)	710 (490–1029)	1577 (1185–2099)	2769 (2120–3615)	5209 (3546–7650)	1041 (896–1210)	1124 (947–1302)

CHD: AMI + SCD + UAP; CVD: CHD + stroke; CHD mortality: Fatal AMI + SCD; CHD: Coronary heart disease; AMI: Acute myocardial infarction; UAP: Unstable angina pectoris; SCD: Sudden cardiac death.

Table 3. Age specific incidence rates of CVD events by subtype in women in 100000 person-years with 95% confidence interval

	Age (years)					Total	
	44–35	54–45	64–55	74–65	≥ 75	Crude	Age adjusted
n	1205	713	467	325	59	2769	
CHD	270 (174–419)	842 (613–1158)	1440 (1064–1949)	2434 (1824–3251)	1197 (449–3189)	880 (750–1032)	887 (738–1037)
AMI	67 (28–162)	175 (88–351)	202 (91–450)	625 (355–1100)	298 (42–2113)	186 (131–263)	189 (120–259)
UAP	176 (102–302)	641 (445–923)	1158 (827–1620)	1148 (756–1743)	589 (147–2355)	584 (480–711)	580 (462–699)
SCD	27 (7–108)	22 (3–155)	67 (17–268)	616 (350–1085)	293 (41–2079)	104 (66–165)	109 (53–164)
CHD mortality	54 (20–143)	66 (21–204)	67 (17–268)	770 (464–1277)	293 (41–2079)	145 (98–214)	148 (86–210)
Stroke	135 (73–251)	375 (233–603)	303 (157–582)	518 (279–963)	587 (147–2348)	279 (211–371)	295 (205–384)
Stroke mortality	0	87 (33–233)	67 (17–268)	154 (50–477)	293 (41–2079)	58 (31–108)	68 (20–116)
CVD	407 (284–582)	1229 (944–1601)	1759 (1337–2315)	2997 (2306–3894)	1800 (809–4008)	1168 (1016–1343)	1194 (1019–1370)
CVD mortality	54 (20–143)	153 (73–321)	134 (50–357)	924 (582–1467)	586 (146–2342)	203 (145–282)	216 (138–295)
All cause mortality	148 (82–267)	350 (214–572)	937 (647–1358)	2259 (1681–3035)	3222 (1784–5818)	637 (528–768)	727 (574–881)

CHD: AMI + SCD + UAP; CVD: CHD + stroke; CHD mortality: Fatal AMI + SCD; CHD: Coronary heart disease; AMI: Acute myocardial infarction; UAP: Unstable angina pectoris; SCD: Sudden cardiac death.

rates to the age structure of the Iranian population in 2006.[10] Age at event was compared using Student's t- and ANOVA tests. Data entry was carried out using EPI info™. Data were analyzed using STATA software (Stata/IC 11.0, StataCorp LP, TX, USA). For all analyses, statistical significance was assessed at a level of 0.05 (two-tailed).

Results

A total of 3168 men and 3336 women were followed up. Table 1 shows the baseline characteristics of the participants. Among baseline participants, 5550 (85.3%) had at least one follow-up with a median of 81 months. There were 4834 (74.3%) participants remained in the study for the duration of the seven years of follow-up. There was no significant difference between available participants and those lost-to-follow-up in terms of sex and traditional risk factors (hypercholesterolemia, hypertension, diabetes mellitus, and smoking), except for central obesity (70.3% vs 67.5%, respectively; P = 0.028). The participants lost-to-follow-up were 1.3 (95%CI: 0.7 – 1.9) year older than the rest of the sample (P < 0.001). The participants who had a history of MI, stroke, or heart failure at baseline were excluded from analysis (n = 181).

After 32893 person-years of follow-up, a total of 427 new cases of CVD events were registered over the follow-up period. Of these, 229 CVD events occurred in men and 198 in women. The confirmed cases of AMI, stroke, UAP, and SCD were 57, 43, 93, and 36 in men and 32, 48, 100, and 18 in women, respectively. Due to the lack of conclusive evidence, CVD death was neither ruled out nor confirmed for 40 (14.2%) deaths (unknown death). Considering all CHDs, SCD constituted 19.3% of these events in men and 12.0% in women (P = 0.063). SCD accounted for 66.7% of CVD mortality in men and 51.4% in women (P = 0.161). In men, 21.2% of all-cause mortality was due to SCD and the corresponding proportion for women was 16.4% (P = 0.311). CVD mortality constituted 31.8% of all-cause mortality in both men and women.

The crude annual incidence rates of CVD events were 1436 and 1168 per 100000 person-years in men and women, respectively. These rates increased with age in both sexes (Tables 2 and 3).

Table 4. Total age specific incidence rates of CVD events by subtype in 100000 person-years with 95% confidence interval

	Age (years)					Total	
	44–35	54–45	64–55	74–65	≥ 75	Crude	Age adjusted
n	2325	1327	946	649	151	5398	
CHD	406 (314–525)	991 (800–1229)	1492 (1209–1840)	2482 (2028–3039)	1699 (1006–2870)	1015 (912–1129)	1027 (913–1141)
AMI	111 (68–182)	236 (152–366)	321 (205–503)	780 (546–1116)	482 (181–1284)	266 (216–328)	269 (211–328)
UAP	251 (181-348)	665 (511–864)	901 (688–1179)	1093 (808–1479)	719 (323–1600)	579 (503–667)	581 (496–665)
SCD	42 (19–93)	82 (39–172)	251 (151–417)	564 (371–857)	476 (178–1268)	161 (123–210)	165 (118–212)
CHD mortality	62 (32–120)	106 (55–203)	285 (177–458)	795 (559–1131)	595 (247–1429)	211 (167–267)	216 (162–270)
Stroke	118 (74–191)	260 (171–395)	372 (245–565)	647 (437–958)	599 (249–1440)	272 (222–334)	280 (219–341)
Stroke mortality	0	47 (18–125)	50 (16–156)	231 (120–444)	238 (59–951)	53 (34–85)	59 (29–89)
CVD	526 (420–660)	1264 (1044–1530)	1887 (1564–2277)	3176 (2654–3801)	2324 (1483–3644)	1298 (1181–1427)	1322 (1192–1452)
CVD mortality	62 (32–120)	153 (89–263)	335 (216–519)	1026 (753–1399)	833 (397–1746)	265 (215–326)	275 (214–336)
All cause mortality	181 (123–265)	517 (385–695)	1257 (1002–1576)	2514 (2062–3064)	4402 (3189–6075)	833 (741–937)	933 (815–1052)

CHD: AMI + SCD + UAP; CVD: CHD + stroke; CHD mortality: Fatal AMI + SCD; CHD: Coronary heart disease; AMI: Acute myocardial infarction; UAP: Unstable angina pectoris; SCD: Sudden cardiac death.

Table 5. Age at events

	Men			Women			P-value
	n	Mean ± SD	Median	n	Mean ± SD	Median	
UAP	93	60.2 ± 12.2	58.0	100	62.5 ± 10.2	64.2	0.165
AMI	57	62.1 ± 11.8	64.7	32	63.0 ± 11.0	65.1	0.710
SCD	36	64.4 ± 11.0	66.0	18	68.3 ± 10.5*	71.2	0.213
Stroke	43	63.5 ± 11.5	65.0	48	59.1 ± 11.5*	57.5	0.076
P-value for all		0.237			0.020		0.073
Fatal CVD	54	66.4 ± 10.4	68.1	35	65.8 ± 11.4	69.7	0.810
Nonfatal CVD	175	60.6 ± 11.9	60.8	163	61.5 ± 10.6	62.2	0.440
P-value†		< 0.001			0.034		0.757
Other mortality	99	66.2 ± 12.3	67.33	52	67.7 ± 11.7	68.3	0.459
P-value†		0.929			0.442		0.654
All cause mortality	170	66.6 ± 11.7	68.1	110	66.9 ± 11.8	69.1	0.869

CHD: AMI + SCD + UAP; CVD: CHD + stroke; CHD: Coronary heart disease; AMI: Acute myocardial infarction; UAP: Unstable angina pectoris; SCD: Sudden cardiac death; * Post-hoc test: $P = 0.013$; † In comparison with fatal CVD.

Table 4 shows the incidence rates in the whole sample. No significant difference was found in age at fatal and nonfatal CVD events between men and women (Table 5). On average, fatal CVDs in men occurred at six years older compared to nonfatal CVDs. In women, this difference was four years.

Discussion

In this large prospective cohort of Iranians without serious disease at entry to the study, a high incidence of CVD was found with a considerable number of events in the younger participants especially in women, relative to some other populations. To our knowledge, there are no other comparable data for most CVD events from Iran or other Middle Eastern countries. Cancer mortality was estimated to be 53 per 100000 in Iran in 2004 – 2005.[14] It is one-fifth of CVD mortality when findings of this study were adjusted for age distribution of Iranian population.

The CHD incidence rates of Western countries were between 200 and 500 in men and 60 and 150 in women (per 100000 person-years).[15–17] According to our study, the corresponding figures were as high as two times more in men and almost six times more in women compared with the highest report from these countries. The CHD mortality rates from the current study were more than two times higher than recent reports from countries of the European Union and even reports in two decades ago.[18] However, with regard to former Soviet Union countries with very high rates,[18] our rates were relatively lower.

Considering AMI, the reported incidence rates were much lower in populations from UK[15] and Japan,[19] but Netherlands[5] and Spain[20] had closer rates to our sample. The SCD incidence rate was at least three times higher compared with reports from the USA, Japan, Ireland, and Canada.[21] The rate was also double in men than that in the women. The higher vulnerability of men was consistent in all age groups except for 65 – 75 years where the women's SCD rate peaked and exceeded the rate found in men. SCD accounted for more than half of CVD mortality. Apart from the primary prevention, it seems that health system had little opportunity to take action in more than half of the deaths due to CVD events because they were sudden and took place out of hospitals. The large proportion of SCDs shown in our study reinforces the importance of improvements in primary prevention of AMI.

With regards to stroke, the rate for men in our sample was between the highest reported rates of European countries[22] and Japan, a well-known high- risk region for stroke.[19] For women, it was more than both regions. Mashhad Stroke Incident Study (MSIS) in the north east of Iran reported stroke rates for all ages as 144 in men and 113 in women per 100000.[6] For those aged more than 35 years, the corresponding rates were as high as 445 and 422 per 100000 in men and women, respectively (based on our calculation). These higher rates suggest that stroke incidence might be even higher in other areas of Middle East. However, the stroke mortality rate was considerably lower than that in Russia which has the highest global stroke mortality rate, and approximately half the median global stroke mortality rate.[23] While stroke incidence was reported to be generally 33% more in men in almost all ages,[24] overall stroke rate as well as stroke mortality rate was

similar in both sexes in this study. This finding was in line with the MSIS in which the expected 10 years lag for women compared to men was absent.[6] Furthermore, in contrast to expectation that stroke is less frequent than AMI, it constituted higher incidence rate in women in all age groups which is similar to the Japanese populations[19] but is in contrast with most Western countries.[25] In young ages, even AMI in combination with SCD yielded similar inferiority in women. In men, the reverse was true especially when SCD is taken into account. A projection study estimated that in 2030, cerebrovascular diseases would be the leading cause of death in middle-income countries with 14.4% of total deaths followed by CHD with 12.7%. This ranking was projected to reverse in rest of the world.[2] Accordingly, the Iranian community may face a worsening situation in terms of stroke in the future, especially taking into account that hypertension as the most important risk factor for stroke[26] was controlled only in about 15% of the population in Iran.[27]

The age distribution of these events in this study differed from the aforementioned populations. As expected, the incidence of major CVD increased exponentially with ageing but peaking in those aged 65 – 74 years. The same pattern was also seen for the CVD components, except for stroke in women, and SCD in men where incidence increased continuously with age. This finding is in contrast with reports from other countries[5,15,19,28] in which the incidence increased throughout the last decades of life. It supports the fact that there was a tendency for these events to occur at younger ages in the ICS population. For instance, the incidence rate of AMI in the youngest age group in Netherlands[5] was about four and 5.5 times less in comparison to the findings of this study in men and women, respectively. As with CHD, and consistent with the MSIS,[6] the stroke events tended to occur at younger ages in both sexes relative to all European countries.[29] Our incident rates in 35 – 44 years age group were approximately three and six times higher than a sample in UK[15] in men and women, respectively.

However, age at events did not show much of difference in this study. In Spain, AMI occurred at age 59 and 62 years in men and women, respectively[20] and it was 60 years in Denmark[16] which are very close to ours. There was the same median value of age at AMI in UK[15] for men but not for women. However, out-of-hospital death due to AMI in Netherlands occurred at 72 years in men and 80 in women[5] which were eight and 12 years older than the age at SCD in this study. Although the occurrence of CVD at younger age might partly reflect a demographic artifact owing to the lower age distribution in Iran, however, the individual and macroeconomic implications of premature CVDs for the workforce and national productivity are serious. The resulted economic constraints along with the loss of productive years of life impinge on both the private and public sectors.

We showed that the widespread assumption that coronary events occur at younger ages compared to stroke[15] was not true in our sample. As SCD, on average, occurred nine years later in women, the reverse may be true in some cases. It is important to note that the expected age gap between men and women was not seen in any of main events. This contrasts with many other reports that showed these events happen 10 – 20 years later in women as in the UK where only 16% of AMIs in women occurred before median event age of men (65 years).[15] The reason might be that in comparison to men, women had relatively higher prevalence rates of hypertension, diabetes, and hypercholesterolemia in Iran.[30] More importantly, obesity was almost two times more prevalent in women and central obesity was four times higher.[31] Except for diabetes that the prevalence rates were comparable in men and women, the same pattern was seen in the whole Middle East region.[32] Obesity is known to play a central role and be the only modifiable factor that influences all the other cardiovascular risk factors.[33] The excess of obesity in women was partly ascribed to the low physical activity.[31,32]

Over the past two centuries, infectious diseases and malnutrition as the main causes of death at the beginning have gradually been supplanted in most high- income countries by CVD and cancer which is known as the epidemiological transition.[34,35] Owing to the considerable burden of CVD deaths in this study and their occurrence at young ages, in line with the estimates for Middle Eastern countries,[36] Iran is seemingly about to enter the third phase of epidemiological transition or is already in its early phase. It means that Iran will probably face even higher rates, which might be true about the region at large. It necessitates substantial investments in public health and researches to primarily prevent these diseases and their risk factors and provide diagnostic and treatment facilities. It seems an equivocal fact that negligence will exact heavy price.

Several potential shortcomings of ICS merit consideration. First, the total burden of vascular diseases was certainly underestimated because we did not consider stable diseases such as heart failure and vascular dementia as well as peripheral vascular diseases. Second, in addition to accurate hospital clinical data, we also used neurological symptoms reports from participants to diagnose stroke for those who were not admitted to a hospital. Hence, this verbal documentation is probably not as accurate as for CHD diagnosis. Third, as there is considerable regional inequality in Iran,[37] our sample from central Iran which to some extent is wealthier than more marginal areas, may not be completely representative of the whole country. Forth, the considerable number of unknown deaths may have resulted in underestimation especially in terms of fatal stroke. Last but not the least, this study has faced to high lost-to-follow-up rate. This was mainly due to nonstandardized regional changes in telephone numbers and inadequate address records that make the probability of bias less. However, no remarkable differences were found in the baseline important characteristics between available and lost-to-follow-up groups.

Our study had also several strengths including the large sample size from three counties with a prospective design. Endpoints were ascertained and confirmed by a panel of specialists based on medical records or their equivalents, which provided more consistency in the outcomes. It was the only multicenter cohort study of Iran that enrolled samples from both urban and rural areas, which makes it unique for the region at large. In contrast to some famous major cardiovascular epidemiology studies that used volunteers and imposed age-restriction for elderly,[15,38] we used a random sampling method without any restriction for elderly that overcame any potential underestimation or volunteer bias.

In conclusion, we found substantially high incidence rates for almost all CVDs and mortality except for stroke mortality in both men and women. Iran needs to urgently deal with current high CVD rates and be ready for probable increasing rates in future. This study yielded one of the rare reports of CVD incidence in the Middle East. It highlights the need for careful monitoring of events to determine trends in CVD occurrence especially in other areas of the country as well as other countries of the region.

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Statement of Contributions

Research idea: *The whole project (Isfahan Cohort Study) was the idea of NS;* ***Design of study:*** *MT (the ICS follow-up projects; design of baseline survey was the same as IHHP by NS and colleagues);* ***Questionnaire design:*** *MT;* ***Data collection:*** *MT and RI; MS and SO were key members of diagnostic panel;* ***Data analysis:*** *MT;* ***Drafting:*** *MT;* ***Revising the manuscript:*** *TM, GNT, NS, and SO.*

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