ORIGINAL ARTICLE

Incidence of metabolic syndrome and determinants of its progression in Southern Iran: A 5-year longitudinal follow-up study

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Background: Metabolic syndrome (MetS) is a cluster of conditions increasing the risk of serious diseases. This study aimed to define the predictors of MetS incident in a community-based cohort in Southern Iran, during a mean follow-up period of 5.1 years. **Materials and Methods:** During the mean follow-up period of 5.1 years, a cohort study was conducted on 819 Iranian adults aged ≥18 years at baseline and followed to determine the incidence and predictors of MetS progression in Shiraz, a main urban region in the southern part of Iran. The International Diabetes Federation Guideline was used to detect the MetS. Multiple Cox's proportional hazards models were also used to estimate the predictors of new-onset MetS. **Results:** The prevalence of MetS was 25.9% at baseline, and the overall incidence of subsequent MetS was 5.45% (95% confidence interval [CI]: 4.47–6.59). The incidence of MetS was significantly higher in women (7.12% [95% CI: 5.52–9.05]) than in men (3.92% [95% CI: 2.80–5.34]). Moreover, it increased by 5.02 (95% CI, 3.75–6.58) among individuals who had one metabolic component and by 12.65 (95% CI, 9.72–16.18) for those who had three or more components ($P < 0001$). The incidence of MetS was also analyzed using the multiple Cox's proportional hazards model for potential risk factors, and it was revealed that female gender (hazard ratio [HR] 2.45; 95% CI: 1.33, 4.50; $P = 0.004$), higher body mass index (HR 3.13; 95% CI: 1.43.6.84; $P = 0.012$), increased abdominal obesity (HR 1.45; 95% CI 0.85, 2.46; $P = 0.045$), smoking (HR 4.79; 95% CI 2.09, 10.97; $P < 0.001$), and lower high-density lipoprotein (HR 0.53; 95% CI: 0.29, 1.00;$P = 0.044$) significantly predicted the onset of MetS at baseline; however, age, systolic and diastolic blood pressure, serum uric acid, fasting blood glucose, cholesterol, triglyceride and creatinine, estimated glomerular filtration rate, marital status, level of education, and level of physical activity did not independently predict the onset of MetS when other covariates were considered. **Conclusion:** This study showed the high-incidence rates of MetS in males and females residing in Southern Iran. Therefore, the prevention through community-based lifestyle modification should be implemented to reduce the burden of MetS and its complications.

Keywords: Incidence, metabolic syndrome, risk factors

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INTRODUCTION

Metabolic syndrome (MetS) is a collection of inter-connected metabolic abnormalities such as glucose metabolism, lipid metabolism, elevated blood pressure (BP), and central obesity.[1] MetS increases the risk of serious diseases such as Type-2 diabetes, cardiovascular diseases, and eventually all-cause

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mortality.[2] It is also associated with nonalcoholic steatohepatitis, reproductive diseases, and certain types of cancers.[3] Numerous definitions and diagnostic criteria have been used to identify MetS. However, regardless of the used criteria, it is well acknowledged that the prevalence of MetS is increasing in epidemic extents in both developed and developing countries.[2] The prevalence of MetS in the adult population is estimated to be 20%–25%.[4] The specific cause of MetS is not clear; however, it is considered as a combination of genetic, metabolic, and some environmental factors. The pathophysiology of MetS is complex, with insulin resistance and disorder in lipid metabolism playing a central role in the pathogenesis.[5] The prevalence of MetS varies considerably worldwide due to the differences in genetics, lifestyle factors, and socioeconomic status.[6] The prevalence of MetS is high in the Middle East, and urgent measures are required to decrease its complications.[7] Recent studies have shown that increasing economic development in developing countries has mainly contributed to the increasing prevalence of obesity, Type-2 diabetes, and cardiovascular diseases.[8] Several cross-sectional studies on the prevalence of MetS have been published in this field.[7-9] Cigarette smoking is proved to play a role in the emergence of various MetS components. The existing data from epidemiological studies on this issue are inconsistent and controversial.[10] Some observational studies have reported an independent association between MetS and chronic kidney disease.[11] Hyperuricemia could deteriorate the insulin resistance. Sequentially, insulin resistance is thought to play a pivotal role in MetS.[12] Recent reports have revealed that raised uric acid may be a predictor for MetS in different individuals; however, the results of these studies are controversial.[13] We sought to determine the association between serum uric acid levels and MetS prevalence and incidence. Better understanding of the incidence of MetS and determinants of its progression in a prospective study would result in a better evaluation of populations at higher risk to implement effective preventive strategies among the population in Southern Iran.

MATERIALS AND METHODS

Setting and study design

This community-based prospective study was an ongoing population-based longitudinal study carried out in Shiraz, the capital of Fars province, Southern Iran, under the auspices of health policy research center, Shiraz University of Medical Sciences, Shiraz, Iran. According to the national census 2016, the overall population of Shiraz was estimated to be 1869001 persons. The study procedures were performed in two phases from November 2011 to September 2012 and from October 2016 to November 2017.

Sample size and data collection

The sample size was determined using the following formula:

$$n=\frac{(Z_{1-\frac{\alpha}{2}}+Z_{1-\beta})^2\, p(1-p)}{d^2}=504; d=0.05; P=0.28\ [14];$$

$$Z_{1-\alpha/2}=1.96; Z_{1-\beta}=0.53$$

However, considering the loss rate of 35%, the final sample size was 819 persons.

The participants took part in two phases. In the first phase, the participants were selected by a stratified multistage probability sampling method, with selections made from the sampling units based on the geographical area, gender, and age groups from seven municipality regions in Shiraz. The participants were selected using the cluster random sampling. The probability proportional to the size sampling methodology was used on the home addresses, postal zip codes, and municipality regions to select the study population from each municipality. Individuals aged ≥18 years were selected and invited by phone calls to participate in the study. The exclusion criteria were non-Iranian nationality, pregnancy, or baby delivery within the previous 6 months. The cohort of 819 residents who participated in the baseline survey was re-assessed after a mean period of 5.1 years. The data from the second phase of the study were obtained in the same as well. The relevant period was considered to start on the date when the baseline examination was performed until either the onset of MetS, death, or the end of the follow-up period. The study proposal was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. 397433), and written informed consent was obtained from each participant. Among 819 participants meeting the criteria for the follow-up study, 577 (70.5%) persons returned for follow-up examinations during October 2016 to November 2017. During the 5.1 year follow-up period, 11 persons died, and 231 persons quitted the study. In this regard, 180 individuals had a change in address or had migrated and were no further accessible, and 51 persons refused to participate even after repeated attempts. Figure 1 depicts the composition of the study population.

Clinical and nutritional assessments

A standard questionnaire addressing demographic characteristics, level of education, medical history, and health-related behaviors was administered by the trained research staff. Past smokers were defined as those who had abstained from smoking for > 3 months at the examination time. The participants' heights and weights were assessed while the participants were wearing light clothing and no

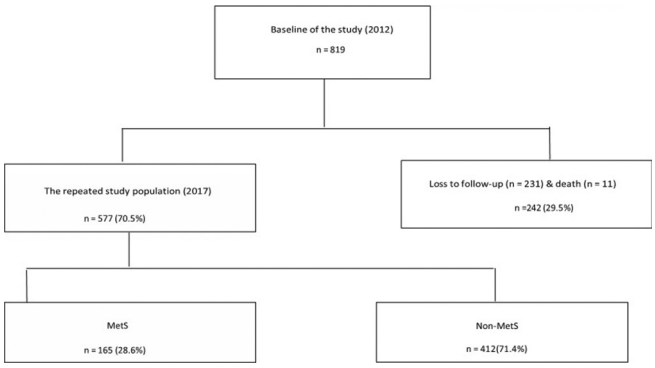

Figure 1: Flow diagram showing the process of participants attending the 5-year follow-up study

shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters (kg/m^2). After a 15-min rest in the sitting position, the BP was recorded using a standardized mercury sphygmomanometer as an average of two consecutive readings. The dietary intake from a 24-h food recall was assessed by the food frequency questionnaire. Data entry and interviews were performed by a trained dietitian, and the participants' intake was analyzed in terms of energy, macronutrients, and micronutrients contents by the Nutritionist-4 software (First Databank Inc., Hearst Corp., San Bruno, CA, USA).

Blood sampling and laboratory measurements

Blood samples were collected after an overnight fasting and were then analyzed. The intra- and inter-assay coefficients of variation were 2.1% and 2.2% for FBS, 0.8% and 3.1% for total cholesterol, 0.9% and 2.1% for triglyceride (TG), and 2.1% and 3.4 for high-density lipoprotein cholesterol (HDL-C), respectively. The assessments were performed using the enzyme or radioimmunoassay methods. Serum creatinine (Cr) was measured by Jaffe's kinetic method. The intra- and inter-assay coefficients of variation were 2.4 and 3.1%, respectively. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15]

Outcome variables

MetS was defined using the International Diabetes Federation Guideline. Individuals with central obesity defined as waist circumference ≥ 94 cm for men and ≥80 cm for women plus any two of the following four factors were defined as having MetS: (1) Raised TG level: ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality; (2) Reduced HDL-C: <40 mg/dL in males and <50 mg/dL in females, or specific treatment for this lipid abnormality; (3) Raised BP: Systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension; (4) Raised fasting plasma glucose ≥100 mg/dL, or previously diagnosed Type 2 diabetes;[4] and BMI was categorized according to the World Health Organization's guidelines. The active individuals were recommended to do physical activity based on the CDC/ACSM guidelines of either ≥30 min of moderate-intensity physical activity on ≥5 days/week or ≥20 min of vigorous-intensity physical activity on ≥3 days/week.[16]

Data analysis

Mean (standard deviation [SD]) or frequency (percentage) values of the baseline characteristics were achieved. The baseline characteristics of follow-ups and non-follow-ups (those without any follow-up data) are shown as mean (SD) or frequency (%). A comparison between two groups was performed using the statistical methods such as Student's *t*-test, Chi-squared test, analysis of variance or Kruskal–Wallis tests for normally or not normally distributed continuous variables, respectively. The progression rates were estimated as the number of cases, who developed MetS per 100 person-years of follow-up. The incidence rates were calculated by dividing the number of events by the years at risk for the whole population. To facilitate interpretations, the progression rates are reported in terms of percentage per year. The relevant period date for the incident cases of MetS was defined as the date of completion of the baseline examination until the date when the MetS was diagnosed for the first time, the date of the last completed follow-up, death, or end of follow-up in the second phase. Hazard ratio (HR) was determined based on the incidence rates and adjusted HR with 95% CI using Cox-proportional hazard regression analysis, which simultaneously is adjusted for other covariates. According to this analysis, age, fasting blood glucose, systolic and diastolic BP, BMI, waist-to-hip ratio (WHR), cholesterol, TG and creatinine, eGFR and uric acid, gender, marital status, cigarette smoking, level of education, and physical activity were considered as dichotomous variables. For the risk factors with more than two categories, the first category was considered as the reference group. All the statistical significance analyses were two-tailed, the confidence intervals (CIs) were set at 95%, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS, version 20; SPSS Inc., Chicago, Illinois, USA).

RESULTS

Characteristics of the participants

Among 819 participants, 58.5% of the participants were women, and 41.5% were men. The mean (SD) age of the participants was 43.0 (14.0) years. Table 1 shows the baseline characteristics of the individuals after stratification according to follow-up status. The participants at the follow-up phase differed significantly from the participants with no follow-up regarding some baseline characteristics

Table 1: The characteristics of the baseline variables of the followed up versus nonfollow-up participants

Characteristics	Mean (SE)			*P*
	Baseline (*n*=819)	Nonfollow-up (*n*=242)	Follow-up (*n*=577)	
Age (year)	43.0 (0.49)	40.6 (1.01)	44.0 (1.06)*	0.004
Height (cm)	163.7 (0.37)	163.8 (0.68)	163.7 (0.44)	0.853
Weight (kg)	70.0 (0.44)	68.6 (0.88)	70.5 (0.51)*	0.048
BMI (kg/m^2)	26.1 (0.15)	25.5 (0.29)	26.3 (0.18)*	0.018
WC (cm)	89.2 (0.39)	87.8 (0.74)	89.8 (0.47)*	0.020
Hip circumference (cm)	102.4 (0.33)	101.8 (0.63)	102.6 (0.39)	0.256
WHR	0.87 (0.024)	0.86 (0.004)	0.87 (0.002)*	0.017
Fasting glucose baseline (mg/dl)	93.1 (1.01)	89.9 (1.4)	94.4 (1.2)*	0.021
Cholesterol (mg/dl)	190.0 (1.50)	187.8 (2.91)	191.0 (1.74)	0.340
LDL-cholesterol (mg/dl)	106.8 (1.21)	103.9 (2.30)	108.1 (1.42)	0.121
HDL-C (mg/dl)	49.9 (0.39)	50.2 (0.73)	49.8 (0.46)	0.711
TG (mg/dl)	140.8 (2.71)	132.7 (4.31)	144.1 (3.39)*	0.55
Systolic BP (mmHg)	115.5 (0.50)	115.5 (1.03)	115.4 (0.56)	0.931
Diastolic BP (mmHg)	74.4 (0.31)	74.7 (0.60)	74.3 (0.36)	0.563
eGFR (ml/min/1.73 m^2)	79.4 (0.75)	81.3 (1.48)	78.6 (0.86)	0.119
Cr (mg/dl)	1.0 (0.008)	1.0 (0.01)	1.0 (0.01)	0.210
Uric acid (mg/dl)	4.5 (0.04)	4.3 (0.08)	4.5 (0.06)	0.104
Men	41.5	26.3	37.9	0.263
Obesity	19.3	17.2	20.2	0.055
DM drug	4.3	4.6	4.2	0.473
Lipid drug	9.8	7.9	10.5	0.153
HTN drug	9.4	9.6	9.3	0.499
Marital status				
Married	84.1	73.6	88.5	<0.001
Single	15.9	26.4	11.5	
HCVD	5.3	4.6	5.6	0.338
FHDM	26.9	23.3	28.5	0.077
Smoking				
Never	92.6	94.2	91.9	0.165
Current/past	7.4	5.8	8.1	
Education level				
Illiterate/primary school	6.4	6.8	6.3	0.811
Diploma/below diploma	60.8	62.2	60.3	
Higher than diploma	32.8	33.1	33.5	
Physical activity				
No	30.9	29.8	31.4	0.210
<2 time in week	26.0	22.7	27.4	
≥3 time in week	43.1	47.5	41.2	

The difference in the mean or percentage of the variables between nonfollow-up and attendees at follow-up. *P<0.05. BMI=Body mass index; HDL-C=High-density lipoprotein cholesterol; TG=Triglyceride; eGFR=Estimated glomerular filtration rate; CR=Creatinine; HTN=Hypertension; DM=Diabetes mellitus; HCVD=History of cardiovascular disease; FHDM=Family history of diabetes mellitus; BP=Blood pressure; WC=Waist circumference; WHR=Waist-to-hip ratio; SE=Standard error

such as age, fasting glucose, waist circumference, TG, weight, marital status, and BMI. However, the follow-up sample was similar to the baseline sample.

Prevalence and incidence

During the study, the overall prevalence of MetS increased from 25.9% in 2012 to 28.6% in 2017. Out of 405 individuals with no MetS in the first stage, 107 (26.4%) (40 men and 67 women) developed MetS in 1960 (1020 men and 940 women) person-years of 5.1 year follow-up.

The overall incidence of subsequent MetS was 5.45% (95% CI: 4.47–6.59) per year. The incidence of MetS among women (men, 3.92%;[95% CI: 2.80–5.34]) was significantly higher, compared to women (7.12% [95% CI: 5.52–9.05] ;P < 0001). The incidence of MetS showed a significant increase with an increase in the number of MetS components at the baseline. The incidence of MetS increased by 5.02 (95% CI, 3.75–6.58) for individuals who had a metabolic component and by 12.65 (95% CI, 9.72–16.18) for those who had three or more components (P < 0001).

Risk factors

Table 2 shows the compares the baseline characteristics of the participants with and without MetS. The participants who developed MetS were older and female with higher

Table 2: The baseline characteristics between participants who did and did not develop metabolic syndrome

Variables	Mean (SE)		Difference (95% CI)	*P*
	Developed MetS	Not developed MetS		
Age (year)	44.0 (1.09)	39.9 (0.74)	4.1 (1.37-6.83)	0.003
Height (cm)	162.7 (1.08)	165.5 (0.59)	−2.8 (−5.11-0.48)	0.018
Follow-up (year)	4.9 (0.05)	4.8 (0.02)	0.1 (0.004-0.23)	0.042
Weight (kg)	71.2 (1.07)	67.8 (0.68)	3.3 (0.82-5.96)	0.010
BMI (kg/m^2)	26.9 (0.38)	24.7 (0.23)	2.1 (1.31-3.06)	<0.001
WC (cm)	89.9 (0.79)	86.0 (0.55)	3.9 (1.87-5.94)	<0.001
Hip circumference (cm)	103.3 (3.)	100.1 (0.46)	3.2 (1.37-5.14)	0.001
WHR	0.53 (0.04)	0.41 (0.02)	0.1 (−0.006-0.22)	0.038
Systolic BP (mm Hg)	114.4 (1.47)	112.3 (0.67)	2.0 (−0.78-4.85)	0.157
Diastolic BP (mm Hg)	73.9 (0.79)	74.3 (0.40)	1.6 (−0.13-3.42)	0.070
FBS	90.4 (1.98)	86.6 (1.06)	3.7 (−0.39-7.96)	0.076
TG (mg/dl)	146.8 (6.17)	114.5 (2.82)	32.3 (20.61.44.09)	<0.001
Cholesterol (mg/dl)	195.0 (3.47)	184.6 (2.42)	10.3 (1.47-19.24)	0.022
HDL-C (mg/dl)	50.0 (0.95)	51.3 (0.70)	1.1 (−3.58-0.98)	0.264
LDL cholesterol (mg/dl)	112.4 (2.87)	107.2 (2.06)	5.2 (−2.31-12.7)	0.174
eGFR (ml/min/1.73 m^2)	78.9 (1.95)	84.2 (1.28)	−5.2 (−10.03-−0.48)	0.031
Cr (mg/dl)	1.0 (0.02)	1.0 (0.01)	0.001 (−0.05-0.05)	0.959
Uric acid (mg/dl)	11.5 (4.42)	6.2 (0.74)	5.38 (−0.40-11.17)	0.048
Protein (g/dL)	59.2 (2.57)	60.9 (1.52)	2.9 (−7.59-4.03)	0.548
Carbohydrate (g/dL)	175.8 (7.26)	167.7 (3.46)	8.0 (−7.80-23.98)	0.316
Fat (g/dL)	56.6 (2.85)	60.3 (1.59)	−3.6 (−9.84-2.51)	0.245
Energy intake (kcal)	1448.8 (57.14)	1448.9 (28.77)	−0.1 (−115.51-115.30)	0.999
Men	37.4	51.2	−13.8 (−24.8-−2.2)	0.017
Obesity	20.8	11.2	9.6 (1.9-17.2)	<0.001
Smoking				1.000
Never-smoker	91.6	91.3	0.6 (−5.9-6.5)	
Past/current	8.4	8.7	−0.3 (−10.6-4.6)	
Education				
Under diploma	27.5	32.3	−4.8 (−15.0-5.4)	0.771
diploma	38.8	33.5	5.3 (−5.7-15.3)	
Matriculation or above	33.7	34.2	−0.5 (−11.0-10.00)	
Physical activity (time in week)				
<3	53.5	58.6	−5.1 (−16.4-6.2)	0.408
≥3	46.5	41.4	−1.6 (−9.3-6.1)	

MetS=Metabolic syndrome; BMI=Body mass index; HDL-C=High-density lipoprotein cholesterol; TG=Triglyceride; eGFR=Estimated glomerular filtration rate; CR=Creatinine; HTN=Hypertension; DM=Diabetes mellitus; HCVD=History of cardiovascular disease; FHDM=Family history of diabetes mellitus; BP=Blood pressure; WC=Waist circumference; WHR=Waist-to-hip ratio; SE=Standard error; CI=Confidence interval

BMI, WC, HC, WHR, TG, and uric acid and higher percentage of obesity at the baseline; however, they had lower eGFR compared to the participants free of MetS at the end of follow-up phase ($P < 0.05$ for all measures). Table 3 shows the HR of MetS with regard to age, gender, MetS components, hypertension, diabetes, abdominal obesity, and other potential risk factors for Mets such as baseline eGFR, uric acid, smoking, physical activity, marital status, and level of education. A univariate analysis showed that female gender, age, increased total cholesterol, TG, uric acid, BMI, and abdominal obesity were significantly associated with the risk of developing MetS. The incidence of MetS was also analyzed using multiple models for the potential risk factors of MetS. After adjusting the covariates, Cox's proportional hazards model showed that female gender (HR 2.45; 95% CI: 1.33,4.50), higher BMI (HR 3.13; 95% CI: 1.43.6.84), increased WHR (HR 1.45; 95% CI: 0.85,2.46), smoking 4.79; 95% CI: 2.09,10.97), and lower HDL (HR 0.53; 95% CI: 0.29,1.00) at the baseline significantly predicted the onset of MetS; however, the other variables were not significant.

DISCUSSION

During the last three decades, the prevalence of MetS increased worldwide. The incidence and prevalence rates of MetS show remarkable differences among the general populations in various studies from different countries.[17] In this cohort study, the incidence of MetS was 5.45% (3.92% in men and 7.12% in women). This rate is close to the reported incidence rate of MetS (5.5%) in the northern region of Iran. However, in comparison to our study, the incidence rate of

Table 3: Hazard ratio and 95% confidence intervals of potential risk factors in relation to metabolic syndrome incidence

Variables	At risk (*n*)	Cases (*n*)	Person-year	Incidence/100 person-year (95% CI)	HR (95% CI)	*P*	Multiple-adjusted HR (95% CI)	*P*
All	396	107	1960	5.45 (4.47-6.59)	-			
Gender								
Men	188	40	941	4.25 (3.036-5.788)	1.00		1.00	0.004
Women	208	67	1020	6.56 (5.090-8.341)	1.62 (1.09-2.41)	0.015	2.45 (1.33-4.50)	
Age (year)								
<35	139	24	680	3.52 (2.261-5.251)	1.00		1.00	
35-50	146	44	721	6.10 (4.434-8.192)	1.67 (1.01-2.76)	0.044	1.30 (0.61-2.80)	0.960
≥50	111	39	560	6.96 (4.952-9.520)	1.81 (1.08-3.02)	0.023	1.19 (0.69-2.05)	0.531
Fasting glucose (mg/dl)								
<100	354	93	1753	5.30 (4.281-6.499)	1.00		1.00	0.403
≥100	35	13	173	7.51 (4.001-12.849)	1.310 (0.731-2.34)	0.364	0.70 (0.30-1.61)	
Systolic BP (mmHg)								
<130	341	85	1671	5.076 (4.063-6.289)	1.00		1.00	0.171
≥130	36	14	176	7.95 (4.348-13.346)	1.55 (0.88-2.75)	0.126	1.78 (0.77-4.07)	
Diastolic BP (mmHg)								
<85	356	89	1743	5.106 (4.100-6.283)	1.00		1.00	0.501
≥85	21	10	103	9.708 (4.655-17.854)	1.57 (0.81-3.03)	0.174	0.70 (0.25-1.94)	
Cholesterol (mg/dl)								
<200	253	57	1268	4.495 (3.404-5.824)	1.00		1.00	0.376
>200	137	48	663	7.23 (5.338-9.598)	1.83 (1.24-2.69)	0.002	1.350 (0.67-2.67)	
HDL (mg/dl)								
Men≥40 and women ≥50	277	76	1353	5.617 (4.425-7.030)	1.00	0.029	1.00	0.044
Men <40 and women <50	112	29	574	5.052 (3.383-7.255)	0.61 (0.39-0.95)		0.53 (0.29-1.00)	
LDL (mg/dl)								
<130	292	74	1458	5.075 (3.985-6.371)	1.00		1.00	0.571
≥130	98	31	473	6.553 (4.453-9.302)	1.50 (0.98-2.29)	0.059	0.80 (0.37-1.72)	
TG (mg/dl)								
<150	244	50	1222	4.16 (4.091-5.394)	1.00		1.00	0.168
≥150	144	55	699	7.86 (5.927-10.241)	2.26 (1.53-3.34)	≤0.001	1.45 (0.85-2.46)	
BMI (kg/m^2)								
<25 normal	190	27	944	2.860 (1.884-4.161)	1.00		1.00	
25-29.9 overweight	147	57	733	7.776 (5.889-10.075)	2.17 (1.37-3.45)	0.001	2.41 (1.31-4.41)	0.008
≥30 obese	113	22	260	8.46 (5.302-12.81)	3.66 (2.08-6.47)	≤0.001	3.13 (1.43.6.84)	0.012
Increased (WHR)								
No	211	49	1047	4.680 (3.462-6.187)	1.00		1.00	0.045
Yes	171	56	850	6.588 (4.976-8.555)	1.52 (1.03-2.23)	0.033	1.59 (0.95-2.67)	
Marital status								
Married	339	100	1684	5.938 (4.831-7.222)	2.03 (0.94-4.38)	0.070	1.00	0.547
Single	57	7	277	2.52 (1.016-5.206)	1.00		0.75 (0.30-1.88)	
Smoking								
Never	361	98	1791	5.471 (4.442-6.668)	1.00	0.097	1.00	<0.001
Past/current	34	9	164	5.487 (2.509-10.417)	1.79 (0.89-3.60)		4.79 (2.09-10.97)	
Education level								
Illiterate	26	6	124	4.838 (1.775-10.53)	1.00		1.00	
Below diploma	86	21	424	4.952 (3.065-7.570)	0.89 (0.36-2.23)	0.819	0.33 (0.13-1.49)	0.191
Diploma	126	38	630	6.031 (4.268-8.279)	0.85 (0.35-2.02)	0.718	0.55 (0.18-1.70)	0.303
Higher than diploma	123	33	599	5.509 (3.792-7.736)	1.02 (0.42-2.44)	0.960	0.48 (0.15-1.52)	0.214
eGFR (ml/min/1.73 m^2)								
≥90	119	25	589	4.244 (2.746-6.265)	1.00		1.00	0.196
≥60 and<90	212	64	1043	6.136 (4.725-7.835)	1.46 (0.91-2.34)	0.114	1.14 (0.61-2.10)	

Contd....

Table 3: Contd....

Variables	At risk (*n*)	Cases (*n*)	Person-year	Incidence/100 person-year (95% CI)	HR (95% CI)	*P*	Multiple-adjusted HR (95% CI)	*P*
<60	46	15	231	6.493 (3.634-10.710)	1.70 (0.89-3.25)	0.108	1.65 (0.72-3.79)	0.297
Uric acid (mg/dl)								
Men <7.3 and women <6.2	375	99	2563	3.862 (3.139-4.702)	1.00		1.00	
Men≥7.3 and women ≥6.2	14	6	125	4.8 (1.761-10.447)	4.11 (1.77-9.51)	0.001	2.14 (0.80-5.72)	0.129
Physical activity time in week								
<3	216	53	1079	4.911 (3.679-6.424)	0.82 (0.54-1.24)		0.74 (0.46-1.19)	0.224
≥3	111	34	543	6.261 (4.336-8.749)	1.00	0.352	1.00	

Multiple analyses of the risk of incident MetS in subjects without MetS at baseline. Multiple model was adjusted for each component of MetS and other potential risk factors for MetS: age, gender, abdominal obesity and, base line eGFR, uric acid, smoking, physical activity marital status and education level. BMI=Body mass index; HDL=High-density lipoprotein; TG=Triglyceride; eGFR=Estimated glomerular filtration rate; CR=Creatinine; HTN=Hypertension; DM=Diabetes mellitus; HCVD=History of cardiovascular disease; FHDM=Family history of diabetes mellitus; BP=Blood pressure; WHR=Waist to hip ratio; SE=Standard error; CI=Confidence interval; HR=Hazard ratio; MetS=Metabolic syndrome

the reported value was significantly higher among men than women (7.49% vs. 4.33%).[9] Similar to this study, in a cohort study conducted the central part of Iran, the incidence rate of MetS was reported to be 5.65%. The study showed that the incidence rates of MetS among males and females were 5.6% and 5.8%, respectively. These values were larger than the value in our study on males and smaller than that among females.[18] In a study conducted in Korea by Hwang *et al*., the incidence rates of MetS during a 5-year follow-up were 3% among males and 4.6% among females, respectively. Accordingly, the incidence of MetS in the present study was higher, compared to the study in Korea.[19] In a study conducted in an urban south European population as Santos' cohort study, the incidence rate of MetS (4.72%) was close to the reported value in the present study; however, the incidence rates were similar among men and women.[20] The results of the present study showed that the incidence of MetS was higher than that of the Coronary Artery Risk Development in Young Adults (CARDIA) (1%). This might be explained with regard to the age distribution of the study population. The participants in the CARDIA study aged 18–30 years.[21] The incidence rates of MetS increased in China throughout the past decade. The incidence of MetS increased from 8% to 10.6% in the urban regions and from 4.9% to 5.3% in the rural regions.[22] The differences in the incidence of MetS between studies conducted in Iran's regions and other studies may be attributed to different inclusion criteria, different age groups, and different prevalence rates of MetS components. The present study showed that the incidence of MetS was higher in females than in males.

The reason of such a gender variance in MetS has not yet been determined; however, some studies have proposed that female sex hormones may contribute to the changes in glucose tolerance and all MetS components. Moreover, metabolic changes associated with menopause might explain the increased prevalence of MetS in women. More stringent cutoffs employed for waist circumference and HDL among women partly explain this variation.[23] The present study revealed that higher age, BMI, WHR, TG, and lower HDL at baseline significantly increased the incidence of MetS. In this study, the incidence of MetS increased with age. The result was similar to a 5-year follow-up study in Korea.[19] The adoption of a more sedentary lifestyle and dietary changes that occur with urbanization and westernization following the socioeconomic rise in developing countries, seem to be the main factors leading to obesity and the MetS pandemic.[24] Many studies have indicated that obesity is closely associated with hypertension, Type 2 diabetes, and dyslipidemia.[25] In obesity, the serum concentrations of leptin and resistin increase, whereas adiponectin decreases. The increased production of leptin and resistin and the decreased secretion of adiponectin increase the risk of developing the MetS components.[26] Insulin resistance enhances hypertriglyceridemia and low HDL-C.[27] In this study, no association was detected between eGFR and the incidence of MetS. Consistent with our findings, some studies report that MetS is not significantly associated with reduced eGFR.[28] In humans, the uric acid is the end compound of purines catabolism. The overproduction of uric acid is observed to play an emerging role in human disease. Some studies have found a positive relationship between serum uric acid levels and the prevalence of MetS. However, it is not yet clear whether the increase in uric acid level is an independent risk factor or just a biomarker in the development and progression of MetS. Greater awareness and identification of the MetS trend in this region would facilitate the prioritization and implementation of interventions to optimize the risk factors that could have a positive effect on MetS and treat these metabolic risk factors. To the best of our knowledge, this is the first study assessing the relationship between uric acid and the incidence of MetS in Iranian population. Our study demonstrated that elevated uric acid was positively associated with the incidence of MetS in univariate analysis, whereas the

increased uric acid concentration was not independently associated with the incidence of MetS. There are several arguments suggesting that uric acid may not be a real risk factor for metabolic diseases. There is ample evidence indicating that even acutely raising uric acid concentrations improves the endothelial function. The improvement in the endothelial function is supposed to be due to the potentials of the uric acid to function as an antioxidant. In addition, other studies have documented that uric acid levels are significantly enhanced in individuals with abdominal obesity, low HDL-C, and hypertension. Accordingly, hyperuricemia can be considered as an insulin resistance marker as such some studies have shown that decreased insulin resistance by some interventions such as diets or medications decreases the uric acid levels.[29]

The present study showed that smoking in our population was associated with the incidence of MetS. A remarkable association between abdominal obesity and smoking with the increased incidence of MetS in the Iranian population highlights the significance of implementing lifestyle intervention programs to promote healthy eating habits, physical activities, and awareness of the risk of abdominal obesity and smoking.

One of the strengths of the present study is that it was a population-based study covering a wide age range of participants, representative sampling methodology, and the use of standardized data collection protocols. Furthermore, the incidence of MetS was estimated in accordance with the most frequently used definitions. Selection bias was minimized since this study was a continuous survey of randomly selected individuals. The use of population-based sample would also enhance the likelihood of generalizability.

The study was considered the most recent data of the potential risk factors available in our region and provided decision-makers with valuable information regarding the health promotion areas that should be reinforced. The measures aimed at improving adherence to preventive recommendations for obesity. Adequate measures are required with a special focus on dietary recommendations, increased physical activity, and smoking cessation.

The present study had several limitations. First, 29.5% loss in the follow-up phase might have caused selection bias. However, in further analysis, the follow-up sample was similar to the baseline sample in terms of the frequency distributions of the participants' baseline characteristics, including age, gender, level of education, and behaviors (i.e., smoking and physical activity) as such they might have had some slight effects on the present findings due to the loss to follow-up. Researchers in a cohort study on the Korean population also reported that they had 30.4% subject attrition in the follow-up phase.[19] Regardless of these limitations, the major strength of this study includes a prospective cohort study on the general population in one of the urban region in Iran. To the best of our knowledge, this study describes the relationship between uric acid concentration and the incidence of MetS among Iranian population for the first time. In addition, given that many factors influence the progression of MetS, a variety of risk factors, in terms of type and number, used in the present work, can serve as a significant advantage.

CONCLUSION

In conclusion, this study provides information about the incidence of MetS in an urban region in southern Iran as men, 3.92%; women, 7.12%. Cox's proportional hazards model showed that female gender, increased TG, BMI, abdominal obesity, and smoking at baseline significantly predicted the onset of MetS after the mean period of 5.1 years. These data further confirmed the need for future research, public health, and clinical collaboration against MetS in the Iranian population.

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Conflicts of interest

There are no conflicts of interest.

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