Original Article

Prevalence of Metabolic Syndrome in Amol and Zahedan, Iran: A Population Based Study

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Abstract

Purpose: So far, a variety of prevalence rates have been reported for the metabolic syndrome (MetS) according to several definitions. The aim of this study was to assess the prevalence of MetS in Iran according to two definitions and compare the characteristics of the subjects who met the MetS criteria according to the different definitions.

Methods: Participants were recruited from family registries of public health centers. After obtaining demographic and clinical data, the subjects underwent anthropometric measurements and laboratory evaluations. MetS was defined according to the NCEP-ATPIII and IDF criteria. The subjects were then categorized into 3 groups: 1) Healthy non-MetS subjects based on either definition, 2) Individuals with MetS according to only one of the definitions, and 3) Individuals who met both NCEP-ATPIII and IDF criteria for MetS.

Results: Totally, 5826 subjects in Amol and 2243 subjects in Zahedan were enrolled in the study. The weighted prevalence of MetS according to the NCEP-ATPIII and IDF criteria was 27.8% and 26.9% in Amol and 12% and 11.8% in Zahedan, respectively. Overall, 18.9% of the subjects fulfilled both criteria for MetS. However, a considerable proportion (8.5%) met the MetS criteria according to only one definition but not both.

Conclusions: MetS is increasingly prevalent in Iran as well as other parts of the world. Due to non-uniform definitions of MetS, some of the subjects who meet MetS according to one set of criteria might be considered healthy according to another definition and consequently would not receive the preventive health services.

Keywords: Epidemiology, Iran, metabolic syndrome X, prevalence

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Introduction

According to the World Health Organization, cardiovascular disease (CVD) was responsible for approximately 17 million deaths in 2008.[1] In recent years, Westernization of life style along with economic development has been followed by substantial increase in the prevalence of CVD, especially in developing countries.[1] Metabolic syndrome (MetS) is a measure of CVD, defined as the clustering of multiple cardio-metabolic risk factors along with adipose tissue dysfunction and insulin resistance as core pathophysiology.[2,3] The role of metabolic syndrome in increasing the risk of mortality, CVD, and stroke has been already described.[4] Furthermore, MetS is associated with diabetes mellitus type 2,[5] fatty liver[6] and even cancers.[7]

Currently, there are 2 widely used definitions for MetS. First, the National Cholesterol Education Panel-Adult Treatment Panel III (NCEP-ATPIII) defines MetS by the presence of abdominal obesity, dyslipidemia, elevation of arterial blood pressure and glucose intolerance.[8] After emerging strong evidence supporting the role of central obesity as the culprit of MetS as well as the major ethnic differences in definition of central obesity, the International Diabetes Federation (IDF) proposed another set of criteria for MetS to highlight the impact of central obesity and ethnic diversity.[9] However, non-uniform definitions for MetS potentially give rise to concerns that many people who are at risk of CVD and non-communicable diseases might not receive preventive health care since they do not meet the diagnostic criteria of a specific definition.

On the other hand, the prevalence of MetS has been reported quite variably in different worldwide and Iranian studies. For instance, Zabetian, et al. reported a prevalence of 32% for MetS among 10368 Iranian adults[10] while its prevalence in Zanjan was 23.7%.[11]

In this large population-based study, we aimed to assess the prevalence of MetS and its components according to two distinct definitions (NCEP-ATPIII and IDF) in two major districts located in different geographical areas in Iran (Zahedan in the southeast and Amol in the north). We also compared the characteristics of the subjects who met the MetS criteria according to both or only one of the NCEP-ATPIII and IDF definitions.

Patients and Methods

Study population

This was a cross-sectional study on subjects above 16 years of age in Amol and Zahedan districts, Iran. In order to have a random and representative sample, the family registries of public health centers were considered as sampling frame and two clusters with

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an average size of 30 individuals were selected from each public health center. The selected subjects were interviewed at home by two trained interviewers to obtain demographic and clinical characteristics, after an informed consent was obtained. Venous blood sampling and anthropometric measurements were performed on the day following the day of the interview. We excluded the individuals who did not consent and substituted them by other random subjects. The study protocol was approved by the ethics committees of the Zahedan and Mazandaran Universities of Medical Sciences and the Digestive Disease Research Institute to conform to the guidelines of the Declaration of Helsinki.

Measurements and definitions

Venous blood sample was taken after tourniquet application following at least 8-hours of fasting to assess fasting plasma glucose (FPG), plasma insulin (PI), and lipid profile. Insulin resistance was quantified using homeostasic model assessment of insulin resistance (HOMA-IR) calculated as (FPG×PI)/405.[12] Diabetes mellitus was defined as FPG ≥ 126 mg/dL or receiving antihyperglycemic drug therapy.[13]

Weight was measured with light clothes to the nearest 0.1 Kg in upright position. Height was measured without shoes with a standard height rule to the nearest 0.1 cm and waist circumference was measured halfway the lower costal margin and the iliac crest to the nearest 0.5 cm. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressure (BP) measurement was performed following 5 minutes of relaxation in sitting position; subjects on antihypertensive medications or those with systolic or diastolic blood pressure of higher than 140 and 90 mmHg, respectively, were considered hypertensive.[14]

MetS was defined according to the NCEP-ATPIII and IDF criteria, as summarized in Table 1. Subjects were then categorized into 3 groups: 1) Healthy non-MetS subjects based on either definition; 2) Individuals with MetS only by one of the definitions, and 3) Individuals who met both NCEP-ATPIII and IDF criteria for MetS.

Statistical analysis

STATA software (version 11, StataCorp, College Station, TX, USA) was used for statistical analysis allowing for the complex survey sampling design. Variance estimation took into account the stratification of the sample at the district level and design weights were applied to adjust each district to its correct proportion of the population by gender and age groups. Data were presented as mean (standard error of the mean) or count (%), as appropriate. The difference between groups was tested using one-way analysis of variance (ANOVA) or Pearson's Chi-square tests. For the variables which did not meet the assumptions of normality and homogeneity of variance, the log-transformed values were used in statistical analysis.

Multinomial logistic regression analysis was undertaken to assess for independent predictors of being diagnosed with MetS according to only one (group 2) or both (group 3) of the MetS definitions compared to healthy non-MetS individuals (group 1). Due to heterogeneity of effect, two separate regression models were fitted for 2 districts while taking into account the male gender as referent. Regression modeling followed a stepwise selection procedure. P-value < 0.05 was considered statistically significant.

Results

Totally, 8069 subjects (5826 subjects in Amol and 2243 subjects in Zahedan) were enrolled in the study. The mean age of the participants was 40.1 (0.24) years in Amol and 36.5 (0.39) years in

Table 1. Criteria for metabolic syndrome according to NCEP-ATPIII and IDF

	NCEP-ATP III	IDF*
Abdominal obesity	> 102 cm for males and > 88 cm for females	Ethnic specific cut-offs for Iranian population (1)
High TG	≥ 150 mg/dL or treatment for hypertriglyceridemia	> 150 mg/dL or treatment for hypertriglyceridemia
High HDL-C	< 40 mg/dL foe males or < 50 mg/dL for females	< 40 mg/dL for males or < 50 mg/dL for females
High Blood pressure		
• Systolic	≥ 130 mmHg	> 130 mmHg
• Diastolic	≥ 85 mmHg	> 85 mmHg
High FPG	≥ 100 mg/dL or treatment for hyperglycemia	> 100 mg/dL or previously diagnosed type 2 diabetes

NCEP-ATP III = National Cholesterol Education Panel-Adult Treatment Panel III; IDF = International Diabetes Federation; TG = triglyceride; HDL-C = high density lipoprotein-cholesterol; FPG = fasting plasma glucose. *According to IDF, MetS is diagnosed with presence of abdominal obesity plus two of the other criteria

Table 2. Baseline qualitative characteristics of the participants, *n*(%)

Variable			Total prevalence‡	Group 1€	Group 2€	Group 3€
Gender*	Amol	Male	3282 (50.0)	2234 (70.5)	430 (12.4)	618 (17.1)
		Female	2544 (50.0)	1527 (65.2)	191 (6.8)	826 (27.9)
	Zahedan	Male	1165 (48.7)	992 (88.0)	91 (6.2)	82 (5.7)
		Female	1078 (51.3)	825 (82.9)	66 (4.5)	187 (12.5)
Marriage*	Amol		4741 (75.9)	2873 (70.2)	551 (85.7)	1317 (88.8)
	Zahedan		1821 (73.4)	1405 (69.4)	150 (92.4)	266 (98.5)
Hypertension*	Amol		1503 (23.1)	480 (11.1)	230 (36.3)	793 (53.8)
	Zahedan		504 (19.4)	262 (12.9)	72 (46.7)	170 (63.6)
Diabetes*	Amol		716 (10.7)	165 (3.6)	115 (17.0)	436 (29.2)
	Zahedan		155 (5.2)	39 (1.7)	34 (19.7)	82 (28.5)
Smoking*	Amol		839 (12.0)	563 (12.2)	118 (17.3)	158 (9.4)
	Zahedan		97 (3.8)	80 (3.8)	8 (4.9)	9 (3.3)

Group 1: Healthy non-MetS subjects based on both definitions; Group 2: Individuals with MetS according to only one of the definitions; Group 3: Individuals who met both NCEP-ATPIII and IDF criteria for MetS. ‡ Prevalence of each variable in Amol and Zahedan. € Percentages add to 100 in row. **P*-value <0.001 for the difference between 3 groups

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Table 3. Baseline quantitative characteristics of the participants, Mean (standard error of mean)

			Total	Group 1	Group 2	Group 3
Age *	Amol		40.1 (0.24)	36.1 (0.3)	44.9 (0.7)	49.9 (0.5)
	Zahedan		36.5 (0.39)	34.2 (0.4)	47.4 (1.5)	51.7 (0.9)
TC*	Amol		179.5 (0.59)	170.3 (0.7)	190.9 (1.8)	202.2 (1.2)
	Zahedan		176.9 (0.90)	172.6 (0.9)	204.3 (3.9)	200.3 (2.7)
FPG*	Amol		99.0 (0.44)	91.1 (0.3)	109.5 (2.1)	118.4 (1.3)
	Zahedan		88.5 (0.59)	83.6 (0.4)	108.9 (4.3)	121.5 (3.9)
TG *	Amol		130.7 (1.2)	98.5 (1.0)	186.5 (4.1)	203.9 (3.2)
	Zahedan		124.6 (1.7)	110.7 (1.6)	208.4 (9.2)	203.6 (7.4)
HDL-C*	Amol	Male	42.6 (0.26)	46.0 (0.3)	35.9 (0.6)	33.1 (0.5)
		Female	46.3 (0.34)	50.8 (0.4)	38.2 (0.9)	37.7 (0.5)
	Zahedan	Male	49.8 (0.17)	49.6 (0.2)	51.3 (0.5)	51.6 (0.6)
		Female	50.8 (0.16)	51.0 (0.2)	49.4 (0.5)	49.6 (0.4)
LDL-C *	Amol		101.0 (0.49)	97.0 (0.6)	105.5 (1.6)	111.1 (1.1)
	Zahedan		101.5 (0.78)	100.1 (0.8)	112.1 (3.7)	108.1 (2.5)
PI*	Amol		9.9 (0.10)	8.9 (0.1)	10.7 (0.3)	12.6 (0.2)
	Zahedan		11.3 (0.23)	10.3 (0.2)	17.1 (1.7)	17.5 (1.2)
HOMA-IR*	Amol		2.5 (0.03)	2.0 (0.03)	2.8 (0.1)	3.7 (0.1)
	Zahedan		2.6 (0.06)	2.2 (0.05)	4.5 (0.5)	5.2 (0.3)
BMI*	Amol		27.6 (0.08)	25.9 (0.09)	28.1 (0.17)	32.5 (0.12)
	Zahedan		24.2 (0.12)	23.3 (0.12)	27.4 (0.37)	30.5 (0.30)
Waist* circumference	Amol	Male	89.6 (0.23)	85.4 (0.2)	94.2 (0.4)	104.0 (0.4)
		Female	89.7 (0.29)	84.1 (0.3)	89.9 (0.7)	102.6 (0.4)
	Zahedan	Male	86.6 (0.41)	84.5 (0.4)	97.3 (0.6)	107.7 (1.4)
		Female	83.8 (0.46)	80.8 (0.5)	90.5 (1.6)	101.3 (0.6)

TC = total cholesterol level; FPG = fasting plasma glucose; TG = triglyceride level; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; PI = plasma insulin; HOMA-IR = homeostatic model assessment of insulin resistance; BMI = body mass index; Group 1: Healthy non-MetS subjects based on either definition; Group 2: Individuals with MetS only by one of the definitions; Group 3: Individuals who met both NCEP-ATPIII and IDF criteria for MetS. **P*-value <0.001 for the difference between 3 groups

Table 4. Prevalence of metabolic syndrome (Overall and by gender).

		Total		Male (%)	Female (%)	*P*-value*
		N	Prevalence (95% CI)			
NCEP-ATP III Criteria	Amol	1762	27.78 (26.6–29.0)	745 (20.8)	1017 (34.7)	< 0.001
	Zahedan	346	12.05 (10.7–13.4)	93 (6.8)	253 (17.1)	< 0.001
	Overall	2108	23.55 (22.6–24.5)	838 (17.1)	1270 (29.9)	< 0.001
IDF Criteria	Amol	1747	26.86 (25.7–28.0)	921 (25.8)	826 (27.9)	0.064
	Zahedan	349	11.80 (10.5–13.1)	162 (10.9)	187 (12.5)	0.233
	Overall	2096	22.81 (21.9–23.7)	1083 (21.8)	1013 (23.7)	0.047

NCEP-ATP III = National Cholesterol Education Panel-Adult Treatment Panel III; IDF = International Diabetes Federation; CI = confidence interval. **P*-value for the difference between males and females

Table 5. Prevalence of components contributed to metabolic syndrome among those who met the diagnostic criteria

			Total (%)	Male (%)	Female (%)	P-Value*
NCEP-ATP III	Amol	Abdominal obesity	1304 (76.0)	362 (48.8)	942 (92.3)	< 0.001
		Low HDL-C	1541 (88.0)	642 (86.9)	899 (88.6)	< 0.001
		High TG	1245 (70.4)	581 (78.5)	664 (65.6)	0.003
		High BP	1122 (62.9)	532 (71.7)	590 (57.6)	0.002
		High FPG	1067 (58.4)	437 (55.3)	630 (60.2)	0.01
	Zahedan	Abdominal obesity	292 (85.1)	66 (72.4)	226 (89.9)	< 0.001
		Low HDL-C	150 (43.5)	0 (0)	150 (59.6)	< 0.001
		High TG	245 (70.9)	81 (87.9)	164 (64.6)	< 0.001
		High BP	269 (78.5)	85 (91.1)	184 (73.9)	< 0.001
		High FPG	191 (52.9)	67 (69.3)	124 (46.8)	0.026
IDF**	Amol	Low HDL-C	1490 (85.6)	758 (82.4)	732 (88.6)	< 0.001
		High TG	1216 (69.7)	666 (72.6)	550 (67.0)	0.003
		High BP	906 (51.0)	491 (53.0)	415 (49.2)	0.013
		High FPG	931 (51.1)	431 (42.9)	500 (58.7)	0.001
	Zahedan	Low HDL-C	111 (32.9)	1 (0.004)	110 (59.7)	< 0.001
		High TG	262 (74.7)	138 (85.3)	124 (66.0)	< 0.001
		High BP	237 (67.3)	124 (76.0)	113 (60.2)	< 0.001
		High FPG	185 (51.7)	96 (59.4)	89 (45.4)	0.053

NCEP-ATP III = National Cholesterol Education Panel-Adult Treatment Panel III; IDF = International Diabetes Federation; TG = triglyceride level; HDL-C = high density lipoprotein-cholesterol; BP = blood pressure; FPG = fasting plasma glucose, **P*-value for the difference between males and females. **all subjects who met the IDF criteria had abdominal obesity according to the definition

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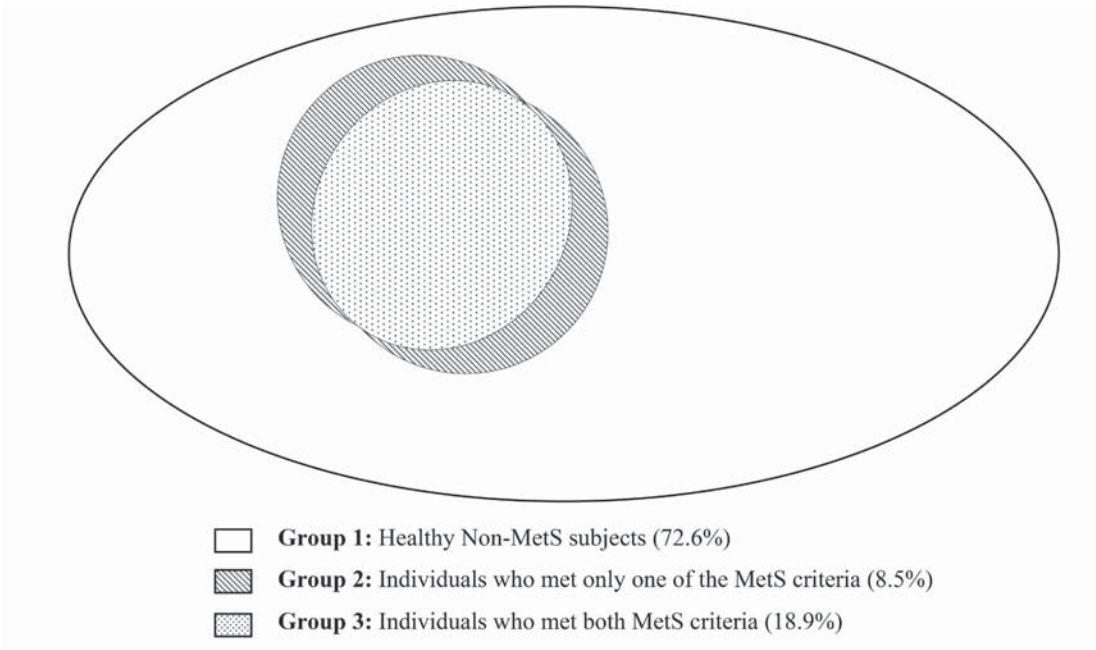

Figure 1. Subjects with MetS according to only one or both NCEP-ATPIII and IDF definitions compared to healthy non-MetS individuals.

Table 6. Multinomial logistic regression analysis of metabolic syndrome and its correlates.

	Age	Female gender	BMI		TC	HOMA-IR
			25–29.9	≥30		
Amol						
Group 1	Referent	Referent	Referent	Referent	Referent	Referent
Group 2	1.03 (1.02–1.04)*	0.46 (0.37–0.57)*	2.88 (2.2–3.7)*	2.62 (1.9–3.6)*	1.008 (1.005–1.01)*	1.33 (1.2–1.4)*
Group 3	1.05 (1.04–1.06)*	0.85 (0.72–1.01)	14.28 (9.2–22.1)*	58.2 (37.4–90.6)*	1.01 (1.008–1.012)*	1.43 (1.3–1.5)*
Zahedan						
Group 1	Referent	Referent	Referent	Referent	Referent	Referent
Group 2	1.04 (1.03–1.05)*	0.88 (0.6–1.3)	3.98 (2.5–6.3)*	4.57 (2.5–8.3)*	1.01 (1.006–1.016)*	1.20 (1.09–1.3)*
Group 3	1.07 (1.06–1.09)*	2.74 (1.9–4.0)*	10.06 (5.4–18.8)*	36.2 (19.0–69.1)*	1.006 (1.001–1.01)*	1.23 (1.12–1.4)*

BMI = body mass index; TC = total cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; Group 1: Healthy non-MetS subjects based on both definitions; Group 2: Individuals with MetS only by one of the definitions; Group 3: Individuals who met both NCEP-ATPIII and IDF criteria for MetS. * *P*-value < 0.05

Zahedan. Females constituted 2544 (50.0%) and 1078 (51.3%) of participants in Amol and Zahedan, respectively. The baseline demographic and clinical characteristics of the participants are outlined in Tables 2 and 3. The overall weighted prevalence of MetS according to the NCEP-ATPIII and IDF criteria was 27.8% (1762 participants) and 26.9% (1747 participants) in Amol and 12.0% (346 participants) and 11.8% (349 participants) in Zahedan, respectively. Females tended to exhibit higher prevalence of MetS in both districts (Table 4).

Table 5 outlines the prevalence of components contributing to MetS. Low HDL-C level was the least frequent component contributing to MetS in Zahedan while it was the most common component in Amol.

Totally, 2491 of the participants (27.4%) met either the NCEP-ATPIII or IDF criteria for MetS, but only 1713 (18.9%) fulfilled both (Group 3). A considerable fraction (778 subjects, 8.5%) met the MetS criteria according to only one of the definitions but not both (group 2, Figure 1).

All demographic, clinical and laboratory variables differed significantly between the 3 study groups (P < 0.001) (Tables 2 and 3). Compared to males, a higher proportion of females met both definitions of MetS in both Amol and Zahedan. Hypertension, diabetes mellitus and marriage were more prevalent in group 3 compared to groups 2 and 1. The mean age of the participants, body mass index (BMI), PI, HOMA-IR, and waist circumference were significantly higher in group 3 than groups 2 and 1, and also in group 2 than group 1 (P < 0.001 for both). The mean values of FPG, total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) in groups 3 and 2 were higher compared to group 1 (P < 0.001).

Table 6 presents the multinomial logistic regression analysis on the 3 study groups. Adjusted relative risk ratios indicate the relative risk of meeting only one or both definitions of MetS versus being categorized as healthy non-MetS individual as referent. Females had a higher risk of MetS with both NCEP-ATPIII and IDF definitions (group 3) in Zahedan but not in Amol. Interestingly in Amol, females tended to exhibit an inverse association with MetS according to only one of its definitions (Group 2). Older age, higher BMI, TC and HOMA-IR were also independently associated with the risk of MetS based on both or only one of the diagnostic set of criteria.

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Discussion

Despite the wealth of epidemiologic studies on MetS in Iran, studies in the literature reported a variety of prevalence rates.[10,11,16] In the present study, we observed the prevalence of 27.8% and 26.9% in Amol and 12.0% and 11.8% in Zahedan according to NCEP-ATPIII and IDF criteria, respectively. This was lower than previously reported prevalence rates in the country. In a study on 10368 adults in Tehran, Iran, the prevalence of MetS was 32.1% (95% CI: 31.2 – 33.0) and 33.2% (95% CI: 32.3 – 34.1) according to the IDF and NCEP-ATPIII definitions, respectively.[10] In another population based study on 3,024 Iranian adults aged 25 – 64 years from 30 provinces, the age-adjusted prevalence of MetS was about 34.7% (95% CI: 33.1 – 36.2) and 37.4% (95% CI: 35.9 – 39.0) based on the NCEP-ATPIII and IDF definitions, respectively.[16] Similarly, studies in other parts of the world revealed a great variability in the prevalence of MetS ranging from about 4% in a rural area in Japan[17] up to 63.7% in an urban area in Pakistan.[18] Apart from various definitions, such disparity is more probably due to the heterogeneity of study samples even within a country as we observed in the present study. The prevalence of MetS in our study also differed from an earlier study in Zahedan among 1802 individuals which reported prevalence rates of 21.0% and 24.8% according to NCEP-ATPIII and IDF definitions, respectively.[19] However, unlike Kaykhaei, et al. who recruited subjects over 19 years of age, our study population comprised individuals over 16 years of age which could potentially result in a lower prevalence rate due to the lower risk of metabolic syndrome in younger individuals. Furthermore, different cut-off values for waist circumference in IDF criteria might have contributed to the discrepancy between the studies.

Several definitions for MetS have been introduced over the past decade. NCEP-ATPIII[8] and IDF[9] are two of the most widely used. The non-uniform definitions of MetS have resulted in less comparative data on the prognostic value of different criteria proposed so far. Each definition arbitrarily includes subjects who might be excluded according to another. Consequently, there is a gray zone of subjects who meet one definition but not others. The gray zone (group 2) is at increased risk of developing MetS-related disorders compared to healthy individuals. As observed in our study, these subjects have totally exclusive metabolic characteristics compared to healthy population (group 1). So, evaluation of subjects based on various available criteria might hamper the health care providers from supplying health care services to a substantial number of the people at risk. It is undoubtedly of a great value to follow major cardiovascular outcomes in this borderline group (group 2) to arrive at a uniform definition of MetS or to switch to a risk scoring system rather than categorization of subjects into MetS and non-MetS groups.

In accordance with the previous studies, we observed that the components which constitute MetS vary in the rates in which they occur in different populations. The major abnormality contributing to MetS in Amol was low HDL-C. In contrast, it was the least frequent component of MetS in Zahedan. Surprisingly, there was not even one male in Zahedan to meet the low HDL-C criterion. The diversity in HDL-C level might be related to differences in lifestyle (e.g. smoking[20] and exercise[21]), diet (e.g. alcohol consumption[22]), as well as genetic predisposition and ethnicity of the indigenous people in two geographical regions in Iran. There are some reports in the literature that deal with the impact of ethnicity on HDL-C level. Previous studies showed that Africans have higher rates of HDL-C level compared with Caucasians.[23,24] In a study conducted in Singapore, Indians had a significantly lower level of HDL-C than Chinese subjects.[25] These findings question the generalizability of the currently used HDL-C cut-off values in definitions of MetS and necessitate further studies to decide whether it is essential to consider ethnic diversities for abnormal HDL-C cut-off values.

In line with previous studies in the literature,[10,16,17] females tended to exhibit higher prevalence of MetS than males in both Zahedan and Amol districts. However, the female preponderance faded out to some extent after adjustment for the effect of the other variables while comparing subject who met only one or both of the definitions for MetS compared to healthy individuals. The gender preponderance might be partly explained by females' sedentary life style compared to males, considering the cultural context of the Iranian society, and males' responsibility to maintain family expenses.

A potential limitation of the study was that although the study sample constituted individuals from 2 different districts with respect to ethnicity, life style and climate, it did not represent the whole Iranian population since Iran is home to diverse ethnic populations. The results of the present study should be then interpreted cautiously for other parts of the country.

In conclusion, MetS is increasingly prevalent in Iran and other parts of the world. In addition to the genetic predisposition, different socio-demographic factors influence its emergence. Due to non-uniform definitions of MetS, some of the subjects who meet MetS according to one definition might be considered healthy according to another. This hampers the health care providers from supplying preventive health services to a substantial number of individuals at risk. Consequently, it is essential to conduct further studies in order to unify the definitions of MetS or to switch to a more flexible risk scoring system rather than labeling subjects as MetS or non-Mets. The need to consider ethnic diversity in defining cut-off values of waist circumference in MetS definitions has been already addressed in the literature. Our study proposes that ethnic differences should be also taken into account while defining the abnormal HDL-C cut off values.

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Author Contributions

**MRO and FZ contributed equally to this article. FZ, AAM, HP and RM provided administrative support. MRO, MS and NAK conducted the experiments and analyzed the data. FSS, ZR, NM and MM conducted the measurements. All authors were involved in writing the paper and had final approval of the submitted manuscript.*

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