BMJ Open

Potential of four definitions of metabolic syndrome to discriminate individuals with different 10-year cardiovascular disease risk scores: a cross-sectional analysis of an Iranian cohort

Mohammad Javad Zibaeenezhad,[1] Mehrab Sayadi,[1] Ali Karimi-Akhormeh,[1] Ali Ardekani,[2] Nader Parsa,[1] Iman Razeghian-Jahromi [ID] [1]

¹Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, Iran (the Islamic Republic of)
²Student Research Committee, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran (the Islamic Republic of)

Correspondence to
Dr Iman Razeghian-Jahromi; razejahromi@yahoo.com

ABSTRACT

Objective We aimed to reveal the potential of four different metabolic syndrome (Mets) definitions to differentiate subjects according to 10-year risk of cardiovascular disease.

Design A cross-sectional analysis of a prospective cohort.

Setting This study used baseline data from the Shiraz Heart Study, a prospective cohort study in Shiraz, Iran. Participants were screened against Mets definitions including modified WHO, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), American Heart Association (AHA) and International Diabetes Federation (IDF). Also, Framingham risk score (FRS) and atherosclerotic cardiovascular disease (ASCVD) risk score were determined for each participant.

Participants A total number of 7225 participants of both genders entered the study. They were selected through defined family physician centres in different geographical areas. Urban residents with no migration plan were included. Those who were far from study centres or with disabilities that made them incapable to cooperate were excluded.

Results Participants were 47.68% (N=3445) male with the mean age of 52.13±8.00 years. The number of subjects with Mets identified by WHO was the lowest (N=1676), while the percentage of subjects with high risk score was the highest, 17.1% (N=282) in FRS and 9.8% (N=162) in ASCVD risk score. There were statistically significant differences in the mean risk scores between participants with and without Mets according to AHA, WHO and NCEP ATP III definitions (p<0.001). In IDF definition, the risk scores of subjects with Mets were not statistically different compared with peers without Mets, neither based on FRS (p=0.247) nor ASCVD risk score (p=0.193).

Conclusions IDF was not the appropriate definition for discrimination of subjects with Mets and/or those at high risk of future cardiovascular events. AHA, WHO and NCEP ATP III definitions were effective to discriminate subjects with Mets from peers without Mets.

INTRODUCTION

Worldwide escalation of metabolic syndrome (Mets) makes it a burgeoning health concern, and this rising trend is expected

Strengths and limitations of this study

► This study is extracted from the baseline data of a prospective cohort with a sizeable sample of the general urban population.
► This study possesses added value in terms of demonstration of specific country/regional differences in the field of metabolic syndrome definitions and 10-year cardiovascular risk scores.
► This study suffers from inherent limitations of cross-sectional design.

to continue in the future.[1] Mets has a strong relation to cardiovascular disorders, mainly coronary heart disease.[2] Indeed, Mets could be assigned as a predictor of poor cardiovascular outcomes and all-cause mortality.[3] It is defined as the concomitant occurrence of several cardiovascular risk factors including abdominal obesity, insulin resistance, elevated blood pressure and dyslipidaemia.[4]

Despite considerable efforts to define Mets, there are still disagreements over its definition.[5] There are four main definitions proposed by different expert panels: the WHO in 1998[6] (revised in 1999[7]); the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) in 2001[8 9] (revised in 2004[10]); the NCEP ATP III definition has subsequently been revised by the American Heart Association (AHA)/National Heart, Lung, and Blood Institute[11]; and lastly, the International Diabetes Federation (IDF) consensus group in 2005.[12 13]

Uncertainty about the most appropriate definition among different populations has challenged identification of subjects with Mets. Although main features are identical among these definitions, existence of critical differences in some components as well as

diverse threshold measures result in non-homogeneous identification of subjects with Mets leading to different reports on Mets prevalence.[14] Also, this discrepancy lowers differentiation potential of Mets from subjects without Mets, and consequently, decreases the efficiency of established therapeutic and preventive strategies. In other words, it is of utmost importance to precisely identify subjects who have cardiovascular risk factors, and accordingly, at high risk of cardiovascular events.

Cardiovascular risk prediction models play a crucial role in the prevention and management of cardiovascular disease (CVD), especially in clinical settings. Traditionally, Framingham risk score (FRS) has been widely used to estimate the risk of coronary events in a 10-year interval considering different variables.[15] Another distinct algorithm that has been developed to predict 10-year CVD risk is atherosclerotic cardiovascular disease (ASCVD) risk score that was provided by the AHA/American College of Cardiology.[16] In previous studies, different definitions of Mets have been tested for their potential to predict CVD which showed inconsistent results.[17–21] These inconsistencies include, but are not limited to, determination of the superior or inferior definition with respect to identification of high-risk subjects.[19 21]

In the present study, the potential of four Mets definitions was compared for discrimination of patients with different 10-year cardiovascular risk scores according to Framingham and ASCVD criteria.

METHODS
Study population
This is a cross-sectional analysis that was founded on the baseline data (obtained during 2016–2019) of the Shiraz Heart Study (SHS). SHS is a cardiovascular-oriented prospective cohort that is being conducted to scrutinise cardiovascular risk factors and incidence of cardiovascular events, mainly coronary heart disease, for 10 years in a middle-aged urban population in Shiraz, Iran. SHS protocol including the method of participants' selection as well as inclusion and exclusion criteria have been published previously.[22]

Definitions of Mets, FRS and ASCVD risk score
Four definitions of Mets with their components are provided in table 1. It should be noted that modified WHO criteria were used in the present study due to the lack of data about microalbuminuria in our dataset. FRS has traditionally been used to evaluate the risk of cardiac events in a 10-year interval by the aid of incorporating certain data including gender, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, diabetes and smoking status.[15] Scores were classified into low (<10%), intermediate (10%–20%) and high risk (>20%).[23–25] An ASCVD risk score calculator is another valuable tool to predict the risk of cardiovascular events in the upcoming 10 years. Practically, it is used clinically to identify high-risk patients to implement preventive strategies.[16] Age, gender, systolic blood pressure, total and HDL cholesterol, smoking status and treatment for hypertension (HTN) were considered in risk score calculation. All ASCVD calculators provide the risk score in numerical values. Risk scores were then categorised into low-risk (<5%), borderline-risk (5%–7.4%), intermediate-risk (7.5%–19.9%) and high-risk (≥20%) groups.[26] In this way, association of each risk level with subjects with and without Mets could be assessed in different definitions. Furthermore, based on the NCEP ATP III definition, different clusters of Mets components were defined, and occurrence of the clusters was sought in each gender. Expected prevalence of each cluster was calculated based on independent occurrence of five alterations.[27]

Table 1	Four definitions of metabolic syndrome			
	AHA	**WHO**	**NCEP ATP III**	**IDF**
Criteria	**At least any three of the five criteria below**	**Number 2*+at least any two of the criteria below**	**At least any three of the five criteria below**	**Number 1*+at least any two of the criteria below**
1	Waist circumference: ≥102 cm (M), ≥89 cm (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m²	Waist circumference: >102 cm (M), >88 cm (F)	Central obesity (waist circumference): ≥94 cm (M), ≥80 cm (F)
2	Fasting glucose ≥100 mg/dL or Rx	Glucose intolerance, IGT, diabetes, and/or other evidence of IR	Fasting glucose ≥110 mg/dL or Rx	Fasting glucose ≥100 mg/dL or Rx
3	TG ≥150 mg/dL or Rx	TG ≥150 mg/dL or HDL-C: <35 mg/dL (M), <39 mg/dL (F)	TG ≥150 mg/dL or Rx	TG ≥150 mg/dL or Rx
4	HDL-C: <40 mg/dL (M), <50 mg/dL (F) or Rx	–	HDL-C: <40 mg/dL (M), <50 mg/dL (F) or Rx	HDL-C: <40 mg/dL (M), <50 mg/dL (F) or Rx
5	≥130 mm Hg systolic or ≥85 mm Hg diastolic or Rx	≥140/90 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or Rx	≥130 mm Hg systolic or ≥85 mm Hg diastolic or Rx

WHO[6 7]; National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[8 51]; American Heart Association (AHA)[52] and International Diabetes Federation (IDF).[12 13]
*Obligatory criterion.
BMI, body mass index; F, female; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; IR, insulin resistance; M, male; Rx, on treatment; TG, triglycerides.

Table 2 The prevalence of Mets according to four definitions stratified by gender

Gender	N	AHA (N, %)	WHO (N, %)	NCEP ATP III (N, %)	IDF (N, %)
Total	7225	3582 (49.6)	1676 (23.2)	3294 (45.5)	4940 (68.4)
Female	3780	2120 (56.1)	876 (23.2)	2010 (53.2)	3091 (81.8)
Male	3445	1462 (42.4)	800 (23.2)	1284 (37.3)	1849 (53.7)
P value		**<0.001**	0.962	**<0.001**	**<0.001**

Bold values imply statistical significance.
AHA, American Heart Association; IDF, International Diabetes Federation; Mets, metabolic syndrome; N, number; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Statistical analysis

Continuous and categorical variables are presented as mean±SD and number (%), respectively. X^2 test was used for comparison of categorical variables. Independent sample t-test as well as analysis of variance were used for comparison of continuous variables. Presence of within-groups association in each Mets age-stratified definition was evaluated by trend test. Q kappa agreement coefficient was carried out to assess concordance between Mets definitions. P value of less than 0.05 was considered statistically significant.

Patient and public involvement

The present study was conducted on previously collected data. In the original study, participants were not involved in the development of research questions, nor the outcome measures/the design of the study. Also, they were not involved in the recruitment to or conduct of the study. In the original cohort, the participants are informed about their blood parameters, and the results of other examinations are gradually shared with them. The overall findings and benefits of the study will be disseminated through public media.

RESULTS

This study included 7225 participants with 3445 men (47.68%) and a mean age of 52.13±8.00 years. Table 2 demonstrates the prevalence of Mets in both genders.

The prevalence rates of Mets were 49.6%, 23.2%, 45.5% and 68.4% according to the AHA, WHO, NCEP ATP III and IDF, respectively. Unlike in WHO, the prevalence of Mets was significantly different between genders in favour of female dominance.

Mets prevalence was significantly different among age groups in all four definitions (X^2 test) (table 3). In fact, the prevalence of Mets and age are in a positive association in a way that the elderly participants were more likely to have Mets (trend test). Increasing trend of Mets prevalence with age is substantiated from 36.4% to 61.6% for AHA, 12.2% to 38.6% for WHO, 32.3% to 58.1% for NCEP ATP III, and 63.8% to 71.4% for IDF in those younger than 45 years to peers older than 65 years.

In order to measure the extent of agreement between definitions, kappa agreement coefficient was used. Levels of agreement could be grouped into six categories according to kappa coefficient: none (0–0.20), minimal (0.21–0.39), weak (0.40–0.59), moderate (0.60–0.79), strong (0.80–0.90) and perfect (above 0.90).[28] As demonstrated in table 4, AHA and NCEP ATP III are in perfect agreement (0.909), while WHO and IDF are in non-agreement situation (0.147). Other definitions are in weak or minimal agreements with each other.

Table 5 demonstrates the prevalence of Mets components in each definition. High HDL was the prevalent disorder according to the AHA and NCEP ATP III definitions. The most prevalent feature in the WHO and IDF

Table 3 The prevalence of Mets according to the four definitions stratified by age groups

Age group	N	AHA (N, %)	WHO (N, %)	NCEP ATP III (N, %)	IDF (N, %)
40–45	1840	669 (36.4)	224 (12.2)	595 (32.3)	1174 (63.8)
45–50	1513	683 (45.1)	277 (18.3)	628 (41.5)	998 (66.0)
50–55	1356	758 (55.9)	359 (26.5)	698 (51.5)	971 (71.6)
55–60	1213	673 (55.5)	345 (28.4)	619 (51.0)	856 (70.6)
60–65	845	517 (61.2)	294 (34.8)	488 (57.8)	614 (72.7)
65–70	458	282 (61.6)	177 (38.6)	266 (58.1)	327 (71.4)
P value	X^2 test	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Trend test	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Bold values imply statistical significance.
AHA, American Heart Association; IDF, International Diabetes Federation; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Table 4 Kappa agreement coefficient between four definitions of Mets

Definition	AHA	WHO	NCEP ATP III
IDF	0.424	**0.147**	0.402
NCEP ATP III	**0.909**	0.401	
WHO	0.347		

Bold values imply highest and lowest agreements.
AHA, American Heart Association; IDF, International Diabetes Federation; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

definitions was high waist circumference (WC). Diabetes is the least prevalent component among all definitions.

FRS and ASCVD risk score in relation to Mets

FRS and ASCVD risk score were 10.81±8.72 and 5.54±6.16 for all the participants, respectively. Correlation between these two scores was 0.834 (figure 1). Tables 6 and 7 depict the mean of FRS and ASCVD risk score for subjects with and without Mets for all definitions. There are statistically significant differences in the risk scores between the two groups according to AHA, WHO and NCEP ATP III definitions (p<000.1). In contrast, the IDF definition considered no significant difference in the risk score between subjects with Mets and without Mets (p=0.247 for FRS, and p=0.193 for ASCVD risk score).

In tables 8 and 9, FRS and ASCVD risk score were classified into different categories, and each category was compared between subjects with Mets and without Mets for each definition. The only definition in which subjects with Mets and without Mets were not differentially grouped with respect to the categorised risk score was that of the IDF (p=0.845 for FRS and p=0.853 for ASCVD risk score). However, there are significant differences in all the categories, either FRS or ASCVD risk score, between subjects with Mets and without Mets in three other definitions (AHA, WHO and NCEP ATP III) (p<0.001).

Table 5 The prevalence of Mets components in each definition

Feature	AHA (N, %)	WHO (N, %)	NCEP ATP III (N, %)	IDF (N, %)
WC	3955 (54.7)	**5886 (81.5)**	4039 (55.9)	**5592 (77.4)**
TG	3826 (53.0)	3826 (53.0)	3826 (53.0)	3826 (53.0)
HDL	**4308 (59.6)**	2696 (37.3)	**4308 (59.6)**	4308 (59.6)
HTN	3129 (43.3)	2299 (31.8)	3129 (43.3)	3129 (43.3)
DM	2853 (39.5)	1724 (23.9)	1724 (23.9)	2853 (39.5)

Bold values imply the component with the highest prevalence in each definition.
AHA, American Heart Association; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; IDF, International Diabetes Federation; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; TG, triglycerides; WC, waist circumference.
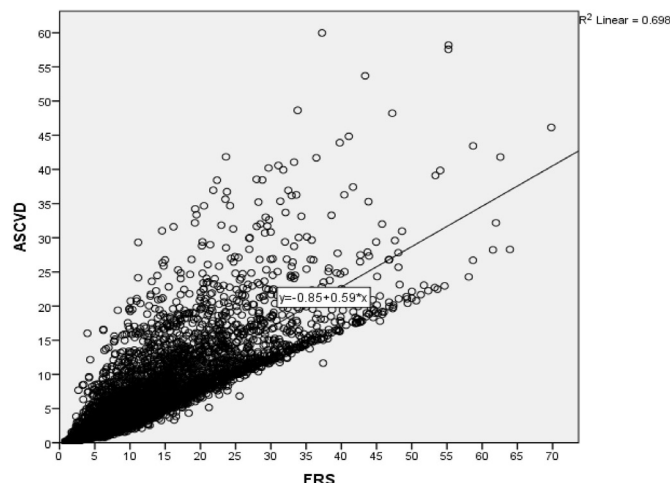
Figure 1 Correlation between Framingham risk score (FRS) and atherosclerotic cardiovascular disease (ASCVD) risk score (correlation coefficient=0.834).

Furthermore, comparison of FRS and ASCVD risk score showed that the former identified a greater proportion of subjects as high-risk patients in all definitions (15.3% vs 5.6% in AHA, 17.1% vs 9.8% in WHO, 15.2% vs 6.0% in NCEP ATP III, and 12.1% vs 3.5% in IDF) (figures 2 and 3).

Table 10 shows that the most prevalent cluster in men was triglycerides (TG)+HDL+HTN, while the cluster WC+TG+HDL was the prevalent one in women (NCEP ATP III). Other than dyslipidaemia, it seems that HTN and high WC were the major culprits in the prevalent clusters in men and women, respectively. As it was shown, observed and expected prevalence of cluster components were significantly different in both genders. In spite of clear association between high blood pressure and early arterial ageing, the extent to which HTN contributes to the elevated risk of cardiovascular events should be further investigated.[29]

DISCUSSION
Metabolic syndrome
This study was a cross-sectional analysis of a prospective cohort which has been detailed elsewhere.[30 31] In the current study, 7225 participants were screened against four different Mets definitions. The prevalence of Mets

Table 6 Framingham risk score in subjects with and without Mets in the four definitions

	Mets (mean±SD)		
Definition	No	Yes	P value
AHA	9.90±8.31	11.71±9.01	**<0.001**
WHO	10.34±8.62	12.37±8.84	**<0.001**
NCEP ATP III	10.09±8.43	11.66±8.97	**<0.001**
IDF	10.74±9.35	10.48±8.39	0.247

Bold values imply significant differences.
AHA, American Heart Association; IDF, International Diabetes Federation; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Table 7 ASCVD risk score in subjects with and without Mets in the four definitions

Definition	Mets (mean±SD)		P value
	No	**Yes**	
AHA	4.23±4.73	6.85±7.08	**<0.001**
WHO	4.54±4.85	8.84±8.44	**<0.001**
NCEP ATP III	4.32±4.79	6.97±7.19	**<0.001**
IDF	5.40±6.18	5.61±6.15	0.193

Bold values imply significant differences.
AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; IDF, International Diabetes Federation; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

was found to be close for the AHA (49.6%) and NCEP ATP III (45.5%), while the highest (68.4%) and the lowest (23.2%) subjects with Mets were identified by the IDF and WHO definitions, respectively. It is not, however, a concluding remark to classify the latter definitions into the strongest or the weakest ones for Mets diagnosis as they use different criteria, and reasonably, differences in the prevalence of Mets are not an unexpected phenomenon. The prevalence of Mets is widely varied between different populations. Studies reported Mets prevalence of 21.5% in France,[32] 33.5% in Turkey,[33] 34.1% among American adults[34] and 54.8% in Mexico.[35] The prevalence of Mets (NCEP ATP III) among 8698 US adults was reported to be 34.3%±0.8%, which remained unchanged during 2007–2014. Regarding trend of Mets components, there was a significant increase in abdominal obesity, especially in women, while the prevalence of raised triglyceridaemia and fasting hyperglycaemia

decreased.[36] During 2011–2016, Mets prevalence was estimated to be 34.7% among 17 048 US adults, which shows a remarkable increase in young adults and high prevalence in those older than 60 years.[37] In a pooled analysis on 26 609 participants from 34 studies, the most prevalent Mets (NCEP ATP III) component was low HDL, which was followed by HTN, abdominal obesity, raised TG and elevated fasting glucose.[38] According to the NCEP ATP III definition, low HDL was the most prevalent component in our population as well. It is closely followed by elevated WC and hypertriglyceridaemia. Also, the cluster of low HDL and hypertriglyceridaemia, either combined with HTN in male or with raised WC in female, was the prevalent one in the present study.

A systematic review reported the pooled estimate of 25% for Mets prevalence in Middle East countries.[39] Mets is considered as a frequent disorder in Iranian population as well,[40] and people living in urban areas were recognised as more risky ones in comparison with rural residents.[41 42] In Iran, multiple studies reported the prevalence of Mets differently; 34.7% by NCEP ATP III and 37.4% by IDF,[43] 37% by IDF and 33.8% by NCEP ATP III,[44] 42.87% by IDF and 40.68% by NCEP ATP III.[45] According to the Isfahan Healthy Heart Program, the age-adjusted prevalence of Mets was reported to be 23.3% according to the NCEP ATP III definition in urban and rural populations of three cities of Iran.[41] In all definitions, except WHO, the prevalence of Mets was higher in women.

In one large European multicentre study, arterial stiffness was compared between four different age groups and in individuals with or without Mets as well (according to the revised version of NCEP ATP III). They concluded that arterial stiffness was correlated with age, and patients with Mets had higher arterial stiffness in all age groups.

Table 8 Comparison of categorised Framingham risk score between subjects with Mets and without Mets in the four definitions

Definition	Risk score	Mets		P value
		No (n, %)	**Yes (n, %)**	
AHA	Low	2245 (64.1)	1991 (56.2)	
	Intermediate	847 (24.2)	1007 (28.4)	**<0.001**
	High	408 (11.7)	542 (15.3)	
WHO	Low	3392 (62.9)	844 (51.2)	
	Intermediate	1332 (24.7)	522 (31.7)	**<0.001**
	High	668 (12.4)	282 (17.1)	
NCEP ATP III	Low	2396 (63.3)	1840 (56.5)	
	Intermediate	934 (24.7)	920 (28.3)	**<0.001**
	High	456 (12.0)	494 (15.2)	
IDF	Low	1348 (62.3)	3054 (62.6)	
	Intermediate	541 (25.0)	1231 (25.2)	0.845
	High	275 (12.7)	591 (12.1)	

Bold values imply significant differences. Low (<10%), intermediate (10%–20%) and high risk (>20%). Some data may contain missing values.
AHA, American Heart Association; IDF, International Diabetes Federation; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Table 9 Comparison of categorised ASCVD risk score between subjects with Mets and without Mets in the four definitions

| Definition | Risk score | Mets | | P value |
		No (n, %)	Yes (n, %)	
AHA	Low	2463 (70.3)	1942 (54.8)	
	Borderline	373 (10.7)	469 (13.2)	**<0.001**
	Intermediate	623 (17.8)	931 (26.3)	
	High	41 (1.2)	199 (5.6)	
WHO	Low	3697 (68.5)	708 (42.9)	
	Borderline	603 (11.2)	242 (14.7)	**<0.001**
	Intermediate	1017 (18.9)	537 (32.6)	
	High	78 (1.4)	162 (9.8)	
NCEP ATP III	Low	2641 (69.7)	1764 (54.2)	
	Borderline	415 (11.0)	430 (13.2)	**<0.001**
	Intermediate	687 (18.1)	867 (26.6)	
	High	46 (1.2)	194 (6.0)	
IDF	Low	1350 (62.3)	3055 (62.6)	
	Borderline	267 (12.3)	578 (11.9)	0.853
	Intermediate	481 (22.2)	1073 (22.0)	
	High	69 (3.2)	171 (3.5)	

Bold values imply significant differences. Low (<5%), borderline (5%–7.5%), intermediate (7.5%–20%) and high (≥20). Some data may contain missing values.
AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; IDF, International Diabetes Federation; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Interestingly, among Mets components, only hyperglycaemia and HTN were in a positive association with arterial stiffness, and dyslipidaemia (low HDL and high TG components) was not associated with arterial stiffness. More unexpectedly, there was an association between high WC and lower arterial stiffness.[46]
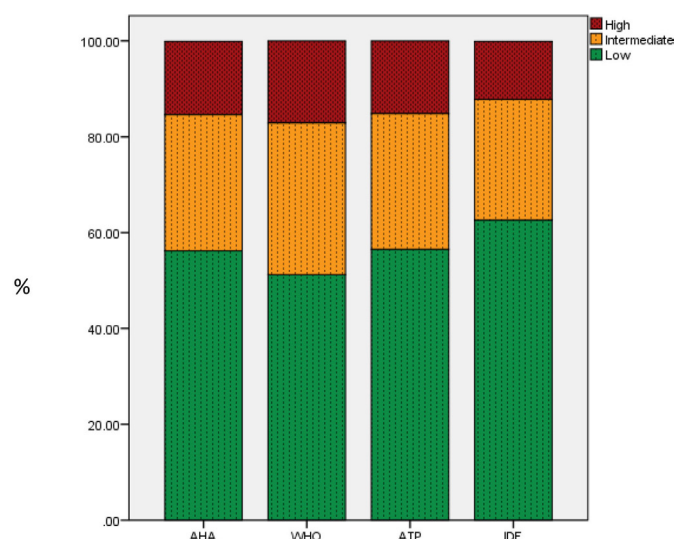
Following or in conjunction with coronary artery disease and other cardiovascular complications, components of Mets like central obesity, hyperlipidaemia and insulin resistance are all risk factors of endothelial function[47]
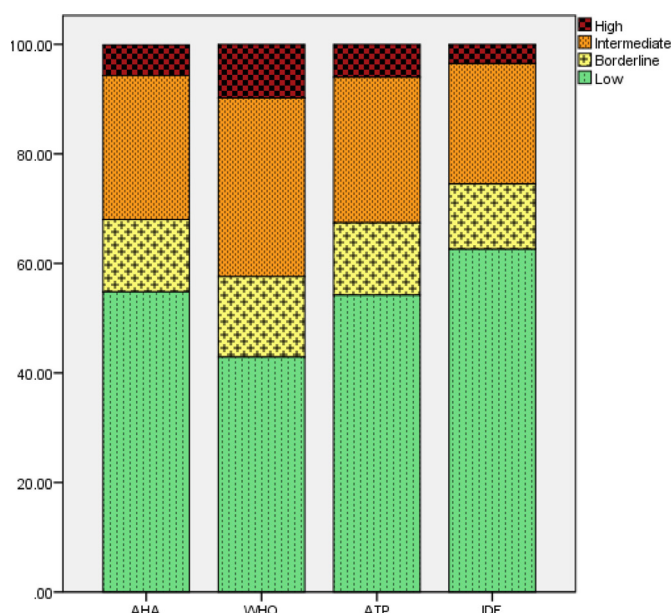

Figure 2 Comparison of different categorisations of Framingham risk score for each definition. AHA, American Heart Association; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Figure 3 Comparison of different categorisations of atherosclerotic cardiovascular disease risk score for each definition. AHA, American Heart Association; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Table 10 Observed and expected prevalence of specific clustering of Mets components in both genders according to NCEP ATP III definition

Components	Male		Female	
	Observed	Expected	Observed	Expected
WC+TG+HDL	8.4	9.6	24.5	22.9
WC+TG+HTN	5.7	7.7	3.6	7.7
WC+TG+DM	1.2	2.6	1.0	3.7
WC+HDL+HTN	4.1	7.2	9.1	14.1
WC+HDL+DM	0.9	2.6	2.9	6.7
WC+HTN+DM	2.4	2.1	2.3	2.2
TG+HDL+HTN	21.8	21.7	2.1	3.3
TG+HDL+DM	9.5	7.9	1.2	1.5
TG+HTN+DM	3.3	6.3	0.2	0.5
HDL+HTN+DM	2.6	5.9	0.2	0.9
WC+TG+HDL+HTN	10.4	8.4	21.3	15.4
WC+TG+HDL+DM	3.6	3.0	9.3	7.3
WC+TG+HTN+DM	1.2	2.4	1.0	2.5
WC+HDL+HTN+DM	2.1	2.3	2.4	4.5
TG+HDL+HTN+DM	12.3	6.9	1.6	1.0
WC+TG+HDL+HTN+DM	11.6	2.7	18.4	4.9
X^2	42.28		50.90	
P value	**<0.001**		**<0.001**	

Bold values imply statistical significance.

DM, diabetes mellitus; HDL, high density lipoprotein; HTN, hypertension; Mets, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; TG, triglycerides; WC, waist circumference.

that possibly lead to kidney impairments.[48] Studies revealed that subjects with four or more Mets components had significantly decreased glomerular filtration rate compared with those with one or no components at all.[49] To substantiate, obesity increases the risk of diabetic nephropathy, hypertensive nephrosclerosis, and focal and segmental glomerular sclerosis. Furthermore, obesity accelerates development and progression of chronic kidney disease. Early manifestation of Mets-associated kidney injury is microalbuminuria. In fact, Mets deteriorates renal physiology and metabolism through certain mechanisms including change in adipokine levels, oxidative stress and inflammation.[48]

FRS and ASCVD risk score

The correlation between FRS and ASCVD risk score is high, which is also evident in the next analyses. However, the numerical value of FRS mean is nearly double that of ASCVD risk score for all the participants. Having calculated FRS and ASCVD risk score, subjects with Mets in AHA, WHO and NCEP ATP III definitions showed significantly higher scores compared with subjects without Mets. This finding revealed that, unlike IDF, the criteria of the other three definitions are efficient enough to differentiate subjects with Mets from their counterparts without Mets. Lack of potential to make differentiation between subjects with Mets and without Mets could be assumed

as a negative point for IDF definition since subjects with Mets are logically at greater risk of experiencing cardiovascular events.

Mets association with FRS and ASCVD risk score

It can be concluded that IDF definition is not only unsuitable for our population for identification of subjects with Mets, but also, it did not reveal any significant difference between subjects with Mets and without Mets in categorised risk score groups. Percentage of high-risk subjects was higher in WHO definition, which can be attributed to the lower number of subjects with Mets in this group. This case is completely opposite of IDF definition. The discrepancies in detecting subjects with Mets or high risk score may be originated from dissimilar threshold values of different components which are determinant factors for defining Mets and calculation of risk scores. For instance, an absolutely required component in WHO definition is insulin resistance while significance of WC is emphasised as a key feature in IDF definition. Accordingly, the best definition for detecting high-risk individuals still remains elusive.

The lower predictive value of IDF definition for CVD has been mentioned in previous studies.[18 50] On the other hand, NCEP ATP III criterion has been identified as a useful tool to predict CVD in several studies.[18 20] In a population sample from Germany,[50] the IDF definition is

recognised to have lower predictive ability for CVD than the NCEP ATP III, despite the fact that the prevalence of Mets was higher according to IDF definition. In the meanwhile, some other studies reported no superiority for any of the definitions over the others, and suggested further longitudinal investigations should be implemented to obtain a clearer picture.[17 21] The present study showed that there may be differences in the 10-year estimated risk of developing CVD among identified subjects with Mets depending on the type of Mets definition. The complex multistage probability sample design of our original study, besides a good sample size, provides a suitable representation of the urban population in the country.

The study suffers from inherent limitations subjected to its cross-sectional design such as inability to assess incidence and to make causal inference. Longitudinal prospective assessments are more useful to clearly measure the incidence of cardiovascular events and their degree of association with Mets definitions as well as with every component of each definition. Thereafter, selection of the most precise definition is feasible for detection of subjects with Mets and those with high risk of life-threatening incidents. As we did not examine the participants for microalbuminuria at the baseline survey of the original cohort, modified WHO definition was used that may have imposed some deviations from the real values.

Conclusion

Mets is an outstanding feature to identify high-risk individuals, particularly in the general population. Our findings revealed that the IDF definition was not the appropriate one to identify subjects with Mets and subjects with high risk of cardiovascular events. However, AHA, WHO and NCEP ATP III were able to discriminate between subjects with Mets and without Mets according to FRS and ASCVD risk score. To assess the validity of this classification, further longitudinal studies are required to determine which Mets definition is effective for prognostication of future cardiovascular events.

REFERENCES

1 GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;377:13–27.
2 Zhou J, Gao Q, Wang J, et al. Comparison of coronary heart disease risk assessments among individuals with metabolic syndrome using three diagnostic definitions: a cross-sectional study from China. *BMJ Open* 2018;8:e022974.
3 Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;56:1113–32.
4 Cornier M-A, Dabelea D, Hernandez TL, et al. The metabolic syndrome. *Endocr Rev* 2008;29:777–822.
5 Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech* 2009;2:231–7.
6 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a who consultation. *Diabet Med* 1998;15:539–53.
7 World Health Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a who consultation. Part 1, diagnosis and classification of diabetes mellitus*. Geneva: World Health Organization, 1999.
8 Detection NCEPEPo, Adults ToHBCi. Third report of the National cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III): national cholesterol education program, National heart, lung and blood 2002.
9 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486.
10 Grundy SM, Brewer Jr HB, Cleeman JI. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433–8.
11 Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005;112:2735–52.
12 Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *The Lancet* 2005;366:1059–62.
13 Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. *Diabet Med* 2006;23:469–80.
14 Delavari A, Forouzanfar MH, Alikhani S, et al. First nationwide study of the prevalence of the metabolic syndrome and optimal cutoff points of waist circumference in the middle East: the National survey of risk factors for noncommunicable diseases of Iran. *Diabetes Care* 2009;32:1092–7.
15 Santos ASAC, Rodrigues APS, Rosa LPS, et al. Cardiometabolic risk factors and Framingham risk score in severely obese patients: baseline data from DieTBra trial. *Nutrit Metabol Cardiovas Dis* 2020;30:474–82.
16 Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:S1–45.
17 Hosseinpanah F, Asghari G, Barzin M, et al. Prognostic impact of different definitions of metabolic syndrome in predicting cardiovascular events in a cohort of non-diabetic Tehranian adults. *Int J Cardiol* 2013;168:369–74.

18 Kastorini C-M, Panagiotakos DB, Georgousopoulou EN, *et al*. Metabolic syndrome and 10-year cardiovascular disease incidence: the ATTICA study. *Nutr Metab Cardiovasc Dis* 2016;26:223–31.

19 Qiao Q, Group DS, DECODE Study Group. Comparison of different definitions of the metabolic syndrome in relation to cardiovascular mortality in European men and women. *Diabetologia* 2006;49:2837–46.

20 Zhou H, Guo Z-rong, Yu L-gang, *et al*. Evidence on the applicability of the ATPIII, IDF and CDS metabolic syndrome diagnostic criteria to identify CVD and T2DM in the Chinese population from a 6.3-year cohort study in mid-eastern China. *Diabetes Res Clin Pract* 2010;90:319–25.

21 Suzuki T, Zeng Z, Zhao B, *et al*. Comparison of coronary heart disease risk among four diagnostic definitions of metabolic syndrome. *J Endocrinol Invest* 2016;39:1337–46.

22 Zibaeenezhad MJ, Ghaem H, Parsa N, *et al*. Analysing cardiovascular risk factors and related outcomes in a middle-aged to older adults population in Iran: a cohort protocol of the Shiraz heart study (SHS). *BMJ Open* 2019;9:e026317.

23 Wilson PWF, D'Agostino RB, Levy D, *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–47.

24 D'Agostino Sr RB, Vasan RS, Pencina MJ. General cardiovascular risk profile for use in primary care: the Framingham heart study 2008;117:743–53.

25 Jellinger PS, Handelsman Y, Rosenblit PD. American association of clinical endocrinologists and American College of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease 2017;23:1–87.

26 Arnett DK, Blumenthal RS, Albert MA, *et al*. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;74:e177–232.

27 Scuteri A, Najjar SS, Orru' M, *et al*. The central arterial burden of the metabolic syndrome is similar in men and women: the Sardinia study. *Eur Heart J* 2010;31:602–13.

28 McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med* 2012;22:276–82.

29 Scuteri A, Morrell CH, Orru' M, *et al*. Gender specific profiles of white coat and masked hypertension impacts on arterial structure and function in the Sardinia study. *Int J Cardiol* 2016;217:92–8.

30 Zibaeenezhad MJ, Ghaem H, Parsa N, *et al*. Analysing cardiovascular risk factors and related outcomes in a middle-aged to older adults population in Iran: a cohort protocol of the Shiraz Heart Study (SHS). *BMJ Open* 2019;9:e026317.

31 Parsa N, Zibaeenezhad MJ, Trevisan M, *et al*. Magnitude of the quality assurance, quality control, and testing in the Shiraz cohort heart study. *Biomed Res Int* 2020;2020:8179795.

32 Vernay M, Salanave B, de Peretti C, *et al*. Metabolic syndrome and socioeconomic status in France: the French nutrition and health survey (ENNS, 2006-2007). *Int J Public Health* 2013;58:855–64.

33 Gündogan K, Bayram F, Capak M, *et al*. Prevalence of metabolic syndrome in the Mediterranean region of Turkey: evaluation of hypertension, diabetes mellitus, obesity, and dyslipidemia. *Metab Syndr Relat Disord* 2009;7:427–34.

34 Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. *Diabetes Care* 2011;34:216–9.

35 Salas R, Bibiloni MdelM, Ramos E, *et al*. Metabolic syndrome prevalence among Northern Mexican adult population. *PLoS One* 2014;9:e105581.

36 Shin D, Kongpakpaisarn K, CJljoc B. Trends in the prevalence of metabolic syndrome and its components in the United States 2007–2014 2018;259:216–9.

37 Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011-2016. *JAMA* 2020;323:2526–8.

38 Nolan PB, Carrick-Ranson G, Stinear JW, *et al*. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: a pooled analysis. *Preventive Medicine Reports* 2017;7:211–5.

39 Ansarimoghaddam A, Adineh HA, Zareban I, *et al*. Prevalence of metabolic syndrome in Middle-East countries: meta-analysis of cross-sectional studies. *Diabetes Metab Syndr* 2018;12:195–201.

40 Jahangiry L, Farhangi MA, Rezaei F. Framingham risk score for estimation of 10-years of cardiovascular diseases risk in patients with metabolic syndrome. *J Health Popul Nutr* 2017;36:36.

41 Sarrafzadegan N, Kelishadi R, Baghaei A, *et al*. Metabolic syndrome: an emerging public health problem in Iranian women: Isfahan healthy heart program. *Int J Cardiol* 2008;131:90–6.

42 Eftekhari MH, Sohrabi Z, Parsa N, *et al*. Role of gender in the prevalence of metabolic syndrome and its related risk factors in Shiraz healthy heart center population. *Int Cardiovasc Res J* 2015;9:231–7.

43 Delavari A, Forouzanfar MH, Alikhani S, *et al*. First nationwide study of the prevalence of the metabolic syndrome and optimal cutoff points of waist circumference in the Middle East: the national survey of risk factors for noncommunicable diseases of Iran. *Diabetes Care* 2009;32:1092–7.

44 Nikbakht H-A, Rezaianzadeh A, Seif M, *et al*. Prevalence of metabolic syndrome and its components among a population-based study in South of Iran, Persian Kharameh cohort study. *Clin Epidemiol Glob Health* 2020;8:678–83.

45 Naghipour M, Joukar F, Nikbakht H-A, *et al*. High prevalence of metabolic syndrome and its related demographic factors in North of Iran: results from the Persian Guilan cohort study. *Int J Endocrinol* 2021;2021:8862456.

46 Topouchian J, Labat C, Gautier S, *et al*. Effects of metabolic syndrome on arterial function in different age groups. *J Hypertens* 2018;36:824–33.

47 Avogaro A, de Kreutzenberg SV. Mechanisms of endothelial dysfunction in obesity. *Clinica Chimica Acta* 2005;360:9–26.

48 Tesauro M, Canale MP, Rodia G, *et al*. Metabolic syndrome, chronic kidney, and cardiovascular diseases: role of adipokines. *Cardiol Res Pract* 2011;2011:653182

49 Ninomiya T, Kiyohara Y, Kubo M, *et al*. Metabolic syndrome and CKD in a general Japanese population: the Hisayama study. *Am J Kidney Dis* 2006;48:383–91.

50 Assmann G, Guerra R, Fox G, *et al*. Harmonizing the definition of the metabolic syndrome: comparison of the criteria of the adult treatment panel III and the International diabetes Federation in United States American and European populations. *Am J Cardiol* 2007;99:541–8.

51 Expert Panel on Detection EJJ. Executive summary of the third report of the National cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) 2001;285:2486–97.

52 Grundy SM, Brewer HB, Cleeman JI, *et al*. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433–8.