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Association between Metabolic Syndrome and Its Components with Cardiovascular Disease Risk in the MASHAD Cohort Study Population

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ABSTRACT

Introduction: The primary aim of this study was to evaluate the association of metabolic syndrome (MetS), based on different definitions, with the risk of total cardiovascular disease (CVD), unstable angina (UA), stable angina (SA), and myocardial infarction (MI). Additionally, we aimed to investigate which definition of MetS is a better predictor of CVD events in a large sample of Iranian adults.

Methods: The analysis was conducted among 7,910 adults from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) cohort study. The presence of MetS at baseline was defined using the following criteria: International Diabetes Federation (IDF 2005), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and World Health Organization (WHO). Hazard ratios (HR) and 95% confidence intervals (CI) were used to estimate the association of MetS and its components with CVD events.

Results: The prevalence of MetS among CVD patients was 56.40%, 52.30%, and 23.90% based on the IDF, NCEP ATP III, and WHO criteria, respectively. The highest HR for total CVD (HR: 2.29; 95% CI: 1.54–3.40; P<0.001), UA (HR: 2.13; 95% CI: 1.22 – 3.72; P<0.01), and MI (HR: 3.11; 95% CI: 1.33–7.26; P<0.01) was found when using the WHO definition. The highest HR for SA (HR: 2.56; 95% CI: 1.37 – 4.81; P<0.001) was found when using the NCEP ATP III definition.

Conclusion: Having MetS based on the WHO definition was a significant predictor for the incidence of total CVD, MI, and UA, while having MetS based on the ATP III criteria was associated with a higher risk of SA in the MASHAD study population.

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Introduction

Metabolic Syndrome (MetS) is a common clustering of metabolic and anthropometric risk factors for cardiovascular disease (CVD) events (1). Various professional groups have proposed several criteria for MetS, including the International Diabetes Federation (IDF, 2005) (2), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III, 2001) (3), and World Health Organization (WHO,1998) (4). Despite variations in the threshold parameters for each definition, there is a general agreement between different groups on the main components of MetS, which include obesity, impaired glucose tolerance, dyslipidemia, and hypertension (5, 6). In a sample of 3,024 Iranian adults, the prevalence of MetS was reported at 37.4% according to the IDF and 34.7% based on the NCEP ATP III in a national survey (7). A high degree of concordance in the prevalence of MetS was reported using the NCEP ATP III and IDF in an Iranian population (8). However, even based on the lowest prevalence of 34.6%, the prevalence of MetS in Iran is interestingly higher than the estimated worldwide prevalence (20 - 25%) (9). The prevalence of MetS based on the ATP III definition in the Tehran Lipid and Glucose Study (TLGS) was reported to be 33.7% which was higher in women than men (10). Among 6,578 participants of the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study, the prevalence of MetS based on the IDF definition was reported at 37% and 58% in the age range of < 46 and ≥ 46 years old, respectively (11). An increasing rate of CVD events in Iran has been reported in recent studies (12) and is now the leading cause of mortality in Iran and responsible for 50% of all deaths annually (12, 13). Individuals with MetS have twice the risk of death and are three times more likely to have a heart attack or stroke compared to healthy individuals (14). In a population study among elderly Iranians, the prevalence of MetS according to three definitions (IDF, ATP III, and WHO) was high and associated with an increased risk of coronary heart disease (8). The association of MetS with a high risk of CVD has been documented worldwide (15). However, this relationship varies in different populations according to age, sex, and ethnicity (16). The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) with corroboration from the British Regional Heart Study (BRHS) explored the association of MetS (based on the NCEP ATP III definition) with CVD risk in non-diabetic individuals over three years of follow-up. In the BRHS, MetS was moderately correlated with increased CVD, while no association with CVD was detected in PROSPER (17, 18). Several cohort studies have evaluated the association of MetS with CVD events in an Iranian population, most of which used a single definition of MetS (19-21). We aimed to compare the prevalence of MetS using three different definitions and also to investigate the association of MetS by each definition and its constituent components with CVD risk in a representative population sample from Mashhad, in Northeastern Iran.

Materials and Methods

Study population

The MASHAD study is a prospective cohort study involving 9,704 men and women aged 35–65 years, all of whom were free from chronic diseases (e.g., CVD, cancer, and chronic kidney disease) at baseline. This cohort study was designed to investigate the association between various CVD risk factors (including nutritional, environmental, and genetic factors) and the incidence of CVD. Participants were recruited into the study using a stratified cluster random sampling method from three locations in Mashhad, northeastern Iran. Each location was divided into nine regions, organized around the divisions of Mashhad Healthcare Centers. At baseline, all information, including demographic data, anthropometric measurements, and biochemical factors (blood pressure, fasting blood glucose, and lipid profile), was collected and used in the present study to identify MetS among the study population (22). All participants were recruited in 2010 and subsequently followed up over the next 5–6 years. After six years of follow-up, CVD events in participants were confirmed by a cardiologist, which took place from April 2015 to May 2016 (23). Participants who did not complete the follow-up stages or had incomplete data on MetS

components were excluded from the analysis. Consequently, 7,910 participants were included in the study (Figure 1). The study protocol, written consent form, and other documents related to the study were reviewed and approved by the Human Research Ethics Committee of Mashhad University of Medical Sciences (MUMS). All participants were able to provide written informed consent.

Metabolic syndrome diagnosis

The baseline characteristics were compared among participants who did or did not experience a CVD event during the follow-up period. Three different definitions of MetS were used in this study: (1) IDF (2005): central obesity [waist circumference (WC) ≥ 80 cm for women or ≥ 94 cm for men] and two more components including fasting blood glucose (FBG) ≥ 100 mg/dl, blood pressure (BP) 130/85 mmHg or higher, serum high-density lipoprotein cholesterol (HDL-C) < 50mg/dl for women or < 40mg/dl for men, and serum triglyceride (TG) ≥ 150 mg/dl. (2) NCEP ATP III (2001): three or more components including FBG ≥ 110 mg/dl, BP 130/85 mmHg or higher, serum HDL-C < 50mg/dl for women or < 40mg/dl for men; serum TG ≥ 150 mg/dl; and WC > 88 cm for women or > 102 cm for men (3) WHO (1998): insulin resistance based on having type 2 diabetes, impaired fasting glucose (> 100 mg/dl) or impaired glucose tolerance with two more components including BP 140/90 mmHg or higher, serum TG ≥ 150 mg/dl; serum HDL-C < 35 mg/dl in men and < 39 in women; waist-to-hip ratio (WHR) > 0.90 in men, and > 0.85 in women or body mass index (BMI) > 30 (24) (Supplementary Table 1).

Diagnosis of cardiovascular disease

CVD presence among patients was determined by electrocardiography (ECG), physical examination, and medical history assessed by a cardiologist. Individuals whose diagnosis was unclear were also assessed by echocardiography, stress echocardiography, radioisotope, angiography, computed tomography angiography (CTA), and exercise tolerance test (ETT) as a further follow-up medical examination. Finally, a definite diagnosis was made based on a consensus decision by a team of experts. A diagnosis of CVD was made in 235 patients, including 120 individuals with unstable angina (UA), 75 individuals with stable angina (SA), and 40 individuals with myocardial infarction (MI). Asymptomatic individuals (n=8,524) were considered the control group. Among CVD patients, those with incomplete data (e.g., lipid profile FBG, WC, and BP) were excluded from the study. Therefore, 218 CVD patients (including 108 subjects with UA, 73 subjects with SA, and 37 subjects with MI) were finally included in the case group. The remaining 7,692 individuals were categorized as the control group (see Figure 1).

Anthropometric assessments

Height (in cm), weight (in kg), BMI (in kg/m2), WC (in cm), hip circumference (HC in cm), WHR, and mid-arm circumference (MAC in cm) were measured in all subjects. Height, WC, HC, and MAC were measured to the nearest millimeter with a tape measure. Weight was measured to the nearest 0.1 kg using electronic scales (720, BIOSPACE, Seoul, Korea).

Laboratory evaluation

Blood samples were collected from all participants in vacuum tubes (20 ml) after a 14-hour overnight fast. FBG, total cholesterol (TC), serum low-density lipoprotein cholesterol (LDL-C), serum HDL-C, and TG were measured enzymatically using an automated analyzer (Auto analyzer BT 3000). BP was measured twice with a 30-minute interval using a standard mercury sphygmomanometer, and the average of these two measurements was reported as the final blood pressure.

Assessment of other variables

Health care professionals collected information about demographic variables, including age, sex, education level, and marital status, as well as medical history and lifestyle behaviors such as cigarette smoking, through face-to-face interviews. Physical activity level (PAL) was assessed using the James and Schofield human energy requirements equations (25).

Statistical analysis

The normality of the data was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were performed for all variables, including mean and standard deviation (mean ± SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. The Chi-square test and analysis of variance (ANOVA) were used to compare qualitative and quantitative variables, respectively. The Mann-Whitney U test was used for serum TG since it was a continuous non-normal variable. Hazard ratio (HR) and 95% confidence interval (CI) were used to estimate the association of MetS and its components with CVD events. The HR was adjusted for age, BMI, PAL, smoking status (never, former and current), education level, marital status, and total energy intake. Statistical analysis was performed using SPSS version 18.0 (SPSS, Chicago, IL). A P-value < 0.05 was considered statistically significant.

Results

The prevalence of classical risk factors for CVD was higher at the baseline in subjects with a CVD event

The baseline characteristics of the participants according to CVD occurrence are shown in Table 1. CVD patients were older than healthy subjects. Educational attainment, non-smoking status, PAL, and serum HDL-C concentration were higher in healthy individuals than in CVD patients. BMI, WC, WHR, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, TC, serum TG, and serum LDL-C concentrations were higher in CVD patients compared to healthy subjects.

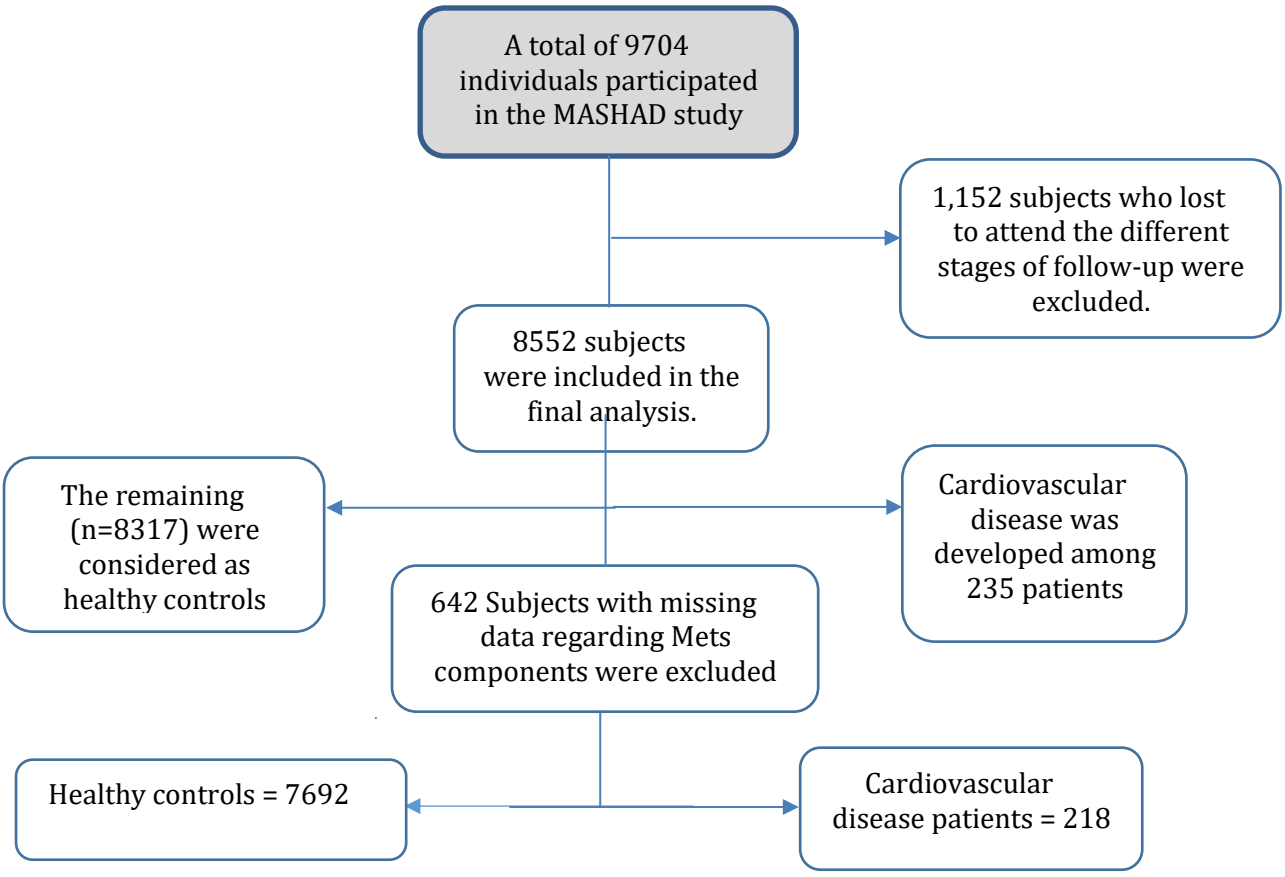

Figure 1. Participants follow diagram

Postmenopausal women had a higher CVD event rate compared to premenopausal women. Furthermore, the prevalence of diabetes mellitus, hypertension, and dyslipidemia was higher among CVD patients.

Table 1. Comparison of baseline characteristics in participants who developed cardiovascular disease in prospective MASHAD Study.

Variable	Incident CVD		P-value
	Yes (n = 218)	No (n = 7692)	
Gender, % (N) **Female**	 51.80 (113)	 56.70 (4362)	 0.151
Age, year	54.22 ± 6.76	47.51 ± 8.10	<0.001
Marital status, % (N) **Single/divorced/widow** **Married**	 6.90 (15) 93.10 (203)	 5.80 (448) 94.20 (7242)	 0.513
Educational attainment, % (N) **Low (trade school)** **Moderate (high school)** **High (university)**	 64.70 (141) 26.10 (57) 9.20 (20)	 50.60 (3891) 37.10 (2851) 12.20 (941)	 <0.001
Smoking status, % (N) **Non-smoker** **Ex-smoker** **Current smoker**	 61 (133) 17.40 (38) 21.60 (47)	 69.20 (5318) 9.80 (753) 21 (1615)	 0.001
Menopausal status, %(N) **Premenopausal** **post-menopausal**	 26.50 (30) 73.50 (83)	 61.80 (2695) 38.20 (1667)	 <0.001
BMI (kg/m^2)	28.76 ± 4.63	27.49 ± 4.60	<0.001
WC (cm)	98.67 ± 10.86	94.15 ± 11.82	<0.001
HC (cm)	103.89 ± 9.58	103.07 ± 9.09	0.190
WHR	0.95 ± 0.07	0.91 ± 0.08	<0.001
MAC (cm)	30.50 ± 3.64	30.40 ± 3.94	0.731
PAL	1.52 ± 0.28	1.59 ± 0.29	0.001
SBP (mmHg)	132.40 ± 20.65	118.59 ± 16.07	<0.001
DBP (mmHg)	83.01 ± 10.62	77.48 ± 10.50	<0.001
FBG (mg/dl)	121.88 ± 64.31	92.19 ± 38.47	<0.001
Serum Cholesterol (mg/dl)	199.64 ± 42.03	189.85 ± 38.57	<0.001
Serum TG (mg/dl)	139 (100.75, 216)	118 (83, 169)	<0.001
Serum LDL-C (mg/dl)	121.82 ± 35.66	115.39 ± 34.94	0.007
Serum HDL-C (mg/dl)	40.07 ± 8.99	42.87 ± 9.93	<0.001
Diabetes, % (N)	29.80 (65)	9 (691)	<0.001
Hypertension, % (N)	40.80 (89)	14.80 (1134)	<0.001
Dyslipidemia, % (N)	92.20 (201)	84.40 (6489)	0.002

- Abbreviations: PAL: physical activity level; **BMI:** body mass index, **WC:** waist circumference, **HC:** hip circumference, **WHR:** waist-to-hip ratio; **MAC:** mid-upper arm circumference, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure, **FBG:** fasting blood glucose, **TG:** triglyceride, **LDL-C:** low-density lipoprotein cholesterol, **HDL-C:** high-density lipoprotein cholesterol.

- Data are presented as means ± standard deviations or median (interquartile range) for continuous variables and as numbers and percentages for categorical variables.

- Hypertension was defined as systolic blood pressure ≥ 140 mmHg, and diastolic blood pressure ≥ 90 mmHg.

- Diabetes was defined as fasting blood glucose ≥126 /mg/dl.

- Dyslipidemia was defined as total cholesterol ≥ 200, or triglycerides ≥150, or low-density lipoprotein cholesterol (LDL-C) ≥130, or high-density lipoprotein cholesterol (HDL-C) <40 (for men) and HDL-C <50 (for women).

- Independent sample t-test and Mann-Whitney U tests are used where appropriate.

The prevalence of MetS and the hazard ratio for a CVD event in the MASHAD cohort differed according to the definition used

The prevalence of MetS based on the three definitions and its components in all participants, is shown in Table 2. According to the IDF, ATP III, and WHO definitions, 34.30%, 27.20%, and 7% of subjects had MetS, respectively, with at least three MetS abnormalities at baseline. Compared to the controls, CVD patients had a significantly higher prevalence of MetS, higher serum TG, higher WC, and higher FBG based on all three definitions. The prevalence of low serum HDL-C was substantially higher in CVD patients according to the WHO definition ($P < 0.05$), while high BP and high FBG, according to the IDF and ATP III definitions, were more frequent in individuals who developed CVD ($P < 0.001$). The HR and 95% CI of CVD events concerning the presence of MetS for each definition or its components, after adjusting for potential confounding factors, are shown in Table 3. This table shows that MetS, high FBG, elevated BP (depending on these three criteria), and low serum HDL-C defined by the WHO increased the risk of total CVD ($P < 0.01$). A high FBG based on the three definitions increased the risk of MI, SA, and UA among all participants ($P < 0.01$). On the other hand, the MetS definition by the WHO increased the risk of MI and UA ($P < 0.01$), while the presence of MetS by the IDF and NCEP ATP III definitions only increased the risk of SA in the study population ($P < 0.05$). We also found that high BP defined by the WHO increased the risk of SA ($P < 0.001$), and elevated BP based on the IDF and NCEP ATP III criteria was associated with a higher incidence of UA ($P < 0.01$)

The hazard ratio for a CVD event differed significantly by sex

High FBG and serum TG, as defined by all three definitions, were associated with a higher total of CVD events ($P < 0.05$) in men. Elevated fasting serum TG defined using all three definitions and higher FBG according to IDF and NCEP ATP III definitions were associated with an increased risk of MI ($P <0.05$). Moreover, the MetS definition based on NCEP ATP III and elevated FBG according to IDF criteria were associated with an increased risk of SA in men ($P < 0.05$). The risk of UA was not associated with any of these definitions or their constituent components among men (Table 4).

Supplementary Table 1. Metabolic syndrome definitions from WHO, NCEP, and IDF.

	WHO (1998)	NCEP (2001)	IDF (2005)
Required	Insulin resistance*	None	WC† ≥ 94 cm in men or ≥ 80 cm in women
No. of abnormalities	≥ 2 of:	≥ 3 of:	≥ 2 of:
Obesity	WHR > 0.9 in men or > 0.85 in women; BMI ≥ 30 kg/m2	WC ≥ 102 cm in men or ≥ 88 cm in women	Central obesity already required
Triglycerides	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
HDL cholesterol	< 35 mg/dL in men or < 39 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women
Hypertension	≥ 140/90 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg
Glucose	Insulin resistance already required	≥ 110 mg/dL‡	≥ 100 mg/dL
Microalbuminuria	Albumin/creatinine ratio > 30 mg/g; Albumin excretion rate > 20 mcg/min		

- **Abbreviations: WHO:** World Health Organization; **NCEP:** National Cholesterol Education Program; **IDF:** international diabetes federation; **WC:** waist circumference; **WHR:** waist to hip ratio; **BMI:** body mass index; **HDL:** high-density lipoprotein.
*Insulin resistance in top 25%; glucose ≥ 110 mg/dL; 2-hour glucose ≥ 140 mg/dL.
†Waist circumference for Europids (someone of European Extraction, even if living elsewhere).
‡The American Diabetes Association recently suggested lowering this threshold to 100.

Table 2. Participants of the MASHAD study who had metabolic syndrome or its components according to different definitions at baseline.

	MetS	High TG (mg/dl)	High WC (cm)	Low HDL-C (mg/dl)	High FBG (mg/dl)	High BP (mmHg)
All participants,% (N)						
IDF	34.30 (2713)	33 (2607)	72.20 (5707)	64.40 (5092)	19.10 (1514)	28.70 (2265)
NCEP ATP III	27.20 (2155)	33 (2607)	46.50 (3677)	64.40 (5092)	13.90 (1099)	28.70 (2625)
WHO	7 (556)	33 (2607)	71.50 (5645)	28.90 (2289)	9.70 (767)	15.50 (1223)
CVD patients, % (N)						
IDF	56.40 (123)	43.60 (95)	79.40 (173)	69.30 (151)	45.90 (100)	61 (133)
NCEP ATP III	52.30 (114)	43.60 (95)	58.70 (128)	69.30 (151)	36.70 (80)	61 (133)
WHO	23.90 (52)	43.60 (95)	83.90 (183)	36.20 (79)	29.80 (65)	40.80 (89)
Healthy controls, % (N)						
IDF	33.70 (2590) ***	32.70(2512) ***	72(5534) *	64.30(4941)	18.40(1414) ***	48.10(3692)***
NCEP ATP III	26.50 (2041) ***	32.70(2512) ***	46.20(3549) ***	64.30(4941)	13.20(1019) ***	48.10(3692) ***
WHO	6.60 (504) ***	32.70(2512) ***	71.10(5462) ***	28.70(2210) *	9.10(702) ***	14.80(1134) ***

- Data are % (number).
- **Abbreviations: MetS:** metabolic syndrome; **TG:** triglyceride; **WC:** waist circumference; **HDL-C:** high-density lipoprotein cholesterol; **FBG:** fasting blood glucose; **BP:** blood pressure; **IDF:** international diabetes federation, **NCEP ATP III:** national cholesterol education program adult treatment panel III; **WHO:** world health organization.
- *P<0.05; ** P<0.01; ***P<0.001; from comparing healthy controls with CVD patients.

The MetS based on WHO criteria in women was associated with a higher CVD risk. According to all three definitions, MetS, high FBG, and elevated BP were associated with a higher total CVD event rate in women (P < 0.001). Moreover, a high WC and low serum HDL-C based on the WHO definition were directly associated with an increased risk of CVD in women (P < 0.05). Furthermore, the risk of MI was increased in women with MetS, high WC, and low serum HDL-C as defined by WHO criteria (P < 0.05). High FBG based on IDF criteria and elevated BP defined by WHO were associated with a higher risk of SA in females (P < 0.05). lastly, the presence of MetS and elevated BP according to all three definitions, low serum HDL-C based on WHO criteria, and high FBG according to IDF and WHO definitions were associated with an increased risk of UA in women (P < 0.05) (Table 5).

Discussion

After six years of follow-up in 35- to 65-year-old individuals in the MASHAD study, MetS was strongly associated with a higher incidence rate of new CVD events based on three different definitions: IDF, NCEP ATP III, and WHO. It is important to note that each component of MetS is considered a major risk factor for CVD (26). While previous studies have explored the link between MetS and CVD incidence (27-29), our study was the first to compare various MetS definitions and evaluate the association between their individual components and CVD incidence in Iran. We aimed to identify which criteria serve as the best predictors for CVD events and to assess the risk while considering sex stratification in this population. Our results demonstrated a higher risk of developing CVD using the WHO definition for MetS compared to the other two definitions; these results are similar to those of a prospective cohort

study in Middle Eastern elderly subjects by Mozaffary et al. (30). However, another study stated that MetS based on the WHO criteria was not a predictor of cardiovascular mortality among older and diabetic patients (31). A possible explanation for this might be the limited sample size. We showed that CVD risk is approximately 2.29 times higher in individuals with MetS defined by WHO criteria compared to those without MetS at the baseline. This result was consistent with three previous European studies which reported more than a 2-fold risk using the WHO definition (32-34). In contrast, in a large multiethnic cohort study, it was reported that the NCEP ATP III, IDF, and WHO criteria had a similar ability to predict the occurrence of CVD outcomes (35). As the present study indicated, some prospective studies have highlighted significant sex and gender differences in CVD risk associated with MetS, reporting that CVD risk is not only equal but also higher in women with MetS than in men with MetS (36, 37).

Table 3. Hazard ratios (95% CIs) for events of cardiovascular disease associated with metabolic syndrome and its components according to different definitions in total study population.

Total population (n=7910)	MS	High TG (mg/dl)	High WC (cm)	Low HDL-C (mg/dl)	High FBG (mg/dl)	High BP (mmHg)
Total CVD						
IDF	1.66 (1.18 – 2.34) **	1.28 (0.92 – 1.77)	1.24 (0.78 – 1.96)	1.26 (0.89 – 1.79)	2.27 (1.64 – 3.16) ***	1.56 (1.12 – 2.16) **
ATP III	1.86 (1.31 – 2.62) ***	1.28 (0.92 – 1.77)	1.41 (0.91 – 2.20)	1.26 (0.89 – 1.79)	2.05 (1.45 – 2.90) ***	1.56 (1.12 – 2.16) **
WHO	2.29 (1.54 – 3.40) ***	1.28 (0.92 – 1.77)	1.24 (0.81 – 1.89)	1.43 (1.03 – 1.99) *	2.43 (1.67 – 3.48) ***	1.99 (1.42 – 2.80) ***
MI						
IDF	2.10 (0.95 – 4.63)	1.81 (0.87 – 3.78)	2 (0.70 – 5.74)	1.16 (0.54 – 2.50)	3.34 (1.59 – 7.03) **	1.39 (0.66 – 2.91)
ATP III	1.64 (0.74 – 3.63)	1.81 (0.87 – 3.78)	1.21 (0.45 – 3.29)	1.16 (0.54 – 2.50)	3.26 (1.53 – 6.94) **	1.39 (0.66 – 2.91)
WHO	3.11 (1.33 – 7.26) **	1.81 (0.87 – 3.78)	2.77 (0.81 – 9.47)	1.89 (0.91 – 3.93)	3.22 (1.47 – 7.06) **	2.06 (0.96 – 4.40)
SA						
IDF	1.95 (1.04 – 3.65) *	1.24 (0.69 – 2.24)	2.54 (0.99 – 6.54)	1.22 (0.65 – 2.30)	2.55 (1.40 – 4.62) **	1.61 (0.89 – 2.92)
ATP III	2.56 (1.37 – 4.81) **	1.24 (0.69 – 2.24)	2.45 (1.07 – 5.62)	1.22 (0.65 – 2.30)	1.93 (1.02 – 3.65) *	1.61 (0.89 – 2.92)
WHO	2.05 (0.97 – 4.34)	1.24 (0.69 – 2.24)	1.60 (0.72 – 3.55)	1.03 (0.55 – 1.94)	2.14 (1.09 – 4.19) *	2.74 (1.49 – 5.04) ***
UA						
IDF	1.36 (0.84 – 2.20)	1.13 (0.72 – 1.79)	0.69 (0.37 – 1.28)	1.32 (0.81 – 2.17)	1.81 (1.13 – 2.90) *	1.59 (1 – 2.53) *
ATP III	1.57 (0.97 – 2.56)	1.13 (0.72 – 1.79)	1.05 (0.56 – 1.95)	1.32 (0.81 – 2.17)	1.74 (1.06 – 2.86) *	1.59 (1 – 2.53) *
WHO	2.13 (1.22 – 3.72) **	1.13 (0.72 – 1.79)	0.83 (0.48 – 1.45)	1.53 (0.97 – 2.44)	2.31 (1.39 – 3.84) ***	1.61 (0.99 – 2.63)

- Abbreviations: CI: confidence interval; **MS:** metabolic syndrome; **TG:** triglyceride; **WC:** waist circumference; **HDL-C:** high-density lipoprotein cholesterol; **FBG:** fasting blood glucose; **BP:** blood pressure; **CVD:** cardiovascular disease; **MI:** myocardial infarction; **SA:** stable angina; **UA:** unstable angina.
- HRs were adjusted for age, sex, BMI, physical activity level, smoking status, education level, marital status, and energy intake.
- * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

Table 4. Hazard ratios (95% CIs) for events of cardiovascular disease associated with metabolic syndrome and its components according to different definitions in males.

Males (n=3343)	MS	High TG (mg/dl)	High WC (cm)	Low HDL-C (mg/dl)	High FBG (mg/dl)	High BP (mmHg)
Total CVD						
IDF	1.47 (0.89 – 2.43)	1.67 (1.06 – 2.65) *	1.08 (0.61 – 1.91)	1.02 (0.65 – 1.60)	2.05 (1.28 – 3.30) **	1.03 (0.65 – 1.63)
ATP III	1.59 (0.95 – 2.66)	1.67 (1.06 – 2.65) *	1.28 (0.68 – 2.43)	1.02 (0.65 – 1.60)	1.99 (1.19 – 3.32) **	1.03 (0.65 – 1.63)
WHO	1.84 (0.97 – 3.49)	1.67 (1.06 – 2.65) *	1.04 (0.59 – 1.83)	0.99 (0.61 – 1.61)	1.96 (1.11 – 3.45) *	1.27 (0.78 – 2.07)
MI						
IDF	2.44 (0.92 – 6.48)	2.99 (1.16 – 7.69) *	1.60 (0.50 – 5.14)	1.01 (0.41 – 2.48)	3.91 (1.58 – 9.68) **	1.20 (0.49 – 2.96)
ATP III	1.42 (0.52 – 3.89)	2.99 (1.16 – 7.69) *	0.71 (0.20 – 2.56)	1.01 (0.41 – 2.48)	3.07 (1.21 – 7.80) *	1.20 (0.49 – 2.96)
WHO	2.15 (0.68 – 6.76)	2.99 (1.16 – 7.69) *	2.81 (0.61 – 12.88)	1.21 (0.48 – 3.09)	2.24 (0.79 – 6.37)	1.63 (0.65 – 4.08)
SA						
IDF	2.37 (0.83 – 6.76)	1.65 (0.63 – 4.34)	1.88 (0.55 – 6.36)	0.83 (0.32 – 2.11)	3.08 (1.17 – 8.09) *	1.51 (0.58 – 3.92)
ATP III	3.98 (1.39 – 11.39) *	1.65 (0.63 – 4.34)	3.37 (0.95 – 11.92)	0.83 (0.32 – 2.11)	2.11 (0.72 – 6.19)	1.51 (0.58 – 3.92)
WHO	2.22 (0.60 – 8.17)	1.65 (0.63 – 4.34)	1.97 (0.52 – 7.53)	0.85 (0.30 – 2.40)	2.36 (0.74 – 7.47)	2.45 (0.94 – 6.40)
UA						
IDF	0.88 (0.42 – 1.85)	1.27 (0.66 – 2.44)	0.72 (0.33 – 1.57)	1.15 (0.55 – 2.39)	0.80 (0.41 – 1.54)	0.73 (0.34 – 1.55)
ATP III	1.07 (0.49 – 2.31)	1.27 (0.66 – 2.44)	1.08 (0.43 – 2.71)	1.48 (0.69 – 3.19)	0.80 (0.41 – 1.54)	0.73 (0.34 – 1.55)
WHO	1.51 (0.57 – 3.99)	1.27 (0.66 – 2.44)	0.60 (0.29 – 1.24)	1.65 (0.71 – 3.80)	0.78 (0.36 – 1.66)	1.31 (0.65 – 2.62)

- **Abbreviations: CI:** confidence interval; **MS:** metabolic syndrome; **TG:** triglyceride; **WC:** waist circumference; **HDL-C:** high-density lipoprotein cholesterol; **FBG:** fasting blood glucose; **BP:** blood pressure; **CVD:** cardiovascular disease; **MI:** myocardial infarction; **SA:** stable angina; **UA:** unstable angina.
- HRs were adjusted for age, BMI, physical activity level, smoking status, education level, marital status, and energy intake.
- * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

However, this difference diminishes when adjusted for the presence of overt diabetes mellitus (36, 38-40). This inconsistency may be due to variations in inclusion criteria, the exclusion of diabetic patients and differences in outcome measures. Although MetS, based on all three criteria (with WHO being the most robust), was a predictor of CVD in women in the current study, no significant association was observed in men. This outcome broadly aligns with the work of another study on a multi-ethnic U.S. population, which demonstrated that the WHO definition was not predictive of a higher risk of CVD in males (41); however, the findings of the current study do not support this research as they report that MetS was less predictive in women compared to men (41). In a cohort study, Dekker et al. reported that after age adjustment in MetS patients according to the NCEP ATP III definition, there was an approximately 2-fold increase in the risk of fatal CVD in men and nonfatal CVD in women, but the HR for the WHO definition of MetS was slightly lower (42). This was also the finding of the San Antonio Heart Study, with a follow-up of up to 12.7 years, indicating that the NCEP ATP III criteria tended to be more predictive than the WHO criteria in lower-risk subjects and females (38). The components of MetS have a different impact on CVD risk in men compared to women.

Table 5. Hazard ratios (95% CIs) for events of cardiovascular disease associated with metabolic syndrome and its components according to different definitions in females.

Females (n=4475)	MS	High TG (mg/dl)	High WC (cm)	Low HDL-C (mg/dl)	High FBG (mg/dl)	High BP (mmHg)
Total CVD						
IDF	1.76 (1.07 – 2.88) *	0.91 (0.57 – 1.45)	2.07 (0.62 – 6.88)	1.70 (0.96 – 3)	2.37 (1.48 – 3.78) ***	2.34 (1.46 – 3.74) ***
ATP III	2.01 (1.24 – 3.27) **	0.91 (0.57 – 1.45)	1.48 (0.76 – 2.89)	1.70 (0.96 – 3)	2.01 (1.25 – 3.24) **	2.34 (1.46 – 3.74) ***
WHO	2.62 (1.57 – 4.37) ***	0.91 (0.57 – 1.45)	3.10 (1.93 – 4.96) ***	2.12 (1.34 – 3.36) **	2.81 (1.74 – 4.52) ***	3.10 (1.93 – 4.96) ***
MI						
IDF	1.42 (0.37 – 5.44)	0.64 (0.16 – 2.56)	–	1.64 (0.34 – 7.84)	2.37 (0.64 – 8.83)	1.85 (0.50 – 6.90)
ATP III	1.95 (0.50 – 7.52)	0.64 (0.16 – 2.56)	3.39 (0.37 – 31.54)	1.64 (0.34 – 7.84)	3.53 (0.95 – 13.20)	1.85 (0.50 – 6.90)
WHO	5.09 (1.32 – 19.64) *	0.64 (0.16 – 2.56)	2.34 (0.28 – 19.38)	4.43 (1.22 – 16.07) *	5.60 (1.53 – 20.46) **	3.34 (0.88 – 12.71)
SA						
IDF	1.55 (0.71 – 3.37)	0.95 (0.44 – 2.04)	3.81 (0.48 – 30.07)	1.66 (0.67 – 4.12)	2.13 (1.01 – 4.52) *	1.65 (0.78 – 3.48)
ATP III	1.83 (0.85 – 3.93)	0.95 (0.44 – 2.04)	1.72 (0.62 – 4.80)	1.66 (0.67 – 4.12)	1.74 (0.79 – 3.82)	1.65 (0.78 – 3.48)
WHO	1.82 (0.72 – 4.61)	0.95 (0.44 – 2.04)	1.25 (0.46 – 3.36)	1.19 (0.54 – 2.64)	1.92 (0.84 – 4.40)	2.84 (1.30 – 6.17) **
UA						
IDF	2.14 (1.01 – 4.52) *	0.96 (0.50 – 1.85)	1 (0.22 – 4.49)	1.77 (0.77 – 4.04)	2.59 (1.32 – 5.08) **	3.37 (1.65 – 6.89) **
ATP III	2.20 (1.07 – 4.50) *	0.96 (0.50 – 1.85)	1.11 (0.42 – 2.93)	1.77 (0.77 – 4.04)	1.91 (0.97 – 3.77)	3.37 (1.65 – 6.89) **
WHO	2.81 (1.38 – 5.72) **	0.96 (0.50 – 1.85)	1.59 (0.55 – 4.58)	2.72 (1.42 – 5.21) **	3.09 (1.58 – 6.03) **	3.18 (1.63 – 6.19) **

- **Abbreviations: CI:** confidence interval; **MS:** metabolic syndrome; **TG:** triglyceride; **WC:** waist circumference; **HDL-C:** high-density lipoprotein cholesterol; **FBG:** fasting blood glucose; **BP:** blood pressure; **CVD:** cardiovascular disease; **MI:** myocardial infarction; **SA:** stable angina; **UA:** unstable angina.
- HRs were adjusted for age, BMI, physical activity level, smoking status, education level, marital status, and energy intake.
- * P-value<0.05, ** P-value<0.01, *** P-value<0.001.

According to the Framingham Heart Study, abnormal serum lipids are considered a CVD risk factor in men, whereas high blood cholesterol has less impact on postmenopausal women (43).

Our study found that elevated BP and high FBG based on three definitions, as well as low serum HDL-C defined by WHO criteria, were strong predictors of higher CVD risk in both sexes. However, while Hari et al. revealed that all determinant components of MetS were strongly associated with a higher CVD risk in men, in women, serum HDL-C and TG showed no association with short-term CVD risk (41). Elevated serum TG and high FBG according to all three definitions were associated with an increased CVD risk in men in our study. Conversely having MetS, high FBG, elevated BP according to all three definitions, high WC, and low serum HDL-C by WHO criteria were associated with an increased CVD risk among women. Njelekela et al. reported that women with CVD had more than three times higher odds of having MetS based on ATP III criteria compared to men, and men with CVD had more than three times higher odds of having high BP than women (44). The predictability of MetS and its components varied depending on the definitions of the different constituents of MetS. The higher risk of MetS in women seems to be due to the lower cut-off point of WC and higher levels of serum HDL-C.

Additionally, sex-specific risk factors could increase CVD incidence in women, including premature menopause, pregnancy-related complications such as preeclampsia, and chronic inflammatory diseases like systemic lupus erythematosus (SLE). Moreover, disparities between men and women may partly be explained by differences in CVD presentations and the protective role of estrogen in women (45, 46). However, in a longitudinal study (n = 2,646) with 7.4 years of follow-up, based on all three MetS definitions, the ORs were similar between men and women (35).

In some studies (47-51), but not all (52), a significant relationship between the presence of Mets and the occurrence of MI and angina pectoris was reported. The current investigation showed that MetS and high FBG based on the WHO definition, were predictive of the risk of MI and UA. These results corroborate the findings of a multi-ethnic population study that demonstrated MetS was associated with an increased risk of MI according to the WHO (OR: 2.69; 95% CI: 2.45 – 2.95) and IDF (OR: 2.20; 95% CI: 2.03 – 2.38). Additionally, two individual components_hypertension and diabetes mellitus_were similarly associated with MetS using the WHO definition and an increased risk of MI (53).

Several strengths of this analysis should be highlighted. First, a cohort study design was conducted among participants, which allows for the establishment of cause-and-effect relationships. The study also benefited from a large sample size and adjusted for all potential confounding factors influencing CVD occurrence, such as older age, smoking, and physical inactivity. By controlling for these risk factors, the study was able to clearly demonstrate the association between MetS and CVD risk. Additionally, the association between MetS and CVD risk was analyzed with stratification by sex and all subtypes of CVD. This approach allows for a more detailed and precise assessment of the association.

Despite these strengths, our study has some limitations, such as wide confidence intervals (CIs), particularly in evaluating MI risk. Additionally, microalbuminuria, a component of MetS under the WHO definition, was not measured. The current study focused exclusively on a population from Mashhad city. Further studies could expand this research by including cohort populations from multiple cities across Iran. Moreover, the follow-up duration of this study was 6 years; therefore, a longer duration might have led to different outcomes.

Taken together, the WHO definition of MetS confers a higher risk of cardiovascular disease in the Iranian population compared to the other two criteria. Therefore, early detection of individuals with MetS based on WHO criteria for risk assessment and treatment is of great importance. Further work is needed to compare different definitions of MetS to identify the best predictor of CVD in this population.

Conclusion

This study aimed to compare the WHO, IDF, and ATP III criteria and their determining components in predicting total and different subtypes of CVD occurrence in a large sample of the Iranian population. The findings of this study suggest that Iranian individuals who have MetS and its constituent components according to the WHO criteria have an approximately twofold increased risk for CVD, which is higher than the calculated risk for other MetS criteria. Moreover, the WHO criteria were more predictive of CVD in women. Additionally, MetS, high FBG, and high BP based on all three definitions were associated with an increased CVD risk among women. In contrast, high serum TG and high FBG were the only two components that were more predictive of CVD in men. MetS has become a significant health issue in developing countries, and therefore efforts should be made to increase community awareness, promote pre-symptomatic detection, and ensure early diagnosis. Notably, more prospective studies are needed to determine the best definition of MetS in Iran.

Ethics approval and consent to participate

Informed consent was obtained from all subjects in accordance with protocols approved by the Ethics Committee of Mashhad University of Medical Sciences. All participants were literate, able to understand

the study requirements, and willing to provide written informed consent. (IR.MUMS.MEDICAL.REC.1386.250).

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Declarations of conflict of interest

The authors have no conflicts of interest to disclose.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Wang J, Ruotsalainen S, Moilanen L, Lepistö P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. European heart journal. 2007 Apr 1;28(7):857-64.
2. Alberti G, Zimmet P, Shaw J, Grundy SM. The IDF consensus worldwide definition of the metabolic syndrome. Brussels: International Diabetes Federation. 2006 May;23(5):469-80.
3. Maria A. Expert panel on detection e, treatment of high blood cholesterol in A. 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(19):2486-97.
4. 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. Diabetic medicine. 1998 Jul;15(7):539-53.
5. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. Diabetic medicine. 2006 May;23(5):469-80.
6. Parsamanesh N, Karami-Zarandi M, Banach M, Penson PE, Sahebkar A. Effects of statins on myocarditis: a review of underlying molecular mechanisms. Progress in cardiovascular diseases. 2021 Jul 1;67:53-64.
7. Delavari A, Forouzanfar MH, Alikhani S, Sharifian A, Kelishadi R. 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 Jun 1;32(6):1092-7.
8. Hadaegh F, Zabetian A, Tohidi M, Ghasemi A, Sheikholeslami F, Azizi F. Prevalence of metabolic syndrome by the Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions and their association with coronary heart disease in an elderly Iranian population. Annals Academy of Medicine Singapore. 2009 Feb 1;38(2):142.
9. Amirkalali B, Fakhrzadeh H, Sharifi F, Kelishadi R, Zamani F, Asayesh H, et al. Prevalence of metabolic syndrome and its components in the Iranian adult population: a systematic review and meta-analysis. Iranian red crescent medical journal. 2015 Dec 27;17(12):e24723.
10. Azizi F, Salehi P, Etemadi A, Zahedi-Asl S. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. Diabetes research and clinical practice. 2003 Jul 1;61(1):29-37.
11. Tayefi M, Saberi-Karimian M, Esmaeili H, Zadeh AA, Ebrahimi M, Mohebati M, et al. Evaluating of associated risk factors of metabolic syndrome by using decision tree. Comparative clinical pathology. 2018 Jan;27:215-23.
12. Sadeghi M, Haghdoost AA, Bahrampour A, Dehghani M. Modeling the burden of cardiovascular diseases in Iran from 2005 to 2025: the impact of demographic changes. Iranian journal of public health. 2017 Apr;46(4):506.
13. Aghasizadeh M, Bizhaem SK, Baniasadi M, Khazdair MR, Kazemi T. Evaluation of LDL goal achievement in statin consumption, south east of Iran. Scientific Reports. 2021 May 24;11(1):10786.
14. Federation I. The IDF consensus worldwide definitionofthemetabolicsyndrome. 2014 r03r26]. http://www. idf. org/webdata/ocs/meta_ syndrome definition. pdf.
15. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. Journal of the American College of Cardiology. 2010 Sep 28;56(14):1113-32.
16. Ju SY, Lee JY, Kim DH. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-

analysis of prospective cohort studies. Medicine. 2017 Nov 1;96(45):e8491.
17. Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. The Lancet. 2008 Jun 7;371(9628):1927-35.
18. Akhondian J, Kiani MA, Jafari SA, Beiraghi Toosi M, Mirzaei Najm Abad M, Ahanchian H, et al. Evaluation of liver enzymes rising in patients treated with sodium valproate (VPA). International Journal of Pediatrics. 2015 Jun 1;3(3.2):685-9.
19. Ramezankhani A, Azizi F, Hadaegh F, Eskandari F. Sex-specific clustering of metabolic risk factors and their association with incident cardiovascular diseases: a population-based prospective study. Atherosclerosis. 2017 Aug 1;263:249-56.
20. Yousefzadeh G, Shokoohi M, Najafipour H, Shadkamfarokhi M. Applying the Framingham risk score for prediction of metabolic syndrome: the Kerman Coronary Artery Disease Risk Study, Iran. ARYA atherosclerosis. 2015 May;11(3):179.
21. Sarrafzadegan N, Gharipour M, Sadeghi M, Nezafati P, Talaie M, Oveisgharan S, et al. Metabolic syndrome and the risk of ischemic stroke. Journal of Stroke and Cerebrovascular Diseases. 2017 Feb 1;26(2):286-94.
22. Ghayour-Mobarhan M, Moohebati M, Esmaily H, Ebrahimi M, Parizadeh SM, Heidari-Bakavoli AR, et al. Mashhad stroke and heart atherosclerotic disorder (MASHAD) study: design, baseline characteristics and 10-year cardiovascular risk estimation. International journal of public health. 2015 Jul;60:561-72.
23. Asadi Z, Shafiee M, Sadabadi F, Heidari-Bakavoli A, Moohebati M, Khorrami MS, et al. Association of dietary patterns and risk of cardiovascular disease events in the MASHAD cohort study. Journal of Human Nutrition and Dietetics. 2019 Dec;32(6):789-801.
24. Huang PL. A comprehensive definition for metabolic syndrome. Disease models & mechanisms. 2009 Apr 30;2(5-6):231-7.
25. James WP, Schofield EC. Human energy requirements. A manual for planners and nutritionists. 1990 Dec 29.
26. Giugliano D, Esposito K. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes: response to Kahn et al. Diabetes care. 2006 Jan 1;29(1):175-6.
27. Yang W, Guo S, Wang H, Li Y, Zhang X, Hu Y, et al. The Association of Metabolic Syndrome with the development of cardiovascular disease among Kazakhs in remote rural areas of Xinjiang, China: a cohort study. BMC Public Health. 2021 Dec;21:1-8.
28. Gustavo de Sousa Barbalho Y, Morato Stival M, Ramos de Lima L, Cristina Rodrigues da Silva I, de Oliveira Silva A, Vieira Gomes da Costa M, et al. Impact of metabolic syndrome components in high-risk cardiovascular disease development in older adults. Clinical Interventions in Aging. 2020 Sep 18:1691-700.
29. Mazloomzadeh S, Zarandi FK, Shoghli A, Dinmohammadi H. Metabolic syndrome, its components and mortality: A population-based study. Medical journal of the Islamic Republic of Iran. 2019 Feb 27;33:11.
30. Mozaffary A, Bozorgmanesh M, Sheikholeslami F, Azizi F, Eskandari F, Hadaegh F. Added value of different metabolic syndrome definitions for predicting cardiovascular disease and mortality events among elderly population: Tehran Lipid and Glucose Study. European journal of clinical nutrition. 2014 Jul;68(7):853-8.
31. Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, et al. Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. Diabetes care. 2004 Nov 1;27(11):2689-94.
32. Isomaa BO, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes care. 2001 Apr 1;24(4):683-9.
33. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Bonadonna RC, et al. Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: prospective data from the Bruneck study. Diabetes care. 2003 Apr 1;26(4):1251-7.
34. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. Jama. 2002 Dec 4;288(21):2709-16.
35. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes care. 2007 Jan 1;30(1):8-13.
36. Pucci G, Alcidi R, Tap L, Battista F, Mattace-Raso F, Schillaci G. Sex-and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature. Pharmacological research. 2017 Jun 1;120:34-42.
37. Onat A, Ceyhan K, Başar Ö, Erer B, Toprak S, Sansoy V. Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels —a prospective and cross-sectional

evaluation. Atherosclerosis. 2002 Dec 1;165(2):285-92.
38. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation. 2004 Sep 7;110(10):1251-7.
39. Schillaci G, Pirro M, Vaudo G, Gemelli F, Marchesi S, Porcellati C, et al. Prognostic value of the metabolic syndrome in essential hypertension. Journal of the American College of Cardiology. 2004 May 19;43(10):1817-22.
40. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes care. 2005 Feb 1;28(2):385-90.
41. Hari P, Nerusu K, Veeranna V, Sudhakar R, Zalawadiya S, Ramesh K, et al. A gender-stratified comparative analysis of various definitions of metabolic syndrome and cardiovascular risk in a multiethnic US population. Metabolic syndrome and related disorders. 2012 Feb 1;10(1):47-55.
42. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation. 2005 Aug 2;112(5):666-73.
43. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease--the Framingham Heart Study. The Canadian journal of cardiology. 1988 Jul 1;4:5A-10A.
44. Njelekela MA, Mpembeni R, Muhihi A, Mligiliche NL, Spiegelman D, Hertzmark E, et al. Gender-related differences in the prevalence of cardiovascular disease risk factors and their correlates in urban Tanzania. BMC cardiovascular disorders. 2009 Dec;9:1-8.
45. Sader MA, Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. Cardiovascular research. 2002 Feb 15;53(3):597-604.
46. DeVon HA, Ryan CJ, Ochs AL, Shapiro M. Symptoms across the continuum of acute coronary syndromes: differences between women and men. American journal of critical care. 2008 Jan 1;17(1):14-24.
47. Kokubo Y, Okamura T, Yoshimasa Y, Miyamoto Y, Kawanishi K, Kotani Y, et al. Impact of metabolic syndrome components on the incidence of cardiovascular disease in a general urban Japanese population: the Suita study. Hypertension Research. 2008 Nov;31(11):2027-35.
48. Noto D, Barbagallo CM, Cefalù AB, Falletta A, Sapienza M, Cavera G, et al. The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: results of a 15 years follow-up in a Mediterranean population. Atherosclerosis. 2008 Mar 1;197(1):147-53.
49. Kim I, Kim MC, Sim DS, Hong YJ, Kim JH, Jeong MH, et al. Effect of the metabolic syndrome on outcomes in patients aged< 50 years versus> 50 years with acute myocardial infarction. The American Journal of Cardiology. 2018 Jul 15;122(2):192-8.
50. Lee SH, Tao S, Kim HS. The prevalence of metabolic syndrome and its related risk complications among Koreans. Nutrients. 2019 Jul 30;11(8):1755.
51. Johans CE, Bajic P, Kirshenbaum E, Blackwell RH, Kothari AN, Kuo PC, et al. Metabolic syndrome increases risk of postoperative myocardial infarction following percutaneous nephrolithotomy. Journal of Endourology. 2018 Nov 1;32(11):1039-43..
52. Lovic MB, Djordjevic DB, Tasic IS, Nedeljkovic IP. Impact of metabolic syndrome on clinical severity and long-term prognosis in patients with myocardial infarction with ST-segment elevation. Hellenic journal of cardiology. 2018 Jul 1;59(4):226-31.
53. Mente A, Yusuf S, Islam S, McQueen MJ, Tanomsup S, Onen CL, et al. Metabolic syndrome and risk of acute myocardial infarction: a case-control study of 26,903 subjects from 52 countries. Journal of the American College of Cardiology. 2010 May 25;55(21):2390-8.