

Frequency of Metabolic Syndrome According to Optimal Cut-Points for Body Mass Index in Saudi Population

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Abstract

Background and Objective: The prevalence of metabolic syndrome (MetS) are increasing worldwide. Body mass index (BMI) cut-off for MetS can vary. The objective of this study is to identify the optimal BMI cut-off that is associated with MetS.

Methods: For the present study, we analyzed participants who are equal to or older than 18 years old. A total of 5498 were analyzed at the present study. Patients were recruited from the population of the primary health care department at King Fahad Armed Forces Hospital. Metabolic risk factors were defined using the 2006 International Diabetes Federation criteria. We collected data personal interview and electronic medical chart review. Physician and nurse interviewers measured the weight (kg) and height (cm) of the participants and BMI was calculated. Receiver operating characteristic curve analysis was used to obtain the optimal sensitivity and specificity using different BMI cut-off values to predict the presence of diabetes.

Results: Of the 5498 participants analyzed, 2049 (37.3%) were male and 3449 (62.7%) were female with female to male ratio 1.7:1. Age was 42.7 ± 15.8 (minimum 18 years and maximum 105 years). MetS was present in 1967 cases (35.8%) where 673 cases (38.8%) were male and 1204 cases (61.2%) were female with female to male ratio 1.6:1, $P=0.08$. Males were significantly older than females in MetS patients (45.5 ± 12.8 vs. 36.1 ± 13.3 respectively, $p < 0.0001$). BMI was significantly higher in MetS patients (31.9 ± 6.6 vs. 28.3 ± 6.7 respectively, $p < 0.0001$). Optimal BMI cut-off values ranged from 28.50 to 29.50 in total population, 27.50 to 28.50 in male and from 28.50 to 29.50 in female. The AUC was 0.615 (95% CI, 0.590-0.639) in male and 0.686 (95% CI, 0.668-0.704) in female. Regression analysis showed that the risk of MetS was significantly increased at BMI values as low as ≤ 15.0 kg/m² and increased progressively as BMI increased for

both genders. Applying this criterion to identify the cut-off values resulted in improvements in sensitivity, false negative rate and worsening in specificity and false positive rate. A very small false negative rate ranging from 0.001 to 0.005 resulted by using these lower BMI cut-offs.

Conclusion: The diagnostic usefulness of BMI alone in defining obesity in patients with MetS is limited among men and women Saudi adults.

Keywords: Metabolic syndrome; Body Mass Index

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic factors that increases the risk of cardiovascular disease (CVD) morbidity and mortality and type 2 diabetes mellitus (T2DM) [1-5]. MetS increases the risk of developing T2DM by three-fold and cardiovascular disease by two-fold, and it has become a major public health challenge around the world [6]. It has been proposed that the association between body mass index (BMI) and the development of T2DM is more complex than a mere a dose-response relationship [7,8]. These factors not only lead to reduced quality of life given their protracted nature, they also lead to premature death [9]. The first official definition of MetS put forward by a working group of the World Health Organization (WHO) in 1999, a number of different definitions have been proposed [10]. Presently, there are three sets of criteria for MetS: the International Diabetes Federation (IDF), the revised National Cholesterol Education Program and the Modified WHO [11].

Obesity is a complex disorder, where genetic predisposition interacts with environmental exposures to produce a heterogeneous phenotype [12]. Obesity is a well-known risk factor for developing T2DM, hypertension, dyslipidaemia and CVD and it was estimated to be the fifth leading cause of mortality at a global level, causing approximately 2.8 million deaths per year [1,13-15]. Although BMI is commonly used to measure somatic obesity, recent findings have reported its conflicting association with CVD and obesity-related health risks [16,17]. The prevalence of MetS is on the rise due to the obesity epidemic [1]. There are many individuals who are not categorized as obese based on BMI but are predisposed to MetS [18]. Screening for MetS among these non-obese individuals is often ignored, as they are assumed to be healthy. The literature shows that normal weight individuals could have MetS, placing them

at elevated risk for chronic diseases that are typically associated with elevated BMI [19]. Evidence also suggests that an abnormal metabolic profile, rather than high BMI, is associated with higher risk of diabetes and CVD [20].

Studies from different countries and ethnicities have different conclusions regarding the cut-off points to diagnose obesity and hence MetS [21-23]. Researchers believe that ethnic and racial variation among population from different regions might need different cut-off points and/or use of different anthropometric measurement to diagnose obesity and MetS [23,24]. As a known risk factor of T2DM, high BMI ($> 30 \text{ kg/m}^2$) is associated with 3-10 times greater risk of developing T2DM compared to low BMI ($< 25 \text{ kg/m}^2$) [25-30]. Although this index has advantages in clinical and epidemiological practice, as a non-invasive and low-cost method, its predictive value for chronic diseases has been questioned, especially when applied to certain population groups [31-33]. Asians are more likely to have a higher percentage of body fat at lower BMI than Europeans, which may lead to the greater prevalence of cardiovascular disease risk factors at a relatively lower BMI in Asian populations [34-36]. The World Health Organization suggests that the cut-off values for public health action for Asians are BMI values $\geq 23 \text{ kg/m}^2$ to represent an increased risk of CVD and BMI values $\geq 27.5 \text{ kg/m}^2$ to represent a high risk of cardiovascular disease [35].

BMI is a valuable tool in clinical care and public health research to identify individuals who are at a significantly higher risk for obesity-associated diseases. However, evidence regarding whether different cut-off BMI values are appropriate in Saudi Arabia and gulf countries are insufficient [37-41]. On the other hand, several studies have attempted to determine the optimal cut-off values for BMI to predict various CVD risk factors based on data from either small-scale or cross-sectional studies. Most of the available data indicate that a cut-off BMI value is

needed for the general population in Saudi Arabia. The objective of this study is to identify the optimal BMI cut-off that is associated with MetS

Methods

We analyzed 5498 participants who are equal to or older than 18 years old. All cases were from the population of the primary health at King Fahad Armed Forces Hospital. All data were collected by personal interview and on the basis of a review of electronic medical records. Physician and nurse interviewers measured and recorded weight (kg) and height (cm). Metabolic risk factors were defined using the 2006 IDF criteria that define elevated triglyceride as ≥ 150 mg/dL (≥ 1.7 mmol/L) and reduced high density lipoprotein cholesterol as < 40 mg/dL (< 1.03 mmol/L) for male and as < 50 mg/dL (< 1.29 mmol/L) for female. ²⁴ Elevated blood pressure was defined when the systolic blood pressure was ≥ 130 mm Hg and/or diastolic blood pressure was ≥ 85 mm Hg in addition to receiving any medication for hypertension. Abnormal glucose metabolism was considered when HbA1c (≥ 5.7) or when patients were known to have type 2 diabetes. A combination of two or more of these risk factors was used to assess cutoff values for BMI.

Statistical Analysis

Unpaired t-test analysis and Chi square (X^2) test (categorical data comparison) were used between variables to estimate the significance of different between groups for demographic and clinical laboratory were used for. The optimal sensitivity and specificity using different BMI cut-off values to predict the presence of MetS were examined by receiver operating characteristic curve (ROC) analysis. A greater area under the curve (AUC) indicates better predictive capability. An AUC=0.5 indicates that the test performs no better than chance, and an AUC=1.0 indicates perfect discrimination. An ideal

test is one that reaches the upper left corner of the graph (100% true positives and no false positives). To determine the optimal BMI cutoff points, we computed and searched for the shortest distance between any point on the curve and the top left corner on the y-axis. Distance was estimated at each one-half unit of BMI according to the equation:

Distance in ROC curve = $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ [42,43]. Additional criteria were also used to select cut-offs, including the greater sum of sensitivity and specificity, the smallest misclassification rate, and the significant associations between BMI and risk factors based on the logistic regression. Diagnostic performance of BMI in predicting MetS was assessed by calculating AUC, sensitivity, specificity, likelihood ratios, false positive, false negative and the total misclassification rate. All results are presented as mean \pm standard deviation or percentage, where applicable. Data analysis was performed in each gender separately. BMI was stratified in unit of 0.5 for both gender. We consider a BMI < 15.0 as the reference. The independent relationship between the stratified BMI and the odds ratio of having MetS were analyzed using logistic regression. All statistical analyses were performed using SPSS Version 22.0. The difference between groups was considered significant when $P < 0.05$.

Results

Of the 5498 participants analyzed, 2049 (37.3%) were male and 3449 (62.7%) were female with female to male ratio 1.7:1. Age was 42.7 ± 15.8 (minimum 18 years and maximum 105 years), Table 1. MetS was present in 1967 cases (35.8%) where 673 cases (38.8%) were male and 1204 cases (61.2%) were female with female to male ratio 1.6:1, $P = 0.08$. Males were significantly older than females in MetS patients (45.5 ± 12.8 vs. 36.1 ± 13.3 respectively, $p < 0.0001$). BMI was significantly higher in MetS patients (31.9 ± 6.6 vs. 28.3 ± 6.7 respectively, $p < 0.0001$).

Parameters		Total	Metabolic syndrome		P value
			Present	Absent	
n (%)		5498	1967 (35.8)	3531 (64.2)	
Gender	Male	2049 (37.3)	673 (38.8)	1286 (36.4)	0.08
	Female	3449 (62.7)	1204 (61.2)	2245 (63.6)	
Age (years)		42.7 ± 15.8	45.5 ± 12.8	36.1 ± 13.3	< 0.0001
Body mass index (kg/m ²)		29.6 ± 6.9	31.9 ± 6.6	28.3 ± 6.7	< 0.0001

Table 1: Population characteristics (means \pm SD or number (%)).

Table 2 displays details of the diagnostic performance of BMI in detecting MetS using optimal BMI cut-off values based on the shortest distance in ROC curve. Optimal BMI cut-off values ranged from 28.50 to 29.50 in total

population, 27.50 to 28.50 in male and from 28.50 to 29.50 in female. The AUC was 0.615 (95% CI, 0.590-0.639) in male and 0.686 (95% CI, 0.668-0.704) in female, Figure 1.

Parameters	Area under curve (95% CI)	Cut-offs BMI kg/m ²	Sensitivity	Specificity	False positive rate	False negative rate	Positive likelihood ratio	Negative likelihood ratio	Misclassification rate
Total	0.659 (0.645-0.674)	29.0	0.63	0.64	0.36	0.37	0.98	0.58	0.73
Male	0.615 (0.590-0.639)	28.0	0.57	0.53	0.47	0.43	1.08	0.81	0.90
Female	0.686 (0.668-0.704)	29.5	0.66	0.64	0.34	0.36	1.03	0.53	0.70

Table 2: Diagnostic performance of BMI in detecting metabolic syndrome using optimal BMI cut-off values based on the shortest distance in ROC curves in Saudi adults.

Table 3 shows the predictive value of BMI in detecting MetS using BMI cut-off values based on the lowest significant association between BMI and the risk factors from the logistic regression analysis. Regression analysis showed that the risk of MetS was significantly increased at BMI values as low as ≤ 15.0 kg/m² and increased

progressively as BMI increased for both genders, Table 4. Applying this criterion to identify the cut-off values resulted in improvements in sensitivity, false negative rate and worsening in specificity and false positive rate. A very small false negative rate ranging from 0.001 to 0.005 resulted by using these lower BMI cut-offs.

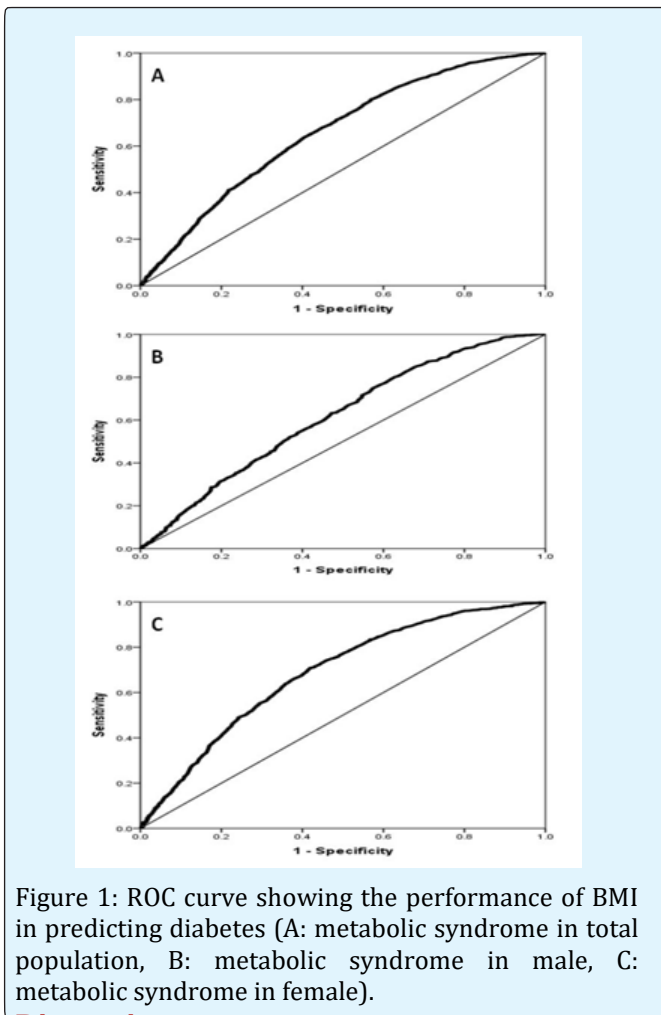
Parameters	Area under curve (95% CI)	Cut-offs BMI kg/m ²	Sensitivity	Specificity	False positive rate	False negative rate	Positive likelihood ratio	Negative likelihood ratio	Misclassification rate
Total	0.659 (0.645-0.674)	16.0	0.997	0.012	0.988	0.003	1.01	0.23	0.99
Male	0.615 (0.590-0.639)	17.0	0.999	0.013	0.987	0.001	1.01	0.08	0.99
Female	0.686 (0.668-0.704)	17.0	0.995	0.031	0.969	0.005	1.03	0.16	0.97

Table 3: Diagnostic performance of BMI in detecting metabolic syndrome using optimal BMI cut-off values based on the significant association using logistic regression in Saudi adults.

BMI (kg/m ²)	Total		Male		Female	
	Odd ratio (95% C I)	P	Odd ratio (95% C I)	P	Odd ratio (95% C I)	P
<15.0	16.3 (2.1-125.7)	0.007	-	-	16.1 (2.1-124.9)	0.008
15.0-15.9	10.9 (3.3-36.5)	<0.0001	-	-	9.9 (2.9-33.7)	<0.0001
16.0-16.9	23.4 (5.6-98.1)	<0.0001	-	-	18.6 (4.4-79.3)	<0.0001
17.0-17.9	19.9 (6.1-64.8)	<0.0001	15.6 (1.9-125.6)	0.01	19.9 (4.7-84.3)	<0.0001
18.0-18.9	11.5 (5.1-25.8)	<0.0001	9.0 (1.9-42.5)	0.005	11.7 (4.5-30.1)	<0.0001
19.0-19.9	8.6 (4.5-16.4)	<0.0001	10.4 (2.8-38.1)	<0.0001	6.9 (3.3-14.5)	<0.0001
20.0-20.9	10.8 (6.0-19.6)	<0.0001	8.5 (2.3-31.4)	0.001	11.2 (5.8-21.7)	<0.0001
21.0-21.9	6.1 (3.9-9.6)	<0.0001	2.4 (1.1-5.2)	0.02	11.5 (5.8-23.0)	<0.0001
22.0-22.9	5.5 (3.5-8.5)	<0.0001	2.4 (1.1-5.1)	0.02	9.4 (4.9-17.9)	<0.0001
23.0-23.9	3.9 (2.7-5.7)	<0.0001	2.3 (1.1-4.7)	0.03	4.7 (3.0-7.4)	<0.0001
24.0-24.9	3.6 (2.6-5.1)	<0.0001	2.1 (1.1-4.2)	0.04	4.4 (2.9-6.6)	<0.0001

25.0-25.9	3.0 (2.2-4.3)	<0.0001	1.6 (0.8-3.1)	0.2	4.2 (2.7-6.5)	<0.0001
26.0-26.9	2.3 (1.7-3.2)	<0.0001	1.3 (0.7-2.5)	0.4	3.1 (2.1-4.8)	<0.0001
27.0-27.9	2.0 (1.5-2.7)	<0.0001	1.2 (0.6-2.2)	0.6	2.6 (2.7-3.8)	<0.0001
28.0-28.9	2.3 (1.7-3.1)	<0.0001	1.4 (0.7-2.6)	0.3	2.8 (1.9-4.1)	<0.0001
29.0-29.9	2.0 (1.5-2.7)	<0.0001	1.2 (0.6-2.3)	0.5	2.3 (1.6-3.4)	<0.0001
30.0-30.9	1.6 (1.2-2.2)	0.003	1.1 (0.6-2.2)	0.7	1.7 (1.2-2.5)	0.006
31.0-31.9	1.7 (1.2-2.3)	0.001	1.1 (0.6-2.2)	0.6	1.8 (1.2-2.6)	0.002
32.0-32.9	1.6 (1.2-2.2)	0.003	1.0 (0.5-2.0)	0.9	1.8 (1.3-2.7)	0.001
33.0-33.9	1.2 (0.9-1.7)	0.2	0.9 (0.4-1.7)	0.7	1.3 (0.9-1.7)	0.2
34.0-34.9	1.2 (0.8-1.6)	0.4	1.0 (0.5-2.1)	0.9	1.1 (0.8-1.6)	0.5
35.0-35.9	1.2 (0.9-1.8)	0.3	0.7 (0.3-1.5)	0.4	1.4 (0.9-2.1)	0.1
36.0-36.9	0.9 (0.6-1.3)	0.5	0.9 (0.4-2.0)	0.8	0.9 (0.6-1.6)	0.8
37.0-37.9	1.3 (0.9-2.1)	0.2	0.6 (0.3-1.4)	0.2	1.2 (0.8-2.0)	0.4
38.0-38.9	1.1 (0.7-1.6)	0.8	0.9 (0.4-2.2)	0.9	1.0 (0.6-1.7)	0.9
39.0-39.9	1.5 (1.0-2.4)	0.08	0.9 (0.3-2.5)	0.8	1.7 (1.0-2.8)	0.05

Table 4: Risk of metabolic syndrome associated with increasing BMI in Saudi adults based on regression analysis.



Discussion

In this hospital-based cohort of Saudi adults, we showed that individuals with a BMI of ≤ 16.0 kg/m² have been significantly at higher risk of developing MetS with optimal BMI cut-off points of 29.5 kg/m² in women and 28.0 kg/m² in men. Our findings also higher to those of other studies conducted in Asian countries [44-54].

MetS is an asymptomatic, pathophysiological state characterised by obesity, insulin resistance, hypertension, dysglycaemia, and dyslipidaemia. The current study shows the prevalence of MetS to be 35.8% according to the IDF criteria, when BMI cutoff values have been implemented [55]. The prevalence of MetS in Saudi Arabia and gulf countries ranged from 33.7% to 40.5% using the same IDF criteria [41,56,57]. The prevalence of MetS was higher with age which was consistent with other studies [58-60]. Our sample shows that female had a higher prevalence of MetS (62.7%) than male (37.3%), a finding contrary to that of Flowers, et al. who found that males had a higher prevalence using the same MetS criteria and ascribed the sex differences to the protective effect of oestrogen [61,62].

The use of BMI with optimal cut-off points for diagnosis of obesity is important to establish consequent public health policies, treatment protocols and to determine the correct optimal cut-off points of BMI for each population. In 2004, the WHO consultation group stated that based on the existing data, Asians may have higher chances of acquiring disease at a BMI cut-off once presumed as low risk for obesity related disease (< 25 kg/m²) and since then multiple studies have been conducted in the Asian region to evaluate the best threshold of BMI regarding risk of disease [63]. Majority

of the studies point to the fact that Asians have a higher risk of developing MetS and CVD and have a higher percent of body fat, compared to their peer Caucasians living in the US and Europe with a similar BMI [64]. In one study in the eastern province of Saudi Arabia among a large population of adults over 30 years old, BMI cut-offs for detecting hypertension and diabetes were defined as 28.5 kg/m² and 29.5 kg/m² for men and 30.5 kg/m² and 31.5 kg/m² for women, although their ROC analysis did not show these cut-off points as having clinical value. Al-Lawati, et al. in 2008, reported the optimum BMI cut-off for the Omani Arab population as 23.2 kg/m² and 26.8 kg/m² for men and women older than 20 years old, respectively [38,39]. In another study evaluating BMI based on metabolic risk factors conducted in Guatemala, as a developing country, they documented BMI cut-offs as 24.7–26.1 kg/m² for men and 26.5–27.6 kg/m² for women. In a sample of the Chinese population Dong and colleagues evaluated 3006 individuals [65].

They documented a cut-off of 25 kg/m² for men and 24.5 kg/m² for women as appropriate for the prediction of metabolic syndrome in the Chinese population. For the Malaysian population, one study in 2009, based on their definition of cardiovascular risk as hypertension, dyslipidemia and diabetes, reported a BMI cut-off of 23.5 and 24.9 kg/m² for men and women, respectively [66]. Wannamethee, et al. in a prospective study in 2010, found that a BMI of between 28–29 kg/m² for men and a BMI of 29–30 kg/m² was optimal for the diagnosis of diabetes in a large sample of residence within the UK [67]. Pan et al. compared the accumulation of different risk factors including hypertension, diabetes, hypertriglyceridemia and hypercholesterolemia considering a similar positive predictive value between a Taiwanese population and a non-Hispanic Caucasian population from the US [46]. They found that with a similar positive predictive value, risk factors are much more prevalent in the Taiwanese population. One of the confounding factors that influence the difference in cut-off points among studies, other than ethnic differences, could be the different age groups selected for the studies. Age can change body composition regarding total and distribution of body fat and the metabolic factors [68].

BMI cut-off points defined by the WHO, are based on the risk factors associated with development of disease, mostly CVD. In light of the WHO expert consultation in 2004, it has become evident that a single BMI cut-off is unlikely to represent an equal accumulation of different risk factors for non-communicable disease among all ethnic groups and different populations worldwide

[63,69,70]. The optimum BMI for definition of disease has been a subject of great consideration among different researches. Studies have shown that Asians are likely to have a higher percent of adipose tissue, especially visceral adiposity, at lower BMI cut-off points than that reported by the WHO as standard cut-off points, which is based on studies in European and American populations [66,71]. A BMI of >30 kg/m², as defined by the WHO criterion was found to be less sensitive for predicting individual metabolic risk factors for MetS in both genders [54]. The important caveat is the BMI cut-off value selected. Our results, and those of others, show that it may not be appropriate to use the BMI cut-offs developed for certain other groups (e.g. European Americans or African Americans) for Saudi population since Saudis seem to experience metabolic abnormalities at lower BMI [72–75]. The suggestion to use different cut-off values is not new. Other studies have also called for lower BMI cut-offs [76]. BMI cut-off values of 25.0 kg/m² and 30.0 kg/m², derived from European populations, are associated with increased co-morbidities in Saudi population and are clearly too high to use. They underestimate the prevalence of MetS and obfuscate the large numbers of Saudis who evince metabolic abnormalities at these higher BMI cut-offs. Some researchers have called for an even lower BMI cut-off (21.0 kg/m²) for overweight in Asians, but this suggestion has failed to gain consensus [77–79].

In our study, the risk of MetS associated with each BMI level was estimated, adjusting for other covariates. To assess the impact of the other covariates, we estimated an unadjusted logistic regression model with BMI level as the only covariate. The Odds Ratios (OR), which approximate the relative risks in the nested case-control analysis, are listed in Table 4. BMI cut-off of 16.0 kg/m² was associated with the highest unadjusted and adjusted prevalence ratio particularly in females. The unadjusted ORs were slightly higher than the adjusted ORs. This implies that some factors, such as age and gender, are associated with both increased BMI and increased risk of MetS, but the impact of these factors on the association between BMI and risk of MetS is limited. Moreover, BMI values were clinically measured in the current study, compared with BMI calculated from self reported height and weight in those earlier studies. Self reported weight and height considerably underestimate the individuals' measured BMI and may thus have weakened the association between obesity and risk of MetS and/or biased the estimated results [80,81]. Self reported diabetes has high specificity and positive predictive value but low sensitivity [82]. This may explain the higher OR

associated with BMI levels in the current study compared to other report [83].

The overall performance of the ROC curve can be quantified by estimating the AUC which ranged from 0.59 to 0.70, Table 2. An area of 1.0 is perfect and an area <0.5 is considered non-informative. Our results indicated that the ROC analysis was close to a non-informative test as shown in the Figure 1. ROC curve analysis showed that the corresponding sensitivities and specificities were poor (<0.63 and <0.64, respectively). This indicates that the percentage of people identified as having the risk factors and the percentage of people who were identified as not being at risk were less than 63% of total population. Both positive likelihood ratio and negative likelihood ratio were close to 1.0, indicating a minimal increase in the likelihood of the presence of the risk factor if the test is positive and a minimal decrease in the likelihood if the test is negative. The false positive and false negative rates were high and close to each other in both women and men. Several reasons may explain the weakness of BMI as a tool to classify obesity in the Saudi Arabian population. First, BMI does not reflect fatness uniformly in all populations and different ethnic groups [76]. This may suggest the importance of including a measure of abdominal obesity in classifying obesity in Saudi populations. Second, the short stature of Saudi women could be limiting the usefulness of BMI in this population [37].

The overall misclassification was high and exceeded 90% of the total population across all the selected BMI cut-off points. Most of the other previous studies that have been conducted in non-Caucasian populations did not assess the misclassification rate [84-87]. However, one study conducted in Asian Indians indicated a high overall misclassification rate, particularly in women [76]. Those authors concluded that the BMI did not accurately predict overweight in that population. This is not the first study to suggest the presence of a significantly increased risk of MetS at BMI values less than 25. However, the use of such low cut-offs would lead to large misclassification of healthy people as being at risk, as indicated by the high values of sensitivities and false positive rates. This fact that could cause unnecessary and costly diagnostic testing. Overall the total misclassification rate was unacceptably high, even with the use of different BMI cut off points. These findings illustrate the significant limitations in using BMI alone for obesity diagnosis in the Saudi Arabian population.

Our results should be interpreted in light of the study's limitations. First, most of the patients enrolled were already on treatment for hypertension, diabetes and hypercholesterolaemia, which imposed some limitations on the study. We tried to overcome these by obtaining the necessary sample size and by using data documented before treatment. Finally, as this was a hospital-based, retrospective study, the findings do not represent the whole Saudi population or the local community. Further larger population-based studies are necessary to support our findings. Another limitation of the present study was having considered only overall obesity (assessed by BMI) and not abdominal obesity (measured by waist circumference), which is known to bear a close relationship with the target diseases.

Conclusion

The diagnostic usefulness of BMI alone in defining obesity in patients with MetS is limited among men and women Saudi adults.

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