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Utility of Continuous Metabolic Syndrome Score in Assessing Risk of Type 2 Diabetes: The Isfahan Diabetes Prevention Study

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Key Words
Diabetes mellitus · Continuous metabolic syndrome score · First-degree relatives · Metabolic syndrome · Risk factors

Abstract
Background/Aim: It is not clear whether levels of continuous metabolic syndrome (cMetS) are associated with type 2 diabetes (T2D). The aim of this study was to determine the ability of the cMetS score to predict progression to T2D in non-diabetic first-degree relatives (FDRs) of patients with T2D in Isfahan, Iran. ***Methods:*** A total of 1,869 non-diabetic FDRs 30–70 years old in 2003–2005 were followed through 2014 for the occurrence of T2D. At baseline and through follow-ups, participants underwent a standard 75 g 2-h oral glucose tolerance test. MetS was defined by the National Cholesterol Education Program-Adult Treatment Panel III. The cMetS score was calculated using age- and gender-standardized Z-score for MetS components. Receiver operating characteristic (ROC) curve was used to assess the association between cMetS and components of MetS with T2D. ***Results:*** During 13,571 person-years of follow-up, 72 men and 210 women developed diabetes. Those in the top quartile of cMetS were 8.0 times more likely to develop diabetes than those in the bottom quartile (OR 7.96; 95% CI 4.88–12.99). On ROC curve analysis, a higher area under the ROC were found for FPG (74.3%; 95% CI 70.8–77.8), than for cMetS (69.4%; 95% CI 66.0–72.8). ***Conclusions:*** The cMetS score is a robust predictor of T2D and may be more effective and efficient than the current binary definition of MetS in predicting progression to T2D in our study population.

Introduction

The metabolic syndrome (MetS), which is a cluster of metabolic risk factors that are associated with insulin resistance, is a complex disorder and increases the risk for all-cause mortality, cardiovascular disease (CVD) morbidity and mortality, type 2 diabetes (T2D), and some cancers [1]. It is highly prevalent worldwide but its clinical value remains unsettled [2].

The World Health Organization report suggested that MetS is a pre-morbid condition for predicting the development of CVD and T2D rather than a clinical diagnosis [3]. However, the current binary definition of MetS has limited practical utility as an evaluative or managerial tool. The question then arises whether the continuous MetS (cMetS) score is a better predictor of T2D risk than binary definition for epidemiological studies. Increasing evidence supports the use of a cMetS score in epidemiological studies [2] because (a) dichotomizing continuous outcome variables reduces statistical power [2, 4]; (b) di-

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abetes risk is a progressive function of several MetS components; (c) T2D risk increase progressively with increasing number of MetS components [5]; and (d) the cMetS score is more sensitive and less error-prone, eliminating the need to dichotomize MetS components [2, 4, 6, 7]. In the joint statement by the American Diabetes Association and European Association for the study of diabetes [2], it was recommended that one area of necessary research was the definition of the MetS based on continuous variables in a multivariate score system. To our knowledge, no cohort studies have described the possible association between cMetS score and the risk of T2D.

The objective of this study, therefore, was to determine the ability of the cMetS score, using the age- and gender-standardized Z-score for MetS components, to predict the incidence of T2D. We hypothesize that increase in the cMetS score is associated with T2D.

Patients and Methods

Data Collection

This study was conducted using the data from the Isfahan Diabetes Prevention Study (IDPS), an ongoing prospective single-center observational study in central Iran to assess the various potential risk factors for diabetes in subjects with family history of T2D (one of the main risk factors for T2D). The recruitment methods and examination procedures of the IDPS have been described previously [8]. The IDPS sample at baseline comprised 3,483 (919 men and 2,564 women) first-degree relatives (FDR) of consecutive patients with T2D. All patients were attendees at clinics at Isfahan Endocrine and Metabolism Research Center, which is affiliated to Isfahan University of Medical Sciences, Iran. The study was conducted between 2003 and 2005. All participants were from Isfahan city and adjoining areas. They completed a standardized medical examination and laboratory tests including a standard 75 g 2-hour oral glucose tolerance test (OGTT), standardized blood pressure (BP), a questionnaire on their health status and on various potential risk factors for diabetes. Participants receive follow-up tests according to Standard of Medical Care in Diabetes [9] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes. Accordingly, if OGTT was normal at baseline, repeat testing was carried out at least at a 3-year interval. Otherwise, repeat testing was carried out annually.

Ethics Statement

The Iranian government's ethical guidelines regarding epidemiological studies in accordance with the current version of the Declaration of Helsinki were followed, and Isfahan University of Medical Sciences ethical committee approval was granted, and an informed consent form was signed by each participant.

Follow-Up and Ascertainment of T2D

Among 3,483 persons who participated at baseline, 319 subjects were excluded because of diagnosis of T2D at baseline and 1,295 did not attend any follow-up examination, leaving 1,869 participants with a mean (SD) age of 43.0 (6.5, range 30–70) for this analysis, all of whom had at least one subsequent review during a mean (SD) follow-up period of 7.3 (2.2, range 1–10) years. Pregnant women were excluded. The most prominent characteristics of individuals who did not attend follow-up visit, such as age, height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), and low-density lipoprotein cholesterol (LDLC), total cholesterol, triglyceride (Tg) and obesity, were similar to the characteristics of those who attended the baseline study. However, non-attendees had slightly lower fasting plasma glucose (FPG; 94.7 vs. 95.7 mg/dl, $p < 0.05$), plasma glucose (PG) at 30 min (139.5 vs. 144.2 mg/dl, $p < 0.001$), 60 min (140.8 vs. 149.8 mg/dl, $p < 0.001$), and 120 min (110.6 vs. 119.5 mg/dl, $p < 0.001$), levels of glycosylated hemoglobin (HbA1c, 5.0 vs. 5.1%, $p < 0.05$), systolic BP (113.2 vs. 115.7 mm Hg, $p < 0.001$), diastolic BP (73.4 vs. 75.7 mm Hg, $p < 0.001$), and higher high-density lipoprotein cholesterol (HDLC, 46.7 vs. 45.0 mg/dl, $p < 0.001$).

Procedures

Information on age, gender, body size, HbA1c, cholesterol, LDLC, HDLC, Tg and BP, family and personal medical history was collected at the baseline and through follow-ups. The same methodology was used for both the prevalence and incidence studies. They included siblings or children and they reported to clinics in the morning after an overnight fast. Subjects were asked to abstain from vigorous exercise in the evening before and in the morning of the investigations. Smokers were encouraged to abstain from smoking in the morning of the investigations. On arrival in the clinic, the information given by the participants in the questionnaire on family history was first verified. Then height and weight were measured with subjects in light clothes and without shoes using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, waist, and HC were measured to the nearest 0.5 cm with a measuring tape. Waist was measured midway between the lower rib margin and the iliac-crest at the end of a gentle expiration. HC was measured over the greater trochanters directly over the underwear. A physician measured BP after subjects had been seated for 10 min by using a mercury sphygmomanometer and appropriately sized cuffs, using standard techniques. FPG was measured using the glucose oxidase method. Subjects with FPG <126 mg/dl underwent a standard OGTT (75 g glucose 2-hour) at baseline and the follow-ups. Venous blood was sampled at fasting, 30, 60, and 120 min after oral glucose administration. Plasma samples obtained after centrifuge were analyzed the same day.

HbA1c (measured by ion-exchange chromatography), total cholesterol, Tg, HDLC, and LDLC (calculated by the Friedewald equation [10] provided total Tgs did not exceed 400 mg/dl) were assessed. All the blood-sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using the enzyme-linked method.

Definitions

We calculated BMI as the ratio of weight (kg) to squared height (m^2), the latter being assessed only at baseline. Those participants with FPG ≥200 mg/dl or pharmacological treatment were considered diabetic. If FPG was ≥126 and <200 mg/dl, a second FPG was measured on another day. If the second FPG was also ≥126 mg/dl, participants were considered diabetic. FPG ≥126 mg/dl or 2-hour PG of ≥200 mg/dl defined diabetes mellitus. The definition of MetS

used in this study is based on the 2009 consensus criteria [11], which was the same as the third report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [12] by the presence of three or more of the following abnormalities: BP ≥130/85 mm Hg or a history of hypertension and current use of antihypertensive treatment; waist girth >102 cm for men and >88 cm for women, serum Tg ≥150 mg/dl and/or HDL cholesterol (<40 mg/dl for men and <50 mg/dl for women), and FPG levels ≥100 mg/dl. The mean arterial pressure (MAP) was calculated using the following formula: MAP = ((systolic BP – diastolic BP)/3) + diastolic BP.

The cMetS score was calculated by the use of standardized residuals (Z-score) of MAP, Tg, FPG, WC and HDLC [7]. The score is a summary measure. By subtracting the overall mean and divided by the standard deviation, a Z-score was obtained. All individuals were assigned this value, reflecting their deviation from the mean. Z-scores for all items in the MetS definition of NCEP-ATP III were then summed. The cMetS ranged from –8.98 to 17.57. Higher scores signify less favourable metabolic profile. The standardized HDLC was multiplied by –1 since it is inversely related to metabolic risk. MAP was used since including both systolic and diastolic would load 2 BP variables into the calculation, and MAP represent both systolic and diastolic BP.

Analysis

Incidence was expressed as the number of cases of T2D per 1,000 person-years of follow-up beginning on the date of completion of the baseline examination in 2003–2005 and continuing until the occurrence of T2D, the date of the last completed follow-up, death, or end of follow-up on March 21, 2014, whichever came first. Statistical methods used included the Student's t test, chi-square test, and multiple logistic regression. The incidence of T2D was calculated according to the quartile of cMetS level and compared the risk of developing T2D in each quartile with the lowest category of risk (reference group). Univariate and multivariate logistic regressions were fitted to identify predictors of new-onset diabetes using the SPSS for Windows (SPSS Inc., Chicago, Ill., USA). Adjustment for age and gender was examined in separate models. Age- and gender-adjusted means were calculated and compared using general linear models. The number of subjects included in the individual analyses varies slightly because of missing values. The ability of cMetS and components of MetS to predict incidence diabetes was examined by receiver operating characteristic (ROC) curve and their respective areas under the curve, in which sensitivity is plotted as a function of 1 – specificity. Areas under the ROC curves were compared by the algorithm developed by DeLong et al. [13]. All tests for statistical significance were 2-tailed, and performed assuming a type I error probability of <0.05.

Results

Characteristics

During the follow-up, a total of 282 (72 men and 210 women) incident cases of T2D occurred during 13,571 (3,460 men and 10,111 women) person-years of follow-up. Baseline characteristics of the 1,587 (84.9%) participants without and 282 (15.1%) with T2D are shown in table 1. As expected, those who developed T2D were older and had higher age- and gender-adjusted mean BMI, WC, HC, FPG, and PG at 30, 60 and 120 min, higher HbA1c, Tg, cholesterol, diastolic BP and cMetS score at baseline, and a higher proportion of overweight and MetS. The mean (SD) age was 44.4 (6.8) for those with and 42.7 (6.4) for those without T2D. The mean (SD) cMetS score was 1.51 (2.7) for those with and –0.27 (2.7) for those without T2D.

Table 1. Age, and age-, gender-adjusted means (SE) and proportions of selected baseline characteristics between 282 first-degree relatives of patients with T2D who did and 1,587 who did not develop diabetes

Variables	Developed diabetes mean (SE)	Not developed diabetes mean (SE)
Age, years	44.4 (0.39)	42.7 (0.16)***
cMetS	1.51 (0.15)	–0.27 (0.06)***
Height, cm	159.4 (0.33)	159.9 (0.14)
Weight, kg	76.9 (0.68)	73.3 (0.29)***
BMI, kg/m^2	30.3 (0.25)	28.7 (0.10)***
WC, cm	92.2 (0.54)	88.7 (0.23)***
HC, cm	109.9 (0.52)	107.0 (0.22)***
WHR	0.84 (0.003)	0.83 (0.001)**
Systolic BP, mm Hg	117.5 (0.95)	115.5 (0.40)
Diastolic BP, mm Hg	77.1 (0.71)	75.5 (0.30)*
Baseline fasting glucose, mg/dl	104.4 (0.67)	94.1 (0.28)***
PG 30 min, mg/dl	164.0 (1.86)	140.6 (0.77)***
PG 60 min, mg/dl	186.5 (2.41)	143.2 (1.01)***
PG 120 min, mg/dl	146.6 (1.84)	114.7 (0.77)***
HbA1c, %	5.4 (0.05)	5.0 (0.02)***
Tg, mg/dl	194.7 (5.96)	161.3 (2.48)***
Cholesterol, mg/dl	200.9 (2.42)	195.7 (1.01)*
HDLC, mg/dl	44.0 (0.71)	45.2 (0.30)
LDLC, mg/dl	120.2 (2.20)	119.4 (0.89)
Women, %	74.5	73.8
Overweight (BMI ≥25)	90.6	82.9***
MetS, %	55.3	34.5***

Age-adjusted means were calculated using general linear models. The difference in the mean or percentage of the variables between diabetes and no diabetes. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The baseline characteristics of the study participants by the cMetS score quartile are shown in table 2. When variables at baseline were compared, it was found that all variables were more likely to increase, and HDLC and follow-up duration were more likely to decrease across all four subject groups.

Incidence of Diabetes

The overall incidence of subsequent diabetes was 20.8 (95% CI 18.4–23.2) per 1,000 person-years. Incidence rates were similar in women (20.8, 95% CI 18.0–23.5 per 1,000 person-years) and men (20.8, 95% CI 16.3–26.2).

Table 2. Age and age-, gender-adjusted mean (SE) and proportion of first-degree relatives of patients with T2D by cMetS score quartile in the IDPS

Characteristic	Total	cMetS at baseline			
		1st quartile (<–1.91)	2nd quartile (–1.92 to –0.13)	3rd quartile (–0.14 to 1.75)	4th quartile (>1.75)
Number, %	1,869 (100)	467 (25.0)	467 (25.0)	468 (25.0)	467 (25.0)
cMetS	0.00 (0.00)	–3.36 (0.05)	–0.95 (0.05)	0.80 (0.05)	3.51 (0.06)**
Age, years	43.0 (0.15)	41.6 (0.30)	41.8 (0.30)	43.9 (0.30)	44.7 (0.30)**
Height, cm	159.8 (0.19)	159.0 (0.26)	159.5 (0.26)	160.3 (0.26)	160.3 (0.27)*
Weight, kg	73.8 (0.28)	65.6 (0.47)	71.4 (0.47)	76.5 (0.46)	81.9 (0.48)**
WC, cm	89.2 (0.22)	81.6 (0.35)	87.2 (0.34)	91.5 (0.35)	96.7 (0.35)**
HC, cm	107.4 (0.21)	102.1 (0.38)	105.8 (0.37)	109.4 (0.37)	112.5 (0.38)**
WHR	0.83 (0.002)	0.80 (0.002)	0.83 (0.002)	0.84 (0.002)	0.86 (0.002)**
BMI, kg/m^2	28.9 (0.10)	26.0 (0.17)	28.1 (0.17)	29.9 (0.17)	31.8 (0.17)**
Follow-up duration, years	7.3 (0.05)	7.6 (0.10)	7.5 (0.10)	7.2 (0.10)	6.8 (0.10)**
FPG, mg/dl	95.6 (0.28)	88.0 (0.50)	93.2 (0.50)	98.5 (0.49)	102.8 (0.51)**
PG 30 min, mg/dl	144.1 (0.51)	131.6 (1.45)	141.3 (1.43)	148.3 (1.44)	155.7 (1.49)**
PG 60 min, mg/dl	149.7 (1.02)	130.6 (1.90)	141.2 (1.89)	156.1 (1.89)	171.5 (1.95)**
PG 120 min, mg/dl	119.5 (0.78)	107.8 (1.50)	115.4 (1.48)	123.0 (1.47)	131.7 (1.52)**
HbA1c	5.1 (0.02)	4.9 (0.04)	5.1 (0.04)	5.2 (0.4)	5.2 (0.04)**
Cholesterol, mg/dl	196.5 (0.95)	192.0 (1.88)	194.2 (1.86)	194.1 (1.85)	205.7 (1.91)**
LDLC, mg/dl	119.5 (0.84)	117.4 (1.66)	119.8 (1.65)	119.8 (1.64)	121.2 (1.78)**
HDLC, mg/dl	45.0 (0.28)	53.2 (0.49)	46.7 (0.49)	42.2 (0.49)	37.8 (0.50)**
Tg, mg/dl	166.3 (2.35)	112.2 (4.10)	141.3 (4.07)	162.8 (4.04)	248.6 (4.14)**
Systolic BP, mm Hg	115.7 (0.38)	105.0 (0.65)	113.4 (0.64)	117.3 (0.65)	127.2 (0.66)**
Diastolic BP, mm Hg	75.7 (0.28)	67.3 (0.49)	73.8 (0.48)	77.7 (0.48)†	84.2 (0.49)**
MAP, mm Hg					
Women, n (%)	1,380 (73.9)	415 (89.1)	383 (82.0)	326 (69.7)	256 (54.8)**
Overweight, n (%)	1,152 (84.1)	358 (77.2)	377 (82.3)	420 (91.5)	447 (96.1)**
MetS, n (%)	704 (37.7)	3 (0.6)	46 (9.9)	243 (51.9)	412 (88.2)**

Data are expressed as mean (SE) or number (%). * $p < 0.01$, ** $p < 0.001$ comparison across all 4 groups.

The incidence of T2D was 39.4 per 1,000 person-years (95% CI 32.8–46.8) for participants in the highest quartile of cMetS score, and 6.2 per 1,000 person-years (95% CI 3.9–9.3) for the lowest quartile. The risk of T2D increased with increasing quartiles of the cMetS score. Compared with participants in the lowest quartile, the risk of T2D was 8.0 times higher in those in the highest quartile at baseline (OR 7.96; 95% CI 4.88–12.99) and 4.7 times higher in those in the 3rd quartile (OR 4.69; 95% CI 2.86–7.69) and 2.4 times higher in those in the 2nd quartile (OR 2.38; 95% CI 1.41–4.01) in age- and gender-adjusted models (table 3).

The ROC curves for the incidence of T2D for the cMetS score and each component of MetS are shown in figure 1. The areas under the ROC curves from the largest to the least area were 0.743 (95% CI 0.708–0.778, $p < 0.001$) for FPG, 0.694 (95% CI 0.660–0.728, $p < 0.001$) for the cMetS score, 0.613 (95% CI 0.578–0.649, $p < 0.001$) for WC, 0.586 (95% CI 0.548–0.525, $p < 0.001$) for Tg, 0.553 (95% CI 0.514–0.593, $p < 0.01$) for MAP, and 0.541 (95% CI 0.502–0.580, $p < 0.05$) for HDLC. All parameters were significant predictors of T2D. HDLC had an area smaller than that of other components of MetS. Pairwise comparison results indicates that the areas under the curves between cMetS score and FPG vs. HDLC, MAP, Tg, and WC were statistically significant ($p < 0.001$). Also, the area under the ROC curves for FPG and cMetS is not significantly different. It is apparent that in this population of FDRs of patients with T2D, the cMetS score was slightly inferior to FPG in identifying those who developed T2D according to area under the ROC curve, although the difference was not statistically significant.

At a cMetS score of zero or higher, the sum of sensitivity and specificity was maximized. Accordingly, the optimal cut-point for detecting T2D was a cMetS score great-

Table 3. Incidence rates and OR of diabetes by cMetS score quartile at baseline, the IDPS

	cMetS at baseline			
	1st quartile (<–1.91)	2nd quartile (–1.92 to –0.13)	3rd quartile (–0.14 to 1.75)	4th quartile (>1.75)
Number of cases, %	22 (4.7)	49 (10.5)	87 (18.6)	124 (26.6)
Person-years	3,549	3,510	3,371	3,150
Incidence/1,000 person-year (95% CI)	6.2 (3.9–9.3)	14.0 (10.3–18.4)	25.8 (20.7–31.7)	39.4 (32.8–46.8)
Unadjusted OR (95% CI)	1.00	2.37 (1.41–3.99)**	4.62 (2.84–7.52)**	7.31 (4.55–11.76)**
Gender-adjusted OR (95% CI)	1.00	2.44 (1.45–4.11)*	5.04 (3.09–8.24)**	8.61 (5.30–14.00)**
Age- and gender-adjusted OR (95% CI)	1.00	2.38 (1.41–4.01)*	4.69 (2.86–7.69)**	7.96 (4.88–12.99)**

OR (with 95% CI) calculated by binary logistic regression. * $p < 0.01$, ** $p < 0.001$.

er than or equal to zero. Of the total sample, 48.2% had a score of zero or higher. At a cMetS score greater or equal to zero, sensitivity was 74.1% and specificity was 56.4%. However, the sensitivity and specificity of binary definition of MetS were 55.3 and 65.5%, respectively. Thus, the Youden's index of optimum cMetS score was higher than the binary-defined MetS.

Discussion

This study showed that the cMetS score is a strong predictor of incident T2D in a cohort of FDR of patients with T2D in Iran. The area under the ROC curve of FPG was higher than other MetS components, further emphasizing the utility of glucose testing alone in predicting T2D. The cMetS score is a slightly weaker diabetes risk predictor than FPG. However, a simple FPG measurement was a better predictor of future diabetes than the expense and inconvenience necessary to measure the cMetS score. No study has assessed the risk of T2D in persons with the cMetS score. Several studies have assessed risks of diabetes in persons with binary definition of MetS, and the results are inconsistent. Some of them showed that the presence of binary MetS was predictive of progression to diabetes [5, 14–22], whereas more recent studies showed no significant association of binary MetS in the development of T2D [23–28]. Our previous study [28] and other studies [5, 17, 23, 27] took into consideration that FPG has a greater impact on the development of T2D than other components of MetS. On the basis of our overall findings, FPG could be argued to be the best and most practical predictor of progression to diabetes.

The possible explanation for the superior predicting ability of the FPG and cMetS score is that the FPG and cMetS score are treated as continuous variables and not dichotomized as in NCEP-ATP III-defined MetS. Similarly, our findings confirm those of other studies [5, 23, 28] that the ability of cMetS scores to predict risk of diabetes can largely be attributed to its glucose component.

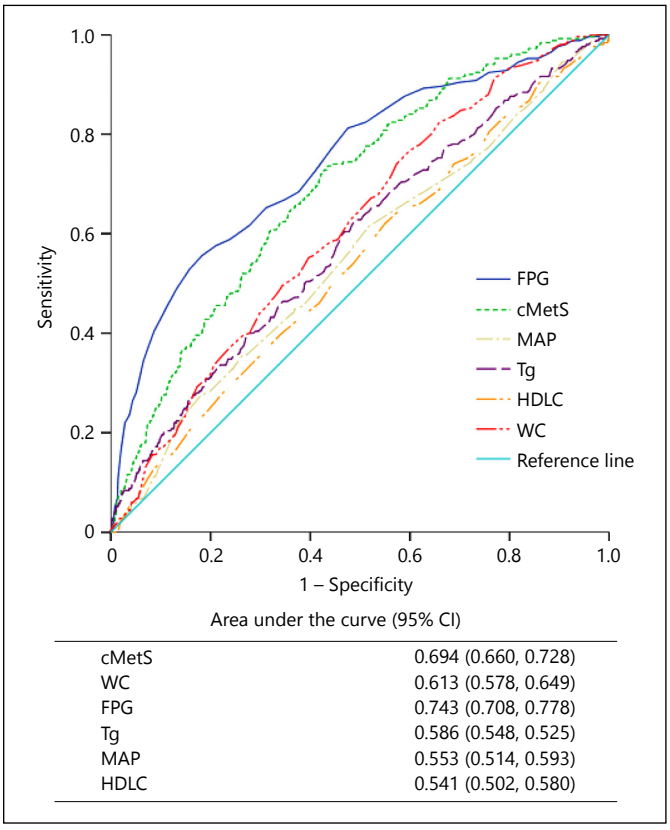

Fig. 1. ROC curves for cMetS score, FPG, WC, Tg, MAP and HDLC to predict T2D in non-diabetic FDRs of patients with T2D. The estimates of the area under the ROC curves and their 95% CIs are shown.

The aim of the original concept for MetS itself was to encourage individuals who were diagnosed as MetS to pay attention to the clustering of often overlooked cardiovascular risk factors with the aim of improving cardiovascular and T2D prevention strategies; it was not intended for conducting clinical diagnosis [3, 29]. On the basis of our overall findings, FPG and the cMetS score could be argued to be the best and FPG could be the most practical predictor of progression to T2D to avoid the costs and inconveniences of a cMetS score.

Our study has several strengths and limitations. This is the first study to examine the association of cMetS score and T2D incidence. Although the use of cMetS score implies population specific results, the cMetS score is more appropriate than using the binary definition of MetS for epidemiological studies. Additional strengths of this study include the prospective cohort design, the sample consisting of both men and women of a wide age range, diagnosis of diabetes based on standard OGTT, and information on potential determinants of diabetes. Selection and information bias were unlikely because of the prospective design. However, some limitations of this study should be addressed. Some selection bias might have occurred because the current sample is not fully representative of the Iranian FDR of patients with T2D.

In conclusion, the results of this study indicates that although the cMetS risk score is a robust predictor of T2D and may be more effective and efficient than the current binary definition of MetS in predicting progression to T2D, FPG appeared to be a more robust predictor of T2D in our study population. More researches are needed to determine the effectiveness of the cMetS score in other regions and populations.

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Declaration of Competing Interests

None to declare.

Authors Contributions

M.J. conceived and designed the study, analyzed the data and wrote the manuscript; M.A. recruited samples and contributed to the discussion and revision of the manuscript and obtained funding for the IDPS.

Disclosure Statement

None.

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