Endocrine (2019) 65:73–80
https://doi.org/10.1007/s12020-019-01970-5

ORIGINAL ARTICLE

Check for updates

Development of a metabolic syndrome severity score and its association with incident diabetes in an Asian population—results from a longitudinal cohort in Singapore

Serena Low[1,2] · Kay Chin Jonathon Khoo[2] · Jiexun Wang[2] · Bastari Irwan[3] · Chee Fang Sum[1] · Tavintharan Subramaniam[1] · Su Chi Lim[1,2,4] · Tack Keong Michael Wong[5]

Received: 8 February 2019 / Accepted: 24 May 2019 / Published online: 3 June 2019

Abstract

Purpose Metabolic syndrome (MetS) is a constellation of clinical factors that indicates elevated risk of diabetes. It is diagnosed based on three or more abnormalities in its components. This does not take into account that MetS can likely present as a continuum of risk. We aim to develop a MetS severity score and assess its association with incident diabetes.

Methods In total, 4149 subjects without baseline diabetes participated in a community screening programme in 2013–2017. MetS was defined according to International Diabetes Federation criteria. A MetS severity z-score was derived from standardised loading coefficients of a confirmatory factor analysis for waist circumference, triglycerides, HDL-cholesterol, blood pressure and fasting plasma glucose (FPG). Multivariable cox proportional hazards regression model was used to assess the risk of diabetes by the score with adjustment for demographics and MetS components.

Results Diabetes occurred in 130 subjects. Quintile 5 of the baseline MetS severity z-score was significantly associated with development of diabetes even in fully adjusted model with HR 2.63 (95% CI: 1.04–6.64; $p = 0.040$). The relationship between MetS and incident diabetes became attenuated and non-significant in fully adjusted model with HR 0.67 (95% CI: 0.34–1.29; $p = 0.228$). Mediation analysis showed that MetS severity z-score accounted 61.0% of the association between increasing body mass index and development of diabetes ($p < 0.001$).

Conclusions The MetS severity z-score is an inexpensive and clinically-available continuous measure of MetS to identify individuals at high risk of diabetes.

Keywords Metabolic syndrome · Diabetes Mellitus · Risk factor · Severity

Introduction

The ongoing rise in prevalence of diabetes mellitus (DM) globally is a major public health concern. In Singapore, there are ~440,000 residents aged 18 years and above with DM in 2014. It is estimated that the number will increase to 1 million in 2050 [1]. The significant morbidity and mortality from the complications engendered by DM [2] warrants an urgent need to understand the risks of DM in an effort to prevent its development.

Notably, metabolic syndrome (MetS) is a constellation of clinical parameters that show elevated risk for Type 2 DM (T2DM) [3]. It is diagnosed when waist circumference (WC) is high and two of the following abnormalities: raised triglycerides (TG), low HDL-Cholesterol (HDL-C), raised blood pressure (BP) and raised fasting plasma glucose (FPG) [4]. The clustering of these risk factors was

These authors contributed equally: Serena Low, Kay Chin Jonathon Khoo

Supplementary information The online version of this article (https://doi.org/10.1007/s12020-019-01970-5) contains supplementary material, which is available to authorized users.

✉ Su Chi Lim
lim.su.chi@ktph.com.sg

1 Diabetes Centre, Admiralty Medical Centre, Singapore, Singapore

2 Clinical Research Unit, Khoo Teck Puat Hospital, Singapore, Singapore

3 Transformation Office, Hospital Administration, Khoo Teck Puat Hospital, Singapore, Singapore

4 Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

5 Family and Community Medicine, Khoo Teck Puat Hospital, Singapore, Singapore

apparently driven by underlying alterations in physiological processes involving insulin resistance such as adipocyte dysfunction, systemic inflammation, oxidative stress and abnormalities of cellular function [5–8]. MetS has been associated with higher risk for diabetes [9]. There are, however, a few drawbacks of using MetS to predict development of DM. Firstly, the binary nature of the MetS components does not reflect the continuum of risk in MetS [10, 11]. Secondly, there is a challenge to track changes in MetS status over time as its dichotomous status—yes or no—can fluctuate depending on whether the cut-off for the components are met at every follow-up [10, 12, 13]. Another drawback is the attribution of equal importance to individual MetS components as this ignores the fact that certain components may be more strongly linked to MetS [14].

To address these gaps, development of MetS severity score has emerged in recent years [3, 7, 11, 14–16]. A few studies have demonstrated that MetS severity score was significantly associated with risk of T2DM [7, 14, 15]. Despite the surge in interest in MetS severity score and its clinical utility, research on development of MetS severity score remains limited in Asia. Furthermore, the mechanism on the role of MetS severity on development of DM is unclear. We therefore aim to develop a baseline MetS severity score, explore its relationship with development of T2DM and elucidate the mechanism for the relationship.

Materials and methods

We carried out a retrospective cohort study on residents who were aged ≥40 years and took part in the Alexandra Health Community Health Screening in the Northern Region of Singapore. During the period September 2013 to December 2017, 18,746 residents had taken part in this screening conducted in the regional hospital, markets and during community events. For the purpose of the analysis, they were excluded if they had fewer than two fasting plasma glucose (FPG) values during the study period ($n =$ 14,250), pre-existing diabetes at baseline or baseline FPG ≥7 mmol/l ($n = 347$). There were 4149 participants who were included in the analysis.

The methodology was described in our earlier paper [17]. The participants were administered a questionnaire on demographics, history of pre-existing diseases, medications, exercise and smoking. Trained nurses assessed blood pressure with standard automated sphygmomanometer when the subjects were sitting up, having rested for 5 min or more. The following anthropometric measurements were taken: height, weight, WC, and body mass index (BMI) derived from weight and height. Fasting blood samples were collected from the participants and measured in the hospital laboratory accredited by the Royal College of the American Pathologists. The following methods were used for quantification: FPG by hexokinase method (Roche cobas® c 701) with intra-assay coefficients of variations (CV) 0.5 to 1.7% and inter-assay CV 0.4 to 1.5% (inter-assay); HDL-C and TG by enzymatic colorimeter test (Roche cobas® c 501) with intra-assay CV 0.4 to 1.0% and inter-assay CV 0.9 to 1.5% for HDL-C and intra-assay CV 0.7 to 1.1% and inter-assay CV 1.6 to 2.0% for TG [18–20].

According to the International Diabetes Federation (IDF), MetS is diagnosed if the following criteria are met: central obesity as defined by WC ≥ 90 cm in males and ≥80 cm in females; and abnormalities in at least two of the following components: TG ≥ 1.7 mmol/l or treatment for this lipid abnormality); HDL-C < 1.03 mmol/l in males and <1.29 mmol/l in females or treatment for this lipid abnormality; systolic BP (SBP) ≥130 mmHg or diastolic BP (DBP) ≥85 mmHg or treatment for previously diagnosed hypertension; and FPG ≥5.6 mmol/l [4].

T2DM was the outcome in this study. Subjects were considered as having developed T2DM if one of the following occurred: (1) FPG ≥ 7.0 mmol/l as recommended by standards of medical care from the American Diabetes Association [20]; (2) diabetes on self-report; or (3) treatment with medication for diabetes [7, 22, 23].

Statistical analysis

The MetS severity was modelled by one-factor confirmatory factor analysis (CFA). For each patient i for $i = 1, 2, 3, \ldots 1000$, we assume

$$\mathrm{WC}_i = \alpha_1 + b_1 \mathrm{MetS}_i + e_{1i},$$

$$\mathrm{In(TG)}_i = \alpha_2 + b_2 \mathrm{MetS}_i + e_{2i},$$

$$\mathrm{HDL} - C_i = \alpha_3 + b_3 \mathrm{MetS}_i + e_{3i},$$

$$\mathrm{BP}_i = \alpha_4 + b_4 \mathrm{MetS}_i + e_{4i},$$

$$\mathrm{FPG}_i = \alpha_5 + b_5 \mathrm{MetS}_i + e_{5i},$$

Where error terms $e_{1i}, e_{2i}, \ldots, e_{5i}$ are assumed to follow normal distributions with same mean of zero and standard deviations $\sigma_1, \sigma_2, \ldots, \sigma_5$, respectively, and assumed to be uncorrelated with model parsimony concern. Note that parameters $\alpha_1, \ldots, \alpha_5, b_1, \ldots, b_5, \sigma_1, \ldots, \sigma_5$ are unknown and need be estimated from data. Recall that MetS severity score is the latent factor which cannot be observed and measured directly. It is common to introduce a scale for the latent factor MetS severity score, e.g., assuming it follows the standard normal distributions with a mean of zero and standard deviation of 1 [24].

Under the above CFA model, we adopted STATA command "sem" for estimating the parameters in the model and command "predict" for predicting MetS score for each participant. Note the command "sem" is used for parameter estimation in structural equation model (SEM), which can model interrelations among multiple latent factors and observable variables. CFA model is a special case of SEM. Specifically, we ran STATA commands below for parameter estimation and MetS score prediction:

sem (MetS-severity → WC TG (natural log transformed) HDL-C BP FPG), stand predict mscore, latent (MetS-severity)

The mscore was converted to *z*-score as MetS severity *z*-score by subtracting mean of mscore from the mscore and dividing by standard deviation of mscore [25].

Metabolic syndrome severity cannot be observable and measureable directly. We assumed WC, TG, HDL-C, BP and FPG are its core components, and considered one-factor CFA model for testing our hypothesis. Different standard regressions, we are not able to evaluate accuracy for each person due to his unknown value of MetS. Instead, we evaluated overall performance of our model across all samples by goodness-of-fit indices commonly used in the field of SEM: comparative fit index, 0.91 (ideal is close to 1); standardized root mean square residual, 0.05 (ideal is ≤0.08); coefficient of determination, 0.77 (ideal is close to 1); and tucker-lewis index, 0.81 (ideal is close to 1) [26]. Generally, our CFA model fits data very well. Repeat confirmatory analyses were done for Chinese, Malay and Indian subgroups, as well as gender and age-specific subgroups.

Independent *t*-test or Wilcoxon Ranksum test and Chi-Square test were used to compare continuous and categorical variables between groups. Multivariable cox proportional hazards regression model was used to estimate hazard ratios (HR) for development of T2DM, adjusting for age, gender, ethnicity and MetS components [7]. Assumption of proportional hazard was tested for all covariates with global test using scale Schoenfeld residuals. The assumption was not violated by the cox regression model in our analysis
($p > 0.05$). The extent of collinearity with the inclusion of MetS components in the model was examined by computing variance inflation factors. Variance inflation factors exceeding 10 are indicative of severe collinearity [7]. The variance inflation factors ranged from 1.10 to 3.79 when the MetS components were added to the model in our study.

The ability of MetS severity *z*-score and MetS to discriminate individuals who developed diabetes and those who did not was compared using area under the receiver-operating characteristics (ROC) curve. The model which included the individual MetS components was also compared with the model without these components for MetS severity *z*-score using ROC curve.

A repeat analysis was done using MetS defined according to Adult Treatment Panel III which requires ≥3 criteria to be met: WC ≥ 102 cm in males and ≥ 88 cm in females; TG ≥ 1.69 mmol/l; HDL-C < 1.04 mmol/l in males and <1.29 mmol/l in females; SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or medication for hypertension; and FPG ≥ 5.55 mmol/l [27]. Repeat analyses were also performed for MetS severity z-scores for ethnic-specific subgroups as well as by gender.

We assessed the role of MetS on the association between baseline BMI and development of diabetes using mediation analysis. The Baron and Kenny three-step framework [28] was used to assess (1) association between baseline BMI and development of diabetes (2) association between baseline BMI and baseline MetS severity *z*-score; and (3) weakening of association between BMI and development of diabetes when MetS severity *z*-score was added to the model. We used the following commands *in Stata 14.0* (StataCorp. Stata Statistical Software: Release 14. 2015, StataCorp LP.: College Station, TX) "*binary_mediation* "and "*bootstrap"*. The outputs were the magnitude of decrease in the proportion of the link between BMI and development of diabetes after including MetS severity *z*-score in the model and the strength of the mediation. All statistical tests were two-sided. The results were deemed significant if $P < 0.05$.

Results

The mean follow-up duration was 1.7 year (±0.8) and the mean number of visits per subject was 2.4 (range 2–7). Figure 1 shows the results of the confirmatory analysis for the overall study population. HDL-C, TG and WC had the largest factor loading coefficients in terms of magnitude. The model met the ideal threshold in terms of Comparative Fit Index, Standardised Root Mean Square Residual and Coefficient of Determination. Supplementary Table 1 shows the loading coefficients from the confirmatory factor analysis specific subgroups. The coefficient was highest in magnitude for HDL-C in Chinese, Malays and Others whereas it was highest in magnitude for TG in Indians and Others. Males had larger coefficient for HDL-C in terms of magnitudes than females. However, the coefficients for SBP and FPG in higher in females than males. The oldest age group had the lowest coefficient for TG, SBP and FPG but the highest coefficient for HDL-C in terms of magnitude compared with the other age groups. Diabetes developed in 130 participants (3.1%). The baseline characteristics were shown in Table 1. Those who developed diabetes tended to be older, male and of non-Chinese ethnicity ($p < 0.05$). Compared with the participants who did not develop diabetes, those who developed diabetes had poorer clinical

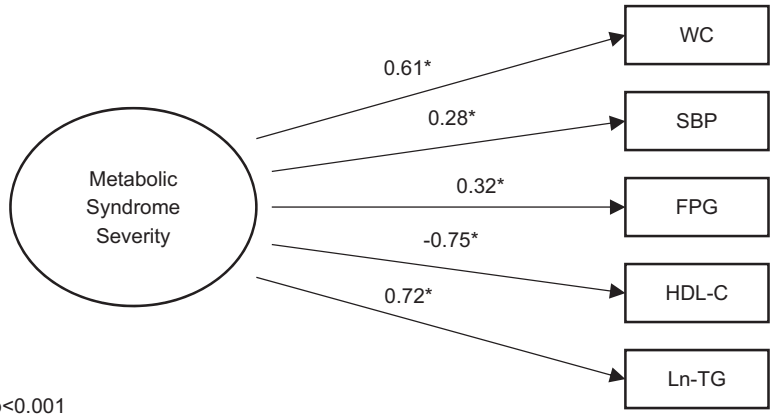

Fig. 1 Results of confirmatory factor analysis

WC waist circumference, Ln-TG natural log-transformed triglycerides, HDL-C high-density lipoprotein – cholesterol, Systolic BP Systolic blood pressure, FPG fasting plasma glucose

Table 1 Baseline characteristics stratified by development of diabetes

Variables	$N = 4149$	Development of diabetes		*P*-value
		No ($n = 4019$)	Yes ($n = 130$)	
Age (%)				0.008
40–49 years	919 (22.2)	900 (22.4)	19 (14.6)	
50–59 years	1700 (41.0)	1655 (41.2)	45 (34.6)	
60–69 years	1182 (28.5)	1131 (28.1)	51 (39.2)	
≥ 70 years	348 (8.4)	333 (8.3)	15 (11.5)	
Male (%)	1398 (33.7)	1338 (33.3)	60 (46.2)	0.002
Ethnicity (%)				0.002
Chinese	3610 (87.0)	3510 (87.3)	100 (76.9)	
Malay	266 (6.4)	253 (6.3)	13 (10.0)	
Indian	178 (4.3)	169 (4.2)	9 (6.9)	
Others	95 (2.3)	87 (2.2)	8 (6.2)	
BMI (kg/m^2)	23.5 ± 3.9	23.4 ± 3.8	26.1 ± 6.0	<0.001
Waist circumference (cm)	82.2 ± 10.2	82.6 ± 10.0	89.7 ± 12.3	<0.001
Systolic BP (mmHg)	126.4 ± 16.6	126.2 ± 16.5	132.3 ± 17.4	<0.001
Diastolic BP (mmHg)	75.3 ± 10.5	75.2 ± 10.4	79.2 ± 11.8	<0.001
HDL-C (mmol/l)	1.6 ± 0.4	1.6 ± 0.4	1.4 ± 0.4	<0.001
TG (mmol/l)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.4 (1.0–1.9)	<0.001
FPG (mmol/l)	5.2 ± 0.5	5.2 ± 0.5	6.0 ± 0.6	<0.001
Hypo-lipid treatment (%)	1061 (25.6)	1022 (25.4)	39 (30.0)	0.240
Hypo-tension treatment (%)	524 (12.6)	484 (12.0)	40 (30.8)	<0.001
MetS (%)	1385 (33.4)	1301 (32.4)	84 (64.6)	<0.001
MetS severity *z*-score	0.0 ± 1.0	−0.0 ± 1.0	0.8 ± 1.0	<0.001
MetS severity *z*-score (%)				<0.001
Quintile 1, −1.4 ± 0.4	830 (20.0)	823 (20.5)	7 (5.4)	
Quintile 2, −0.6 ± 0.2	830 (20.0)	814 (20.3)	16 (12.3)	
Quintile 3, 0.0 ± 0.2	830 (20.0)	810 (20.2)	20 (15.4)	
Quintile 4, 0.6 ± 0.2	830 (20.0)	811 (20.2)	19 (14.6)	
Quintile 5, 1.4 ± 0.4	829 (20.0)	761 (18.9)	68 (52.3)	

BMI body mass index, *WC* waist circumference, *Systolic BP* Systolic blood pressure, *Diastolic BP* Diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *FPG* fasting plasma glucose, *MetS* Metabolic Syndrome

profile in terms of BMI, WC, SBP, DBP, HDL-C, TG and FPG ($p < 0.001$). They also had higher proportion of MetS and MetS severity z-score ($p < 0.001$).

MetS as defined according to IDF criteria was associated with development of diabetes in the unadjusted model and in the model adjusted for age, gender and ethnicity. The corresponding HRs were 3.80 (95% CI: 2.65–5.44; $p < 0.001$) and 3.32 (95% CI: 2.30–4.77; $p < 0.001$). However, the association between MetS and development of diabetes was markedly attenuated and lost statistical significance upon addition of the individual MetS components in the model. The corresponding HR was 0.67 (95% CI: 0.34–1.29; $p = 0.228$). See Table 2.

Similar findings were obtained when MetS as defined by ATP III Panel was used. MetS was associated with development of diabetes when unadjusted and adjusted for age, gender and ethnicity. The corresponding HRs were 5.46 (95% CI: 3.86–7.70; $p < 0.001$) and 4.86 (95% CI: 3.42–6.90; $p < 0.001$). Statistical significance was lost upon inclusion of the individual MetS components in the model with HR 0.99 (95% CI: 0.53–1.88; $p = 0.982$). See Supplementary Table 2.

MetS severity z-score in quintiles for the overall population was associated with development of diabetes in the unadjusted and in the model adjusted for age, gender and ethnicity. The corresponding HRs for the highest quintile were 10.02 (95% CI: 4.60–21.83; $p < 0.001$) and 9.41 (95% CI: 4.22–20.99; $p < 0.001$). The association remained statistically significant even upon addition of the individual MetS components in the model with HR 2.63 (95% CI: 1.04–6.64; $p = 0.040$). See Table 2. The area under the ROC curve was 0.84 (95% CI: 0.81–0.87) for MetS severity z-score. This was higher than the area for MetS (0.83; 95% CI: 0.80–0.86) ($p = 0.032$). The model which included the individual MetS components had a higher area under the ROC curve than the model without these components for MetS severity z-score (0.84 vs. 0.74; $p < 0.001$).

Supplementary Table 3 shows the results of cox regression model relating ethnic-specific MetS severity z-score in quintiles to development of diabetes. The HRs for the highest quintile were 8.20 (95% CI: 3.93–17.12; $p < 0.001$) and 7.99 (95% CI: 3.75–17.04; $p < 0.001$) when unadjusted and adjusted for age and gender. The association between the ethnic-specific MetS severity z-score lost statistical significance upon additional adjustment for the individual MetS components with HR 1.96 (95% CI: 0.82–4.69; $p = 0.130$).

Supplementary Table 4 shows the results of cox regression model stratified by gender. The highest quintile of MetS severity z-score in females was associated with development of diabetes with HRs 12.16 (95% CI: 5.06–29.22; $p < 0.001$), 11.20 (95% CI: 4.62–27.17; $p < 0.001$) and 3.28 (95% CI: 1.08–9.99; $p = 0.036$) when unadjusted, adjusted for age and ethnicity and additionally adjusted for the individual MetS components respectively. There was no association between MetS severity z-scores and development of diabetes in males in the fully adjusted model. Using the Baron and Kenny Framework [25], three steps have been fulfilled (Fig. 2). (1) Increasing BMI was associated with development of T2DM; (2) Increasing BMI at baseline was associated with MetS severity z-score; and (3) the association between increasing BMI and development of T2DM is attenuated with addition of MetS severity z-score in the model. MetS severity z-score accounted for 61.0% of association between BMI and T2DM development, having adjusted for age, gender and ethnicity ($p < 0.001$).

Discussion

Our study showed that MetS severity z-score was significantly associated with development of diabetes. This supported the findings in the few earlier studies [7, 14, 15]. When MetS as a dichotomous measure defined according to ATP III Panel was used, the results were similar to the model with MetS as defined by IDF, i.e., the relationship with development of diabetes was much attenuated when adjusted for the individual MetS components. The AUC of MetS severity z-score was also higher than MetS in our study. The findings suggested that MetS severity z-score provides further prediction of development of diabetes in addition to individual MetS components and is a stronger predictor than MetS. MetS severity score was significantly associated with development of diabetes in females but not in males in the fully adjusted models. There was no association between ethnic-specific MetS severity z-score and development of diabetes. In view of the relatively short follow-up duration and low incidence of diabetes, further research with longer follow-up is needed to confirm the findings.

To the best of our knowledge, this was the first time Asian-specific MetS severity score was developed and examined in the prediction of future diabetes. The higher loading coefficients of HDL-C, TG and WC in terms of magnitude from the confirmatory factor analysis demonstrates that the individual MetS components exerted different level of influence on MetS. This supports a need to take into account individualised weightage rather than even distribution of weightage of the MetS components. Interestingly, the Chinese, Malays and Others had the highest coefficient in terms of magnitude for HDL-C whereas the Indians and Others had the highest coefficient for TG. As there was a much higher proportion of Chinese compared with the other ethnic groups, further research was needed to confirm ethnic-specific disparity in the differential influence

Table 2 Risk factors associated with development of diabetes

	Hazards ratio (95% Confidence) *p*-value					
	MetS model			MetS severity *z*-score model		
	Unadjusted	Model 1[a]	Model 2[b]	Unadjusted	Model 1[a]	Model 2[b]
MetS	3.80 (2.65–5.44) < 0.001	3.32 (2.30–4.77) < 0.001	0.67 (0.34–1.29) 0.228			
MetS severity z-score						
Quintile 1				1.00	1.00	1.00
Quintile 2				2.24 (0.92–5.45) 0.075	2.28 (0.94–5.56) 0.069	1.90 (0.78–4.67) 0.159
Quintile 3				2.86 (1.21–6.77) 0.017	2.70 (1.13–6.41) 0.025	1.68 (0.69–4.08) 0.252
Quintile 4				2.82 (1.19–6.71) 0.019	2.63 (1.10–6.31) 0.030	1.17 (0.46–2.94) 0.745
Quintile 5				10.02 (4.60–21.83) <0.001	9.41 (4.22–20.99) <0.001	2.63 (1.04–6.64) 0.040
Age						
40–49 years		1.00	1.00		1.00	1.00
50–59 years		1.36 (0.79–2.34) 0.264	1.25 (0.72–2.15) 0.430		1.44 (0.84–2.48) 0.186	1.26 (0.73–2.17) 0.404
60–69 years		2.32 (1.36–3.97) 0.002	1.78 (1.03–3.08) 0.040		2.77 (1.62–4.74) <0.001	1.89 (1.09–3.28) 0.022
≥70 years		2.22 (1.12–4.42) 0.023	1.65 (0.81–3.35) 0.164		2.81 (1.42–5.57) 0.003	1.87 (0.92–3.79) 0.082
Male		1.54 (1.09–2.17) 0.015	1.47 (1.03–2.11) 0.036		1.00 (0.69–1.44) 0.998	1.23 (0.83–1.81) 0.301
Ethnicity						
Chinese		1.00	1.00		1.00	1.00
Malay		1.87 (1.04–3.35) 0.035	1.69 (0.94–3.04) 0.080		1.63 (0.91–2.93) 0.101	1.58 (0.87–2.84) 0.131
Indian		1.74 (0.87–3.47) 0.116	1.27 (0.63–2.55) 0.502		1.34 (0.67–2.68) 0.403	1.21 (0.60–2.44) 0.591
Other		3.23 (1.57–6.66) 0.002	3.02 (1.44–6.32) 0.003		3.02 (1.46–6.25) 0.003	2.97 (1.42–6.21) 0.004
High WC			1.53 (0.97–2.42) 0.070			1.10 (0.72–1.69) 0.650
High TG			1.10 (0.67–1.81) 0.708			0.89 (0.56–1.40) 0.608
Low HDL-C			1.72 (1.04–2.84) 0.034			1.43 (0.91–2.25) 0.124
High BP			1.83 (1.14–2.94) 0.013			1.44 (0.96–2.16) 0.078
High FPG			9.20 (5.97–14.15) <0.001			7.72 (5.07–11.75) <0.001

BMI body mass index, *WC* waist circumference, *Systolic BP* Systolic blood pressure, *Diastolic BP* Diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *FPG* fasting plasma glucose, *MetS* Metabolic Syndrome

[a]Model 1 adjusted for age, gender and ethnicity

[b]Model 2 adjusted for age, gender, ethnicity, high WC, high TG, low HDL-C, high BP and high FPG

[c]The reference category was Chinese

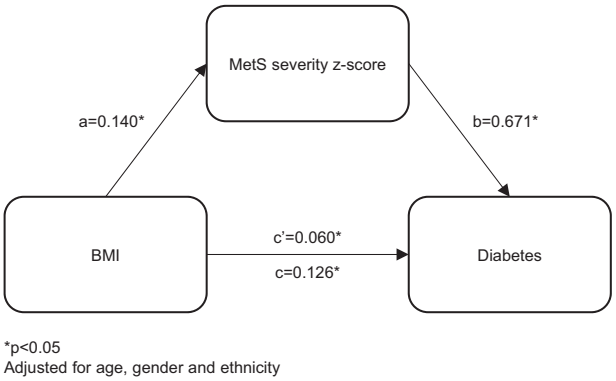

Fig. 2 Mediation of metabolic syndrome severity *z*-score between baseline body mass index and development of diabetes

of the components on MetS. The findings may inform healthcare providers in strategizing preventive interventions tailored to different ethnic groups.

MetS severity *z*-score was shown to have mediated the link between baseline BMI and incident diabetes. Our study demonstrated the partial contribution of the MetS severity *z*-score to the relationship between baseline BMI and incident diabetes. Interestingly, we also observed the mediation effect of triglyceride–glucose index in the relationship between baseline BMI and incident diabetes in a previous study [17]. Our current results add to our previous finding about the deleterious impact of baseline BMI on development of diabetes [17]. It is therefore essential to ensure appropriate weight is sustained and prevent obesity in order to protect against T2DM.

Our findings have brought about a few clinical implications. MetS severity *z*-score is an inexpensive and can easily be derived from routine clinical practice. It can be utilised to determine baseline risk of future DM and track changes in MetS severity over time. This will facilitate the healthcare providers in tracking individuals at high risk of DM and initiate therapy, tracking response to treatment with MetS severity score and improving MetS-related risk with lifestyle modifications involving physical activity and/or dietary changes.

The strengths of our study are as follows: (1) an overall large community-based sample; (2) the use of clinical measurements in addition to self-reported outcomes; and (3) the inclusion of binary mediation analysis to elucidate the role of MetS severity *z*-score in the development of diabetes; (4) the high quality of our standardised clinical and laboratories procedures.

There are limitations in our study. Firstly, the follow-up period was relatively short, and the event rate was low at 3.1%. Secondly, the time between baseline and endpoint in the study may not be the real latent time (subclinical stage) for each individual. The measurement of baseline may be done at different stages of the journey towards the development of diabetes. Thirdly, the design of the study was retrospective and future prospective studies are needed to examine the relationship between MetS severity *z*-score and development of T2DM. There were also limited numbers of Malays and Indians in the study population. This might have limited the generalizability of findings to these ethnic groups. There was lack of 2-h oral glucose tolerance test and Haemoglobin A1c (HbA1c) to aid in the diagnosis of T2DM. Additionally, a repeat measurement in an asymptomatic individual with a single fasting glucose ≥7.0 mM was unavailable for the confirmation of diabetes. However, this form of mis-classification is probably random and less likely to lead to any bias. We also lacked data on family history of diabetes, history of gestational diabetes as possible risk factors of future diabetes. Furthermore, the sample size in the Malays and Indian subgroups is too small to determine cut-off value of MetS severity *z*-score. Future larger studies for the subgroups may be needed to generate the cut-off values for predicting risk of diabetes.

In conclusion, MetS severity *z*-score is an independent predictor of development of diabetes. It provides further prediction of development of diabetes in addition to individual MetS components. It is a stronger predictor than MetS. There is potential for use of MetS severity *z*-score to determine the baseline risk of diabetes and track changes in MetS severity over time in clinical practice.

Acknowledgements We would like to thank Colleagues from Population Health Department for making their kind assistance.

Compliance with ethical standards

Ethical approval The National Healthcare Group Domain Specific Review Board in Singapore approved this study. Since it excluded all identifiable personal information, the Board waived the requirement for informed consent and ethical review of the study (DSRB reference 2017/00735, date 11.04.2017).

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Ministry of Health S. Better health, better care, better life. The war on diabetes. (2016). https://www.moh.gov.sg/content/dam/moh_web/PressRoom/Highlights/2016/cos/factsheets/COS_Factsheet%20-%20Diabetes.pdf. Accessed 1 May 2018
2. Ministry of Health S. Singapore burden of disease study 2010. (2014). https://www.moh.ov.sg/content/moh_web/home/Publications/Reports/2014/singaporeburden-of-disease-study-2010.html. Accessed 1 Aug 2018
3. M.J. Gurka, C.L. Ice, S.S. Sun, M.D. Deboer, A confirmatory factor analysis of the metabolic syndrome in adolescents: an

examination of sex and racial/ethnic differences. Cardiovasc. Diabetol. **11**, 128 (2012)
4. Federation ID. The IDF consensus worldwide definition of the metabolic syndrome. (2006). https://www.idf.org/component/attachments/attachments.html?id=705&task=download. Accessed 2 Oct 2018
5. S. de Ferranti, D. Mozaffarian, The perfect storm: obesity, adipocyte dysfunction, and metabolic consequences. Clin. Chem. **54**, 945–955 (2008)
6. M.D. DeBoer, Obesity, systemic inflammation, and increased risk for cardiovascular disease and diabetes among adolescents: a need for screening tools to target interventions. Nutrition **29**, 379–386 (2013)
7. M.J. Gurka, S.H. Golden, S.K. Musani et al. Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk In Communities Study and Jackson Heart Study. Diabetologia **60**, 1261–1270 (2017)
8. G.I. Shulman, Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N. Engl. J. Med. **371**, 1131–1141 (2014)
9. C. Lorenzo, M. Okoloise, K. Williams, M.P. Stern, S.M. Haffner, The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. Diabetes Care **26**, 3153–3159 (2003)
10. M.D. DeBoer, M.J. Gurka, Clinical utility of metabolic syndrome severity scores: considerations for practitioners. Diabetes Metab. Syndr. Obes. **10**, 65–72 (2017)
11. B.D. Dimitrov, K.M. Bahchevanov, P.A. Atanassova et al. Metabolic syndrome severity score: range and associations with cardiovascular risk factors. Arch. Med. Sci. Atheroscler. Dis. **1**, e90–e97 (2016)
12. J.K. Gustafson, L.B. Yanoff, B.D. Easter et al.The stability of metabolic syndrome in children and adolescents. J. Clin. Endocrinol. Metab. **94**, 4828–4834 (2009)
13. C. Li, E.S. Ford, T.T. Huang, S.S. Sun, E. Goodman, Patterns of change in cardiometabolic risk factors associated with the metabolic syndrome among children and adolescents: the Fels Longitudinal Study. J. Pediatr. **155**, S5.e9–e16 (2009)
14. M.D. DeBoer, M.J. Gurka, J.G. Woo, J.A. Morrison, Severity of the metabolic syndrome as a predictor of type 2 diabetes between childhood and adulthood: the Princeton Lipid Research Cohort Study. Diabetologia **58**, 2745–2752 (2015)
15. M.J. Gurka, S.L. Filipp, T.A. Pearson, M.D. DeBoer, Assessing baseline and temporal changes in cardiometabolic risk using metabolic syndrome severity and common risk scores. J. Am. Heart Assoc. **7**, e009754 (2018)
16. C.G. Magnussen, S. Cheriyan, M.A. Sabin et al. Continuous and dichotomous metabolic syndrome definitions in youth predict adult type 2 diabetes and carotid artery intima media thickness: The cardiovascular risk in young finns study. J. Pediatr. **171**, 97–103.e1-e3 (2016)
17. S. Low, K.C.J. Khoo, B. Irwan et al. The role of triglyceride glucose index in development of type 2 diabetes mellitus. Diabetes Res. Clin. Pract. **143**, 43–49 (2018)
18. Roche. *Glucose H. K. Gen.3: Cobas*. (Roche Diagnostics GmBH, Mannheim, Germany, 2016)
19. Roche. *Triglycerides: Cobas*. (Roche Diagnostics GmbH, Mannheim, Germany, 2016)
20. Roche. *HDL-Cholesterol Plus Generation: Cobas*. (Roche Diagnostics GmBH, Mannheim, Germany, 2016)
21. American Diabetes Association, Standards of medical care in diabetes—2017. Diabetes Care **40**, S1–S135 (2017)
22. V.S. Effoe, A. Correa, H. Chen, M.E. Lacy, A.G. Bertoni, High-sensitivity C-reactive protein is associated with incident type 2 diabetes among African Americans: The Jackson heart study. Diabetes Care **38**, 1694–1700 (2015)
23. M.I. Schmidt, B.B. Duncan, H. Bang et al. Identifying individuals at high risk for diabetes: The atherosclerosis risk in communities study. Diabetes Care **28**, 2013–2018 (2005)
24. T.A. Brown. *Confirmatory Factor Analysis for Applied Research.* (The Guildford Press, New York, 2006)
25. R.D. De Veaux, P.F. Velleman, D.E. Bock. *Stats: Data and Models.* (Pearson, Boston, 2016)
26. StataCorp. *Structural Equation Modeling Reference Manual: Release 13*. (Stata Press, Texas, 2013)
27. S.M. Grundy, J.I. Cleeman, S.R. Daniels et al.Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation **112**, 2735–2752 (2005)
28. R.M. Baron, D.A. Kenny, The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J. Pers. Soc. Psychol. **51**, 1173–1182 (1986)