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Assessing the validity of METS-IR for predicting the future onset of diabetes: an analysis using time-dependent receiver operating characteristics

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Abstract

Background The Metabolic Insulin Resistance Score (METS-IR) is a non-invasive proxy for insulin resistance (IR) that has been newly developed in recent years and has been shown to be associated with diabetes risk. Our aim was to assess the predictive value of METS-IR for the future development of diabetes and its temporal differences in people of different sex, age, and body mass index (BMI).

Methods The current study included 15,453 baseline non-diabetic subjects in the NAGALA cohort and then grouped according to the World Health Organization's (WHO) recommended criteria for age and BMI. Multivariate Cox regression and time-dependent receiver operator characteristics (ROC) curves were used to analyze the value of METS-IR in assessing and predicting the risk of diabetes in people of different sexes, ages, and BMIs.

Results 373 individuals developed diabetes during the observation period. By multivariate COX regression analysis, the development of future diabetes was significantly associated with increased METS-IR, and this positive association was stronger in women than in men and in individuals < 45 years than in individuals ≥ 45 years; while no significant differences were observed between non-obese and overweight/obesity individuals. Using time-dependent ROC analysis we also assessed the predictive value of METS-IR for future diabetes at a total of 11-time points between 2 and 12 years. The results showed that METS-IR had a higher predictive value for the future development of diabetes in women or individuals < 45 years of age compared to men or individuals ≥ 45 years of age for almost the entire follow-up period. Furthermore, across different BMI categories, we also found that in the short term (3–5 years), METS-IR had a higher predictive value for the development of diabetes in individuals with overweight/obesity, while in the medium to long term (6–12 years), METS-IR was more accurate in predicting the development of diabetes in non-obese individuals.

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Conclusions Our study showed that METS-IR was independently associated with the development of future diabetes in a non-diabetic population. METS-IR was a good predictor of diabetes, especially for women and individuals < 45 years old for predicting the future risk of developing diabetes at all times.

Keywords METS-IR, Prediction, Diabetes, Non-invasive, Temporal differences, Time-dependent ROC

Background

The prevalence of diabetes is increasing year on year and has become a major public health challenge worldwide, with an estimated 783.2 million people, or approximately 12.2% of the global population, expected to have diabetes by 2045 [1]. To make matters worse, the long duration of diabetes and its various complications place a huge burden on the individual, both mentally and physically, and on the family finances of those with diabetes [2]. Thankfully, however, people at high risk of diabetes can prevent/delay disease progression through early lifestyle interventions [3, 4], and the core of prevention strategies is the early identification and screening of individuals at high risk of diabetes [5]. Therefore, finding simple and effective screening and risk prediction tools for at-risk populations can inform clinical decision-making by physicians and public health policy formulation, thereby reducing the incidence of diabetes in the population and ultimately improving public health.

IR, defined as reduced insulin sensitivity, is a major pathophysiological feature of type 2 diabetes [6], usually precedes the onset of diabetes [7], and is an important driver of the onset of diabetes in the future [8]. Therefore, accurate measurement of IR can not only improve the identification of individuals at high risk of diabetes but also enhance the prediction of future diabetes. However, the euglycemic-hyperinsulinemic clamp (EHC), the gold standard for measuring IR, is not only expensive and invasive [9], but its use as a health screening tool in clinical practice seems less applicable. As an alternative, many researchers have developed indirect methods for assessing IR, including insulin homeostasis models and quantitative insulin sensitivity check indices [10]. However, the clinical application of these methods is limited due to the atypical measurement of serum insulin [11, 12], so there is a need to find simpler, inexpensive alternative methods suitable for widespread health screening.

METS-IR is a new cardiometabolic risk score recently developed by Prof. Bello-Chavolla OY, and the score includes glucose parameters (fasting plasma glucose: FPG), lipid parameters [triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C)], and obesity parameters (BMI), which has a good fit with EHC and is considered to be a promising alternative to IR [13]. To date, several studies have pointed to the METS-IR as a useful indicator for assessing the risk of diabetes and have suggested that the METS-IR should be used in large epidemiological surveys as well as clinical screening [14–17]; it is important to note that, given a large number of components of the METS-IR, which may vary considerably in different populations, identifying the METS-IR for assessing/predicting the applicable groups for diabetes is necessary. To address this issue, the current study pre-grouped sex, age, and BMI according to WHO-recommended criteria by constructing time-dependent ROC curves at multiple follow-up time points to assess the predictive value of baseline METS-IR for the future development of diabetes and its variability in different populations.

Methods

Data sources

The data used in the current study was sourced from the Dryad public database and the original data was uploaded and shared by Professor Okamura's team (https://doi.org/10.5061/dryad.8q0p192) [18]. Under the terms of the Dryad database service, all researchers can use the data in the database for in-depth analysis and dissemination of new knowledge.

The dataset used for the current study contained data from a longitudinal cohort study conducted at Murakami Memorial Hospital in Japan between 1994 and 2016. The design and implementation steps of the study have been described in detail by Professor Okamura et al. in a previous study [19]. In summary, the cohort was established in 1994 and has continued to date; the study population was the general population enrolled consecutively during the study period for health screening at the Murakami Memorial Hospital Health Screening Centre and the aim of the study was to investigate common risk factors for the onset of diabetes and fatty liver disease. Based on the previous study, the current study aimed to use this publicly available dataset to further assess the predictive value of the baseline METS-IR for future diabetes and its changes in different populations, and thus provide more accurate health advice for diabetes prevention and treatment in the population. We extracted data from this dataset of 20,944 individuals who underwent health screening between 1994 and 2016, including demographic variables (sex, age), lifestyle variables (exercise, smoking, and drinking habits), and health status questionnaires (diabetes and history of liver disease), as well as the results of medical examinations at health screening centers [including laboratory test data, measured height, weight, waist circumference (WC), and blood pressure, etc.]

For the purposes of the current study, we excluded participants with a combination of the following characteristics: 323 participants with diabetes at baseline, 808 participants with FPG over 6.1 mmol/L, 416 participants with liver disease (other than fatty liver), 739 participants with excessive alcohol consumption (over 60 g/day for men and 40 g/day for women), 2,321 participants using medication at baseline (including but not limited to antidiabetic drugs, lipid-lowering drugs, antihypertensive drugs, and hormone), 874 participants with missing data and 10 participants who withdrew for unknown reasons. Ultimately, we included 15,453 eligible participants for subsequent study analysis, and the exact exclusion process was shown in Fig. 1.

Ethical approval and consent to participate

Informed consent for the use of study data has been reported in previous studies where participant authorization was obtained and research ethics was approved by the Ethics Committee of Murakami Memorial Hospital [19]. The present study was conducted as a secondary analysis and the identifiable information of the participants was de-identified. The ethics committee of the authors' research institution (Jiangxi Provincial People's Hospital) reviewed and approved the protocol of the current study (IRB2021-066), waived duplicate applications for informed consent from participants, and supervised the entire study See STROBE statement (S1 Text).

Data acquisition and collection

As reported in the previous article [19], a standardized questionnaire was used to collect information on

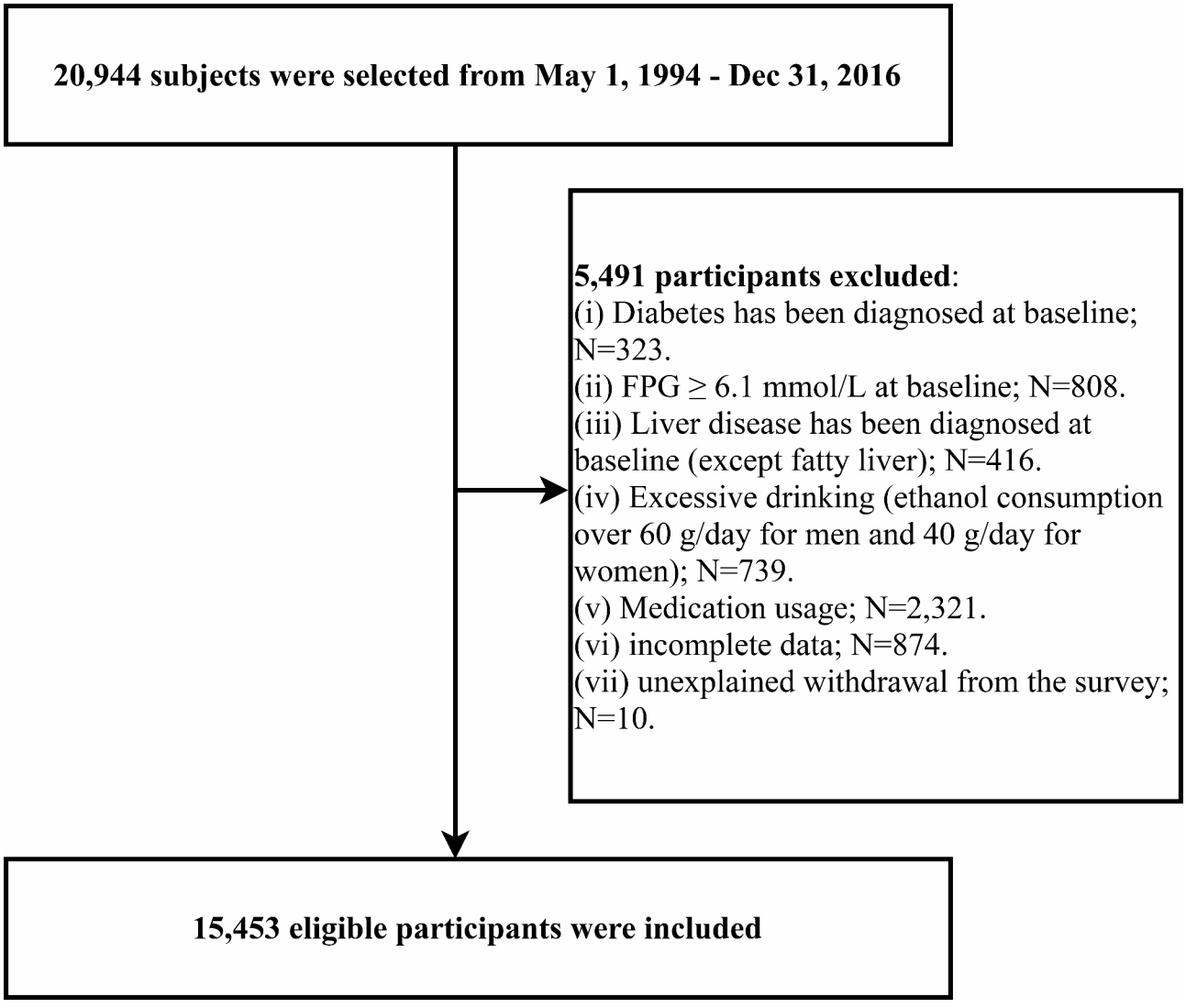

Fig. 1 Flowchart of the selection process of study participants

demographic characteristics, lifestyle (exercise habits, smoking and drinking status), and health status (including disease history and medication use). Physical measurement parameters including height, weight, WC, blood pressure, and other information were measured by standard methods in a quiet environment. Laboratory test data included blood lipids [total cholesterol (TC), TG, HDL-C], blood glucose parameters [FPG and hemoglobin A1c (HbA1c)], liver function enzymes indicators [aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alanine aminotransferase (ALT)] were measured by an automated biochemical analyzer using an 8-hour overnight fasted venous blood sample; additionally, low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald equation.

The diagnosis of fatty liver was made on the basis of ultrasound. After the abdominal ultrasound images have been acquired by a trained technician, the four main assessment criteria of deep attenuation, hepatorenal echo contrast, liver brightness, and vascular blurring were analyzed and diagnosed by an experienced gastroenterologist [20].

Calculations and definitions

METS-IR = (Ln ((2*FPG) + TG)*BMI)/(Ln (HDL-C)). Triglyceride-Glucose (TyG) index = Ln((TG × FPG)/2). Note: The measurement unit of FPG and TG was mg/dl [13].

Exercise habits: Participants were categorized into those with exercise habits (>1 time per week) and those with no exercise habits (<1 time per week), based on participants' weekly exercise [21].

Drinking status: Participants were categorized into non/small drinking (<40 g/week), light drinking (40–140 g/week), moderate drinking (140–280 g/week), and heavy drinking (>280 g/week), based on their alcohol consumption in the month prior to the baseline survey [22].

Smoking status: Participants were classified into non-smokers, past smokers, and current smokers, based on their self-reported smoking history at baseline.

Outcome

The primary outcome was diabetes diagnosed during the follow-up period. According to the American Diabetes Association criteria [23], participants were diagnosed as having diabetes if they had one of the following criteria: (1) FPG ≥ 7.0 mmol/L; (2) HbA1c ≥ 6.5%; and (3) diabetes diagnosed by other medical personnel.

Predefined subgroups

Sex subgroups: All participants were divided into men and women groups.

Age subgroups: Based on the standard of WHO in 2012 [24], people were divided into two groups: age ≥ 45 years old and age < 45 years old.

BMI subgroups: The population was divided into two groups, overweight/obesity (BMI ≥ 25 kg/m^2) and non-obese (BMI < 25 kg/m^2), based on the WHO recommended criteria for classifying BMI in Asians [25].

Statistical analysis

We compared participants' baseline data in groups according to whether they developed diabetes in the future. Clinical variables that were skewed distributed (including ALT, AST, GGT) were expressed as median (interquartile range), normally distributed variables were expressed as mean [standard deviation (SD)], and categorical variables were expressed as frequency (%). The inverse probability of treatment weighting method was used to calculate the standardized difference to quantify the size of the difference between groups, and a standardized difference > 10% was considered significant [26, 27].

The association of METS-IR with diabetes in different sexes, BMIs, and age groups was analyzed using Cox proportional hazard regression models, with hazard ratios (HRs) per SD increase and 95% confidence intervals (CIs) used to record the results. Before building the models, we used the Kaplan-Meier method to plot the log-integrated hazard versus time to assess the proportional hazards assumption (Supplementary Fig. 1) [28], and calculated the variance inflation factor to evaluate the collinearity of METS-IR with other covariates when diabetes was used as the dependent variable [29]. For a variance inflation factor of less than 5 was considered acceptable in the current study (Supplementary Table 1). Three stepwise adjusted multivariate Cox proportional hazards regression models were constructed to explore the association between METS-IR and diabetes risk [30]. In the Model 1, we mainly considered the impact of general demographic factors and lifestyle factors on the outcome, in which covariates such as height, smoking status, drinking status, exercise habits, and fatty liver were included in the Cox model for adjustment; In the Model 2, we further adjusted the liver enzyme indexes ALT, AST and GGT on the basis of Model 1; and in the final model (Model 3), we further adjusted the blood lipid parameters TC and TG, blood pressure parameter (systolic blood pressure) and blood glucose parameter HbA1c. In addition, based on the Model 3, we also examined the differences in METS-IR-related diabetes risk among different subgroups using the likelihood ratio test.

In order to evaluate the predictive value of METS-IR for the onset of diabetes at different times in the future, we used the survival ROC package to draw time-dependent ROC curves to evaluate the predictive ability of METS-IR for the onset of diabetes in different subgroups

and recorded prediction thresholds for corresponding time points. To minimize the impact of reverse causality on the association, we evaluated the predictive value of METS-IR for the onset of diabetes at a total of 11-time points between 2 and 12 years in a time-dependent ROC analysis [31]. Then, we used the R-ggplot2 package to draw the line graphs of the area under the ROC curves (AUC) and prediction thresholds of different subgroups over time to visually show the trend of AUC and prediction thresholds in different subgroups over time. In addition, to further assess the performance of METS-IR in predicting future diabetes, we also compared it with other established surrogates for IR in diabetes risk, such as the TyG index.

R language statistical software (version 4.2.1) was used for time-dependent ROC analysis and picture drawing. Empower(R) software (version 2.20) was used for all other statistical analyses. In all analyses, a P value less than 0.05 was considered significant.

Table 1 Baseline demographic, lifestyle, and laboratory characteristics in participants with and without diabetes

	Nondiabetic	Diabetes	Standardized Difference (95% CI), %
Participants (n)	15,080	373	
Age (years)	43.63 (8.89)	47.14 (8.52)	40 (30, 51)
Sex			49 (39, 59)
Women	6947 (46.07%)	87 (23.32%)	
Men	8133 (53.93%)	286 (76.68%)	
Height (m)	1.65 (0.08)	1.67 (0.09)	19 (9, 29)
Weight (kg)	60.41 (11.48)	69.84 (13.32)	76 (66, 86)
BMI (kg/m2)	22.04 (3.07)	25.03 (3.82)	86 (76, 97)
ALT (IU/L)	17.00 (13.00–23.00)	24.00 (18.00–39.00)	67 (56, 77)
AST (IU/L)	17.00 (14.00–21.00)	20.00 (16.00–26.00)	44 (34, 55)
GGT (IU/L)	15.00 (11.00–22.00)	24.00 (17.00–36.00)	47 (37, 58)
HDL-C (mg/dl)	56.81 (15.54)	45.92 (12.72)	77 (66, 87)
TC (mg/dl)	197.93 (33.33)	209.95 (34.68)	35 (25, 46)
TG (mg/dl)	79.50 (56.58)	132.76 (86.65)	73 (62, 83)
LDL-C (mg/dl)	119.06 (28.82)	134.35 (29.43)	53 (42, 63)
HbA1c (%)	5.16 (0.32)	5.53 (0.37)	107 (97, 118)
FPG (mg/dl)	92.76 (7.34)	101.14 (6.43)	121 (111, 132)
METS-IR	30.98 (6.36)	38.58 (7.74)	107 (97, 118)
SBP (mmHg)	114.31 (14.91)	122.03 (15.59)	51 (40, 61)
DBP (mmHg)	71.44 (10.47)	77.18 (10.23)	55 (45, 66)
Fatty liver	2514 (16.67%)	223 (59.79%)	99 (89, 109)
Exercise habits	2655 (17.61%)	51 (13.67%)	11 (1, 21)
Drinking status			21 (11, 31)
Non/small	11,536 (76.50%)	266 (71.31%)	
Light	1714 (11.37%)	40 (10.72%)	
Moderate	1320 (8.75%)	37 (9.92%)	
Heavy	510 (3.38%)	30 (8.04%)	
Smoking status			45 (35, 55)
None	8882 (58.90%)	145 (38.87%)	
Past	2872 (19.05%)	77 (20.64%)	
Current	3326 (22.06%)	151 (40.48%)	

Values were expressed as mean (SD) or median (interquartile range) or n (%). Abbreviations: BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; METS-IR: metabolic score for insulin resistance; SBP: systolic blood pressure; DBP: diastolic blood pressure

Results

Baseline characteristics of the study population

This study included 15,453 participants whose baseline characteristics met the criteria. During a mean observation period of 6.13 years (Min-Max: 0.46–13.14), 373 participants developed diabetes. Overall, there were significant differences in baseline characteristics between those who would develop diabetes in the future and those who would not (all standardized differences were >10%). In terms of demographic data, participants who had developed diabetes during the follow-up period were generally older at baseline and more likely to be men (76.68%); in terms of physical measurements, participants who had developed diabetes during the follow-up period had relatively higher height, weight, and blood pressure at baseline; in terms of lifestyle, participants who had developed diabetes during the follow-up period usually had a higher proportion of smoking (61.13%) and drinking habits at baseline, while a lower proportion of exercising habits; in terms of laboratory data, participants who had developed diabetes during the follow-up period had lower levels of baseline HDL-C and higher levels of baseline ALT, AST, GGT, TC, TG, LDL-C, HbA1c, and FPG than those without diabetes. Moreover, we also found that participants with diabetes had significantly higher baseline METS-IR than those without (Tables 1 and 38.58 vs. 30.98).

Association between METS-IR and diabetes

The association between METS-IR and diabetes was explored in the total population and subgroup populations, respectively (Table 2). The results showed that METS-IR was positively correlated with diabetes in the total population, regardless of whether confounders were adjusted for in the models (Crude model: HR=2.26, 95%CI=2.10–2.43; Mode 1: HR=1.76, 95%CI=1.59–1.94; Mode 2: HR=1.72, 95%CI=1.55–1.91; Mode 3: HR=1.41, 95%CI=1.24–1.61). In addition, we further assessed the association of METS-IR quartiles as categorical variables with diabetes. The results showed that the high METS-IR group presented a significantly higher risk of developing diabetes in all models. In the final model, subjects in the highest quartile of the METS-IR group

Table 2 Cox regression analyses for the association between METS-IR and incident diabetes in different models grouped by sex, age and BMI

	Hazard ratios (95% confidence interval)					
	Crude Model	Model 1	Model 2	Model 3	Interaction coefficient	*P* for interaction
METS-IR (Total)	2.26 (2.10, 2.43) **	1.76 (1.59, 1.94) **	1.72 (1.55, 1.91) **	1.47 (1.30, 1.68) **		
METS-IR quartiles						
Q1	Ref	Ref	Ref	Ref		
Q2	2.69 (1.46, 4.95)	2.53 (1.37, 4.65)	2.54 (1.38, 4.67)	2.27 (1.23, 4.18)		
Q3	4.99 (2.82, 8.81)	3.57 (2.00, 6.40)	3.50 (1.96, 6.27)	2.31 (1.28, 4.16)		
Q4	15.52 (9.05, 26.60)	6.61 (3.70, 11.82)	6.18 (3.45, 11.08)	3.15 (1.71, 5.77)		
Sex					-0.22 (-0.42, -0.02)	0.03
Women (per SD increase)	2.84 (2.42, 3.33) **	1.97 (1.59, 2.45) **	1.93 (1.55, 2.40) **	1.62 (1.24, 2.13) **		
Men (per SD increase)	2.08 (1.90, 2.28) **	1.67 (1.49, 1.87) **	1.61 (1.42, 1.81) **	1.40 (1.20, 1.64) **		
Age (years)					0.20 (0.03, 0.38)	0.02
≥ 45 (per SD increase)	2.11 (1.87, 2.37) **	1.65 (1.42, 1.92) **	1.60 (1.38, 1.87) **	1.26 (1.04, 1.51) *		
< 45 (per SD increase)	2.49 (2.26, 2.75) **	1.88 (1.64, 2.16) **	1.83 (1.58, 2.12) **	1.72 (1.43, 2.07) **		
BMI (kg/m^2)					0.01 (-0.23, 0.26)	0.91
≥ 25 (per SD increase)	1.99 (1.73, 2.29) **	1.64 (1.40, 1.93) **	1.61 (1.37, 1.91) **	1.59 (1.29, 1.95) **		
< 25 (per SD increase)	2.62 (2.21, 3.11) **	1.98 (1.60, 2.45) **	1.92 (1.55, 2.38) **	1.33 (1.01, 1.76) *		

For all Cox regression models in the current study, our data passed the assumptions of proportional hazards and multicollinearity

Abbreviations: METS-IR: metabolic score for insulin resistance; BMI: body mass index

Crude model adjusted for none

Model 1 adjusted for height, fatty liver, exercise habits, drinking status and smoking status

Model 2 adjusted for height, fatty liver, exercise habits, drinking status, smoking status, ALT, AST and GGT

Model 3 adjusted for height, fatty liver, exercise habits, drinking status, smoking status, ALT, AST, GGT, TC, TG, HbA1c and SBP

*represents $p<0.05$; **represents $p<0.01$

had a 215% increased risk of diabetes compared to the lowest quartile group.

We further conducted stratified analyses according to the pre-defined subgroups, and the results showed that diabetes risk associated with METS-IR was higher in women than in men (Model 3, HR: 1.62 vs. 1.40), higher in the population younger than 45 years than in those≥45 years (Model 3, HR: 1.72 vs. 1.26), and higher in the population with overweight/obesity than that in the non-obese population (Model 3, HR: 1.59 vs. 1.33). While in the subsequent interaction tests, we identified significant differences in the association of METS-IR with diabetes risk between the sex and age subgroups (P for interaction < 0.05), but not in the BMI subgroups (P for interaction = 0.78).

Predictive value of the baseline METS-IR for the onset of future diabetes in different populations

The effectiveness of METS-IR in predicting the onset of diabetes over the next 2–12 years was assessed using time-dependent ROC curves. Tables 3, 4 and 5 show the results of time-dependent ROC analysis in the sex, age, and BMI subgroups, respectively, and the corresponding AUC curves were shown in Fig. 2.

In the sex subgroups, we observed that METS-IR was more accurate in predicting the future onset of diabetes in women than in men, regardless of time variation [AUC: year-2: (women) 0.68 > 0.62 (men); year-3: (women) 0.70 > 0.67 (men); year-4: (women) 0.72 > 0.64 (men); year-5: (women) 0.73 > 0.67 (men); year-6: (women) 0.76 > 0.68 (men); year-7: (women) 0.76 > 0.70 (men); year-8: (women) 0.77 > 0.70 (men); year-9: (women) 0.76 > 0.70 (men); year-10: (women) 0.75 > 0.71 (men); year-11: (women) 0.76 > 0.70 (men); year-12: (women) 0.76 > 0.67 (men)]. In addition, further analysis revealed that the predictive accuracy of METS-IR tended to increase in the short term (2–6 years) in women (AUCs of 0.68,0.70,0.72,0.73,0.76 for year-2 to year-6, respectively) and remained high in the medium to long term (7–12 years).

In the age subgroups, we found that METS-IR was more accurate in predicting the future onset of diabetes in individuals aged < 45 years compared to those aged ≥ 45 years, except in year-2 [AUC: year-3: (age ≥ 45) 0.67 < 0.76 (age < 45); year-4: (age ≥ 45) 0.65 < 0.76 (age < 45); year-5: (age ≥ 45) 0.69 < 0.78 (age < 45); year-6: (age ≥ 45) 0.70 < 0.79 (age < 45); year-7: (age ≥ 45) 0.71 < 0.81 (age < 45); year-8: (age ≥ 45) 0.73 < 0.79 (age < 45); year-9: (age ≥ 45) 0.71 < 0.78 (age < 45); year-10: (age ≥ 45) 0.71 < 0.79 (age < 45); year-11: (age ≥ 45) 0.69 < 0.79 (age < 45); year-12: (age ≥ 45) 0.66 < 0.79 (age < 45)], and

Table 3 Prediction threshold, sensitivity, specificity and areas under the time-dependent receiver operating characteristic curves for METS-IR predicting future diabetes risk for women and men

	Women				Men			
	Prediction threshold	Sensitivity	Specificity	AUC	Prediction threshold	Sensitivity	Specificity	AUC
METS-IR								
2-years	28.58	0.71	0.63	0.68	36.94	0.52	0.72	0.62
3-years	29.31	0.64	0.68	0.70	36.94	0.60	0.72	0.67
4-years	27.90	0.75	0.58	0.72	36.74	0.54	0.71	0.64
5-years	27.90	0.76	0.58	0.73	37.02	0.55	0.73	0.67
6-years	29.20	0.71	0.68	0.76	37.39	0.52	0.74	0.68
7-years	29.31	0.72	0.69	0.76	36.74	0.61	0.72	0.70
8-years	29.22	0.73	0.68	0.77	36.74	0.60	0.72	0.70
9-years	27.50	0.86	0.55	0.76	36.83	0.58	0.72	0.70
10-years	29.00	0.73	0.67	0.75	36.49	0.61	0.71	0.71
11-years	29.33	0.72	0.69	0.76	34.81	0.67	0.63	0.70
12-years	29.33	0.71	0.70	0.76	37.42	0.50	0.76	0.67
TyG index								
2-years	7.90	0.77	0.64	0.64	8.77	0.47	0.79	0.62
3-years	7.92	0.84	0.62	0.71	8.51	0.60	0.66	0.64
4-years	7.98	0.76	0.69	0.72	8.51	0.60	0.66	0.64
5-years	7.92	0.81	0.64	0.73	8.49	0.61	0.65	0.65
6-years	7.98	0.73	0.69	0.73	8.26	0.75	0.50	0.65
7-years	7.99	0.74	0.69	0.73	8.49	0.63	0.65	0.67
8-years	7.98	0.73	0.69	0.73	8.49	0.63	0.65	0.67
9-years	7.99	0.75	0.70	0.74	8.50	0.60	0.66	0.66
10-years	8.01	0.72	0.71	0.73	8.25	0.75	0.50	0.65
11-years	8.00	0.74	0.71	0.74	8.25	0.73	0.50	0.65
12-years	8.01	0.76	0.71	0.76	8.50	0.56	0.67	0.64

Abbreviations: AUC: area under the curve; TyG: Triglyceride-Glucose; other abbreviations as in Table 1

still maintained high accuracy in the medium to long term (AUCs for year-6 to year-12 were above 0.79).

Similarly, we also reported the findings in the BMI subgroups; time-dependent ROC analysis showed that in the short term (3–5 years), METS-IR was more accurate in predicting the future onset of diabetes in population with overweight/obesity[AUC: year-3: (BMI≥25 kg/m^2) 0.67>0.64 (BMI<25 kg/m^2); year-4: (BMI≥25 kg/m^2) 0.67>0.64 (BMI<25 kg/m^2); year-5: (BMI≥25 kg/m^2) 0.66>0.65(BMI<25 kg/m^2)], whereas in the medium to long term, METS-IR had higher accuracy in predicting the future onset of diabetes in non-obese population [AUC: year-6: (BMI≥25 kg/m^2) 0.65<0.69 (BMI<25 kg/m^2); year-7: (BMI≥25 kg/m^2) 0.68<0.70 (BMI<25 kg/m^2); year-8: (BMI≥25 kg/m^2) 0.69<0.71 (BMI<25 kg/m^2); year-9: (BMI≥25 kg/m^2) 0.68<0.70 (BMI<25 kg/m^2); year-10: (BMI≥25 kg/m^2) 0.66<0.70 (BMI<25 kg/m^2); year-11: (BMI≥25 kg/m^2) 0.66<0.70 (BMI<25 kg/m^2); year-12: (BMI≥25 kg/m^2) 0.66<0.68 (BMI<25 kg/m^2)].

Threshold analysis of baseline METS-IR for predicting the future onset of diabetes in different populations

Data on threshold values of METS-IR for predicting the future onset of diabetes in the sex, age, and BMI subgroups were also shown in Tables 3, 4 and 5, and Fig. 3 describes the trend of METS-IR predictive thresholds over time in different subgroups. As seen in Fig. 3, the predictive thresholds of METS-IR for predicting future diabetes were consistently higher in men than in women regardless of time changes and were less fluctuated in both sexes in different time points, suggesting that the threshold values of METS-IR for predicting future diabetes were relatively stable in both sexes and METS-IR had good application value (range of predictive thresholds: men: 34.81–37.42; women: 27.50-29.33). In contrast, the difference in predictive thresholds of METS-IR was not significant between the two age subgroups, but the fluctuations were relatively larger in the group of age<45 years (range of predictive threshold: age≥45: 32.98–35.95; age<45: 31.46–38.06). Similar trends were observed in the BMI subgroups as in the sex subgroups, and as expected, the predictive thresholds of METS-IR were greater in the population with overweight/obesity than in the non-obese population, and were less fluctuated in both overweight/obesity and non-obese populations at all time points (range of predictive threshold: overweight/obesity: 38.42–42.31; non-obese: 27.36–30.77).

Table 4 Prediction threshold, sensitivity, specificity and areas under the time-dependent receiver operating characteristic curves for METS-IR predicting future diabetes risk for age ≥ 45 and < 45 years

	Age, years							
	≥ 45				**< 45**			
	Prediction threshold	Sensitivity	Specificity	AUC	Prediction threshold	Sensitivity	Specificity	AUC
2-years	35.73	0.48	0.75	0.66	38.06	0.37	0.86	0.64
3-years	35.95	0.48	0.76	0.67	37.29	0.63	0.84	0.76
4-years	35.70	0.45	0.75	0.65	36.15	0.63	0.81	0.76
5-years	33.91	0.59	0.67	0.69	36.15	0.62	0.81	0.78
6-years	33.78	0.63	0.67	0.70	31.67	0.81	0.62	0.79
7-years	33.91	0.65	0.68	0.71	35.57	0.69	0.79	0.81
8-years	33.46	0.69	0.66	0.73	31.46	0.85	0.62	0.79
9-years	34.45	0.60	0.71	0.71	31.67	0.81	0.63	0.78
10-years	32.98	0.68	0.63	0.71	31.66	0.84	0.63	0.79
11-years	32.98	0.65	0.63	0.69	31.67	0.84	0.63	0.79
12-years	33.36	0.57	0.65	0.66	31.75	0.84	0.64	0.79
TyG index								
2-years	8.47	0.54	0.70	0.63	8.67	0.45	0.86	0.63
3-years	8.47	0.52	0.70	0.64	8.30	0.69	0.73	0.75
4-years	8.49	0.50	0.72	0.63	8.20	0.74	0.68	0.73
5-years	8.45	0.57	0.69	0.66	8.17	0.72	0.66	0.72
6-years	8.23	0.71	0.56	0.66	8.27	0.71	071	0.73
7-years	8.23	0.70	0.56	0.67	8.22	0.75	0.69	0.76
8-years	8.23	0.73	0.56	0.69	8.24	0.6*	0.70	0.73
9-years	8.18	0.74	0.53	0.67	8.27	0.69	0.72	0.74
10-years	8.18	0.76	0.53	0.68	8.23	0.69	0.70	0.73
11-years	8.20	0.71	0.54	0.67	8.20	0.71	0.69	0.73
12-years	8.20	0.70	0.55	0.65	8.21	0.71	0.69	0.74

Abbreviations: AUC: area under the curve; TyG: Triglyceride-Glucose; other abbreviations as in Table 1

Comparison of predictive value between METS-IR and TyG index

The results of time-dependent ROC analysis comparing METS-IR with TyG for predicting future diabetes were presented in Tables 3, 4 and 5. The results showed that the AUC values for the prediction of future diabetes by METS-IR were higher at the vast majority of time points compared to the TyG index, demonstrating relatively better predictive performance.

Discussion

In this current retrospective cohort study, we further validated previous findings showing that METS-IR was significantly associated with diabetes risk. After adjusting for confounders that may have influenced the results, the results of the stratified analysis showed that the positive association between METS-IR and diabetes was stronger in women than in men and in population < 45 years of age than in population ≥ 45 years of age (P-interaction < 0.05), while no significant differences were observed between non-obese population and population with overweight/obesity (P-interaction = 0.78). In addition, as the main analysis results, the time-dependent ROC analysis showed that: (1) METS-IR was more accurate in predicting the future onset of diabetes in women than in men, and remained more accurate in the medium to long term; (2) at almost all time points, METS-IR was more accurate in predicting the future onset of diabetes in people aged less than 45 years than in those aged ≥ 45 years; (3) in the short term (3–5 years), METS-IR was more accurate in predicting new diabetes events in the population with overweight/obesity, while in the medium to long term (6–12 years), METS-IR was more accurate in the non-obese population.

In recent years, METS-IR has gained much attention as an emerging alternative index of IR. Compared with methods such as EHC, insulin homeostasis model, and quantitative insulin sensitivity check index, METS-IR is more convenient to be obtained and can be calculated using some routine laboratory biochemical indicators, which seems more suitable for a wide range of health screening. METS-IR was developed in 2018 by Bello-Chavolla OY et al. They verified in three cohorts that METS-IR has a good correlation with IR by fat-free mass; furthermore, they assessed the relationship between METS-IR and diabetes risk and showed that diabetes risk increased with the increase of METS-IR percentile [13]. Specifically, participants in the highest quartile group had a 291% increased risk of diabetes compared to participants in the lowest METS-IR quartile group.

Table 5 Prediction threshold, sensitivity, specificity and areas under the time-dependent receiver operating characteristic curves for METS-IR predicting future diabetes risk for BMI ≥ 25 and < 25 kg/m^2

	BMI, kg/m^2							
	≥ 25				**< 25**			
	Prediction threshold	Sensitivity	Specificity	AUC	Prediction threshold	Sensitivity	Specificity	AUC
2-years	38.42	0.86	0.32	0.61	27.36	0.85	0.38	0.62
3-years	40.22	0.83	0.48	0.67	27.38	0.89	0.39	0.64
4-years	40.55	0.77	0.52	0.67	27.38	0.87	0.39	0.64
5-years	42.31	0.60	0.67	0.66	27.47	0.87	0.39	0.65
6-years	41.54	0.64	0.61	0.65	27.80	0.87	0.42	0.69
7-years	42.15	0.64	0.66	0.68	28.63	0.80	0.49	0.70
8-years	42.25	0.63	0.68	0.69	30.67	0.67	0.64	0.71
9-years	42.26	0.60	0.68	0.68	30.67	0.66	0.64	0.70
10-years	42.25	0.55	0.68	0.66	30.77	0.67	0.65	0.70
11-years	42.07	0.57	0.67	0.66	30.19	0.71	0.61	0.70
TyG index								
2-years	8.77	0.67	0.68	0.69	7.61	0.87	0.30	0.60
3-years	8.73	0.58	0.66	0.66	8.45	0.38	0.80	0.62
64-years	8.73	0.59	0.66	0.64	8.24	0.51	0.70	0.64
5-years	8.74	0.49	0.67	0.60	8.42	0.45	0.79	0.65
6-years	8.24	0.84	0.33	0.60	8.29	0.56	0.72	0.67
7-years	8.74	0.51	0.68	0.63	8.24	0.58	0.70	0.68
8-years	8.32	0.80	0.39	0.63	8.00	0.71	0.55	0.67
9-years	8.32	0.82	0.39	0.64	7.97	0.73	0.54	0.67
10-years	8.32	0.81	0.40	0.63	8.06	0.70	0.60	0.68
11-years	8.32	0.79	0.40	0.61	7.98	0.76	0.55	0.68
12-years	8.76	0.51	0.70	0.64	8.17	0.61	0.67	0.67

Abbreviations: AUC: area under the curve; TyG: Triglyceride-Glucose; other abbreviations as in Table 1

Subsequently, similar evidence of positive association was provided in two cross-sectional studies completed in China [14, 17] and validated in further longitudinal studies: In a 6-year longitudinal follow-up period of 12,107 rural Chinese people, each SD increase in METS-IR was strongly associated with an 82% increase in diabetes risk [16]. In the current study, we conducted some longitudinal analyzes based on the Japanese physical examination population cohort. We found that elevated METS-IR was associated with an increased risk of diabetes in the Japanese population; After adjusting for potential confounders, there was a 47% increase in the risk of future diabetes per SD increase in the METS-IR; compared to the lowest quartile group, subjects in the highest quartile group of the METS-IR had a 215% increased risk of diabetes. To summarize, the data on the association between METS-IR and future diabetes in the current study are consistent with those reported in previous studies, both as categorical and continuous variables [13, 14, 16, 17]. In the present study, we further performed stratified analyses for pre-defined age, sex, and BMI subgroups, and after adjusting for multiple confounders, we found that METS-IR was an independent risk factor for the onset of diabetes in all subpopulations. This was consistent with the findings of a previously conducted study of a non-obese population defined by their BMI and WC (BMI≤25 kg/m2 and WC≤90 cm in men or WC≤80 cm in women) [15]. In short, the vast majority of studies supported the association of METS-IR with the risk of type 2 diabetes, and the results of our study, which used data from a large cohort study with a general population and a long follow-up period, provided new evidence for the previous findings. These findings underscored the concept that METS-IR is a valid alternative to IR for assessing diabetes risk in the general population.

The predictive value of METS-IR for future diabetes was previously reported only in a study by Cai XT et al. [15], who specifically assessed the predictive value of METS-IR for future new-onset diabetes in a non-obese population. Given that the current understanding of the predictive value of METS-IR for diabetes is based only on the non-obese population, we further performed a predictive value analysis in different subgroups of the general population, and the results were as expected, supporting the feasibility and validity of METS-IR for future diabetes prediction. In the current study, we evaluated the predictive value of METS-IR for the onset of diabetes over the next 2–12 years using time-dependent ROC in pre-specified subgroups of sex, age, and BMI. Overall, METS-IR had good predictive power for the future onset of diabetes in different populations. By sex subgroups, METS-IR was more accurate in predicting diabetes events in the

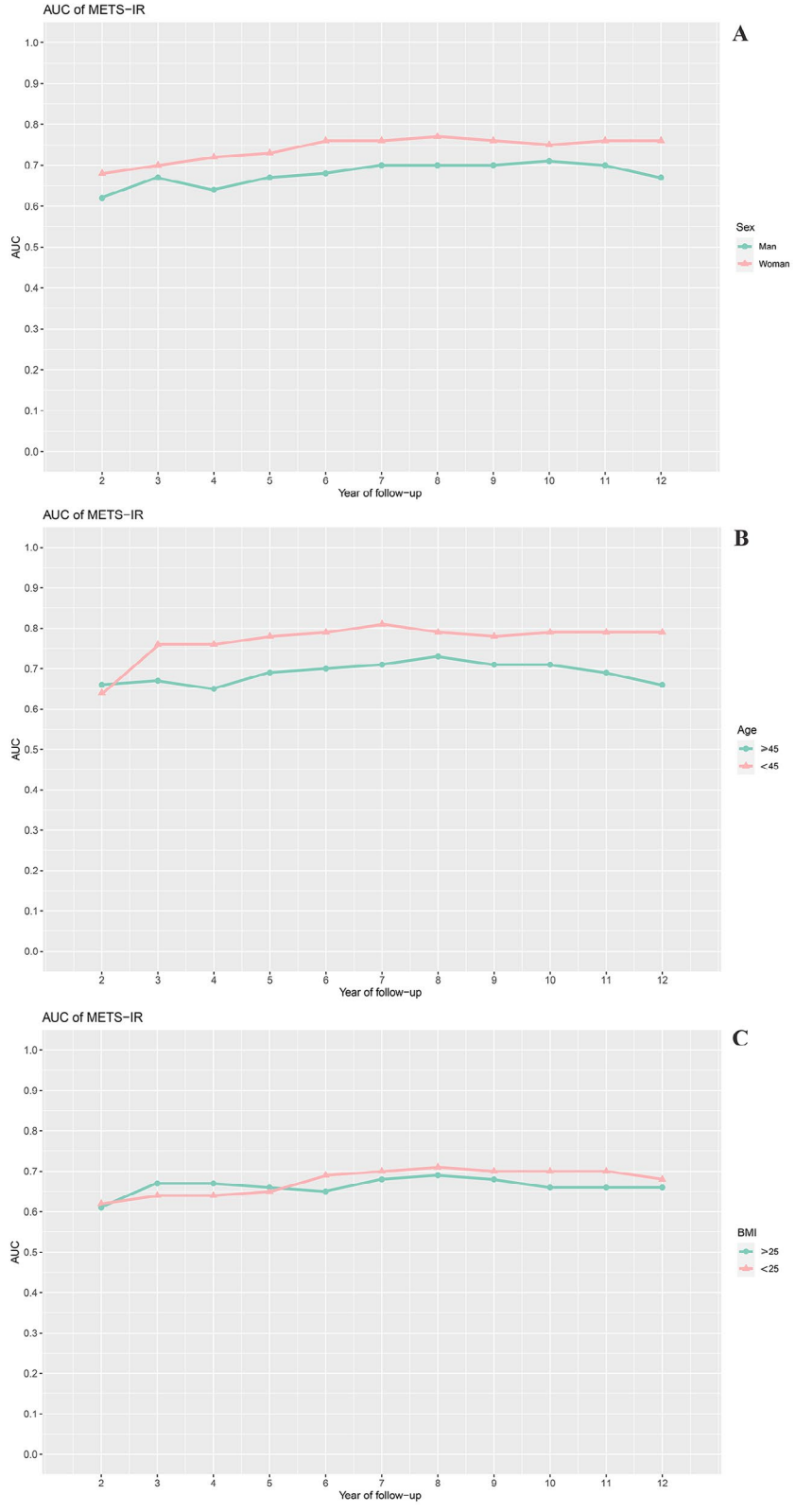

Fig. 2 The area under the receiver operator characteristics curve of METS-IR varying with time to predict the future diabetes in the subgroup populations of sex (**A**), age (**B**), and BMI (**C**). AUC: area under the curve

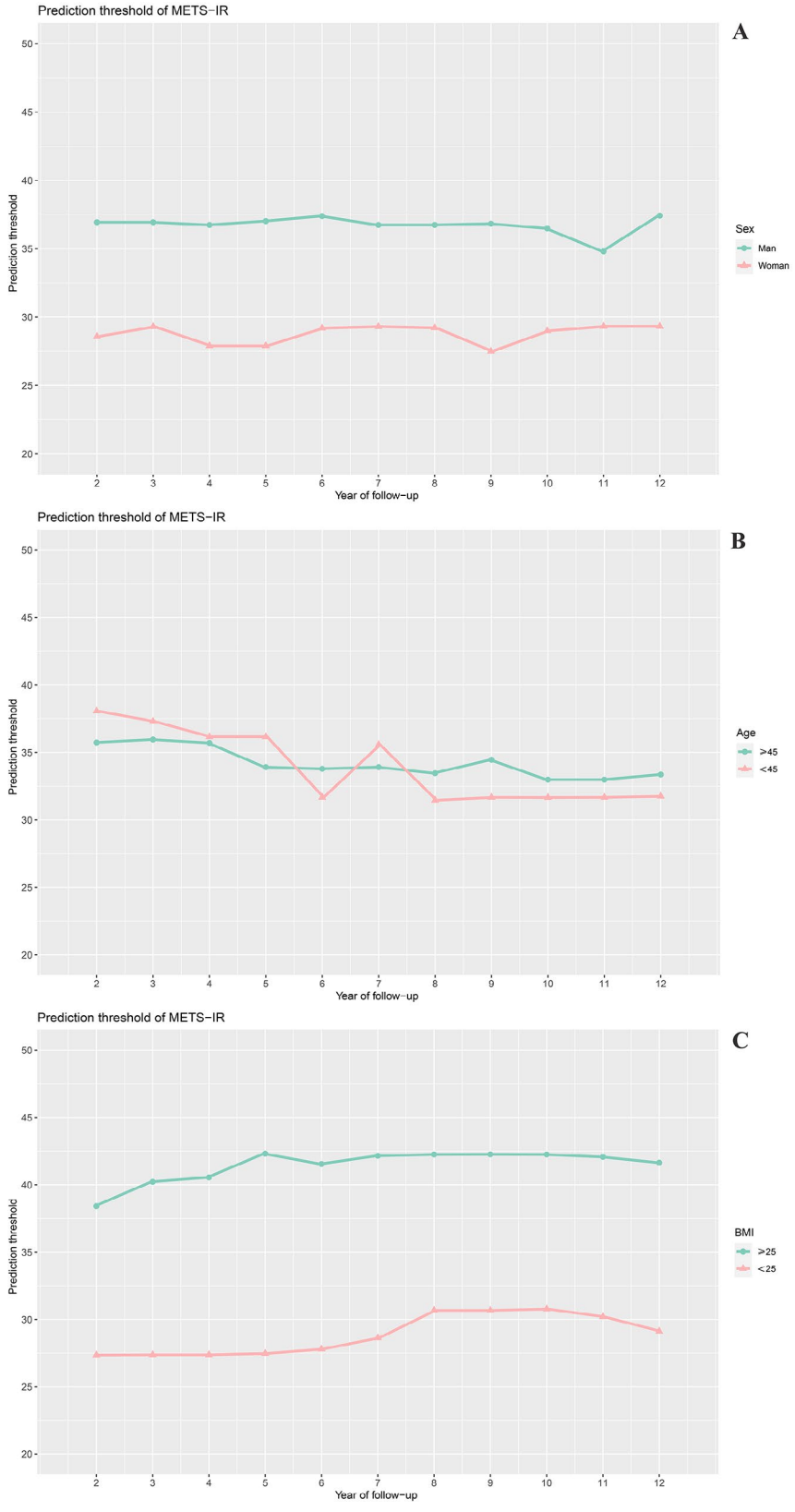

Fig. 3 Threshold fluctuations of METS-IR which was used to predict future diabetes in the subgroup populations of sex (**A**), age (**B**), and BMI (**C**)

women population and remained stable over a longer period of time (AUC remained around 0.76). In terms of age subgroups, METS-IR was more accurate in predicting diabetes events in people younger than 45 years of age and remained more accurate in the next 7–12 years (AUC remained around 0.79). In contrast, there were temporal differences in the predictive value of METS-IR in BMI subgroups, with higher predictive accuracy for the development of diabetes in the population with overweight/obesity in the short term, while higher in the non-obese population in the medium-to long-term. It should be noted that in the age subgroups of the current study, the incidence of diabetes in people older than 45 years (2.78/1000 person-years) is actually higher than that of people younger than 45 years (1.39/1000 person-years); however, in terms of diabetes prediction, the METS-IR demonstrated significantly higher predictive accuracy for individuals younger than 45 years old than for those older than 45 years old. Regarding the differences in the results of the above subgroups, we have the following considerations: (1) It is well known that there are significant differences in body composition between males and females; in general, males have a relatively higher lean body mass while females have a relatively higher fat mass [32]. It should be pointed out that high lean body mass is an important protective factor for diabetes [33], while high-fat mass is a risk factor for diabetes [34]. In fact, the METS-IR formula includes BMI, and typically males have higher lean body mass and females have higher fat mass at the same BMI level. Therefore, compared to males, the same METS-IR level may indicate a higher risk of developing diabetes in females, thereby demonstrating greater accuracy in predicting diabetes. In addition, it is important to note that females are generally less physically active than males [35], and physical activity can help reduce the risk of diabetes [36]. (2) For age subgroup differences, we consider the following factors: It is well-known that increasing age is an important non-modifiable risk factor in the development of diabetes [37]. Studies have shown that with aging, insulin secretion and insulin sensitivity well decline, and impaired glucose metabolism may lead to an increased incidence of diabetes [38, 39]. Additionally, older participants may already have a certain degree of IR, with compensatory increased pancreatic beta-cell function [40], which could reduce the sensitivity of METS-IR in reflecting their IR. On the other hand, age is an important factor affecting lipid metabolism, and there is evidence that HDL-C decreases gradually with aging [41]. Therefore, aging may lead to an increase in fasting blood glucose and a decrease in HDL-C levels, both of which are important components of METS-IR, potentially reducing its accuracy in predicting diabetes. Lastly, age, as an independent risk factor for diabetes, may lead to diabetes development through pathways other than IR in some patients, which could lower the predictive accuracy of METS-IR for diabetes in this subset of patients. (3) For the differences observed in BMI subgroups we considered that they might be related to the following: As is well known, obesity is a disorder of energy balance leading to fat accumulation, primarily characterized by early abnormalities in glycolipid metabolism [42], and METS-IR contains a variety of indicators related to glycolipid metabolism, which better reflects the resulting IR. However, with prolonged exposure to obesity, insulin resistance is no longer induced solely through the glycolipid metabolism pathway; Studies have shown that a significant increase in metabolites, such as branched-chain amino acids, is an important factor contributing to IR in obese compared to non-obese populations [43, 44]. Therefore, the accuracy of MEST-IR in estimating IR may decrease when exposed to obesity for a longer period of time, resulting in decreased accuracy in predicting new-onset diabetes in obese individuals in the medium and long term. In addition, over a longer follow-up period, a proportion of obese individuals may lose weight through various methods, potentially transforming previously obese, high-risk individuals into lean, low-risk individuals. This could ultimately lead to misclassification of future diabetes by the baseline METS-IR, thereby decreasing predictive accuracy.

No previous studies have reported on the predictive threshold of METS-IR for predicting future diabetes. In the present study, we analyzed the trends over time in the predictive thresholds of METS-IR used to predict future diabetes. In terms of the magnitude of the prediction thresholds, the thresholds of METS-IR for predicting future diabetes were slightly higher in men than in women, and slightly higher in people with overweight/obesity than in non-obese people, while the difference of the threshold values among people younger than 45 years old and those aged ≥ 45 years was not significant; in terms of predictive threshold fluctuation intervals, METS-IR prediction thresholds fluctuated relatively little for both men and women, for both the non-obese population and the population with overweight/obesity and for those aged ≥ 45 years.

The results of the current study may provide some reference for the prevention of diabetes in the population, clinical decision-making by physicians, and the development of relevant government policies. Currently, diabetes prevention programs, as a fundamental policy for protecting public health, have obtained certain achievements in various countries [45–47]. However, it should be noted that the rate of mass participation in ongoing prevention programs is still low, and one of the possible reasons for this is lack of awareness of the risks and financial pressures [45]. China is one of the countries with the largest number of diabetes patients worldwide, and over the past

few decades, the prevalence of diabetes has risen sharply [48, 49]. Similar to other countries, in response to the rapidly growing burden of diabetes, the Chinese government has swiftly implemented a number of public health policies, including increasing government investment in primary healthcare, adjusting medical reimbursement policies, initiating the national family doctor program, and leading the establishment of "medical alliances" within counties [50–52]. Indeed, these favorable policy changes have been effectively improving access to better medical care for the general public in recent years. At the same time, they have also contributed to an increased awareness among the general population regarding diabetes and other chronic diseases [48]. However, it is important to note that in some remote or rural areas, due to insufficient medical resources, a shortage of healthcare workers, as well as transportation, economic constraints and time conflicts, people still face challenges in terms of awareness, prevention, and treatment of diabetes [48, 53, 54]. Therefore, identifying a precise, easily measurable, and durable IR surrogate parameter (METS-IR) that suits different populations becomes of great practical significance. This can potentially reduce the economic burden on the population and decrease the healthcare expenditure and resource allocation for diabetes prevention at the national level.

Strengths and limitations

The present study has several advantages: First, the participants of the current study is from a medical screening center more in line with the general population setting relative to the diseased population and is more widely applicable. In addition, the current study has a large sample size and a long follow-up period, and the research evidence can be considered relatively reliable. Second, we included a time factor in the ROC analysis to assess METS-IR prediction of the onset of diabetes at different time points rather than at a fixed time in order to compare longitudinally the temporal differences in METS-IR used to predict future diabetes.

There are, of course, some limitations to our study: First, the retrospective study design, based on single-center data, may introduce some unavoidable selection bias, although on the other hand, single-center data are better at maintaining the homogeneity of the study population, which strengthens the validity of the results [55]. Second, due to the inherent limitations of the data source, we only assessed the predictive power of baseline METS-IR for future diabetes, whereas changes in various factors, including METS-IR, may alter the association of METS-IR with diabetes over a longer follow-up period [2, 56, 57], and such dynamic changes should be further evaluated in the future. Third, the diagnosis of diabetes was determined based on FPG and HbA1c, and the absence of testing for 2-h postprandial glucose may have underestimated the prevalence of diabetes [58, 59], however, our results in data that may be lower than the actual prevalence population may better justify the robustness of the findings of this study. Fourth, the current assessment of the predictive power of METS-IR was based on the general Japanese population, and further validation in other ethnic populations is needed in the future. Fifth, we excluded a portion of subjects (4.17%) due to missing data, which may have resulted in partial selection bias. Fifth, the current study is based on a secondary analysis of public data. Since information on the prevalence of nutritional state was not provided in the original data set, the potential impact of nutritional state on the study results cannot be further assessed in the current research. Finally, the types of diabetes were not distinguished in the current study; however, according to a large number of published research evidence, the results of this study were more applicable to type 2 diabetes, because patients with type 2 diabetes account for more than 95% of all diabetic patients [60, 61].

Conclusions

In conclusion, our study showed that METS-IR was positively associated with diabetes risk in the general population, and METS-IR was effective in predicting the future onset of diabetes in different populations at different times points, with a high predictive value especially for women and those aged less than 45 years. As a new risk screening and prediction tool, the METS-IR index can provide patients, physicians, and healthcare policymakers with better-informed decisions.

Abbreviations

METS-IR	Metabolic insulin resistance score
IR	Insulin resistance
WHO	World Health Organization
EHC	Euglycemic-hyperinsulinemic clamp
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	Gamma-glutamyl transferase
HDL-C	High-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglyceride
LDL-C	Low-density lipoprotein cholesterol
HbA1c	Glycated hemoglobin A1c
FPG	Fasting plasma glucose
ROC	Receiver operating characteristic
HR	Hazard ratio
CI	Confidence interval
AUC	Area under the curves

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
YZ and GT-S: conceptualization. JJ-Q and GT-S: writing-original draft preparation. YZ, SM-H, CH-Y, RJ-Y, MB-K and YZ: writing-reviewing and editing. YZ, MB-K, JJ-Q and GT-S: formal analysis and validation. GT-S and YZ: data curation and validation. YZ and GT-S: Supervision. All authors read and approved the final manuscript.

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Data availability
The data used in this study have been uploaded to the "Dryad" database (https://datadryad.org/stash/dataset/doi:10.5061/dryad.8q0p192).

Declarations

Ethics approval and consent to participate
The analysis of the data of all subjects in the current study complied with the Declaration of Helsinki, See STROBE statement (S1 Text), and was approved by the Ethics Committee of Jiangxi Provincial People's Hospital (IRB2021-066).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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