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The combination of insulin resistance and visceral adipose tissue estimation improves the performance of metabolic syndrome as a predictor of type 2 diabetes

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Abstract

Aims To assess the performance of metabolic syndrome as a predictor of type 2 diabetes in a model that also includes both a measure of insulin resistance and a metabolic score for visceral fat, and to propose a novel metabolic syndrome definition.

Methods In a prospective Metabolic Syndrome Cohort (n=6143), we evaluated improvements in type 2 diabetes risk prediction using International Diabetes Federation-defined and Adult Treatment Panel III-defined metabolic syndrome, after inclusion in the model of updated homeostatic model assessment of insulin resistance and a metabolic score for visceral fat. We also developed a modified metabolic syndrome construct, 'MS-METS', which used the metabolic score for visceral fat instead of waist circumference to evaluate improved predictive performance for risk of developing type 2 diabetes.

Results Participants who had metabolic syndrome as defined by both the Adult Treatment Panel III and the International Diabetes Federation criteria had a higher risk of type 2 diabetes compared to participants who did not meet these criteria. Addition of updated homeostatic model assessment of insulin resistance and metabolic score for visceral fat to both metabolic syndrome definitions increased predictive performance for type 2 diabetes risk. Homeostatic model assessment of insulin resistance was the only additional predictor of type 2 diabetes in participants without metabolic syndrome. Conversely, in participants with metabolic syndrome, the use of the metabolic score for visceral fat was the stronger added predictor for type 2 diabetes. When evaluating participants using the MS-METS definition we observed the largest improvement in predictive ability for type 2 diabetes risk and a significant reduction in risk overestimation compared to evaluation using metabolic syndrome defined according to the International Diabetes Federation and Adult Treatment Panel III criteria alone.

Conclusion Inclusion of updated homeostatic model assessment of insulin resistance and metabolic score for visceral fat increases performance of metabolic syndrome in prediction of type 2 diabetes. Assessment of insulin resistance could be more useful than conventional metabolic syndrome and assessment of visceral adipose tissue could be more useful in people with metabolic syndrome. Metabolic syndrome as defined using our modified MS-METS construct improved the accuracy of type 2 diabetes prediction.

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What's new?

- The metabolic syndrome has been used clinically to identify people at risk of cardiometabolic diseases; nevertheless, some pathophysiological components of the metabolic syndrome are not explicitly included in current definitions.
- Insulin resistance was a better predictor of type 2 diabetes in participants without metabolic syndrome and visceral dat in participants with metabolic syndrome. We also developed a metabolic syndrome definition which substituted waist circumference for METS-VF(MS-METS) for which we observed the largest improvement in predictive ability for type 2 diabetes risk without risk overestimation.
- Complementary clinical assessment of insulin resistance using HOMA2-IR and visceral fat using METS-VF increased predictive performance for type 2 diabetes risk. The MS-METS definition could reduce risk overestimation for type 2 diabetes.

Introduction

The metabolic syndrome (MS) construct comprises a constellation of metabolic risk factors linked to insulin resistance. MS has been used clinically to identify people at risk of cardiometabolic diseases including type 2 diabetes, hypertension and atherosclerosis [1–3]. Insulin resistance is a key component of MS because of its association with impaired glucose metabolism, atherogenic dyslipidaemia, increased vascular resistance and adipose tissue dysfunction, even before the onset of type 2 diabetes, atherosclerosis or hypertension [4–7]. Several epidemiological and clinical criteria have been used to define MS, including the Adult Treatment Panel III (ATP-III) and International Diabetes Federation (IDF) criteria, which are amongst the most widely used in clinical and research settings. Nevertheless, these criteria do not explicitly involve estimation of insulin resistance and its complications; in this context, estimation of insulin resistance and visceral adipose tissue (VAT) could be complementary approaches in people with MS [8–10]. VAT accumulation interacts with insulin resistance as a result of dysregulation in adipose tissue lipolysis, increasing the availability of free fatty acids and decreasing the clearance of triglyceride-rich lipoproteins [11]; therefore, accumulation of VAT leads to increases in cardiometabolic risk, independently of subcutaneous fat deposits [12]. Recently, a metabolic score for visceral fat (METS-VF), a novel VAT estimator, which includes a non-insulin-based metabolic score for insulin resistance (METS-IR), was developed by our group. METS-VF showed notable performance compared to imaging methods and is a predictor of incident type 2 diabetes and arterial hypertension independent of BMI [13]. In the present study, we aimed to evaluate the role of adding assessment of an insulin resistance index and a VAT estimator to current clinically validated MS definitions to improve the predictive performance for incident type 2 diabetes in an open-population cohort and to develop an improved MS definition aimed at reflecting increased type 2 diabetes risk by incorporating a VAT estimator.

Participants and methods

Metabolic Syndrome Cohort

The MS cohort was developed to evaluate the risk of MS components in people who develop incident type 2 diabetes, arterial hypertension and cardiovascular mortality in an urban population living in nine different cities in Mexico. Complete and detailed assessment of measurements and results obtained in this MS cohort are published elsewhere [14,15]. Inclusion and exclusion criteria, as well as biochemical and anthropometrical assessment are presented in the Supporting Information. We recruited 7636 participants at baseline, of whom a total of 6144 participants agreed to continue with a follow-up visit; we also registered 22 deaths after this period of follow-up. For the purposes of the present study, we included all participants for whom all evaluation data were available at baseline and follow-up (n=6144).

METS-IR was calculated using the formula:

$$[\mathrm{LN}((2 * G_0) + TG_0)] * \mathrm{BMI}/[\mathrm{LN}(\text{HDL cholesterol})],$$

where G_0 and TG_0 are fasting glucose and triglycerides, respectively [13].

METS-VF was calculated using the formula:

$$4.466 + 0.011 * [\mathrm{Ln}(\mathrm{METS} - \mathrm{IR})]^3 + 3.239 * [\mathrm{Ln}(\mathrm{WHtr})]^3 + 0.319 * (\text{male sex}) + 0.594 * [\mathrm{Ln}(\text{age})],$$

where WHtr is weight–height ratio and age is given in years [16]. Because METS-IR is essential in estimating METS-VF, we chose the updated homeostasis model assessment for insulin resistance (HOMA2-IR) index to evaluate the contribution of insulin resistance to improving the predictive performance of MS for type 2 diabetes. HOMA2-IR was calculated using fasting glucose and insulin using the HOMA2 calculator released by the Diabetes Trials Unit, University of Oxford: HOMA Calculator [17]. Incident type 2 diabetes was defined as previous medical diagnosis of type 2 diabetes, taking hypoglycaemic medication and/or fasting glucose levels ≥7.0 mmol/dl (≥126 mg/dl) according to American Diabetes Association guidelines. Time to follow-up was estimated from time of recruitment up to the last follow-up or type 2 diabetes diagnosis, whichever occurred first. Finally, we defined MS according to IDF and ATP-III criteria. MS considered

according to the IDF criteria was defined as the presence of central obesity plus two other components and MS considered according to the ATP-III criteria was defined as the presence of three or more components [18].

Statistical analysis

Study population at baseline and follow-up

To evaluate concordance between the IDF and ATP-III MS criteria, we used Cohen's κ coefficient. Next, to evaluate inter-group differences in sociodemographic and biochemical measures, we used Student's *t*-test and the Mann–Whitney *U*-test, as appropriate. Categorical variables were reported as frequencies and percentages, and were compared between groups using chi-squared tests. For measurements in follow-up studies we used Student's paired *t*-test and Wilcoxon's signed rank tests, where appropriate. Data are presented as mean ± SD or as median and interquartile ranges.

Risk of type 2 diabetes assessed using metabolic syndrome constructs and individual components

We evaluated differences in survival using Kaplan–Meier curves compared with log-rank tests and compared differences in time to type 2 diabetes incidence between participants without MS (no MS), those who had MS only according to ATP-III (ATP-III-defined MS) or IDF criteria (IDF-defined MS), and those who had MS according to both sets of criteria (ATP-III + IDF-defined MS). To evaluate the risk of incident type 2 diabetes related to MS, we used Cox proportional risk regression analyses, adjusted for family history of type 2 diabetes, physical activity and smoking status, which have been previously reported to modify type 2 diabetes prediction [19–21]. We hypothesized that type 2 diabetes risk would have a graded response in direct relation to increased number of MS components; to test this hypothesis, we evaluated risk of incident type 2 diabetes using individual MS components from both MS definitions. Furthermore, we explored the capacity of HOMA2-IR and METS-VF to predict incident type 2 diabetes, adjusted for covariates.

Predictive improvement after combining metabolic syndrome, HOMA2-IR and METS-VF

Our main objective was to demonstrate whether using HOMA2-IR and METS-VF would improve the performance of both MS constructs for the prediction of type 2 diabetes. First, we fitted models including METS-VF and/or HOMA2-IR as linear predictors to individual components of each MS definition, and evaluated increases in predictive performance using sequential Cox proportional risk regression analyses. We obtained calibration and discrimination indices from the models, including the likelihood ratio chi-squared test and Harrel's *C*-statistic. To evaluate if the inclusion of the cardiometabolic indicators played a role in type 2 diabetes risk reclassification, we calculated the net reclassification improvement index (NRI), using thresholds of 5%, 10%, 15% and 20%, and estimated 95% CIs using bootstrapping (n=1000). Model selection was carried out using the changes in Bayesian information criterion (ΔBIC); lower BIC values indicated the better fit for each model. Treatment of multicollinearity is presented in the Supporting Information.

Development of a novel metabolic syndrome definition including visceral adipose tissue estimation

The IDF MS definition, and to a lesser extent the ATP-III MS definition, is founded on assessment of waist circumference as a surrogate of abdominal obesity. The use of waist circumference to define at-risk abdominal obesity does not distinguish appropriately between subcutaneous or visceral adipose tissue, thus influencing risk prediction and potentially overestimating risk associated with the MS criteria. We propose a modified definition, substituting waist circumference for the VAT surrogate METS-VF. In this modified definition, we include the previously validated METS-VF threshold of ≥7.18 [16] instead of waist circumference to define visceral obesity as a predictor instead of waist circumference in the ATP-III criteria, a construct which we termed MS-METS. Our novel MS definition considers MS as the presence of three or more criteria, similar to the ATP-III definition. As described above, we evaluated added model performance using calibration indices, BIC and NRI. Statistical analyses were performed using SPSS (version 24.0), R software (version 3.5.2), and GraphPad Prism (version 7.0).

Results

Study population and concordance of metabolic syndrome definitions with respect to type 2 diabetes risk

At baseline, we identified 2695 participants (43.9%) with IDF-defined MS and 2038 participants (33.2%) with ATP-III-defined MS. After follow-up we identified 331 participants who developed incident type 2 diabetes (Table 1). Next, we assessed the prevalence of individual components of MS at baseline. In participants with MS who developed type 2 diabetes we found a high prevalence of low HDL cholesterol and hypertriglyceridaemia, as expected in our population (Table 2). With regard to concordance of MS definition, there was moderate agreement (κ=0.70, 95% CI 0.687–0.721) between the IDF-defined MS and the ATP-III-defined MS groups.

Prediction of incident type 2 diabetes using metabolic syndrome and its individual components

We observed significant differences in type 2 diabetes incidence in the four groups according to the concordance between MS definitions (no MS, ATP-III-defined MS, IDF-defined MS, ATP-III + IDF-defined MS). Participants who only fulfilled the ATP-III MS criteria at baseline had 3.5-fold

Table 1 Biochemical and anthropometric characteristics of the whole study population, participants without metabolic syndrome, those who met only the Adult Treatment Panel III (ATP-III) or International Diabetes Federation (IDF) criteria, and those who met both the ATP-III and IDF criteria

Characteristic	Whole population, *N*=6144	No MS, *n*=3342	ATP-III criteria, *n*=108	IDF criteria, *n*=764	Both sets of criteria, *n*=1930	*P*
Age, years	42.6 (10.7)	40.9 (34–47)	45.5 (11)	42.5 (10.91)	45.3 (11.20)	<0.001
Glucose, mmol/l	4.7 (0.61)	4.6 (0.5)	5.2 (0.8)	4.7 (0.6)	5.1 (0.7)	<0.001
Triglycerides, mmol/l	1.8 (1.2–2.5)	1.4 (1.0–1.9)	2.3 (1.9–3.1)	2.2 (1.8–3.1)	2.3 (1.8–3.1)	<0.001
HDL cholesterol, mmol/l	1.1 (0.9–1.3)	1.3 (1.1–1.5)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	0.9 (0.8–1.1)	<0.001
Systolic blood pressure, mmHg	114 (110–120)	114 (110–119)	119 (110–130)	119 (110–120)	120 (110–130)	<0.001
Diastolic blood pressure, mmHg	78 (70–80)	75 (70–80)	78 (70–82)	78 (70–80)	80 (75–86)	<0.001
Waist circumference, cm	92 (85–100)	88.5 (82–95)	81.5 (78–88)	91 (85–96.5)	99 (93–106)	<0.001
BMI, kg/m^2	27.9 (25.5–31.1)	26.7 (24.58–29.38)	25.8 (24.58–28.07)	27.1 (25.60–28.88)	31.1 (28.44–34.24)	<0.001
Waist–hip ratio	0.9 (0.8–0.9)	0.9 (0.79–0.91)	0.9 (0.76–0.89)	0.8 (0.81-0.93)	0.9 (0.88–0.99)	<0.001
Waist–height ratio	0.6 (0.5–0.6)	0.6 (0.51–0.59)	0.5 (0.50–0.55)	0.6 (0.54-0.58)	0.6 (0.59–0.67)	<0.001
Fasting insulin, pmol/l	70.1 (48.6–102.8)	59.7 (41.7–84)	78.5 (54.2–117.4)	70.8 (52.1–94.2)	96.5 (67.3–134)	<0.001
Total cholesterol, mmol/l	5.2 (4.6–5.9)	5.1 (4.5–5.9)	5.1 (4.6–6.1)	5.3 (4.7-6.0)	5.2 (4.6–6.0)	0.402
LDL cholesterol*, mmol/l	3.3 (2.8–3.9)	3.2 (2.6–3.8)	3.2 (2.8–4.0)	3.4 (2.8–3.9)	3.3 (2.8–3.9)	0.582
Non-HDL cholesterol, mmol/l	4.1 (3.5–4.8)	3.8 (2.2–4.6)	4.1 (3.6–5.0)	4.3 (3.7–4.9)	4.2 (3.7–4.9)	0.278
Apolipoprotein B, mg/dl	106 (89.6–125)	99.6 (83.8–119)	112 (95.3–135.5)	114 (97.1–132)	114 (98.4–131)	0.370
C-reactive protein, mg/dl	1.9 (0.98–4.01)	1.6 (0.82–3.3)	1.7 (0.98–3.4)	1.6 (0.93–3.48)	2.86 (1.48–5.21)	<0.001
METS-IR	43.9 (38.33–50.38)	39.7 (35.75–44.46)	43.1 (39.98–48.69)	44.5 (40.45–47.99)	51.44 (46.36–57.16)	<0.001
METS-VF	6.8 (4.48–7.14)	6.6 (6.29–6.92)	6.7 (6.29–6.85)	6.82 (6.55-7.05)	7.15 (6.90–7.35)	<0.001
HOMA2-IR	1.3 (0.3–1.9)	1.1 (0.77–1.5)	1.5 (1.0–2.2)	1.3 (0.9-1.7)	1.8 (1.2–2.5)	<0.001

HOMA2-IR, updated homeostatic model assessment of insulin resistance; METS-IR, metabolic score for insulin resistance; METS-VF, metabolic score for visceral fat; MS, metabolic syndrome.
P values compared paired comparisons in each group. Data are presented as mean (SD) or median (interquartile range) depending on variable distribution. *Calculated using Martin's formula.

Table 2 Prevalence of individual components of the metabolic syndrome at baseline, stratified by International Diabetes Federation and Adult Treatment Panel III criteria

	Type 2 diabetes at follow-up, *n*=331		No type 2 diabetes at follow-up, *n*=5813	
Components of MS	MS at baseline	No MS at baseline	MS at baseline	No MS at baseline
IDF criteria, *N*	242	89	2453	3360
Central obesity, *n* (%)	242 (100)	52 (58.4)	2452 (100)	2051 (61)
High blood pressure, *n* (%)	129 (53.3)	11 (12.4)	1,160 (47.3)	406 (12.1)
HDL cholesterol, , *n* (%)	184 (76)	34 (38.2)	2,128 (86.8)	1,326 (39.5)
Hyperglycaemia, *n* (%)	131 (54.1)	19 (21.3)	422 (17.2)	109 (3.2)
Hypertriglyceridaemia, *n* (%)	189 (78.1)	42 (47.2)	1991 (81.2)	1038 (30.9)
ATP-III criteria, *N*	217	114	1820	3992
Central obesity, *n* (%)	176 (81.1)	27 (23.7)	1449 (79.6)	989 (24.8)
High blood pressure, *n* (%)	124 (57.1)	16 (14)	1024 (56.3)	542 (13.6)
HDL cholesterol, *n* (%)	172 (79.3)	46 (40.4)	1,639 (90.1)	1,815 (45.5)
Hyperglycaemia, *n* (%)	131 (60.4)	19 (16.7)	416 (22.9)	115 (2.9)
Hypertriglyceridaemia, *n* (%)	171 (78.8)	60 (52.6)	1496 (82.2)	1.533 (38.4%)

ATP-III, Adult Treatment Panel III; IDF, International Diabetes Federation; MS, metabolic syndrome.
Components of MS are defined as follows: IDF central obesity: waist circumference >90 cm in men or 80 cm in women; ATP central obesity: waist circumference >102 cm in men or 88 cm in women; high blood systolic/diastolic blood pressure >130/>85 mmol/L; hyperglycaemia: fasting plasma glucose ≥5.6 to <6.9 mmol/l; hypertriglyceridaemia: fasting triglycerides cholesterol: fasting HDL cholesterol 1.04 mmol/l or 1.3 mmol/l in men and women, respectively.

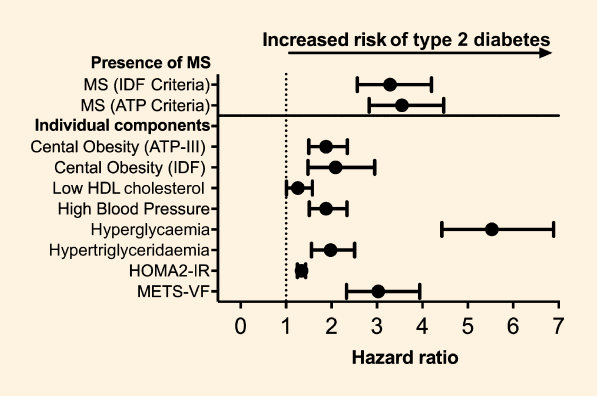

FIGURE 1 Hazard ratio plot for risk of type 2 diabetes using metabolic syndrome (MS) status according to Adult Treatment Panel III (ATP-III) and International Diabetes Federation (IDF) criteria, individual components of MS, updated homeostatic model assessment of insulin resistance (HOMA2-IR) and a metabolic score for visceral fat (METS-VF). Components of MS are defined as follows: IDF central obesity: waist circumference >90 cm in men or 80 cm in women; ATP central obesity: waist circumference >102 cm in men or 88 cm in women; high blood systolic/diastolic blood pressure >130/>85 mmHg; hyperglycaemia: fasting plasma glucose ≥5.5 to <6.9 mmol/l; hypertriglyceridaemia: fasting triglycerides >1.7 mmol/l; low HDL cholesterol: fasting HDL cholesterol 1.0 mmol/l or 1.3 mmol/l in men and women, respectively. IDF criteria for MS consider central obesity + two other risk factors. ATP-III criteria for MS consider ≥3 risk factors.

higher risk and those with only IDF-defined MS had 3.3-fold higher risk of incident type 2 diabetes, compared with those with no MS. When evaluating individual MS components, we observed that participants with impaired fasting glucose had a 5.5-fold higher risk of developing type 2 diabetes, followed by those with central obesity, hypertriglyceridaemia and high blood pressure, adjusted for family history of type 2 diabetes, physical activity and smoking status; low HDL cholesterol was not a significant predictor of incident type 2 diabetes (Fig. 1, Table S1).

Prediction of type 2 diabetes combining continuous metabolic syndrome components, METS-VF and HOMA2-IR

Next, we assessed increases in predictive performance when combining individual components of the ATP-III and IDF MS definitions with METS-VF and HOMA2-IR. When assessing the addition of METS-VF or HOMA2-IR to ATP-III or IDF MS criteria we observed improvements in predictive performance for type 2 diabetes, along with significant decreases in ΔBIC. Inclusion of both HOMA2-IR and METS-VF in both MS definitions resulted in greater improvement in predictive ability, along with the largest decrease in BIC. However, inclusion of continuous METS-VF instead of waist circumference only improved the predictive performance of the ATP-III definition and not the IDF definition of MS, with no improvements in BIC (Table 3). Using penalized ridge Cox regression, we observed similarity in estimated β coefficients compared to non-regularized Cox regression, suggesting no substantial collinearity after inclusion of HOMA2-IR or METS-VF in either MS definitions (Table S2).

Prediction of type 2 diabetes using HOMA2-IR and METS-VF in participants with and without metabolic syndrome

We assessed the use of both HOMA2-IR and METS-VF in participants who had no MS but who had one or two MS components. We observed that an increased risk of type 2 diabetes was associated with increasing HOMA2-IR values, with no significant improvement in predictive ability when including METS-VF; model performance in type 2 diabetes prediction and BIC values were improved after inclusion of HOMA2-IR in participants with no MS but with one or two MS components. Conversely, in participants with MS according to either ATP-III or IDF criteria, inclusion of METS-VF was associated with a higher risk of type 2 diabetes, with no significant improvement in model performance or BIC when including HOMA2-IR, after adjusting for covariates in participants with MS with three, four, and five components (Tables S3–S6).

Inclusion of METS-VF in the definition of metabolic syndrome

As previously stated, we tested whether the substitution of waist circumference for the METS-VF threshold ≥7.18 as one of the ATP-III criteria could improve risk prediction for type 2 diabetes. We identified 1526 participants (24.8%) with MS using the MS-METS definition; among these participants we observed 177 incident cases of type 2 diabetes after follow-up (incidence rate 11.72 cases per 1000 person-years, 95% CI 9.99–13.45). When comparing MS definitions, we observed that use of MS-METS improved predictive performance and decreased BIC values compared to use of the ATP-III and IDF MS criteria (Table 4). Individuals with MS-METS had a 3.4-fold higher risk of type 2 diabetes, adjusted for covariates (hazard ratio 3.35, 95% CI 2.69–4.17). When assessing concordance with other MS criteria, we observed that the Cohen's κ coefficient with ATP-III-defined MS indicated moderate agreement (κ=0.705, 95% CI 0.695–0.715) and with IDF-defined MS it showed lower agreement (κ=0.515, 95% CI 0.505–0.525). Overall, we observed a lower prevalence of MS using MS-METS compared to using the ATP-III and IDF criteria. The proportion of participants with incident type 2 diabetes who met the MS-METS definition at baseline was also lower compared to the proportions that met the ATP-III and IDF criteria (53.5% vs 65.6% and 73.1%, respectively); furthermore, the NRI was negative, implying that it mostly reclassified people who did not develop type 2 diabetes to lower risk categories. This suggests that MS-METS reduces overestimation of type 2 diabetes risk in people who would not otherwise be at risk,

Table 3 Comparison of risk prediction models for incident type 2 diabetes using metabolic syndrome criteria, updated homeostatic model assessment of insulin resistance and a metabolic score for visceral fat, adjusted for family history of type 2 diabetes, physical activity and smoking status.

ATP-III	ATP-III criteria	ATP-III criteria + METS-VF	ATP-III criteria + HOMA-IR	ATP-III criteria + HOMA-IR + METS-VF	Components of ATP-III-defined MS + METS-VF (substitute for waist circumference)
C-statistic	0.674	0.690	0.692	0.696	0.668
Overall NRI (95% CI)	Reference	0.032 (–0.121 to 0.135)	0.038 (–0.049 to 0.240)	0.081 (–0.093 to 0.135)	–0.219 (–0.509 to 0.075)
Likelihood ratio test (*P* value)	136.09 (<0.001)	155.61 (<0.001)	152.00 (<0.001)	166.75 (<0.001)	124.40 (<0.001)
ΔBIC	4836.36 (Reference)	4825.543 (–10.817)	4829.11 (–7.25)	4823.18 (–13.18)	4858.81 (22.45)
IDF	IDF criteria	IDF criteria + METS-VF	IDF criteria + HOMA-IR	IDF criteria + HOMA-IR + METS-VF	Components of IDF-defined MS + METS-VF (substitute for waist circumference)
C-statistic	0.671	0.684	0.689	0.690	0.641
Overall NRI (95% CI)	Reference	0.061 (–0.056 to 0.188)	0.040 (–0.035 to 0.205)	0.051 (–0.014 to 0.190)	–0.486 (–0.532 to 0.152)
Likelihood ratio test (*P* value)	113.46 (<0.001)	134.07 (<0.001)	136.84 (<0.001)	157.74 (<0.001)	101.42 (<0.001)
ΔBIC	4859.01 (reference)	4847.10 (–11.91)	4844.34 (–14.67)	4838.19 (–20.82)	4871.032 (12.022)

ATP-III, Adult Treatment Panel III; BIC, Bayes information criterion; IDF, International Diabetes Federation; MS, metabolic syndrome; NRI, net reclassification improvement index.

which could explain the higher precision and specificity of the MS-METS definition for type 2 diabetes prediction (Fig. 2). This novel MS-METS definition had better predictive performance for type 2 diabetes risk before and a larger decrease in BIC values even after adjusting for covariates (Table 4).

Discussion

In the present study, we report improved performance and risk reclassification for prediction of type 2 diabetes when combining currently validated MS definitions with HOMA2-IR and the novel VAT estimator METS-VF. We also demonstrated that evaluation of insulin resistance using HOMA2-IR for prediction of type 2 diabetes risk could be more beneficial for individuals without MS and evaluation of VAT with METS-VF could lead to improvements in type 2 diabetes prediction for individuals with MS. Finally, we proposed a modified MS definition, substituting waist circumference in the ATP-III criteria for METS-VF >7.18, a definition which showed improved predictive performance for type 2 diabetes when compared to the IDF and the ATP-III MS criteria.

Table 4 Comparison for risk prediction models for incident type 2 diabetes using categorical models and metabolic syndrome definitions

	ATP-III-defined MS	ATP-III-defined MS, adjusted	IDF-defined MS	IDF-defined MS, adjusted	MS-METS*	MS-METS*, adjusted
C-statistic	0.641	0.676	0.671	0.670	0.695	0.713
Overall NRI (95% CI)	Reference	–0.115 (–0.219 to 0.176)	–0.066 (–0.095 to 0.377)	–0.116 (–0.138 to 0.342)	–0.504 (–0.607 to 0.026)	–0.308 (–0.706 to 0.014)
Likelihood ratio test (*P* value)	116.71 (<0.001)	136.09 (<0.001)	113.44 (<0.001)	113.44 (<0.001)	175.70 (<0.001)	182.67 (<0.001)
ΔBIC	4817.794 (reference)	4836.364 (18.57)	4,859.01 (41.216)	4859.017 (41.223)	4783.008 (–34.786)	4801.78 (–16.014)

ATP-III, Adult Treatment Panel III; BIC, Bayes information criterion; IDF, International Diabetes Federation; METS-VF, metabolic score for visceral fat; MS, metabolic syndrome.
Each model comprises five categorical MS components. Model adjusted = Model + covariates. Covariates = family history of type 2 diabetes, physical activity and smoking status.
*MS-METS, modified metabolic syndrome construct, which substituted waist circumference for METS-VF.

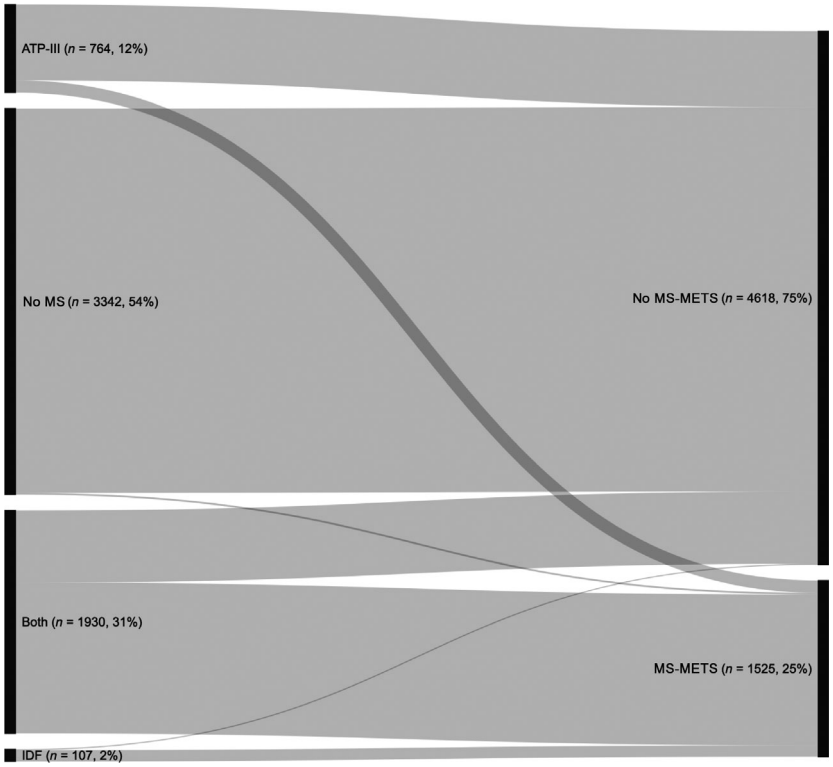

FIGURE 2 Sankey plot for reclassification of participants according to group classification by metabolic syndrome (MS) definition concordance [International Diabetes Federation (IDF) and Adult Treatment Panel III (ATP-III) definitions] compared with the proposed 'MS-METS' construct, which substitutes waist circumference measurements for a metabolic score for visceral fat (METS-VF), a more precise and accurate estimator of visceral adiposity. This novel definition improves the predictive performance for type 2 diabetes in our cohort.

The prevalence of MS in the Mexican population is high compared to other countries, irrespective of the MS definition used, and this trend has continued in the last two decades [22–26]. It has been reported that the use of specific models for the prediction of type 2 diabetes is superior in performance compared with use of the MS construct and its individual components [27,28]. This has led to a clear necessity to identify people at risk of developing type 2 diabetes even when only one or two components of MS are present. The implementation of HOMA2-IR and METS-VF along with the MS construct in clinical practice could be a low-cost strategy to improve cardiometabolic risk estimation, especially in primary care settings where access to specialists and the equipment necessary to evaluate both conditions could be limited.

There is debate about the attributes of MS components and their contribution to cardiometabolic risk prediction [29–32]. Insulin resistance is a major contributor to MS, as shown in studies where people with MS have decreased insulin secretory response as a result of insulin resistance [33]. In the present study, we showed that the inclusion of HOMA2-IR improves the predictive ability of the criteria used to predict type 2 diabetes, especially in people without MS who have none or only one or two MS components. Furthermore, addition of METS-VF to the MS construct showed an increase in the predictive performance for type 2 diabetes in people with MS. In people in whom MS is longstanding, underlying insulin resistance could contribute to the development of cardiometabolic alterations due to dysregulation in several metabolic pathways [34–36]. Inclusion of METS-VF, as a surrogate of VAT, could be of great benefit in primary care to predict the direct consequences of MS and insulin resistance in people without type 2 diabetes or arterial hypertension in whom cardiometabolic risk is deemed to be high.

Our modification of the MS construct to include VAT estimation (MS-METS) instead of waist circumference in the criteria set out by the ATP-III proved successful in improving the ability of this model to predict type 2 diabetes risk. Our rationale for this definition was based on the idea that a more precise evaluation of body fat distribution, as well as assessment of adipose tissue dysfunction and insulin resistance, would offer a more pathophysiologically oriented model which would capture more accurately the associated cardiometabolic risk. Assessment of waist circumference in MS has been criticized because it underestimates VAT as it does not distinguish appropriately between adipose tissue compartments [37]. Furthermore, VAT estimation continues to be limited to clinical research contexts and to settings where equipment and personnel are available [10,38]. The complementary use of METS-VF could offer a novel approach to providing

a quantitative assessment of visceral adiposity complementary to clinical care, and its inclusion in our MS-METS construct could provide better cardiometabolic risk estimation in people with type 2 diabetes. Nevertheless, the MS-METS construct should be validated in non-Latino populations in terms of prediction of cardiometabolic events, which remains the larger area of applicability for this construct.

Strengths of the present study include the fact that the Metabolic Syndrome Cohort included represents the largest open-population cohort in Mexico and Latin America in whom the incidence of type 2 diabetes and arterial hypertension has been evaluated. The improved predictive performance of both indices included in the MS construct could be applicable to other Latin-American populations, who may share similar metabolic susceptibility and in whom large-scale longitudinal epidemiological studies are scarce.

Despite these strengths, some limitations are acknowledged. First, we only estimated the risk and the added performance for incident type 2 diabetes, excluding other relevant events linked to MS. Second, it has been extensively reported that the Mexican population has an increased prevalence of individual MS components [39,40], leading to an elevated prevalence of MS in our study population and decreasing the predictive power of MS. Third, we observed improved performance in our prediction models using both HOMA2-IR and METS-VF; however, the increases did not always result in significant risk reclassification, suggesting that other metabolic factors, which were not directly measured in the present study could be involved in the development of type 2 diabetes. Finally, the threshold used to define increased VAT using METS-VF has only been validated in a Mexican population; external validation is necessary to identify the ideal thresholds for METS-VF in different ethnic groups.

In conclusion, the addition of insulin resistance assessment using HOMA2-IR, along with VAT estimation using METS-VF, increased the ability of the MS construct to predict incident type 2 diabetes in an open-population cohort. The inclusion of HOMA2-IR could be more useful for prediction of type 2 diabetes in people without MS, whereas METS-VF offers better added performance for type 2 diabetes prediction in people with MS. The proposed MS-METS definition, which substitutes waist circumference for METS-VF, is an attractive alternative that increased predictive performance for type 2 diabetes and could be explored for similar MS-related outcomes of interest. Our results could lead to systematic application of HOMA2-IR, METS-VF and the MS-METS construct in a primary care setting to complement routine metabolic assessment.

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Competing interests

None declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Cox regression model for incident type 2 diabetes using individual components of MS, HOMA2-IR, METS-VF, MS status (ATP-III and IDF criteria) and participants who had MS according to both criteria, adjusted for family history of type 2 diabetes, physical activity and smoking status.

Table S2. Comparison of β-coefficient between OLS and ridge regression models for prediction of type 2 diabetes, adjusted for family history of type 2 diabetes, physical activity, smoking status.

Table S3. Cox regression models for prediction of incident type 2 diabetes in participants without metabolic syndrome using ATP-III and IDF criteria, HOMA-IR and METS-VF, adjusted for familiar history of type 2 diabetes, physical activity and smoking status.

Table S4. Comparison of risk prediction models for incident type 2 diabetes in participants without MS (ATP-III and IDF) combining an insulin resistance index (HOMA-IR) and a visceral fat estimator (METS-VF) and one or two components of MS, adjusted for family history of type 2 diabetes, physical activity, smoking status.

Table S5. Cox regression models for prediction of incident type 2 diabetes in participants with metabolic syndrome using ATP-III criteria, HOMA-IR and METS-VF, adjusted

for familiar history of type 2 diabetes, physical activity and smoking status.

Table S6. Comparison of risk prediction models for incident type 2 diabetes in participants with MS (ATP-III and IDF) combining an insulin resistance index (HOMA-IR) and a visceral fat estimator (METS-VF) and three, four or five components of MS, adjusted for family history of type 2 diabetes, physical activity, smoking status.