Waist Circumference and Insulin Resistance Are the Most Predictive Metabolic Factors for Steatosis and Fibrosis

The metabolic-associated fatty liver disease (MAFLD) criteria[1] is aimed at capturing the heterogeneity of the disease with the goal of improving patient stratification and management. However, as is well-known, the metabolic factors used in the nomenclature are complex and correlated, and their nuanced contribution to the definition needs to be quantified to accurately estimate clinical relevance and stratify the population at risk.[2]

In a nationally representative cohort, National Health and Nutrition Examination Survey 2017–2018, we assessed the relative prognostic importance of the 7 key metabolic factors defined per the MAFLD criteria for steatosis and fibrosis outcomes, using separate models, 1 per metabolic factor per outcome (sample size n = 4369) (Supplementary Table 1). We defined hepatic steatosis using controlled attenuation parameter (CAP) at the higher sensitivity cutoff point (CAP ≥290 dB/m), and fibrosis as the median liver stiffness (LSM; ≥8.2 kPa), both measured using vibration-controlled transient elastography.[3] The models were all adjusted for diabetes, overweight status, age, ethnicity, and sex (Supplementary Methods).

The presence of 2 or more metabolic factors conferred increased odds of steatosis and increased odds of fibrosis, independent of elevated body mass index (≥25 kg/m^2 for non-Asians; 23 kg/m^2 for Asians) and diabetes (Figure 1*A* and *B*). Individuals with 2 or more metabolic factors had significantly higher odds of steatosis (adjusted odds ratio [aOR], 5.79; 95% confidence interval [CI], 3.98–8.43; $P = 3.95\ 1 \times 10^{-17}$; CAP ≥290 dB/m) and fibrosis (aOR, 2.5; 95% CI, 1.3–4.81; $P = 7.15\ 1 \times 10^{-3}$; LSM ≥8.2 kPa). Insulin resistance and increased central obesity as measured by elevated waist circumference were the top 2 metabolic factors by odds ratio and Nagelkerke R^2 (Figure 1*C*–*F*) for steatosis. For CAP ≥290 dB/m, elevated waist circumference (≥102 cm/90 cm for non-Asian/Asian men, and waist circumference ≥88 cm/80 cm for non-Asian/Asian women) was associated with aOR of 5.98 (95% CI, 4.54–7.87; $P < .00001$), whereas insulin resistance, as measured by the homeostatic model assessment of insulin resistance (≥2.5) had aOR of 3.96 (95% CI, 2.9–5.4; $P < .00001$). For LSM ≥8.2 kPa, elevated waist circumference was associated with aOR of 4.43 (95% CI, 2.9–6.7; $P < .000001$), whereas insulin resistance had aOR of 2.8 (95% CI, 1.63–4.9, $P < .001$).

The addition of these top 2 metabolic risk factors, elevated waist circumference and insulin resistance, to the diabetes and overweight model improved steatosis classification accuracy, with an overall continuous net reclassification improvement (NRI) of 77% (95% CI, 71–82), with 45% (95% CI, 41–50) for cases and 31% (95% CI, 28–35) for noncases, an area under the curve of 0.81 (95% CI, 0.8–0.83), and a Nagelkerke R^2 of 0.41 (Supplementary Table 2). In comparison, the MAFLD model, 2 or more metabolic factors, diabetes, and overweight status, improved the overall classification accuracy for hepatic steatosis with an overall continuous NRI of 65% (95% CI, 61–70) with 82% (95% CI, 0.79–0.85) for cases but had a reduced NRI of -17% (95% CI, -20 to -13) for noncases when compared with a diabetes and overweight model. The top 2 model exhibited improved classification accuracy for fibrosis with an overall continuous NRI of 61% (95% CI, 52–70) with 50% (95% CI, 41–58) for cases and 12% (95% CI, 8–15) for noncases, area under the curve of 0.75 (95% CI, 0.73–0.76) and Nagelkerke R^2 of 0.16.

The relationship between waist circumference and the risk of developing steatosis[4] has been established, with the underlying hypothesis that visceral fat is a key factor in the development of liver disease, and waist circumference (or increased central obesity) is a surrogate of visceral fat. Similarly, insulin resistance has been studied extensively in patients with nonalcoholic fatty liver disease, but whether insulin resistance is a cause or consequence of nonalcoholic fatty liver disease is still unclear.[5,6] Our findings add to these prior results in 2 significant ways. First, for steatosis and fibrosis, among the entire panel of factors that comprise metabolic dysfunction, higher waist circumference and insulin resistance are the 2 most important factors. Second, although waist circumference and insulin resistance are correlated, including both factors increases the classification accuracy over a model that only includes waist circumference or insulin resistance for steatosis and fibrosis. Given that fatty liver disease remains underdiagnosed in real-world settings[7,8] and the challenge of deploying a screening heuristic requires laboratory tests, our findings highlight the potential of simplifying the

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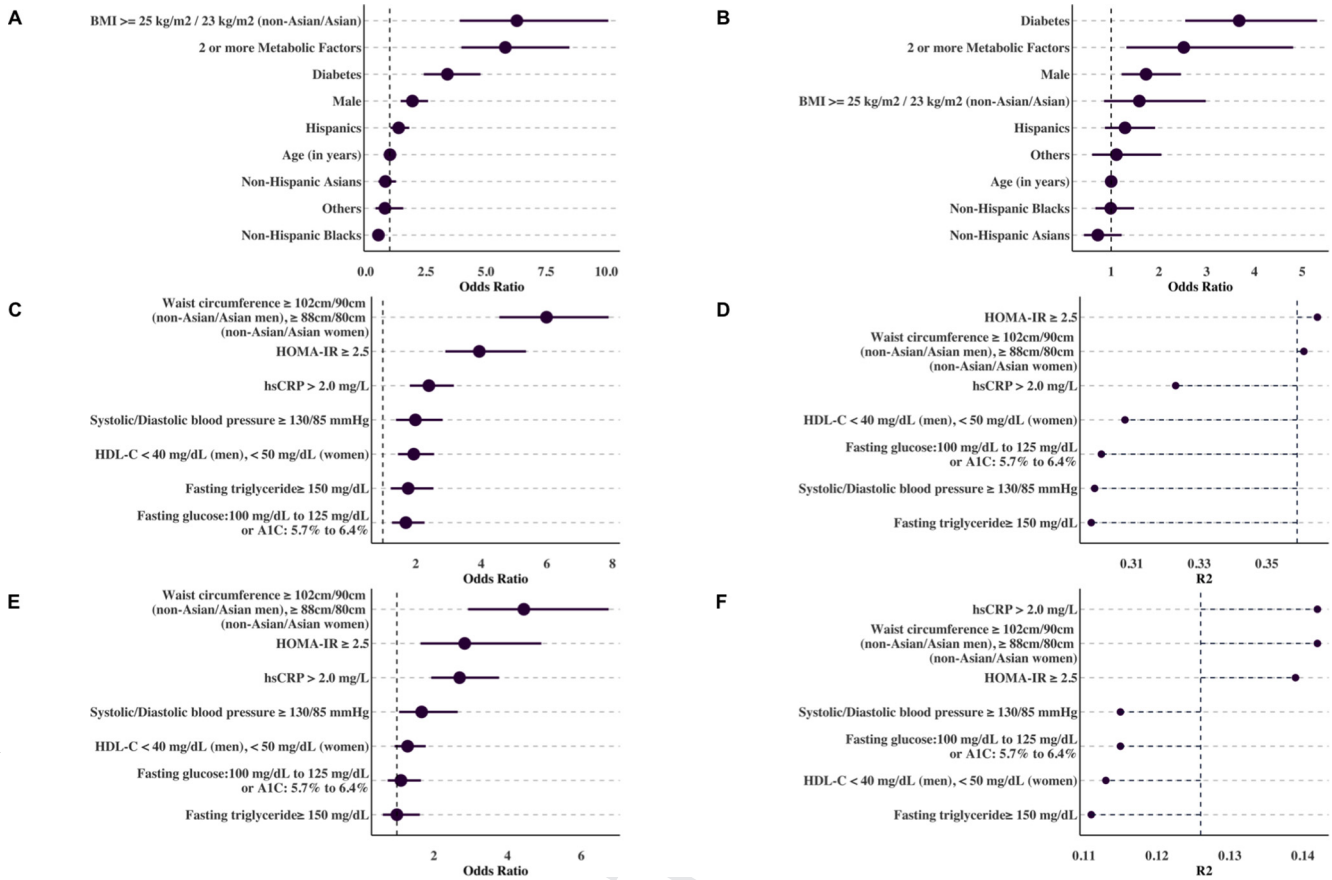

Figure 1. Strength of association for the MAFLD criteria for CAP ≥290 dB/m (*A*) and LSM ≥8.2 kPa (*B*), ordered by odds ratio. An elevated odds ratio suggests that the risk factor has a strong relative importance for steatosis and fibrosis prognosis. Strength of association for each metabolic factor included in the MAFLD criteria for CAP ≥290 dB/m (*C, D*) and LSM ≥8.2 kPa (*E, F*). The risk factors are ordered according to odds ratio (*C, E*), and the estimated variance (R2) explained by each metabolic factor (*D, F*). On *D* and *F*, the *dotted line* indicates the variance explained for the MAFLD criteria model for CAP ≥290 dB/m (*A*) and LSM ≥8.2 kPa (*B*). BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

MAFLD criteria/definition to identify the highest yield groups for screening and risk stratification.

Our study has several strengths. To the best of our knowledge, we are the first to examine the relative and independent contribution of the different metabolic factors defined as risk factors for steatosis and the impact of the factors for fibrosis in a nationally representative sample. We highlight the role of insulin resistance and increased central obesity for steatosis and fibrosis that is independent of diabetes and, interestingly,

Table 1. Definition of the 7 Metabolic Factors as Defined by Eslam et al[1]

Metabolic factor	Definition
Waist circumference	Waist circumference ≥102/88 cm in men/women (or ≥90/80 cm in Asian men/women)
Blood pressure	Blood pressure ≥130/85 mm Hg or specific drug treatment
Plasma triglycerides	Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/L) or specific drug treatment
HDL-cholesterol	HDL-cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment
Prediabetes	Fasting glucose levels 100–125 mg/dL (5.6–6.9 mmol/L), or 2-h postload glucose levels 140–199 mg/dL (7.8–11.0 mmol) or HbA_{1c} 5.7%–6.4% (39–47 mmol/mol)
Insulin resistance	HOMA-IR[9] score ≥2.5
Inflammation	Plasma high-sensitivity C-reactive protein level >2 mg/L

HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance.

Table 2. Characteristics of the Cohort

Characteristic	Healthy CAP <290 dB/m n = 2732	Hepatic steatosis CAP ≥290 dB/m LSM <8.2 kPa, n = 1234	Fibrosis LSM ≥8.2 kPa n = 403
Mean age, *y*	44.3 (42.9 to 45.7)	50.3 (49 to 51.4)	51.6 (49.1 to 54.2)
Sex, %			
Female	55.9 (53.4 to 58.4)	42.9 (39.2 to 46.6)	38.3 (31.5 to 45.2)
Male	44.1 (41.6 to 46.6)	57.1 (53.4 to 60.8)	61.7 (54.8 to 68.5)
Ethnicity, %			
Non-Hispanic Whites	63.3 (58.2 to 68.3)	63.5 (56.7 to 70.3)	61 (52.6 to 69.3)
Non-Hispanic Asians	5.2 (3.3 to 7.1)	4.9 (3.1 to 6.6)	3.7 (1.7 to 5.6)
Non-Hispanic Blacks	12 (8.7 to 15.3)	7.5 (5 to 10)	10.3 (5.4 to 15.2)
Hispanics	14.7 (11.1 to 18.2)	19.9 (14 to 25.8)	19.6 (14 to 25.1)
Others	4.9 (3.5 to 6.3)	4.2 (2.4 to 6)	5.6 (2.6 to 8.5)
Diabetes, %	6.7 (5.5 to 7.9)	23.2 (19.9 to 26.4)	39.5 (32.7 to 46.3)
Lean: BMI ≤25 kg/m^2/23 kg/m^2 (non-Asian/Asian), %	38.8 (34.9 to 42.7)	5 (2.8 to 7.2)	11.3 (5.9 to 16.7)
Overweight: BMI 25–30 kg/m^2/23–25 kg/m^2 (White/Asian), %	34 (31.6 to 36.4)	25 (20.9 to 29.1)	11.1 (7.8 to 14.5)
Obese: BMI ≥30 kg/m^2/25 kg/m^2 (non-Asian/Asian), %	27.2 (23.3 to 31.2)	70 (64.3 to 75.8)	77.5 (71.1 to 84)
Metabolic factors, %			
0 metabolic factors	19 (15.8 to 22.3)	1.9 (0.9 to 2.9)	4.4 (-0.6 to 9.3)
1 metabolic factor	26.2 (22.8 to 29.6)	6.3 (3.9 to 8.8)	7.6 (1.8 to 13.5)
2 or more metabolic factors	54.8 (50.6 to 59)	91.8 (89.2 to 94.4)	88 (81.5 to 94.4)
Waist circumference ≥102 cm/90 cm (non-Asian/Asian men), ≥88 cm/80 cm (non-Asian/Asian women), %	46.1 (41.6 to 50.5)	86.3 (83.3 to 89.2)	85.4 (79.9 to 90.8)
HOMA-IR ≥2.5, %	33.1 (27.7 to 38.6)	74.4 (69.4 to 79.4)	78.6 (71 to 86.1)
hsCRP >2.0 mg/L, %	36.4 (32.2 to 40.6)	60.5 (55.9 to 65.2)	71.6 (66.2 to 76.9)
Fasting glucose: 100–125 mg/dL or A_{1C}: 5.7%–6.4%, %	36.5 (32.7 to 40.2)	44.8 (40.9 to 48.8)	30.6 (23.7 to 37.5)
HDL-C <40 mg/dL (men), <50 mg/dL (women), %	20.9 (18.5 to 23.2)	39.5 (35.3 to 43.8)	38.9 (32 to 45.9)
Fasting triglyceride ≥150 mg/dL, %	7.5 (5.7 to 9.3)	18.6 (14.7 to 22.4)	16.5 (10.6 to 22.4)
Systolic/diastolic blood pressure ≥130/85 mm Hg, %	6.3 (4.6 to 8.1)	13.8 (11.2 to 16.3)	15.6 (11 to 20.2)

NOTE. Cohort was imputed using multivariate imputation by chained equations.[10] All proportions and means are specified together with their 95% confidence interval. Supplementary Table 1 provides the characteristics of the nonimputed dataset with percent missing denoted as [%]. Mean values for the metabolic factors are in Supplementary Table 1.

BMI, body mass index; CAP, controlled attenuation parameter; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LSM median liver stiffness.

overweight status. Second, we leverage survey-weighted logistic regression methods to determine the independent relative importance of the metabolic factors to assess the additive and nonlinear contributions of metabolic variables in a representative US population sample.

Our study has a few limitations. First, in the absence of longitudinal data, it is difficult to assess the directionality of the associations, especially between insulin resistance and fatty liver.[6] Second, we had a high percentage of missing data in self-report use of lipid-lowering drugs and antihypertensive drugs. We can thus only evaluate the relative importance of elevated triglycerides, reduced high-density lipoprotein cholesterol, and elevated blood pressure independent of medication use, and cannot assess the interactions with medications to control the same. Third, our unweighted sample size for CAP and LSM did not allow us to fully dissect the association between ethnicity and the relative importance of metabolic factors in 1 comprehensive model.

Table 3. AUC, Nagelkerke R^2, and Continuous NRI for the Different Models

Model	Features[a]	AUC	R^{2b}	NRI continuous		
				Overall	NRI+	NRI-
CAP ≥290 dB/m						
Diabetes	Diabetes	0.69 (0.67 to 0.7)	0.15			
Overweight	Overweight	0.73 (0.71 to 0.75)	0.25			
Diabetes + overweight	Diabetes, overweight	0.76 (0.74 to 0.77)	0.29			
MAFLD	Diabetes, overweight, 2 or more MF	0.79 (0.77 to 0.8)	0.36	0.65 (0.61 to 0.7)	0.82 (0.79 to 0.85)	-0.17 (-0.2 to -0.13)
WC	Diabetes, overweight, WC	0.79 (0.78 to 0.81)	0.36	0.6 (0.55 to 0.66)	0.54 (0.49 to 0.58)	0.07 (0.03 to 0.1)
Top 2	Diabetes, overweight, WC, IR	**0.81 (0.8 to 0.83)**	**0.41**	**0.77 (0.71 to 0.82)**	**0.45 (0.41 to 0.5)**	**0.31 (0.28 to 0.35)**
Top 4	Diabetes, overweight, WC, IR, BP, inflammation	0.82 (0.81 to 0.84)	0.42	0.75 (0.69 to 0.8)	0.49 (0.44 to 0.53)	0.26 (0.23 to 0.3)
Nonblood markers	Diabetes, overweight, WC, BP	0.8 (0.78 to 0.81)	0.37	0.57 (0.51 to 0.63)	0.48 (0.44 to 0.53)	0.08 (0.05 to 0.12)
LSM ≥8.2 kPa						
Diabetes	Diabetes	0.69 (0.67 to 0.71)	0.1			
Overweight	Overweight	0.66 (0.64 to 0.68)	0.06			
Diabetes + overweight	Diabetes, overweight	0.7 (0.68 to 0.72)	0.11			
MAFLD	Diabetes, overweight, 2 or more MF	0.72 (0.7 to 0.74)	0.13	0.37 (0.3 to 0.45)	0.72 (0.65 to 0.79)	-0.35 (-0.38 to -0.32)
WC	Diabetes, overweight, WC	0.73 (0.71 to 0.75)	0.14	0.4 (0.31 to 0.49)	0.48 (0.4 to 0.57)	-0.08 (-0.11 to 0.05)
Top 2	Diabetes, overweight, WC, IR	**0.75 (0.73 to 0.76)**	**0.16**	**0.61 (0.52 to 0.7)**	**0.5 (0.41 to 0.58)**	**0.12 (0.08 to 0.15)**
Top 4	Diabetes, overweight, WC, IR, BP, inflammation	0.76 (0.74 to 0.78)	0.18	0.58 (0.49 to 0.68)	0.4 (0.31 to 0.49)	0.18 (0.15 to 0.21)
Nonblood markers	Diabetes, overweight, WC, BP	0.74 (0.72 to 0.75)	0.15	0.38 (0.29 to 0.48)	0.34 (0.25 to 0.43)	0.04 (0.01 to 0.07)

NOTE. The overall NRI is the sum of the net reclassifications for cases (P[up|case] - P[down|case]) and noncases (P[down|noncase] - P(up|noncase]). A positive NRI indicated improved reclassification. The base model for the NRI comparison includes diabetes, overweight status, and is adjusted for sex, age, and ethnicity. The 2-category NRI (NRI(p)) is given in Supplementary Table 2.

AUC, area under the receiver operating curve; BP, elevated blood pressure; CAP, controlled attenuation parameter; IR, insulin resistance; LSM, median liver stiffness; MAFLD, metabolic-associated fatty liver disease; NRI, net reclassification improvement; WC, elevated waist circumference.

[a]All models were adjusted for sex, age, and ethnicity.

[b]Nagelkerke R^2.

Metabolic dysfunction as captured by the MAFLD criteria are key risk factors for steatosis and potential progression to fibrosis. This study shines light on the factors that dominate the association (eg, visceral adiposity, and insulin resistance) with steatosis and fibrosis, demonstrating that factors of high prevalence in the United States are also of highest risk for liver disease.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2012.11.00.

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Conflicts of interest
The authors disclose no conflicts. Q6

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Supplementary Methods

The National Health and Nutrition Examination Survey (NHANES) is administered by the National Center of Health Statistics at the Centers for Disease Control and Prevention and is a multistage, ongoing, cross-sectional health survey conducted to assess the health status of the noninstitutionalized civilian population in the United States. We used the 2017–2018 NHANES data for our primary analysis and included all nonpregnant participants 18 years or older with no history of viral hepatitis and no missing examination weights. Based on prior literature,[1] we excluded participants with less than 10 successful vibration controlled transient elastography readings (not valid), and/or with median liver stiffness measure (LSM) $\geq$7.1 kPa and an interquartile range divided by the median LSM $>$0.30 (interquartile range/M $>$0.3) (poorly reliable), resulting in a study sample n = 4369 (Supplementary Table 1). NHANES procedures and protocols were approved by the research ethics review board of the Centers for Disease Control and Prevention, and all participants provided written informed consent.

We defined hepatic steatosis and fibrosis from vibration controlled transient elastography (FibroScan, model 502 V2 Touch, Echosens, Paris, France). We used the higher sensitivity cutoff for the controlled attenuation parameter $\geq$290 dB/m to classify the presence of suspected steatosis.[1] We defined hepatic fibrosis as an LSM of $\geq$8.2 kPa.

We identified individuals with diabetes if they gave a positive response (or said they were borderline) to the question: "Have you ever been told by a doctor that you have diabetes"; or had a fasting blood sugar greater than 126 mg/dL or 2-hour postprandial blood sugar of 200 mg/dL or hemoglobin A_{1C} greater than 6.5%. We defined overweight status as body mass index $\geq$25 kg/m^2/body mass index $\geq$23 kg/m^2, non-Asians/Asians. For each metabolic factor, we coded variables consistent with the definitions by Eslam et al.[2] We had significant missing data for drug treatment for blood pressure (69%), plasma triglycerides (72%), and high-density lipoprotein cholesterol (72%). We omitted specific drug treatments in our definition of these metabolic factors (elevated blood pressure, triglycerides, and reduced high-density lipoprotein cholesterol). We imputed missing data using multivariate imputation by chained equations (MICE)[3] (using MICE R package, version 3.14.0) for variables used to compute the metabolic-associated fatty liver disease criteria in our study sample.

We constructed multivariable- and survey-adjusted regression models (R package *survey*, version 4.1-1) and associated the 7 individual metabolic factors with controlled attenuation parameter and LSM cutoffs to determine the relative importance of the metabolic factors after accounting for diabetes, overweight status, age, sex, and ethnicity. We ranked the metabolic factors by odds ratio and Nagelkerke R^2.

For the top 1, 2, 4, and nonblood based models, we calculated the area under the receiver operating curve, Nagelkerke R^2, and the continuous Net Reclassification Improvement[5] (R packages: *ROCR*, version 1.0-11; and *nricens*, version 1.6). All comparisons were made against a base model that included diabetes and overweight status, and was adjusted for sex, age, and ethnicity.

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Supplementary Table 1. Characteristics of the Cohort

Characteristic	Healthy CAP <290 dB/m n = 2732	Hepatic steatosis CAP ≥290 dB/m LSM <8.2 kPa n = 1234	Fibrosis LSM ≥8.2 kPa n = 403
Mean age, *y*	44.3 (42.9 to 45.7)	50.3 (49 to 51.4)	51.6 (49.1 to 54.2)
Sex, %			
Female	55.9 (53.4 to 58.4)	42.9 (39.2 to 46.6)	38.3 (31.5 to 45.2)
Male	44.1 (41.6 to 46.6)	57.1 (53.4 to 60.8)	61.7 (54.8 to 68.5)
Ethnicity, %			
Non-Hispanic Whites	63.3 (58.2 to 68.3)	63.5 (56.7 to 70.3)	61 (52.6 to 69.3)
Non-Hispanic Asians	5.2 (3.3 to 7.1)	4.9 (3.1 to 6.6)	3.7 (1.7 to 5.6)
Non-Hispanic Blacks	12 (8.7 to 15.3)	7.5 (5 to 10)	10.3 (5.4 to 15.2)
Hispanics	14.7 (11.1 to 18.2)	19.9 (14 to 25.8)	19.6 (14 to 25.1)
Others	4.9 (3.5 to 6.3)	4.2 (2.4 to 6)	5.6 (2.6 to 8.5)
Diabetes, %	6.7 (5.5 to 7.9)	23.2 (19.9 to 26.4)	39.5 (32.7 to 46.3)
Lean: BMI ≤25 kg/m^2/23 kg/m^2 (non-Asian/Asian), %	38.8 (34.9 to 42.7)	5 (2.8 to 7.2)	11.3 (5.9 to 16.7)
Overweight: BMI 25–30 kg/m^2/23–25 kg/m^2 (White/Asian), %	34 (31.6 to 36.4)	25 (20.9 to 29.1)	11.1 (7.8 to 14.5)
Obese: BMI ≥30 kg/m^2/25 kg/m^2 (non-Asian/Asian), %	27.2 (23.3 to 31.2)	70 (64.3 to 75.8)	77.5 (71.1 to 84)
Metabolic factors, %			
0 metabolic factors	19 (15.8 to 22.3)	1.9 (0.9 to 2.9)	4.4 (-0.6 to 9.3)
1 metabolic factor	26.2 (22.8 to 29.6)	6.3 (3.9 to 8.8)	7.6 (1.8 to 13.5)
2 or more metabolic factors	54.8 (50.6 to 59)	91.8 (89.2 to 94.4)	88 (81.5 to 94.4)
Waist circumference ≥102 cm/90 cm (non-Asian/Asian men), ≥88 cm/80 cm (non-Asian/Asian women), %	46.1 (41.6 to 50.5)	86.3 (83.3 to 89.2)	85.4 (79.9 to 90.8)
HOMA-IR ≥2.5, %	33.1 (27.7 to 38.6)	74.4 (69.4 to 79.4)	78.6 (71 to 86.1)
hsCRP >2.0 mg/L, %	36.4 (32.2 to 40.6)	60.5 (55.9 to 65.2)	71.6 (66.2 to 76.9)
Fasting glucose: 100–125 mg/dL or hemoglobin A_{1C}: 5.7%–6.4%, %	36.5 (32.7 to 40.2)	44.8 (40.9 to 48.8)	30.6 (23.7 to 37.5)
HDL-C <40 mg/dL (men), <50 mg/dL (women), %	20.9 (18.5 to 23.2)	39.5 (35.3 to 43.8)	38.9 (32 to 45.9)
Fasting triglyceride ≥150 mg/dL, %	7.5 (5.7 to 9.3)	18.6 (14.7 to 22.4)	16.5 (10.6 to 22.4)
Systolic/diastolic blood pressure ≥130/85 mm Hg, %	6.3 (4.6 to 8.1)	13.8 (11.2 to 16.3)	15.6 (11 to 20.2)

NOTE. All proportions and means are specified together with their 95% confidence interval. Cohort was imputed using multivariate imputation by chained equations.

BMI, body mass index; CAP, controlled attenuation parameter; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LSM median liver stiffness.

Supplementary Table 2. AUC, Nagelkerke R^2, and Continuous NRI for the Different Models

Model	Features[a]	AUC	R^{2b}	NRI continuous		
				Overall	NRI+	NRI-
CAP ≥290 dB/m						
Diabetes	Diabetes	0.69 (0.67 to 0.7)	0.15			
Overweight	Overweight	0.73 (0.71 to 0.75)	0.25			
Diabetes + overweight	Diabetes, overweight	0.76 (0.74 to 0.77)	0.29			
MAFLD	Diabetes, overweight, 2 or more MF	0.79 (0.77 to 0.8)	0.36	0.65 (0.61 to 0.7)	0.82 (0.79 to 0.85)	-0.17 (-0.2 to -0.13)
WC	Diabetes, overweight, WC	0.79 (0.78 to 0.81)	0.36	0.6 (0.55 to 0.66)	0.54 (0.49 to 0.58)	0.07 (0.03 to 0.1)
Top 2	Diabetes, overweight, WC, IR	**0.81 (0.8 to 0.83)**	**0.41**	**0.77 (0.71 to 0.82)**	**0.45 (0.41 to 0.5)**	**0.31 (0.28 to 0.35)**
Top 4	Diabetes, overweight, WC, IR, BP, inflammation	0.82 (0.81 to 0.84)	0.42	0.75 (0.69 to 0.8)	0.49 (0.44 to 0.53)	0.26 (0.23 to 0.3)
Nonblood markers	Diabetes, overweight, WC, BP	0.8 (0.78 to 0.81)	0.37	0.57 (0.51 to 0.63)	0.48 (0.44 to 0.53)	0.08 (0.05 to 0.12)
LSM ≥8.2 kPa						
Diabetes	Diabetes	0.69 (0.67 to 0.71)	0.1			
Overweight	Overweight	0.66 (0.64 to 0.68)	0.06			
Diabetes + overweight	Diabetes, overweight	0.7 (0.68 to 0.72)	0.11			
MAFLD	Diabetes, overweight, 2 or more MF	0.72 (0.7 to 0.74)	0.13	0.37 (0.3 to 0.45)	0.72 (0.65 to 0.79)	-0.35 (-0.38 to -0.32)
WC	Diabetes, overweight, WC	0.73 (0.71 to 0.75)	0.14	0.4 (0.31 to 0.49)	0.48 (0.4 to 0.57)	-0.08 (-0.11 to 0.05)
Top 2	Diabetes, overweight, WC, IR	**0.75 (0.73 to 0.76)**	**0.16**	**0.61 (0.52 to 0.7)**	**0.5 (0.41 to 0.58)**	**0.12 (0.08 to 0.15)**
Top 4	Diabetes, Overweight, WC, IR, BP, inflammation	0.76 (0.74 to 0.78)	0.18	0.58 (0.49 to 0.68)	0.4 (0.31 to 0.49)	0.18 (0.15 to 0.21)
Nonblood markers	Diabetes, overweight, WC, BP	0.74 (0.72 to 0.75)	0.15	0.38 (0.29 to 0.48)	0.34 (0.25 to 0.43)	0.04 (0.01 to 0.07)

NOTE. The overall NRI is the sum of the net reclassifications for cases (P[up|case] - P[down|case]) and noncases (P[down|noncase] - P(up|noncase]). A positive NRI indicated improved reclassification. The base model for the NRI comparison includes diabetes and overweight status, and is adjusted for sex, age, and ethnicity. The 2-category NRI (NRI(p)) is given in Supplementary Table 2.

AUC, area under the receiver operating curve; BP, elevated blood pressure; CAP, controlled attenuation parameter; IR, insulin resistance; LSM, median liver stiffness; MAFLD, metabolic-associated fatty liver disease; NRI, net reclassification improvement; WC, elevated waist circumference.

[a]All models were adjusted for sex, age, and ethnicity.

[b]Nagelkerke R^2.