

## Supplementary Methods

The National Health and Nutrition Examination Survey (NHANES) is administered by the National Center of Health Statistics at the Centers of Disease Control and Prevention (CDC) 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 non-pregnant participants 18 years or older with no history of viral hepatitis and no missing examination weights. Based on prior literature<sup>1</sup>, we excluded participants with less than ten successful VCTE readings (not valid), and/or with median stiffness measure (LSM) greater than or equal to 7.1 kPa ( $LSM \geq 7.1$  kPa) and an interquartile range (IQR) divided by the median LSM greater than 0.30 ( $IQR/M > 0.3$ ) (poorly reliable), resulting in a study sample  $N = 4369$  (Table S1). NHANES procedures and protocols were approved by the research ethics review board of the CDC, and all participants provided written informed consent.

We defined *hepatic steatosis* and *fibrosis* from VCTE (Fibroscan®, model 502 V2 Touch, Paris, France). We used the higher sensitivity cut-off for the controlled attenuation parameter (CAP)  $CAP \geq 290$  dB/m to classify the presence of suspected steatosis<sup>1</sup>. We defined hepatic fibrosis as a median liver stiffness measurement (LSM) of  $\geq 8.2$  kPa.

We identified individuals with *diabetes* if they (1) 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 (2) had a fasting blood sugar greater than 126 mg/dL or 2-hour postprandial blood sugar of 200 mg/dL or A1C greater than 6.5%. We defined overweight status as  $BMI \geq 25$  kg/m<sup>2</sup> /  $BMI \geq 23$  kg/m<sup>2</sup>, non-Asians/Asians. For each metabolic factor, we coded variables consistent with the definitions by Eslam et al<sup>2</sup>. We had significant missing data for drug treatment for blood pressure (69%), plasma triglycerides (72%), and HDL-cholesterol (72%). We omitted specific drug treatments in our definition of these metabolic factors (elevated blood pressure, triglycerides and reduced HDL-cholesterol). We

imputed missing data using multivariate imputation by chained equations (MICE)<sup>3</sup> (using MICE R package, V 3.14.0) for variables used to compute the MAFLD criteria in our study sample.

We constructed multivariable- and survey-adjusted regression models (R package *survey*, V 4.1-1) and associated the seven individual metabolic factors with CAP and LSM cut-offs 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 (OR) and Nagelkerke  $R^2$ .

For the top one, two, four and non-blood based models, we calculated the area under the receiver operating curve (AUC), Nagelkerke  $R^2$ , and the continuous Net Reclassification Improvement (NRI)<sup>5</sup> (R packages: *ROCR*, V 1.0-11 and *nricens*, V 1.6). All comparisons were made against a base model that included diabetes and overweight status and was adjusted for sex, age and ethnicity.

| <b>Characteristic</b>   | <b>Healthy<br/>CAP &lt; 290<br/>dB/m<br/>N = 2732</b> | <b>Hepatic<br/>Steatosis<br/>CAP ≥ 290 dB/m<br/>LSM &lt; 8.2 kPa,<br/>N = 1234</b> | <b>Fibrosis<br/>LSM ≥ 8.2 kPa<br/>N = 403</b> |
|---|---|--|---|
| <b>Mean Age, years</b>  | 44.3 (42.9, 45.7)                                     | 50.3 (49, 51.4)  | 51.6 (49.1, 54.2)                             |
| <b>Sex, %</b>   |   |  |   |
| <i>Female</i>   | 55.9 (53.4, 58.4)                                     | 42.9 (39.2, 46.6)  | 38.3 (31.5, 45.2)                             |
| <i>Male</i>   | 44.1 (41.6, 46.6)                                     | 57.1 (53.4, 60.8)  | 61.7 (54.8, 68.5)                             |
| <b>Ethnicity, %</b>   |   |  |   |
| <i>Non-hispanic Whites</i>  | 63.3 (58.2, 68.3)                                     | 63.5 (56.7, 70.3)  | 61 (52.6, 69.3)                               |
| <i>Non-hispanic Asians</i>  | 5.2 (3.3, 7.1)  | 4.9 (3.1, 6.6)   | 3.7 (1.7, 5.6)                                |
| <i>Non-hispanic Blacks</i>  | 12 (8.7, 15.3)  | 7.5 (5, 10)  | 10.3 (5.4, 15.2)                              |
| <i>Hispanics</i>  | 14.7 (11.1, 18.2)                                     | 19.9 (14, 25.8)  | 19.6 (14, 25.1)                               |
| <i>Others</i>   | 4.9 (3.5, 6.3)  | 4.2 (2.4, 6)   | 5.6 (2.6, 8.5)                                |
| <b>Diabetes, %</b>  | 6.7 (5.5, 7.9)  | 23.2 (19.9, 26.4))   | 39.5 (32.7, 46.3)                             |
| <b>Lean: BMI ≤ 25 kg/m<sup>2</sup> / 23 kg/m<sup>2</sup> (non-Asian/Asian), %</b>                     | 38.8 (34.9, 42.7)                                     | 5 (2.8, 7.2)   | 11.3 (5.9, 16.7)                              |
| <b>Overweight: BMI 25-30 kg/m<sup>2</sup> / 23-25 kg/m<sup>2</sup> (Caucasian/Asian), %</b>           | 34 (31.6, 36.4)                                       | 25 (20.9, 29.1)  | 11.1 (7.8, 14.5)                              |
| <b>Obese: BMI ≥ 30 kg/m<sup>2</sup> / 25 kg/m<sup>2</sup> (non-Asian/Asian), %</b>                    | 27.2 (23.3, 31.2)                                     | 70 (64.3, 75.8)  | 77.5 (71.1, 84)                               |
| <b>Metabolic Factors, %</b>   |   |  |   |
| <i>0 Metabolic Factors</i>  | 19 (15.8, 22.3)                                       | 1.9 (0.9, 2.9)   | 4.4 (-0.6, 9.3)                               |
| <i>1 Metabolic Factor</i>   | 26.2 (22.8, 29.6)                                     | 6.3 (3.9, 8.8)   | 7.6 (1.8, 13.5)                               |
| <i>2 or more Metabolic Factors</i>  | 54.8 (50.6, 59)                                       | 91.8 (89.2, 94.4)  | 88 (81.5, 94.4)                               |
| <b>Waist circumference ≥ 102cm/90cm (non-Asian/Asian men), ≥ 88cm/80cm (non-Asian/Asian women), %</b> | 46.1 (41.6, 50.5)                                     | 86.3 (83.3, 89.2)  | 85.4 (79.9, 90.8)                             |
| <b>HOMA-IR ≥ 2.5, %</b>   | 33.1 (27.7, 38.6)                                     | 74.4 (69.4, 79.4)  | 78.6 (71, 86.1)                               |
| <b>hsCRP &gt; 2.0 mg/L, %</b>   | 36.4 (32.2, 40.6)                                     | 60.5 (55.9, 65.2)  | 71.6 (66.2, 76.9)                             |
| <b>Fasting glucose:100 mg/dL to 125 mg/dL or A1C: 5.7% to 6.4%, %</b>                                 | 36.5 (32.7, 40.2)                                     | 44.8 (40.9, 48.8)  | 30.6 (23.7, 37.5)                             |

|  |                   |                   |                   |
|--|-------------------|-------------------|-------------------|
| HDL-C < 40 mg/dL (men), < 50 mg/dL (women), %      | 20.9 (18.5, 23.2) | 39.5 (35.3, 43.8) | 38.9 (32, 45.9)   |
| Fasting triglyceride ≥ 150 mg/dL, %                | 7.5 (5.7, 9.3)    | 18.6 (14.7, 22.4) | 16.5 (10.6, 22.4) |
| Systolic/Diastolic blood pressure ≥ 130/85 mmHg, % | 6.3 (4.6, 8.1)    | 13.8 (11.2, 16.3) | 15.6 (11, 20.2)   |

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**Table S1. Characteristics of the cohort. Cohort was imputed using multivariate imputation by chained equations<sup>11</sup>. All proportions and means are specified together with their 95% confidence interval.**

NRI Continuous

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

**Table S2. Area under the Receiver Operating Curve (AUCROC), Nagelkerke R<sup>2</sup>, and continuous Net Reclassification Improvement (NRI) for the different models. The overall NRI is the sum of the net reclassifications for cases (P[up|case] - P[down|case]) and non-cases (P[down|non-case] - P(up|non-case)). 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 two-category NRI (NRI(p)) is given in Table S2. WC = Elevated Waist Circumference; IR = Insulin Resistance; BP = Elevated Blood Pressure.**  
**\* All models were adjusted for sex, age, and ethnicity, \*\* Nagelkerke R<sup>2</sup>**

## REFERENCES

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