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Waist circumference and insulin resistance are the most predictive metabolic factors for steatosis and fibrosis

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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, NHANES 2017-2018, we assessed the relative prognostic importance of the seven key metabolic factors defined per the MAFLD criteria for steatosis and fibrosis outcomes, using separate models, one per metabolic factor per outcome (sample size N = 4369, see Supplementary Table S1). We defined hepatic steatosis using controlled attenuation parameter (CAP) at the higher sensitivity cut-off point (CAP ≥ 290 dB/m), and fibrosis as the median liver stiffness (LSM; 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 (see Supplementary Methods).

The presence of two or more metabolic factors conferred increased odds of steatosis as well as increased odds of fibrosis, independent of elevated BMI (BMI ≥ 25 kg/m^2 non-Asians; 23 kg/m^2 for Asians) and diabetes (Figure 1, A-B). Individuals with two or more metabolic factors had significantly higher odds of steatosis (adjusted OR (aOR): 5.79, 95% CI: 3.98, 8.43, p = 3.95 1x10^{-17}, CAP ≥ 290 dB/m), and fibrosis (aOR: 2.5, 95% CI: 1.3,

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Author Contributions

CJP and KC designed the study. KC performed the data analysis. CJP and KC wrote, read and reviewed the manuscripts. MTL critically revised the manuscript. CJP and KC take full responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Interests:

The authors declare that they have no competing interests.

Data Transparency Statement

All data used in this study are publicly available.

4.81, p = 7.15 1x10^{-3}, LSM ≥ 8.2kPa). *Insulin resistance* and *increased central obesity* as measured by elevated waist circumference were the top two metabolic factors by odds ratio and Nagelkerke R^2 (Figure 1, C-F) for steatosis. For CAP ≥ 290 dB/m, elevated waist circumference (WC ≥ 102cm/90cm for non-Asian/Asian men, and WC ≥ 88cm/80cm for non-Asian/Asian women) was associated with aOR: 5.98 (95% CI: 4.54, 7.87, p < 000001) while insulin resistance, as measured by the homeostatic model assessment of insulin resistance (HOMA-IR ≥ 2.5) had aOR: 3.96 (95% CI: 2.9, 5.4, p < 0.00001). For LSM ≥ 8.2 kPa, elevated waist circumference was associated with aOR: 4.43 (95% CI: 2.9, 6.7, p < 0.000001) while insulin resistance had an aOR: 2.8, (95% CI: 1.63, 4.9, p < 0.001).

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 non-cases, an AUC of 0.81 (95% CI 0.8, 0.83), and a Nagelkerke R^2 of 0.41 (Supplementary Table S2). 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 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, −13) for non-cases when compared to 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 non-cases, AUC 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 NAFLD, but whether insulin resistance is a cause or consequence of NAFLD is still unclea[5,6]. Our findings add to these prior results in two significant ways. First, for steatosis and fibrosis, amongst the entire panel of factors that comprise metabolic dysfunction, higher waist circumference and insulin resistance are the two most important factors. Second, while 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 both steatosis and fibrosis. Given that fatty liver disease remains under-diagnosed 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 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 both steatosis and fibrosis that is independent of diabetes and, interestingly, 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 non-linear contributions of metabolic variables in a representative US population sample.

Our study has several 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 HDL-C, 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 one comprehensive model.

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 (e.g, visceral adiposity, and insulin resistance) with steatosis and fibrosis, demonstrating that factors of high prevalence in the US are also of highest risk for liver disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020;158:1999–2014.e1. [PubMed: 32044314]
2. Wai-Sun Wong V, Kanwal F. On the Proposed Definition of Metabolic-Associated Fatty Liver Disease. Clin Gastroenterol Hepatol January 2021.
3. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156:1717–1730. [PubMed: 30689971]
4. Pang Q, Zhang J-Y, Song S-D, et al. Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index. World J Gastroenterol 2015;21:1650–1662. [PubMed: 25663786]
5. Matsuzaka T, Shimano H. Molecular mechanisms involved in hepatic steatosis and insulin resistance. J Diabetes Investig 2011;2:170–175.
6. Gruben N, Shiri-Sverdlov R, Koonen DPY, et al. Nonalcoholic fatty liver disease: A main driver of insulin resistance or a dangerous liaison? Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2014;1842:2329–2343. [PubMed: 25128743]

7. Alexander M, Loomis AK, Fairburn-Beech J, et al. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. BMC Med 2018;16:130. [PubMed: 30099968]
8. Gao E, Hercun J, Heller T, et al. Undiagnosed liver diseases. Transl Gastroenterol Hepatol 2021;6:28. [PubMed: 33824932]
9. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419. [PubMed: 3899825]
10. Azur MJ, Stuart EA, Frangakis C, et al. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 2011;20:40–49. [PubMed: 21499542]

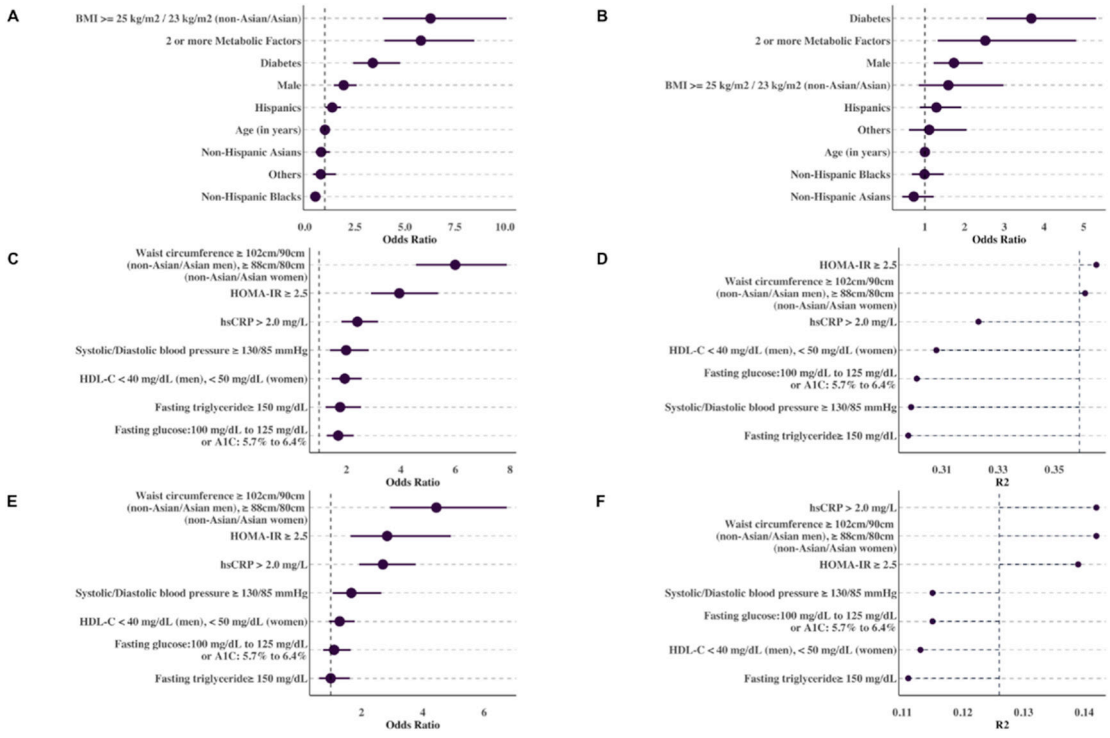

Figure 1.

(A - B): 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 OR suggests that the risk factor has a strong relative importance for steatosis and fibrosis prognosis.

(C - F): 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 figure 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).

Table 1.

Definition of the seven 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 mmHg 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 to 125 mg/dl [5.6 to 6.9 mmol/L], or 2-hour post-load glucose levels 140 to 199 mg/dl [7.8 to 11.0 mmol] or HbA1c 5.7% to 6.4% [39 to 47 mmol/mol]
Insulin Resistance	Homeostasis model assessment of insulin resistance (HOMA-IR)[9] score ≥ 2.5
Inflammation	Plasma high-sensitivity C-reactive protein level >2 mg/L

Table 2.

Characteristics of the cohort. Cohort was imputed using multivariate imputation by chained equations[10]. All proportions and means are specified together with their 95% confidence interval. Table S1 provides the characteristics of the non-imputed dataset with percent missing denoted as [%]. Mean values for the metabolic factors are in Table S1.

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, years	44.3 (42.9, 45.7)	50.3 (49, 51.4)	51.6 (49.1, 54.2)
Sex, %			
Female	55.9 (53.4, 58.4)	42.9 (39.2, 46.6)	38.3 (31.5, 45.2)
Male	44.1 (41.6, 46.6)	57.1 (53.4, 60.8)	61.7 (54.8, 68.5)
Ethnicity, %			
Non-hispanic Whites	63.3 (58.2, 68.3)	63.5 (56.7, 70.3)	61 (52.6, 69.3)
Non-hispanic Asians	5.2 (3.3, 7.1)	4.9 (3.1, 6.6)	3.7 (1.7, 5.6)
Non-hispanic Blacks	12 (8.7, 15.3)	7.5 (5, 10)	10.3 (5.4, 15.2)
Hispanics	14.7 (11.1, 18.2)	19.9 (14, 25.8)	19.6 (14, 25.1)
Others	4.9 (3.5, 6.3)	4.2 (2.4, 6)	5.6 (2.6, 8.5)
Diabetes, %	6.7 (5.5, 7.9)	23.2 (19.9, 26.4))	39.5 (32.7, 46.3)
Lean: BMI ≤ 25 kg/m2 / 23 kg/m2 (non-Asian/Asian), %	38.8 (34.9, 42.7)	5 (2.8, 7.2)	11.3 (5.9, 16.7)
Overweight: BMI 25-30 kg/m2 / 23-25 kg/m2 (Caucasian/Asian), %	34 (31.6, 36.4)	25 (20.9, 29.1)	11.1 (7.8, 14.5)
Obese: BMI ≥ 30 kg/m2 / 25 kg/m2 (non-Asian/Asian), %	27.2 (23.3, 31.2)	70 (64.3, 75.8)	77.5 (71.1, 84)
Metabolic Factors, %			
0 Metabolic Factors	19 (15.8, 22.3)	1.9 (0.9, 2.9)	4.4 (−0.6, 9.3)
1 Metabolic Factor	26.2 (22.8, 29.6)	6.3 (3.9, 8.8)	7.6 (1.8, 13.5)
2 or more Metabolic Factors	54.8 (50.6, 59)	91.8 (89.2, 94.4)	88 (81.5, 94.4)
Waist circumference ≥ 102cm/90cm (non-Asian/Asian men), ≥ 88cm/80cm (non-Asian/Asian women), %	46.1 (41.6, 50.5)	86.3 (83.3, 89.2)	85.4 (79.9, 90.8)
HOMA-IR ≥ 2.5, %	33.1 (27.7, 38.6)	74.4 (69.4, 79.4)	78.6 (71, 86.1)
hsCRP > 2.0 mg/L, %	36.4 (32.2, 40.6)	60.5 (55.9, 65.2)	71.6 (66.2, 76.9)
Fasting glucose:100 mg/dL to 125 mg/dL or A1C: 5.7% to 6.4%, %	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)

Table 3.

Area under the Receiver Operating Curve (AUCROC), Nagelkerke R2, 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.

				NRI Continuous		
Model	**Features***	**AUC**	**R^{2**}**	**Overall**	**NRI+**	**NRI−**
CAP ≥ 290 dB/m						
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	**0.81 (0.8, 0.83)**	**0.41**	**0.77 (0.71, 0.82)**	**0.45 (0.41, 0.5)**	**0.31 (0.28, 0.35)**
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)
LSM ≥ 8.2 kPa						
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	**0.75 (0.73, 0.76)**	**0.16**	**0.61 (0.52, 0.7)**	**0.5 (0.41, 0.58)**	**0.12 (0.08, 0.15)**
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)

*All models were adjusted for sex, age, and ethnicity

**Nagelkerke R^2