

Hepatic Insulin Resistance Syndrome (HIRS): A Proposed Framework for the Classification of Steatotic Liver Disease

Luis Jesuino de Oliveira Andrade

luis_jesuino@yahoo.com.br

Department of Health, Santa Cruz State University, Ilhéus, Bahia, Brazil. <https://orcid.org/0000-0002-7714-0330>

Gabriela Correia Matos de Oliveira

UNAERP - Electro Bonini Hospital and Cidinha Bonini Maternity Hospital - Ribeirão Preto, São Paulo, Brazil. <https://orcid.org/0000-0002-3447-3143>

Alcina Maria Vinhaes Bittencourt

School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil. <https://orcid.org/0000-0003-0506-9210>

Raymundo Paraná

School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil. <https://orcid.org/0000-0002-4019-4597>

Osmário Jorge de Mattos Salles

Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil. <https://orcid.org/0009-0002-1859-0478>

Luis Matos de Oliveira

Department of Health, Santa Cruz State University, Ilhéus, Bahia, Brazil. <https://orcid.org/0000-0003-4854-6910>

Short Report

Keywords: Steatotic liver disease, Insulin resistance, MASLD, Nomenclature

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11285131/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: The authors declare no competing interests.

Abstract

Introduction

The 2023 nomenclature for metabolic dysfunction–associated steatotic liver disease (MASLD) introduced positive diagnostic criteria but requires only one of five heterogeneous cardiometabolic features, and it does not require direct evidence of insulin resistance, a central pathogenic mechanism of hepatic steatosis. A classification anchored on IR may be more biologically coherent and clinically applicable.

Objective

To propose Hepatic Insulin Resistance Syndrome (HIRS) as an IR-based framework for diagnosing and staging steatotic liver disease, and to define a strategy for its validation.

Methods

We developed the framework through narrative synthesis of pathophysiological evidence linking IR to hepatic steatosis, the structure of current MASLD criteria, and published NHANES, UK Biobank, and GSE130970 analyses. We chose elements for measurability and low cost, including use without insulin assays. Validation in NHANES and the UK Biobank is planned and will assess concordance with MASLD, reclassification, and prognostic discrimination, with safeguards against circularity.

Results

This is a conceptual proposal; we report no original empirical results. HIRS requires hepatic steatosis (elastography-based CAP, imaging, validated serum indices, or histology) plus IR (HOMA-IR, triglyceride-glucose index, or a validated surrogate), with adipose-related dysfunction (waist circumference, triglyceride/HDL ratio, uric acid) as a specifier. Significant alcohol intake, other chronic liver diseases, and steatogenic drugs are excluded. Staging comprises metabolic (HIRS 1), inflammatory (HIRS 2), and fibrogenic (HIRS 3) stages, defined by biochemical activity and liver stiffness. Thresholds are provisional pending derivation and validation.

Conclusion

HIRS offers an IR-centered alternative to MASLD with explicit, measurable criteria. Replacing MASLD requires empirical validation and expert consensus.

INTRODUCTION

Steatotic liver disease (SLD) is the most prevalent chronic liver condition worldwide, affecting a large share of the adult population and contributing substantially to liver-related morbidity, cardiometabolic disease, and premature mortality.¹ Its predominant form, formerly termed nonalcoholic fatty liver

disease (NAFLD), results from the interplay of excess adiposity, ectopic lipid deposition, and insulin resistance (IR), the mechanistic core linking hepatic lipid accumulation to dysregulated glucose and lipid metabolism.² In 2023, a multisociety Delphi consensus replaced NAFLD with metabolic dysfunction–associated steatotic liver disease (MASLD), substituting an exclusionary and potentially stigmatizing label with positive diagnostic criteria: hepatic steatosis plus at least one of five cardiometabolic risk factors. The change was intended to reduce stigma, improve awareness, and provide a unifying framework for the broader spectrum of SLD, including its alcohol-related subcategories.³

Meta-analytic evidence indicates that the global prevalence of fatty liver disease has risen steadily over recent decades, in parallel with the obesity and diabetes mellitus epidemics.¹ Population-based studies in the United States and the United Kingdom have more recently characterized the burden of MASLD under the new nomenclature. Analyses of the National Health and Nutrition Examination Survey (NHANES) have described its distribution across demographic groups and its relationship with advanced fibrosis and cirrhosis,⁴ whereas analyses of the UK Biobank have linked MASLD to extrahepatic multimorbidity and excess mortality.⁵ Collectively, these studies establish that the new definition captures a large and clinically consequential population, and that metabolic comorbidities, particularly diabetes mellitus and obesity, shape fibrosis risk and prognosis within it.

Nevertheless, the MASLD framework has conceptual and operational limitations. First, it defines metabolic dysfunction through five heterogeneous cardiometabolic criteria, any one of which suffices, and none of which directly quantifies IR, the mechanism most proximal to hepatic lipid accumulation. Because adiposity-related criteria are met by nearly all affected individuals in large cohorts in which steatosis is ascertained by the fatty liver index (FLI), a score that itself incorporates anthropometric and lipid measures,⁵ the definition constrains recognition of lean disease, which accounts for a substantial fraction of SLD globally and carries meaningful hepatic and extrahepatic risk.⁶ Second, because the criteria are weighted equally, patients who qualify through different pathways are classified as a single entity despite divergent prognoses; within MASLD, glycemic abnormalities appear to stratify mortality risk more strongly than adiposity-related criteria.⁵ Third, accessible indices of IR, including the homeostasis model assessment of IR (HOMA-IR),⁷ the triglyceride–glucose (TyG) index,⁸ and the Metabolic Score for Insulin Resistance (METS-IR),⁹ have been validated against reference methods, yet none is incorporated into the definition. Consequently, the current classification may obscure the pathogenic driver, misclassify patients with discordant metabolic and hepatic phenotypes, and offer limited guidance for staging and therapeutic targeting.

Accordingly, we propose Hepatic Insulin Resistance Syndrome (HIRS) as an etiology-based replacement for MASLD, defined as the hepatic manifestation of systemic IR and anchored on measurable markers of IR together with indicators of adipose-related dysfunction. By making IR an explicit diagnostic requirement, HIRS is intended to align the classification of SLD with its dominant pathophysiology, to improve recognition of patients with steatosis who lack overt obesity, and to support a biologically coherent staging scheme that can inform monitoring and treatment. In this study, we present the

conceptual rationale for HIRS, describe its diagnostic and staging framework, and define a strategy for its empirical validation against MASLD in population-based cohorts, with attention to avoiding circularity between the definition and the outcomes it is meant to predict. We position HIRS not as a nomenclature to be adopted unilaterally, but as a testable proposal whose potential adoption would require independent validation and expert consensus.

METHODS

Study Design and Reporting

This study has two components: (i) development of the HIRS diagnostic and staging framework and (ii) a prespecified analysis plan for its empirical evaluation against MASLD in population-based cohorts. The second component is presented as a protocol; no HIRS-based analyses had been performed at the time of writing. We also summarized published analyses of NHANES, the UK Biobank, and GSE130970 as contextual evidence. This summary was a narrative review without a systematic search and should not be read as a systematic review. Analyses will be reported in accordance with the STROBE statement for observational studies and, for discrimination and reclassification analyses, the TRIPOD guidance.

Framework Development

HIRS was developed through a narrative synthesis, by the authors, of pathophysiological evidence linking IR to hepatic steatosis and of the structure of the 2023 MASLD criteria.³ Candidate diagnostic elements were selected according to four principles: (1) biological proximity to IR; (2) validation against reference methods of insulin sensitivity; (3) availability in routine care, including settings without fasting insulin assays; and (4) availability in the cohorts used for validation. The framework separates three components: hepatic steatosis, IR, and adipose-related dysfunction, the last of which acts as a specifier rather than a diagnostic requirement.

HIRS Diagnostic Criteria

HIRS requires (A) hepatic steatosis and (B) evidence of IR, in the absence of exclusion criteria. Adipose-related dysfunction (C) is recorded as a specifier. Thresholds in Table 1 are provisional, drawn from the literature, and will be refined in the derivation phase described below.

Table 1
Provisional HIRS diagnostic criteria

Component	Criterion (any one suffices within each component)	Provisional threshold
A. Hepatic steatosis (required)	Controlled attenuation parameter (CAP)	≥ 248 dB/m (sensitivity analysis: ≥ 280 dB/m)
	Magnetic resonance imaging–proton density fat fraction (MRI-PDFF)	$\geq 5\%$
	Conventional ultrasound or histology	Per standard clinical criteria
	Fatty liver index (FLI) ¹⁰	≥ 60 (sensitivity analysis only)
B. Insulin resistance (required)	Homeostasis model assessment of IR (HOMA-IR) ⁷	≥ 2.5
	Triglyceride–glucose (TyG) index ⁸	≥ 8.5
	Metabolic Score for Insulin Resistance (METS-IR) ⁹	[Threshold to be derived]
	Prediabetes or type 2 diabetes mellitus (T2DM)	HbA1c $\geq 5.7\%$, fasting glucose ≥ 100 mg/dL, or diagnosis/treatment
C. Adipose-related dysfunction (specifier)	Waist circumference	> 88 cm (women); >94 cm (men)
	Triglyceride-to-HDL cholesterol ratio	> 2.5 [units to be specified]
	Serum uric acid	> 5.5 mg/dL
Exclusions	Alcohol intake	> 20 g/day (women); >30 g/day (men)
	Other causes	Viral hepatitis, steatogenic drugs, other chronic liver diseases

TyG is calculated as $\ln[\text{triglycerides (mg/dL)} \times \text{glucose (mg/dL)} / 2]$, the form for which the 8.5 threshold applies. HOMA-IR is calculated as $\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)} / 22.5$. METS-IR is calculated as $\ln[(2 \times \text{glucose}) + \text{triglycerides}] \times \text{body mass index} / \ln(\text{HDL cholesterol})$, with glucose and lipids in mg/dL.

HIRS Staging

Three stages are proposed. HIRS 1 (metabolic): steatosis without biochemical inflammatory activity. HIRS 2 (inflammatory): alanine aminotransferase $> 1.5 \times$ the upper limit of normal, with a FAST score $>$

0.35 or cytokeratin-18 evidence of steatohepatitis activity. HIRS 3 (fibrogenic): liver stiffness ≥ 8.0 kPa with complementary evidence of fibrogenesis (PRO-C3). Because cytokeratin-18 and PRO-C3 are not available in the planned data sources, staging is presented as a conceptual extension, and only its measurable components (aminotransferases, FAST score, and liver stiffness) will be evaluated.

Data Sources and Study Populations

NHANES. We will use the NHANES cycles from 2017 through March 2020 (prepandemic) and August 2021 through August 2023. Eligible participants are adults aged ≥ 18 years with a valid vibration-controlled transient elastography examination (CAP and liver stiffness) according to National Center for Health Statistics (NCHS) quality criteria. We will exclude pregnant participants and those with missing data required to classify steatosis or the exclusion criteria. HOMA-IR and TyG will be computed in the fasting subsample. NHANES uses a complex, multistage probability design; all estimates will incorporate the appropriate examination and fasting-subsample weights, strata, and primary sampling units, following NCHS guidance for combining cycles.

UK Biobank. We will use UK Biobank participants recruited between 2006 and 2010 who attended the imaging visit with a valid MRI-PDFF measurement. Because fasting insulin is not available, UK Biobank analyses will apply a modified HIRS definition without HOMA-IR (TyG, METS-IR, and glycemic criteria only). Incident outcomes will be ascertained through linkage to death registries and hospital inpatient records.

Variable Definitions

MASLD comparator. MASLD is defined according to the multisociety consensus:³ steatosis plus at least one of five cardiometabolic criteria (adiposity, dysglycemia, elevated blood pressure, hypertriglyceridemia, and low HDL cholesterol, or corresponding treatment), with alcohol intake below the thresholds above. To ensure a fair comparison, MASLD and HIRS will use the same steatosis definition, the same alcohol and other-cause exclusions, and the same participant set.

Fibrosis. Significant fibrosis, advanced fibrosis, and cirrhosis will be defined by liver stiffness thresholds commonly used in NHANES analyses (≥ 8.0 , ≥ 9.7 , and ≥ 13.6 kPa, respectively). Fibrosis-4 (FIB-4) will be computed from age, aspartate aminotransferase, alanine aminotransferase, and platelet count,¹¹ with low-, intermediate-, and high-risk categories at 1.3 and 2.67 (2.0 and 2.67 for participants aged ≥ 65 years).

Lean phenotype. Body mass index < 25 kg/m² (< 23 kg/m² in participants of Asian ancestry).

Covariates. Age, sex, race/ethnicity, socioeconomic indicators, smoking status, physical activity, and, for outcome analyses, baseline comorbidities and medication use.

Threshold Derivation and Validation

Provisional thresholds will be evaluated in a derivation phase and tested in independent data. In NHANES 2017–March 2020, TyG and METS-IR cutoffs will be derived by receiver operating characteristic analysis against $\text{HOMA-IR} \geq 2.5$ as a pragmatic reference, selecting the cutoff that maximizes the Youden index, and HOMA-IR will be examined against its distribution in a metabolically healthy reference subgroup. Derived thresholds will then be tested temporally in NHANES 2021–2023 and externally (TyG, METS-IR) in UK Biobank. Thresholds will not be tuned in the validation data.

Outcomes

In NHANES, the primary outcomes are prevalent significant fibrosis, advanced fibrosis, and high-risk FIB-4. All-cause and cardiovascular mortality will be examined as exploratory outcomes only if public-use linked mortality files with adequate follow-up are available for the included cycles. In UK Biobank, the outcomes are incident T2D, major adverse cardiovascular events (composite of myocardial infarction, ischemic stroke, and cardiovascular death), and all-cause and cardiovascular mortality, defined by ICD-10 codes. Participants with diabetes mellitus at baseline will be excluded from T2D incidence analyses, and participants with prior cardiovascular disease from MACE analyses.

Statistical Analysis

Prevalence and concordance. Survey-weighted prevalence of HIRS and MASLD will be estimated overall, by stage, and in lean individuals, with age standardization to the 2000 US standard population. Concordance will be quantified with Cohen's kappa and cross-classification tables. MASLD prevalence will be benchmarked against published NHANES estimates to verify the analytic pipeline.

Reclassification and discordant groups. We will quantify participants classified as MASLD-positive and HIRS-negative, and vice versa, and compare fibrosis burden and outcome risk in each discordant group with participants meeting neither definition.

Discrimination and reclassification. For each outcome, a base model (age, sex, race/ethnicity, and relevant covariates) will be compared with models adding MASLD, HIRS, or both. For fibrosis, we will use survey-weighted logistic regression and report the area under the receiver operating characteristic curve (AUROC), with differences compared by DeLong's test. For time-to-event outcomes in UK Biobank, we will use Cox proportional hazards models (assumption checked with Schoenfeld residuals) and report Harrell's C-index, time-dependent AUROC, and net reclassification improvement (categorical and continuous) with integrated discrimination improvement. Calibration will be assessed graphically and by calibration slope. Confidence intervals will be obtained by bootstrap.

Safeguards against circularity. (1) The glycemic component of criterion B will be excluded in a strict IR-marker version of HIRS, in which only HOMA-IR, TyG, or METS-IR can satisfy criterion B. (2) Participants

with diabetes mellitus at baseline will be excluded from T2DM incidence analyses. (3) Thresholds will be derived and validated in separate datasets. (4) Overlap among components (for example, triglycerides in TyG, the FLI, and the triglyceride-to-HDL ratio) will be examined, and the FLI will be used only in sensitivity analyses.

Sensitivity analyses. (1) $CAP \geq 280$ dB/m; (2) FLI- and hepatic steatosis index–based steatosis definitions; (3) alternative IR thresholds; (4) exclusion of the first 2 years of follow-up in UK Biobank; (5) exclusion of participants on glucose- or lipid-lowering therapy; and (6) analyses with and without the adipose dysfunction specifier.

Missing data. Variables defining HIRS and MASLD will be analyzed on a complete-case basis. Missing covariates will be handled with multiple imputation by chained equations (20 imputed datasets, pooled with Rubin's rules).

All tests will be two-sided with $\alpha = 0.05$, with false discovery rate adjustment for multiple comparisons in secondary analyses. Analyses will be performed in R (version 4.6.1).

Exploratory Transcriptomic Analysis

To explore biological support, we will analyze the publicly available hepatic expression dataset GSE130970 from the Gene Expression Omnibus. After quality control and normalization, differential expression will be assessed with linear models for microarray/RNA-seq data, comparing groups defined by the clinical annotations available in the dataset. Gene set enrichment analysis will compare enrichment of insulin-signaling gene sets against generic metabolic and inflammatory gene sets, using curated collections (Gene Ontology, KEGG, Reactome, and MSigDB Hallmark) with false discovery rate control. Because the dataset is small and cross-sectional, this analysis is exploratory and hypothesis-generating, and it will not be used to validate the diagnostic criteria.

Ethics and Data Availability

NHANES is conducted by the NCHS with approval from its Research Ethics Review Board and publicly releases de-identified data; secondary analysis is exempt from further review. UK Biobank has approval from the North West Multi-centre Research Ethics Committee. GSE130970 is publicly available.

RESULTS

The current MASLD framework identifies a large but metabolically heterogeneous population

Recent population-based analyses indicate that steatotic liver disease affects a substantial proportion of adults in the United States, but the magnitude of the population identified depends on the operational definition of steatosis and metabolic dysfunction. In NHANES 2017–2023, age-adjusted SLD prevalence was 35.0% (95% CI, 33.4–36.7%), whereas MASLD prevalence was 31.9% (95% CI, 30.4–33.4%). MetALD

and alcohol-associated liver disease accounted for substantially smaller proportions of the population. These findings confirm that the current MASLD framework captures a large segment of the adult population while simultaneously demonstrating that its classification is highly dependent on the coexistence of steatosis with broadly defined cardiometabolic abnormalities.⁴

A second NHANES analysis of 13,538 adults similarly identified substantial disease burden, with SLD defined by CAP > 300 dB/m present in 28.7% of participants, fibrosis defined by liver stiffness > 8 kPa in 11.3%, and MASLD in 25.6%. The difference between the proportions classified according to steatosis, fibrosis, and MASLD illustrates that the presence of a steatotic phenotype and the presence of clinically relevant structural liver disease represent related but non-equivalent dimensions of disease.¹²

Changes in MASLD prevalence do not parallel the burden of hepatic fibrosis

Temporal analyses of NHANES data provide evidence that the prevalence of the diagnostic phenotype and the burden of hepatic fibrosis can change in different directions. Across the 2017–2023 period, the prevalence of SLD and MASLD remained relatively stable in one nationally representative analysis, whereas the prevalence of advanced fibrosis increased from 7.4% to 9.8% when a CAP threshold of 285 dB/m was applied.⁴

A separate serial analysis further illustrated this discordance. MASLD prevalence decreased from 37.6% in 2017–2020 to 32.5% in 2021–2023, while clinically significant fibrosis, advanced fibrosis, and cirrhosis increased during the same period. The same pattern was observed across metabolically defined subgroups, including participants with prediabetes and diabetes.¹³ Thus, temporal changes in the prevalence of the MASLD phenotype do not necessarily reflect corresponding changes in the burden of advanced hepatic disease.

These observations do not demonstrate that MASLD is clinically inadequate. Rather, they identify a potential limitation of a classification system in which steatosis and heterogeneous cardiometabolic features are combined into a single diagnostic category without requiring direct evidence of (Fig. 1).

Metabolic heterogeneity persists even within the MASLD population

The heterogeneity of MASLD is particularly evident among individuals without obesity. In NHANES 2017–2023, lean MASLD was identified in 9.3% of lean adults. Among individuals with lean MASLD, significant fibrosis was present in 5.6%, advanced fibrosis in 2.4%, and cirrhosis in 2.0%.¹⁴ These findings demonstrate that clinically meaningful hepatic disease can occur in individuals who do not meet conventional anthropometric definitions of obesity.

The presence of fibrosis within lean MASLD is relevant to the proposed HIRS framework because body mass index is not itself a measure of insulin action. Consequently, an obesity-centered interpretation of

metabolic dysfunction may fail to distinguish individuals with substantial metabolic impairment from those whose cardiometabolic phenotype is less strongly linked to hepatic IR. Conversely, the presence of metabolic abnormalities without obesity does not establish IR and should not be interpreted as a direct substitute for it.

This distinction provides a rationale for testing whether an IR measure can provide greater biological specificity than the current aggregation of heterogeneous cardiometabolic risk factors (Fig. 2).

MASLD identifies substantial extrahepatic disease burden but does not establish insulin resistance as the organizing variable

The clinical relevance of MASLD extends beyond hepatic manifestations. In the UK Biobank, 131,020 of 438,840 participants with available classification data met criteria for MASLD, corresponding to approximately 29.9% of the cohort.⁵ Participants with MASLD had a higher prevalence of multimorbidity, with two or more long-term conditions present in 21.3% compared with 14.4% among participants without MASLD. Over a median follow-up of approximately 13 years, MASLD was associated with increased all-cause mortality (hazard ratio, 1.16; 95% CI, 1.13–1.19).

The association between MASLD and systemic disease burden strengthens the clinical importance of metabolic classification but does not determine which metabolic abnormality provides the most informative organizing variable. In particular, these observations establish prognostic relevance for the MASLD phenotype but do not demonstrate that IR, rather than adiposity, dysglycemia, hypertension, hypertriglyceridemia, or low HDL cholesterol, is the principal classifier of risk.

The epidemiological evidence therefore points toward a more biologically discriminating metabolic axis, but it cannot by itself show that an IR-based definition performs better.

Hepatic transcriptomic data demonstrate progressive molecular remodeling across histological severity

The publicly available GSE130970 dataset provides complementary molecular evidence because it contains hepatic transcriptomic profiles from 78 human liver biopsies, including six histologically normal samples and 72 samples spanning the spectrum of NAFLD histological severity, with NAS values ranging from 0 to 6 and fibrosis stages ranging from 0 to 4.¹⁵ Published secondary analyses of this dataset have demonstrated reproducible molecular differences across histological phenotypes, including separation of normal liver, steatosis, and steatohepatitis-related profiles and progressive remodeling of metabolic and inflammatory pathways.^{16,17}

Independent analyses have also identified alterations in metabolic pathways within GSE130970 rather than a molecular signature restricted to lipid accumulation alone. For example, published analyses of the dataset identified differential regulation of genes involved in mitochondrial and metabolic processes, with consistent changes in DLD and PDHB among cuproptosis-related genes. These observations

provide biological support for the concept that hepatic steatosis is accompanied by coordinated molecular remodeling involving metabolic, inflammatory, and fibrogenic processes. However, because the present manuscript has not yet performed an original transcriptomic analysis of GSE130970, these findings are considered external exploratory evidence rather than empirical validation of HIRS. Figure 3 should therefore be read as a conceptual summary, not as the output of an original analysis.

The epidemiological and molecular evidence identifies insulin resistance as a testable organizing axis

Taken together, the quantitative evidence identifies four partially independent characteristics of the current disease classification. First, MASLD identifies a large proportion of adults with steatotic liver disease. Second, the prevalence of the MASLD phenotype does not consistently parallel the burden of hepatic fibrosis. Third, clinically relevant liver disease occurs in lean individuals who would not be adequately characterized by obesity-based definitions. Fourth, MASLD is associated with substantial extrahepatic morbidity and mortality, while hepatic transcriptomic studies demonstrate progressive molecular remodeling across histological severity.

These findings converge on a specific unresolved question: whether direct evidence of IR provides a more biologically coherent classifier of steatotic liver disease than the presence of one or more heterogeneous cardiometabolic risk factors.

The available evidence does not establish that HIRS is superior to MASLD. Instead, it identifies a testable hypothesis in which hepatic steatosis and IR are treated as co-primary features, while adipose dysfunction, inflammatory activity, and fibrogenic phenotype are evaluated as modifiers or stages of disease.

The proposed HIRS framework operationalizes an insulin resistance–centered classification

The HIRS framework translates this hypothesis into measurable diagnostic components. Hepatic steatosis is retained as a required structural phenotype, whereas IR becomes the second required component. HOMA-IR is the preferred direct surrogate when fasting insulin is available, while TyG and other validated IR surrogates provide alternatives in settings without insulin measurements. The framework therefore differs from MASLD not by removing metabolic dysfunction, but by requiring that metabolic dysfunction be represented by an explicit IR criterion.

Adipose dysfunction is retained as a phenotypic modifier rather than a mandatory diagnostic component. This distinction permits individuals with hepatic steatosis and demonstrable IR to be classified independently of obesity while preserving anthropometric and lipid-related information as descriptors of metabolic phenotype.

The proposed staging system further separates metabolic disease from subsequent hepatic manifestations. HIRS 1 represents steatosis with IR without established biochemical inflammatory activity; HIRS 2 incorporates evidence of inflammatory activity; and HIRS 3 incorporates evidence of hepatic stiffness and fibrogenic progression. Because cytokeratin-18 and PRO-C3 are not available in the planned population datasets, these latter stages remain partially conceptual and require empirical validation.

The current evidence defines a specific empirical gap for direct HIRS-versus-MASLD validation

The evidence assembled here supports the biological plausibility and testability of an IR-centered classification but does not constitute validation of HIRS. In particular, the available published epidemiological studies do not directly compare the proposed HIRS criteria with MASLD using the same participants, the same steatosis definitions, and prespecified IR thresholds.

The planned NHANES and UK Biobank analyses therefore address a distinct empirical question: whether replacing heterogeneous cardiometabolic entry criteria with an IR requirement produces meaningful differences in disease classification, identifies clinically relevant reclassification groups, and improves discrimination of hepatic fibrosis and longitudinal outcomes. Until those analyses are completed, HIRS should be regarded as a testable classification proposal rather than an established replacement for MASLD.

DISCUSSION

This study aimed to propose an IR-centered framework for classifying steatotic liver disease and to define how it should be tested against the current MASLD construct. The evidence synthesis indicates that MASLD identifies a large and clinically heterogeneous population, those temporal changes in MASLD prevalence do not necessarily parallel fibrosis burden, and that clinically relevant liver disease occurs in lean individuals. Taken together, these observations support IR as a testable organizing axis, but they do not establish HIRS as a validated replacement for MASLD.

These findings are compatible with the rationale behind the current nomenclature. The current MASLD framework intentionally combines hepatic steatosis with cardiometabolic risk factors to provide a positive and clinically practical definition. The 2024 EASL-EASD-EASO guidelines similarly retain this construct while emphasizing sequential fibrosis risk assessment.^{18,19} This position is not uncontested. Commentators have called for formal validation of how well MASLD criteria identify IR,²⁰ whereas the nomenclature steering committee has replied that MASLD overlaps almost entirely with NAFLD and has disagreed with reservations about the cardiometabolic requirement.²¹ Our analysis does not challenge the practical objectives of the nomenclature. Rather, it identifies a potential limitation when obesity, dysglycemia, dyslipidemia, and hypertension are treated as interchangeable proxies for IR, despite representing biologically distinct phenotypes.

The strongest support for this distinction comes from lean populations. A recent NHANES-based study directly associated IR with both MASLD and advanced fibrosis in lean adults, with HOMA-IR remaining independently associated with advanced fibrosis after accounting for excess adiposity.²² This observation is concordant with longitudinal evidence linking baseline HOMA-IR to subsequent fibrosis progression in patients with NAFLD without diabetes.²³ Both sources are observational, however, so they cannot exclude residual confounding. Together, these findings support treating adiposity as a phenotype modifier rather than as a surrogate for IR.

The proposed framework is also physiologically plausible. Hepatic IR can impair suppression of hepatic glucose production while permitting continued lipogenic signaling,² whereas adipose tissue dysfunction increases free-fatty-acid delivery and promotes lipotoxic stress. Recent mechanistic work emphasizes the reciprocal relationship between adipose dysfunction and hepatic IR in MASLD.²⁴ Human fluxomic data further demonstrated that hepatic glucose production increases with inflammation and fibrosis and is associated with hepatic and adipose IR, accompanied by reduced expression of insulin-action genes including IRS1, IRS2, and AKT2 in fibrotic MASH.²⁵ These observations provide a mechanistic bridge between IR, metabolic dysfunction, inflammation, and fibrogenesis.

Clinically, HIRS should initially be regarded as a stratification hypothesis rather than a classification ready for routine implementation. Its potential value would be greatest if direct or validated surrogate measures of IR identify clinically meaningful subgroups currently aggregated within MASLD. Importantly, this approach would complement rather than replace established fibrosis pathways. Comparative studies of IR indices suggest that insulin-based measures may perform particularly well for identifying fibrosis, whereas TyG-derived indices may offer greater feasibility when fasting insulin is unavailable.²⁶

Some limitations require consideration. First, the epidemiological evidence was derived from secondary analyses of NHANES and UK Biobank, introducing differences in population selection, variable definitions, and outcome ascertainment; this could have distorted the apparent relationship between metabolic classification and disease severity. Second, IR was not measured uniformly, and surrogate indices cannot substitute for direct physiological measurements; this could have overestimated or underestimated the biological specificity of an IR-centered classification. Third, the GSE130970 evidence was based on published secondary analyses rather than an original transcriptomic analysis performed in the present study; this could have overinterpreted molecular concordance. Fourth, no prospective HIRS-versus-MASLD reclassification analysis or outcome-prediction model has yet been completed; this could have overestimated the apparent clinical utility of HIRS. In addition, the evidence synthesis was narrative rather than systematic, and the cited analyses used different steatosis thresholds (CAP cutoffs from 280 to 300 dB/m), which introduces selection and measurement bias and could have exaggerated or masked heterogeneity across studies. The cited observational analyses also adjusted for different covariate sets, so residual confounding by diet, physical activity, medications, and alcohol misclassification is likely; this could have overestimated the independent contribution of IR. Finally, the predominantly US and UK datasets limit external validity to populations with different genetic

backgrounds, metabolic phenotypes, and healthcare systems; this could have limited applicability beyond the populations represented in the available evidence.

The principal strength of this study is that it brings population epidemiology, fibrosis phenotyping, lean MASLD, systemic disease burden, and molecular evidence together in a single, falsifiable classification hypothesis, and that it pairs the proposal with explicit safeguards against circularity and a prespecified validation plan. This approach also preserves the clinical utility of established MASLD terminology while identifying a specific biological variable that can be tested prospectively.

Future studies should apply HIRS and MASLD criteria within the same well-characterized cohorts and directly compare their ability to identify significant and advanced fibrosis, predict longitudinal hepatic and extrahepatic outcomes, and improve biological discrimination across lean and non-lean phenotypes. These comparisons should use fasting insulin measured with standardized assays and population-specific cutoffs, and they should include at least one Latin American cohort in which TyG-based criteria can be tested alongside HOMA-IR.

CONCLUSION

In summary, the available evidence supports IR as a plausible and testable organizing variable for steatotic liver disease, while remaining insufficient to demonstrate that HIRS should replace MASLD. Direct comparative validation using standardized IR measurements and clinically meaningful liver outcomes is therefore the necessary next step.

DECLARATIONS

Competing interests:

no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L (2023) The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology* 77(4):1335–1347
2. Petersen MC, Shulman GI (2018) Mechanisms of Insulin Action and Insulin Resistance. *Physiol Rev* 98(4):2133–2223
3. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F et al (2023) A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 79(6):1542–1556
4. Paik JM, Hobbs K, Gupta A, Alkalbani RJ, Reyes MA, Younossi ZM (2025) Prevalence of MASLD, Met-ALD, and ALD and Associated Fibrosis Among US Adults: Insights From NHANES 2017 to 2023.

5. Feng Q, Izzi-Engbeaya CN, Branch AD, Mullish BH, Manousou P, Woodward M (2025) The Relationships Between MASLD, Extrahepatic Multimorbidity, and All-Cause Mortality in the UK Biobank Cohort. *J Clin Endocrinol Metab* 111(1):e58–e69
6. Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y et al (2020) Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 5(8):739–752
7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28(7):412–419
8. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO et al (2010) The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 95(7):3347–3351
9. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, Viveros-Ruiz T, Cruz-Bautista I, Romo-Romo A et al (2018) METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. *Eur J Endocrinol* 178(5):533–544
10. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A et al (2006) The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 6:33
11. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J et al (2006) Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 43(6):1317–1325
12. Unalp-Arida A, Ruhl CE (2025) Prevalence of metabolic dysfunction-associated steatotic liver disease and fibrosis defined by liver elastography in the United States using National Health and Nutrition Examination Survey 2017-March 2020 and August 2021-August 2023 data. *Hepatology* 82(5):1256–1273
13. Bril F, Bolla P, Huynh K, Bobba S (2025) Prevalence of MASLD in People With Diabetes Has Decreased in the US, but Rates of Liver Fibrosis Are Still on the Rise. *J Endocr Soc* 9(8):bvaf110
14. Kim D, Danpanichkul P, Wijarnpreecha K, Cholankeiril G, Loomba R, Ahmed A (2025) Current Burden of Lean Metabolic Dysfunction-Associated Steatotic Liver Disease Among US Adults, 2017–2023. *Aliment Pharmacol Ther* 61(5):891–894
15. Hoang SA, Oseini A, Feaver RE, Cole BK, Asgharpour A, Vincent R et al (2019) Gene Expression Predicts Histological Severity and Reveals Distinct Molecular Profiles of Nonalcoholic Fatty Liver Disease. *Sci Rep* 9(1):12541
16. Wu C, Liu X, Zhong L, Zhou Y, Long L, Yi T et al (2023) Identification of Cuproptosis-Related Genes in Nonalcoholic Fatty Liver Disease. *Oxid Med Cell Longev* 2023:9245667

17. Li J, Zhang Y, Ma X, Liu R, Xu C, He Q et al (2025) Identification and validation of cuproptosis-related genes for diagnosis and therapy in nonalcoholic fatty liver disease. *Mol Cell Biochem* 480(1):473–489
18. European Association for the Study of the Liver (EASL) (2024) European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 81(3):492–542
19. European Association for the Study of the Liver (EASL) (2024) European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). *Obes Facts* 17(4):374–444
20. Cusi K, Younossi Z, Roden M (2024) From NAFLD to MASLD: promise and pitfalls of a new definition. *Ann Hepatol* 29(4):101179
21. Rinella ME, Castro Narro GE, Krag A, Terrault N, Newsome PN, Reply (2024) From NAFLD to MASLD: promise and pitfalls of a new definition. *Hepatology* 79(2):E16–E17
22. Njei B, Abdu M, Al-Ajlouni YA, Mohamed MF, Deng Y, Osta EG et al (2025) Insulin resistance, metabolic dysfunction-associated steatotic liver disease, and advanced liver fibrosis in lean US adults: a population-based study. *Proc (Bayl Univ Med Cent)* 38(5):637–645
23. Koo DJ, Lee MY, Jung I, Moon SJ, Kwon H, Park SE et al (2021) Baseline homeostasis model assessment of insulin resistance associated with fibrosis progression in patients with nonalcoholic fatty liver disease without diabetes: A cohort study. *PLoS ONE* 16(8):e0255535
24. Sancar G, Birkenfeld AL (2024) The role of adipose tissue dysfunction in hepatic insulin resistance and T2D. *J Endocrinol* 262(3):e240115
25. Sabatini S, Sen P, Carli F, Pezzica S, Rosso C, Lembo E et al (2024) Hepatic glucose production rises with the histological severity of metabolic dysfunction-associated steatohepatitis. *Cell Rep Med* 5(11):101820
26. Khamseh ME, Malek M, Jahangiri S, Nobarani S, Hekmatdoost A, Salavatizadeh M et al (2024) Insulin Resistance/Sensitivity Measures as Screening Indicators of Metabolic-Associated Fatty Liver Disease and Liver Fibrosis. *Dig Dis Sci* 69(4):1430–1443

Figures

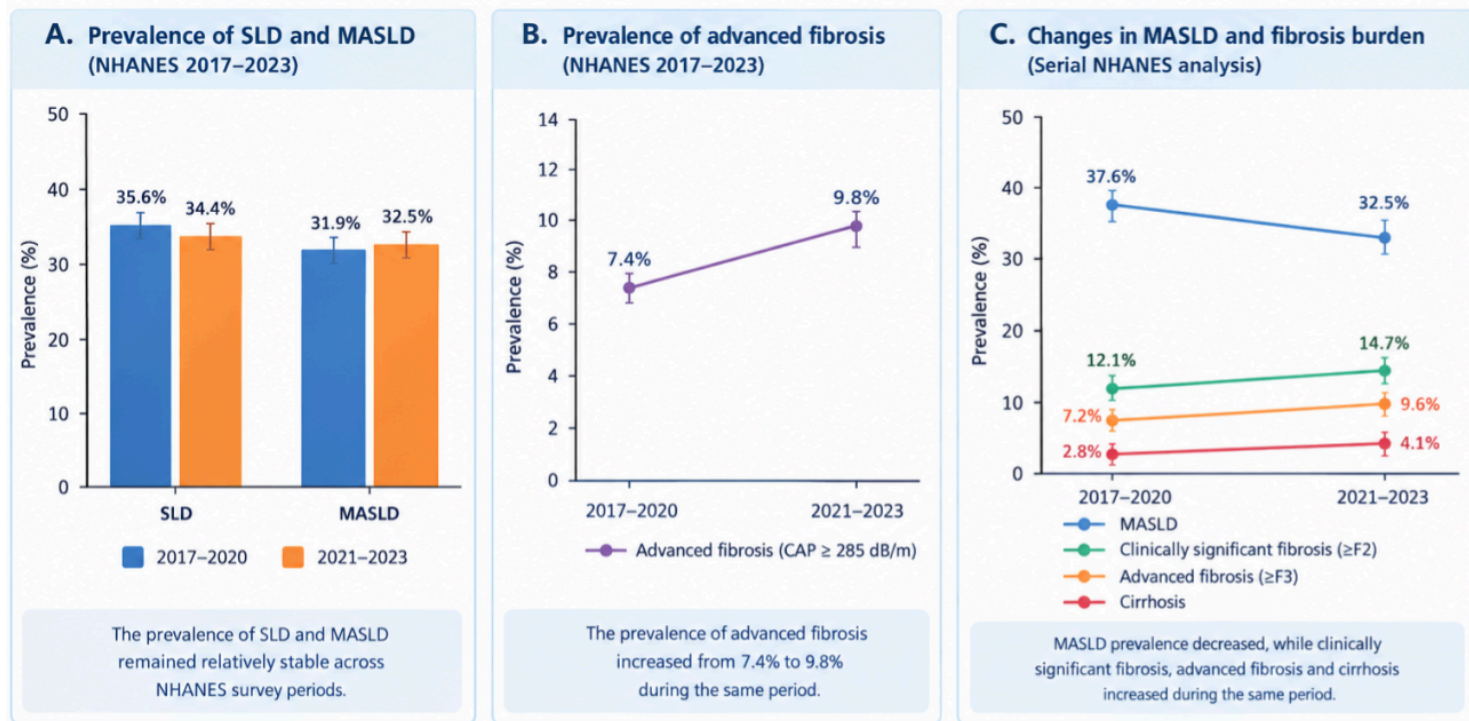


Figure 1

Temporal discordance between steatotic liver disease classification and hepatic fibrosis burden

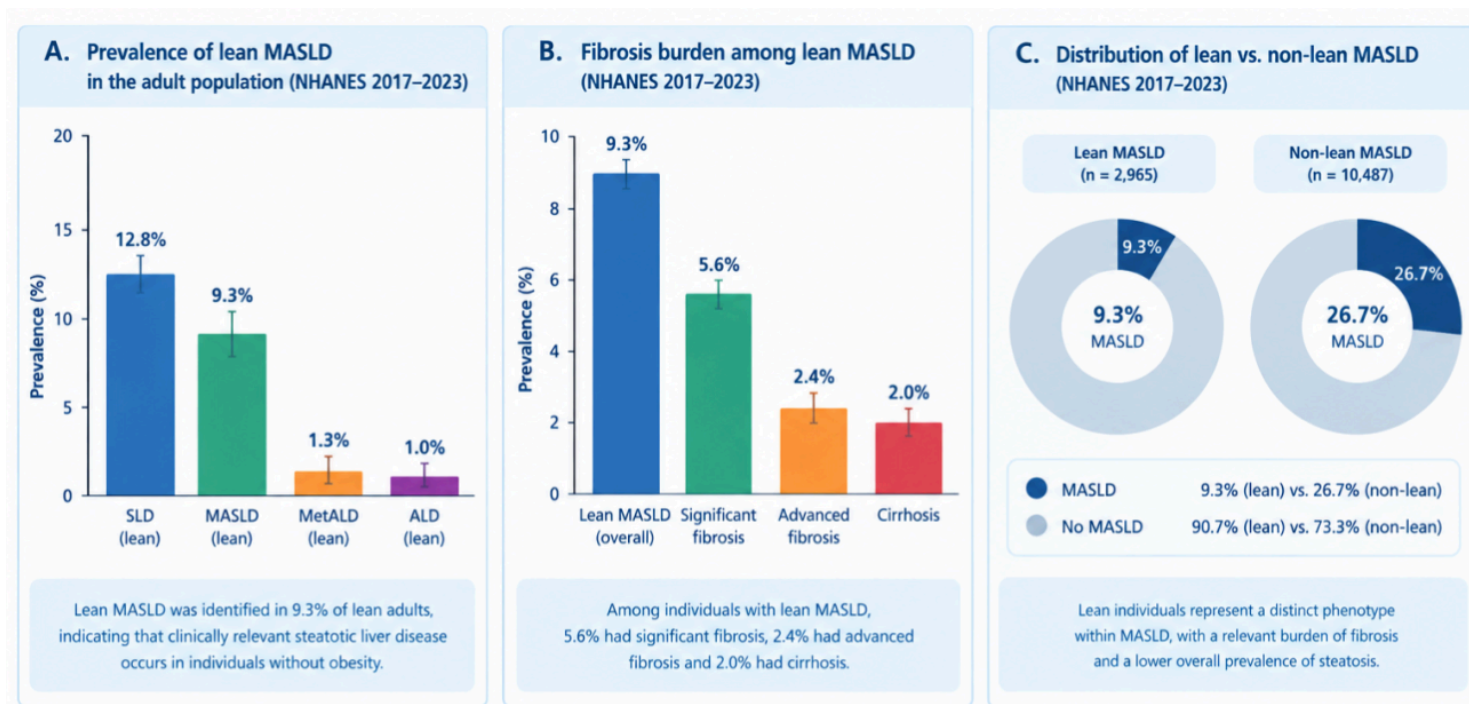


Figure 2

Phenotypic heterogeneity and fibrosis burden within lean MASLD.

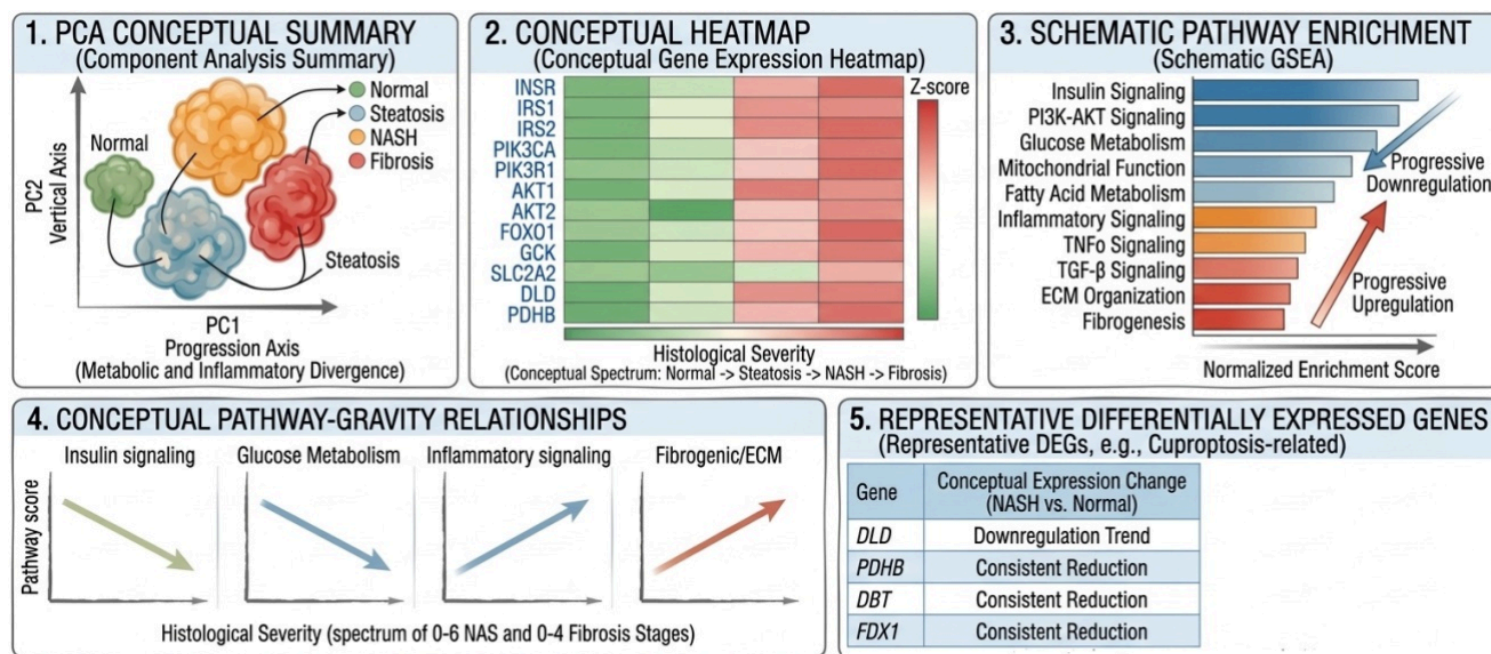


Figure 3

Hepatic molecular remodeling across histological severity in GSE130970