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Metabolic Health Phenotypes Among Middle- to Older-Aged Adults Living With and Without Obesity: Relationships With Hepatic Health Indicators

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Keywords: fatty liver index | liver health biomarkers | metabolic associated fatty liver disease | metabolic health phenotypes | non-alcoholic fatty liver disease | obesity

ABSTRACT

Background: The recent reclassification of nonalcoholic fatty liver disease to metabolic dysfunction-associated steatotic liver disease reflects the central role of metabolic dysfunction in its pathogenesis. Obesity underlies metabolic perturbations; however, liver health risks are not exclusive to individuals with a higher BMI and some individuals with obesity have favorable metabolic health (MH). Thus far, there has been limited examination of liver health indicators among metabolically healthy and unhealthy phenotypes, which is the aim of this study.

Methods: A cross-sectional sample of 2040 middle- to older-aged adults were classified as metabolically healthy obese (MHO), metabolically unhealthy obese (MUO), metabolically healthy nonobese (MHNO), and metabolically unhealthy nonobese (MUNO), according to three MH definitions (MeigsA, MeigsB, and Wildman). Liver biomarkers alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were measured, and the fatty liver index (FLI) was calculated. Crude and adjusted logistic regression models examined associations between liver function indicators and MH phenotypes.

Results: In fully adjusted models, higher FLI scores were consistently associated with lower likelihood of MHO and MHNO (odds ratios and 95% confidence intervals for MHO: 0.947 (0.934, 0.961) [MeigsA], 0.952 (0.938, 0.966) [MeigsB] and 0.945 (0.931, 0.959) [Wildman] and for MHNO: 0.957 (0.950, 0.964) [MeigsA], 0.950 (0.942, 0.958) [MeigsB] and 0.961 (0.955, 0.968) [Wildman] (all $p < 0.001$)). Higher ALT and GGT concentrations were inversely associated with MHO, and AST additionally with MHNO, in all models across the three definitions.

Conclusions: Liver function indicators are linked with MH status in middle- to older-aged adults.

1 | Introduction

Nonalcoholic fatty liver disease (NAFLD), the most common chronic liver condition globally, affects nearly 25% of the population [1]. Recent shifts in understanding of the condition have led to its reclassification, firstly to metabolic dysfunction-associated fatty liver disease (MAFLD) and later to metabolic dysfunction-associated steatotic liver disease (MASLD), emphasizing its strong link with metabolic dysfunction [2]. Overweight and obesity are key drivers of metabolic dysfunction and are linked

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with an increased risk of cardiovascular disease [3]. However, obesity is a heterogeneous disease and metabolic health (MH) phenotypes, including metabolically healthy and unhealthy obese (MHO and MUO) and metabolically healthy and unhealthy nonobese (MHNO and MUNO), have been described [4], with differing cardiometabolic risks between the phenotypes reported [5–7]. These classifications allow for a refined assessment of metabolic status that goes beyond simple measures of body weight or body mass index (BMI) [8]. By distinguishing between MH and obesity, researchers and clinicians may better understand the varying health risks and outcomes associated with each phenotype.

Measures of liver function include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) [9]. These biomarkers provide insights into liver function and potential damage, reflecting the liver's metabolic state [10]. In addition, the fatty liver index (FLI) provides a non-invasive cost-effective way to screen for hepatic steatosis in large populations [11]. It is particularly useful in epidemiological studies and clinical settings where liver biopsy, the gold standard for diagnosing fatty liver, is not feasible [12]. The inter-relationships between MH and liver function measures may play a crucial role in determining health outcomes in individuals with fatty liver disease [13]. Metabolic dysfunction can lead to liver complications such as NAFLD, liver fibrosis and cirrhosis, whereas poor liver health can exacerbate metabolic issues, such as insulin resistance and type 2 diabetes [14].

Previous research has extensively investigated the association between obesity and NAFLD [15, 16]. Thus far, however, limited research has explored the nuanced interplay between liver health indicators and MH phenotypes among adults living with and without obesity [17–19]. Recent emerging evidence suggest that MH phenotypes better predict subclinical atherosclerosis than BMI-based obesity phenotypes in the NAFLD population [19], highlighting the critical role of metabolic status in understanding liver health outcomes. Specifically, metabolic dysfunction such as that reflected in the FLI and liver enzyme profiling are strongly associated with various liver and MH issues [19]. These findings emphasize the need for tailored approaches and the potential value of the concept and examination of obesity phenotypes. Considering the rising prevalence of obesity [20] (including MHO) [21] and MAFLD [22], further research is warranted. Addressing this gap, we investigated the relationships between MH phenotypes, defined using MeigsA, MeigsB, and Wildman definitions [4], and measures of liver health, focusing on the FLI and liver function biomarkers, with a view to improving our understanding of their inter-relationships.

2 | Methods

2.1 | Study Population and Setting

The Cork and Kerry Diabetes and Heart Disease Study (Phase II—Mitchelstown Cohort) was a single center cross-sectional study conducted between 2010 and 2011. Details regarding the study design, sampling procedures and methods of data collection have been reported previously [23]. In brief, stratified sampling was employed to recruit equal numbers of men and women from all registered attending patients in the 45–70-year-old age group. In total, 3807 potential participants were randomly selected from the practice list of a large primary care center in Mitchelstown, County Cork, Ireland. Following the exclusion of duplicates, deaths, and subjects who were incapable of consenting or attending appointment, 3051 were invited to participate in the study, and of these, about two-thirds (2047, 49% male) completed the questionnaire and physical examination components of the baseline assessment. The current analysis included participants ($n = 2040$) with data available for BMI. Ethics committee approval conforming to the Declaration of Helsinki was obtained from the Clinical Research Ethics Committee of University College Cork. A letter signed by the contact GP in the clinic was sent out to all selected participants with a reply slip indicating acceptance or refusal. All participants gave signed informed consent, including permission to use their data for research purposes.

2.2 | Clinical Measures

Anthropometric measurements were recorded with calibrated instruments according to a standardized protocol. Body weight was measured in kilograms without shoes to the nearest 100 g using a Tanita WB100MA weighing scale (Tanita Corporation, IL, USA). Height was measured in centimeters to one decimal place using a Seca Leicester height gauge (Seca, Birmingham, UK). BMI (BMI = weight (kg)/height $(m)^2$) was calculated from measured weight and height. Waist circumference (WC), defined as midway between lowest rib and iliac crest, was measured in centimeters to one decimal place using a Seca 200 measuring tape (Seca, Birmingham, UK). The average of two measurements was used for analyses. Three independent measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained with the subject in a seated position using an Omron M7 digital sphygmomanometer (Omron Healthcare Co Ltd., Japan). The mean of the second and third readings was considered to be a subject's BP.

2.3 | Biochemical Analyses and Liver Health Variables

Study participants fasted for a minimum of 8 h (from 12 midnight or earlier) and were invited to attend the clinic in the morning between 8 and 10 a.m. Fasting blood samples were collected from each participant and biochemical analyses were carried by the Cork University Hospital Biochemistry Laboratory using standardized procedures. Fasting plasma glucose (FPG) concentrations were determined using a glucose hexokinase assay (Olympus Life and Material Science Europa Ltd., Lismeehan Co. Clare, Ireland) and triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels were analyzed using enzymatic colorimetric tests (Olympus Life and Material Science Europa Ltd., Lismeehan Co. Clare, Ireland) on an Olympus 5400 automatic analyzer (Olympic Diagnostica Gmbh, Hamburg, Germany). C-reactive protein (CRP) and insulin were measured using a biochip array system (Evidence Investigator; Randox Laboratories, Crumlin Co. Antrim, United Kingdom).

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Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR) [24]. Liver enzymes (ALT, AST, ALP and GGT) were determined using spectrophotometric enzymatic assays on a Beckman Coulter AU5832 analyzer (Beckman Coulter Diagnostics Limited, Lismeehan Co. Clare, Ireland).

The FLI is a validated tool used to estimate the presence of fatty liver (hepatic steatosis) based on a combination of clinical and biochemical measurements [11]. The FLI was calculated using the following formula:

$$\begin{aligned} \mathrm{FLI} = (&\mathrm{e}\ 0.953 * \log\mathrm{e}\ (\mathrm{TG}) + 0.139 * \mathrm{BMI} \\ &+ 0.718 * \log\mathrm{e}\ (\mathrm{GGT}) \\ &+ 0.053 * \mathrm{WC} - 15.745) / (1 + \mathrm{e}\ 0.953 * \log\mathrm{e}\ (\mathrm{TG}) \\ &+ 0.139 * \mathrm{BMI} + 0.718 * \log\mathrm{e}\ (\mathrm{GGT}) + 0.053 \\ &* \mathrm{WC} - 15.745) * 100. \end{aligned} \quad (1)$$

FLI scores ranged from 2.48 to 99.97. The scores were also categorized as FLI < 30, 30–60 and > 60, indicating low, intermediate and high likelihood of fatty liver.

2.4 | Covariates and Metabolic Health Status

A general health and lifestyle questionnaire assessed demographic variables, lifestyle behaviors and morbidity. These included details on age, sex, education, smoking status, alcohol consumption and use of prescription medications. Physical activity levels were measured using the validated International Physical Activity Questionnaire (IPAQ) [25]. Education was defined as "primary level only" and "secondary or higher". Smoking status was defined as "current smoker" and "non-smoker". Alcohol consumption was measured in units of alcohol consumed on a weekly basis and was categorized into the following levels: (i) nondrinker, that is < 1 drink per week, (ii) moderate drinker, that is between 1 and 14 drinks per week, and (iii) heavy drinker, that is > 14 drinks per week. The definition of "moderate drinker" aligns with criteria from the European Prospective Investigation into Cancer and Nutrition (EPIC) study [26]. For the current analysis, these were then re-categorized as "moderate/non-drinker" or "heavy drinker". Physical activity was categorized as low, moderate and high levels of activity using the IPAQ. This was then recoded as a dichotomous variable: "moderate/high" or "low" physical activity. The presence of cardiovascular disease was obtained by asking study participants if they had been diagnosed with any one of the following seven conditions: Heart Attack (including coronary thrombosis or myocardial infarction), Heart Failure, Angina, Aortic Aneurysm, Hardening of the Arteries, Stroke or any other Heart Trouble. Subjects who reported a diagnosis of any one of these conditions were classified as having cardiovascular disease.

Diet was evaluated using a modified version of the self-completed EPIC food frequency questionnaire (FFQ) [27], which has been validated extensively in several populations [28]. Adapted to reflect the Irish diet, the 150-item semi-quantitative FFQ used in the current study was originally validated for use in the Irish population using food diaries and a protein biomarker in a volunteer sample [29] and incorporated into the SLÁN Irish National Surveys of Lifestyle Attitudes and Nutrition 1998, 2002 and 2007 [30]. The average medium serving of each food item consumed by participants over the last 12 months was converted into quantities using standard portion sizes. Food item quantity was expressed as (g/d) and beverages as (mL/d).

Based on the FFQ, the Dietary Approaches to Stop Hypertension (DASH) score was constructed. DASH is a dietary pattern rich in fruits, vegetables, whole grains, and low-fat dairy foods and is limited in sugar-sweetened foods and beverages, red meat, and added fats. This diet has been promoted by the National Heart, Lung and Blood Institute (part of the National Institutes of Health, a United States government organization) to prevent and control hypertension. For each food group, consumption was divided into quintiles, and participants were classified according to their intake ranking. Component scores were summed, and an overall DASH score was calculated for each person. DASH diet scores ranged from 11 to 42. Lower scores represent poorer and higher scores represent better quality diet [31].

MH status was defined using three definitions: MeigsA (metabolic syndrome phenotype), MeigsB (insulin resistance phenotype), and Wildman (metabolic syndrome plus inflammatory phenotype). The four categories examined were MHO, MUO, MHNO, and MUNO [4]. Details for defining MH status are presented in Supporting Information S1: Table S1. The criteria included BP, TG, HDL-C, FPG, HOMA-IR, WC and CRP levels.

2.5 | Statistical Analysis

Descriptive statistics summarized the study population's characteristics. Categorical data are presented as numbers (n) and percentages (%) and continuous variables are shown as a mean, plus or minus one standard deviation (± SD), or a median and interquartile range (IQR) for skewed data. Comparison across each MH phenotype definition were assessed using chi-square tests, t-tests, or a Mann–Whitney U. Analyses across FLI categories were conducted using chi-square tests, Kruskal–Wallis tests, or a one-way ANOVA, and relationships between BMI, WC, and liver health indicators were assessed using Spearman's rank-order correlation. Binary logistic regression analyses were performed to investigate the associations between liver health indicators and MH status among adults with and without obesity. Three models were run: an unadjusted model (Model 1), an age- and sex-adjusted model (Model 2), and a model which additionally adjusted for education, smoking status, alcohol use, dietary quality (DASH score), physical activity, and cardiovascular disease history (Model 3). Liver health indicator associations with MH phenotypes were additionally assessed using multinomial logistic regression, with the MHNO group used as the reference category. As alcohol consumption is associated with liver function, we conducted additional sensitivity regression analyses excluding study participants who were classified as having heavy alcohol use (n = 195). We also performed sensitivity regression analyses which excluded participants with a cardiovascular disease history (n = 212). In addition, although glucose measures (and treatment data) are

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included in the MeigsA and Wildman MH definitions, we conducted further sensitivity analyses which excluded study participants who had a previous diagnosis of type 2 diabetes (n = 102). Sex-stratified regression analyses were also carried out. Data analyses were carried out using Stata SE Version 13 (Stata Corporation, College Station, TX, USA) for Windows. For all analyses, a p value (two-tailed) of less than 0.05 was considered to show statistical significance.

3 | Results

3.1 | Descriptive Characteristics

Characteristics of study participants (n = 2040) according to MH definitions and phenotypes are presented in Table 1. The prevalence of MH phenotypes varied considerably between definitions. Among adults with obesity, the prevalence of MHO ranged from 24% (Wildman) to 37% (MeigsB) and MUO ranged from 63% (MeigsB) to 76% (Wildman). Among adults without obesity, the prevalence of MHNO ranged from 58% (Wildman) to 78% (MeigsB) and MUNO ranged from 22% (MeigsB) to 42% (Wildman). The prevalence of the metabolically unhealthy phenotype was higher in males than in females, for all definitions. In addition, participants presenting with metabolically healthy phenotypes had a lower BMI and WC than their metabolically unhealthy counterparts, and this was statistically significant across all definitions.

Examination of liver enzymes by MH phenotype revealed consistent trends for ALT and GGT concentrations, both of which were significantly higher among the MUO and MUNO groups compared to their metabolically healthy counterparts, for all MH definitions. Additionally, among adults without obesity, AST and ALP concentrations were significantly higher among the MUNO group compared to their metabolically healthy counterparts, according to all three definitions, with the exception of ALP for Meigs B. FLI scores were consistently greater among the MUO and MUNO groups relative to their MHO and MHNO counterparts (all $p < 0.001$).

In Supporting Information S1: Table S2, analysis of participant characteristics according to FLI categories: FLI < 30 (n = 531), FLI 30–60 (n = 545) and FLI > 60 (n = 878), revealed that subjects with higher FLI scores were more likely to be older, male, to have finished education at primary level only, to be heavy drinkers and have poorer dietary quality, and had lower levels of physical activity. Study participants with higher FLI scores were also more likely to have had a previous history cardiovascular disease. Increasing FLI scores were additionally associated with higher SBP and DBP levels, higher TG and lower HDL-C concentrations, higher FPG levels, greater insulin resistance (HOMA-IR) and higher CRP levels. Significantly higher concentrations of liver enzymes (ALT, AST, ALP, and GGT) were also observed across FLI categories (all $p < 0.001$).

In correlation analyses (Supporting Information S1: Table S3), significant positive correlations between BMI, WC and all liver health indicators were observed. The strongest correlations were observed with FLI (BMI: ρ = 0.855; WC: ρ = 0.884), ALT (BMI: ρ = 0.352; WC: ρ = 0.382) and GGT (BMI: ρ = 0.295; WC: ρ = 0.370). Weaker positive correlations with BMI and WC were observed for AST (BMI: ρ = 0.110; WC: ρ = 0.133) and for ALP (BMI: ρ = 0.094; WC: ρ = 0.075).

3.2 | Logistic Regression Analyses

Tables 2 and 3 present the results of logistic regression analyses examining the associations between liver health indicators and MHO and MHNO phenotypes. Among participants living with obesity (Table 2), FLI and GGT were inversely associated with the MHO phenotype in crude, partially and fully adjusted models, consistently for each of the three MH definitions. In fully adjusted models the odds ratios (ORs) and 95% confidence intervals (95% CIs) for MHO with FLI were 0.947 (0.934, 0.961) [MeigsA], 0.952 (0.938, 0.966) [MeigsB] and 0.945 (0.931, 0.959) [Wildman] (all $p < 0.001$). In fully adjusted models, the ORs and 95% CIs for MHO with GGT were 0.993 (0.987, 1.000; p = 0.042) [MeigsA], 0.994 (0.987, 1.000; p = 0.04) [MeigsB], and 0.991 (0.983, 0.999; p = 0.035) [Wildman]. Higher ALT concentrations were also associated with a lower likelihood of being MHO in fully adjusted models for each of the three MH definitions: 0.984 (0.971, 0.998; p = 0.02) [MeigsA], 0.978 (0.965, 0.992; p = 0.002) [MeigsB] and 0.979 (0.963, 0.995; p = 0.01) [Wildman]. These relationships withstood a sensitivity analysis which excluded participants with heavy alcohol use (Supporting Information S1: Table S4). However, GGT relationships with the MHO phenotype were attenuated in models which examined the MeigsB MH definition (p = 0.05). The same relationships were seen in models which excluded study participants with a cardiovascular disease history (Supporting Information S1: Table S7) and in models which excluded participants with a previous diagnosis of type 2 diabetes (Supporting Information S1: Table S10). No significant associations with the MHO phenotype were observed for AST or ALP.

Among participants without obesity (Table 3), FLI scores, ALT, AST and GGT were inversely associated with the MHNO phenotype in both crude and adjusted models, consistently across the three MH definitions. In fully adjusted models, the ORs and 95% CIs for MHNO with FLI were 0.957 (0.950, 0.964) [MeigsA], 0.950 (0.942, 0.958) [MeigsB], and 0.961 (0.955, 0.968) [Wildman] (all $p < 0.001$), and for GGT were 0.989 (0.984, 0.993) [MeigsA], 0.987 (0.983, 0.992) [MeigsB], and 0.988 (0.983, 0.993) [Wildman] (all $p < 0.001$). Similar direction of associations and effect sizes were observed for ALT, AST, and ALP in all models across all three MH definitions, except for ALP (MeigsB MH definition). In models which excluded heavy alcohol users (Supporting Information S1: Table S5), participants with a cardiovascular disease history (Supporting Information S1: Table S8), and those who had a previous diagnosis of type 2 diabetes (Supporting Information S1: Table S11), the same relationships were observed.

The results from multinomial logistic regression analyses which compared MUNO, MHO, and MUO to MHNO for each phenotype definition are shown in Table 4. In models which adjusted for age, sex, education, smoking, alcohol use, dietary quality, physical activity, and cardiovascular disease history, FLI scores

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TABLE 1 | Characteristics of study participants ($N = 2040$) according to metabolic health phenotypes.

	Obese phenotypes								
	MeigsA			MeigsB			Wildman		
Variable	MHO ($n = 202$)	MUO ($n = 466$)	p	MHO ($n = 234$)	MUO ($n = 405$)	p	MHO ($n = 158$)	MUO ($n = 510$)	p
Age in years (median, IQR)	58.5 (54.0, 63.0)	60.5 (55.0, 64.0)	**0.006**	60.0 (54.8, 64.0)	60.0 (55.0, 64.0)	0.769	59.0 (54.0, 64.0)	60.0 (55.0, 64.0)	0.725
Male (n, %)	102 (50.5)	266 (57.1)	0.116	101 (43.2)	248 (61.2)	**< 0.001**	74 (46.8)	294 (57.6)	**0.017**
Primary education only (n, %)	55 (27.2)	148 (31.8)	0.242	61 (26.1)	130 (32.1)	0.109	43 (27.2)	160 (31.4)	0.321
Current smoker (n, %)	14 (6.9)	52 (11.2)	0.093	20 (8.5)	44 (10.9)	0.347	8 (5.1)	58 (11.4)	**0.02**
Heavy drinker (n, %)	17 (8.4)	43 (9.2)	0.736	20 (8.5)	38 (9.4)	0.723	11 (7.0)	49 (9.6)	0.309
Dietary quality (mean ± SD)	26.9 ± 4.9	26.2 ± 5.3	0.156	27.2 ± 5.3	26.0 ± 5.1	**0.009**	26.9 ± 4.8	26.2 ± 5.2	0.173
Low-level physical activity (n, %)	98 (48.5)	242 (51.9)	0.417	105 (44.9)	224 (55.3)	**0.011**	76 (48.1)	264 (51.8)	0.421
Cardiovascular disease history (n, %)	17 (8.4)	80 (17.2)	**0.003**	24 (10.3)	70 (17.3)	**0.016**	16 (10.1)	81 (15.9)	0.073
BMI, kg/m^2 (mean ± SD)	32.9 ± 2.9	34.2 ± 3.9	**< 0.001**	32.8 ± 3.0	34.3 ± 3.7	**< 0.001**	32.7 ± 3.0	34.2 ± 3.8	**< 0.001**
WC, cm (mean ± SD)	105.9 ± 10.6	110.5 ± 10.4	**< 0.001**	105.0 ± 9.1	111.3 ± 10.7	**< 0.001**	104.8 ± 9.7	110.4 ± 10.6	**< 0.001**
FLI (median, IQR)	77.6 (62.0, 86.0)	88.7 (79.6, 95.0)	**< 0.001**	78.3 (65.0, 86.7)	89.1 (79.9, 95.2)	**< 0.001**	75.0 (58.8, 83.6)	88.2 (78.9, 94.7)	**< 0.001**
ALT, U/L (median, IQR)	26.0 (20.0, 35.0)	30.0 (23.0, 38.0)	**0.001**	25.0 (19.0, 33.0)	30.0 (23.0, 39.0)	**< 0.001**	25.0 (19.0, 32.3)	30.0 (23.0, 39.0)	**< 0.001**
AST, U/L (median, IQR)	25.0 (21.0, 30.0)	26.0 (22.0, 31.0)	0.106	25.0 (21.0, 30.0)	26.0 (22.0, 31.0)	0.183	25.0 (21.0, 29.0)	26.0 (22.0, 31.0)	**0.035**
ALP, U/L (median, IQR)	83.0 (70.0, 96.3)	85.0 (72.0, 101.0)	0.091	84.0 (72.0, 98.0)	85.0 (71.0, 102.0)	0.652	84.5 (71.0, 98.0)	85.0 (72.0, 100.0)	0.772
GGT, U/L (median, IQR)	27.0 (19.0, 38.3)	35.0 (24.0, 52.0)	**< 0.001**	27.0 (18.0, 41.0)	35.0 (25.0, 53.0)	**< 0.001**	26.0 (18.0, 36.0)	35.0 (24.0, 52.0)	**< 0.001**
	Non-obese phenotypes								
	MeigsA			MeigsB			Wildman		
	MHNO ($n = 928$)	MUNO ($n = 444$)	p	MHNO ($n = 1036$)	MUNO ($n = 289$)	p	MHNO ($n = 800$)	MUNO ($n = 572$)	p
Age in years (median, IQR)	57.0 (54.0, 62.0)	61.0 (57.0, 66.0)	**< 0.001**	58.0 (54.0, 63.0)	60.0 (55.5, 64.0)	**0.002**	57.0 (54.0, 62.0)	61.0 (56.0, 65.0)	**< 0.001**
Male (n, %)	421 (45.4)	214 (48.2)	0.325	438 (42.3)	175 (60.6)	**< 0.001**	327 (40.9)	308 (53.8)	**< 0.001**
Primary education only (n, %)	204 (22.0)	128 (28.8)	**0.006**	234 (22.6)	80 (27.7)	0.072	158 (19.8)	174 (30.4)	**< 0.001**
Current smoker (n, %)	149 (16.1)	76 (17.1)	0.619	172 (16.6)	39 (13.5)	0.202	129 (16.1)	96 (16.8)	0.745
Heavy drinker (n, %)	88 (9.5)	47 (10.6)	0.521	98 (9.5)	32 (11.1)	0.415	68 (8.5)	67 (11.7)	**0.049**
Dietary quality (mean ± SD)	27.0 ± 5.5	26.8 ± 5.3	0.469	27.1 ± 5.5	26.1 ± 5.3	**0.007**	27.2 ± 5.5	26.5 ± 5.4	**0.02**
Low-level physical activity (n, %)	387 (41.7)	202 (45.5)	0.184	438 (42.3)	130 (45.0)	0.411	327 (40.9)	262 (45.8)	0.069

(Continues)

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TABLE 1 | (Continued)

	Non-obese phenotypes								
	MeigsA			MeigsB			Wildman		
	MHNO (n = 928)	MUNO (n = 444)	p	MHNO (n = 1036)	MUNO (n = 289)	p	MHNO (n = 800)	MUNO (n = 572)	p
Cardiovascular disease history (n, %)	49 (5.3)	66 (14.9)	**< 0.001**	77 (7.4)	32 (11.1)	**0.046**	48 (6.0)	67 (11.7)	< 0.001
BMI, kg/m^2 (mean ± SD)	25.6 ± 2.6	27.0 ± 2.3	**< 0.001**	25.6 ± 2.6	27.6 ± 1.9	**< 0.001**	25.5 ± 2.6	26.7 ± 2.5	**< 0.001**
WC, cm (mean ± SD)	89.3 ± 9.5	94.9 ± 9.5	**< 0.001**	89.6 ± 9.7	96.6 ± 8.3	**< 0.001**	89.0 ± 9.6	94.0 ± 9.5	**< 0.001**
FLI (median, IQR)	30.1 (15.4, 50.5)	53.6 (35.2, 71.7)	**< 0.001**	31.5 (16.2, 50.0)	61.8 (44.2, 76.8)	**< 0.001**	28.6 (14.8, 46.6)	52.5 (32.3, 71.4)	**< 0.001**
ALT, U/L (median, IQR)	21.0 (17.0, 27.0)	25.0 (19.0, 34.0)	**< 0.001**	21.0 (17.0, 27.0)	27.0 (22.0, 37.0)	**< 0.001**	21.0 (17.0, 26.0)	25.0 (19.0, 33.0)	**< 0.001**
AST, U/L (median, IQR)	24.0 (21.0, 28.0)	25.0 (21.0, 30.0)	**0.002**	24.0 (21.0, 28.0)	25.0 (21.0, 32.0)	**0.001**	24.0 (21.0, 28.0)	25.0 (22.0, 30.0)	**< 0.001**
ALP, U/L (median, IQR)	79.0 (67.0, 95.0)	84.0 (72.0, 98.3)	**0.001**	80.0 (68.0, 96.0)	85.0 (71.0, 96.0)	0.056	79.0 (67.0, 94.0)	84.0 (71.0, 99.0)	**< 0.001**
GGT, U/L (median, IQR)	23.0 (17.0, 33.0)	29.0 (20.0, 44.0)	**< 0.001**	23.0 (17.0, 32.5)	32.0 (23.0, 53.0)	**< 0.001**	22.0 (17.0, 31.0)	29.0 (20.0, 44.0)	**< 0.001**

Note: Categorical variables are presented as numbers (n) and percentages (%). Continuous values are presented as a mean ± one standard deviation (SD) or a median with interquartile range (IQR). The p values represent the MHO versus MUO and MHNO versus MUNO comparisons for each phenotype definition and were determined from a chi-square test, t-test or a Mann Whitney U. Significant p shown in bold.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; FLI, Fatty liver index; GGT, Gamma-glutamyl transferase; MHO, Metabolically healthy obese; MUO, Metabolically unhealthy obese; MHNO, Metabolically healthy nonobese; MUNO, Metabolically unhealthy nonobese; WC, Waist circumference.

TABLE 2 | Logistic regression analysis of associations between liver health indicators and the MHO phenotype.

		MeigsA		MeigsB		Wildman	
Liver health indicator	**Model**	**OR (95% CI)**	p	**OR (95% CI)**	p	**OR (95% CI)**	p
FLI	1	0.949 (0.937, 0.960)	**< 0.001**	0.950 (0.938, 0.962)	**< 0.001**	0.945 (0.933, 0.957)	**< 0.001**
	2	0.945 (0.932, 0.958)	**< 0.001**	0.953 (0.940, 0.965)	**< 0.001**	0.942 (0.929, 0.955)	**< 0.001**
	3	0.947 (0.934, 0.961)	**< 0.001**	0.952 (0.938, 0.966)	**< 0.001**	0.945 (0.931, 0.959)	**< 0.001**
ALT	1	0.986 (0.975, 0.998)	**0.02**	0.972 (0.960, 0.985)	**< 0.001**	0.976 (0.961, 0.990)	**0.001**
	2	0.984 (0.972, 0.997)	**0.014**	0.976 (0.964, 0.989)	**< 0.001**	0.977 (0.962, 0.992)	**0.003**
	3	0.984 (0.971, 0.998)	**0.02**	0.978 (0.965, 0.992)	**0.002**	0.979 (0.963, 0.995)	**0.01**
AST	1	0.990 (0.974, 1.005)	0.19	0.989 (0.975, 1.004)	0.157	0.983 (0.966, 1.001)	0.067
	2	0.990 (0.974, 1.005)	0.191	0.992 (0.977, 1.007)	0.29	0.985 (0.967, 1.003)	0.985
	3	0.992 (0.975, 1.009)	0.347	0.995 (0.980, 1.012)	0.579	0.988 (0.970, 1.007)	0.23
ALP	1	0.995 (0.989, 1.002)	0.159	1.000 (0.993, 1.006)	0.884	1.001 (0.994, 1.008)	0.858
	2	0.994 (0.987, 1.001)	0.096	0.996 (0.990, 1.003)	0.26	0.999 (0.992, 1.006)	0.782
	3	0.997 (0.990, 1.005)	0.466	0.995 (0.988, 1.003)	0.214	1.001 (0.993, 1.009)	0.847
GGT	1	0.990 (0.983, 0.996)	**0.003**	0.991 (0.985, 0.997)	**0.003**	0.985 (0.977, 0.994)	**0.001**
	2	0.990 (0.983, 0.997)	**0.004**	0.993 (0.987, 0.998)	**0.013**	0.987 (0.978, 0.995)	**0.002**
	3	0.993 (0.987, 1.000)	**0.042**	0.994 (0.987, 1.000)	**0.04**	0.991 (0.983, 0.999)	**0.035**

Note: Model 1: Unadjusted. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, education, smoking, alcohol use, dietary quality, physical activity and cardiovascular disease history. Binary logistic regression; models compare MHO to MUO for each phenotype definition. Odds ratios (OR) and 95% confidence intervals (CI) are shown. Significant p shown in bold.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FLI, Fatty liver index; GGT, Gamma-glutamyl transferase; MHO, Metabolically healthy obese.

demonstrated a higher OR for MUO consistently across each MH definition, with ORs and 95% CIs for MUO with the FLI being 1.173 (1.155, 1.191) [MeigsA], 1.172 (1.154, 1.191) [MeigsB], and 1.169 (1.152, 1.186) [Wildman] (all $p < 0.001$). GGT demonstrated stronger associations with both the MUNO and MUO groups than the MHO group across all three MH definitions. These

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TABLE 3 | Logistic regression analysis of associations between liver health indicators and the MHNO phenotype.

		MeigsA		MeigsB		Wildman	
Liver health indicator	**Model**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
FLI	1	0.966 (0.961, 0.971)	**< 0.001**	0.953 (0.946, 0.959)	**< 0.001**	0.964 (0.959, 0.969)	**< 0.001**
	2	0.957 (0.951, 0.963)	**< 0.001**	0.951 (0.944, 0.958)	**< 0.001**	0.961 (0.955, 0.967)	**< 0.001**
	3	0.957 (0.950, 0.964)	**< 0.001**	0.950 (0.942, 0.958)	**< 0.001**	0.961 (0.955, 0.968)	**< 0.001**
ALT	1	0.978 (0.969, 0.987)	**< 0.001**	0.955 (0.943, 0.966)	**< 0.001**	0.965 (0.955, 0.975)	**< 0.001**
	2	0.974 (0.964, 0.984)	**< 0.001**	0.957 (0.945, 0.968)	**< 0.001**	0.965 (0.954, 0.976)	**< 0.001**
	3	0.973 (0.962, 0.983)	**< 0.001**	0.959 (0.947, 0.971)	**< 0.001**	0.962 (0.951, 0.974)	**< 0.001**
AST	1	0.982 (0.971, 0.993)	**0.001**	0.973 (0.961, 0.985)	**< 0.001**	0.975 (0.964, 0.987)	**< 0.001**
	2	0.986 (0.975, 0.997)	**0.01**	0.977 (0.965, 0.989)	**< 0.001**	0.982 (0.971, 0.994)	**0.002**
	3	0.986 (0.975, 0.997)	**0.017**	0.979 (0.967, 0.991)	**0.001**	0.984 (0.973, 0.996)	**0.009**
ALP	1	0.993 (0.989, 0.998)	**0.003**	0.997 (0.992, 1.001)	0.128	0.992 (0.988, 0.996)	**< 0.001**
	2	0.994 (0.990, 0.999)	**0.01**	0.997 (0.992, 1.001)	0.147	0.993 (0.989, 0.997)	**0.001**
	3	0.995 (0.990, 0.999)	**0.018**	0.997 (0.992, 1.001)	0.178	0.993 (0.989, 0.998)	**0.004**
GGT	1	0.990 (0.986, 0.994)	**< 0.001**	0.987 (0.982, 0.991)	**< 0.001**	0.986 (0.981, 0.990)	**< 0.001**
	2	0.989 (0.985, 0.993)	**< 0.001**	0.988 (0.984, 0.992)	**< 0.001**	0.987 (0.982, 0.991)	**< 0.001**
	3	0.989 (0.984, 0.993)	**< 0.001**	0.987 (0.983, 0.992)	**< 0.001**	0.988 (0.983, 0.993)	**< 0.001**

Note: Model 1: Unadjusted. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, education, smoking, alcohol use, dietary quality, physical activity and cardiovascular disease history. Binary logistic regression; models compare MHNO to MUNO for each phenotype definition. Odds ratios (OR) and 95% confidence intervals (CI) are shown. Significant *p* shown in bold.
Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FLI, Fatty liver index; GGT, Gamma-glutamyl transferase; MHNO, Metabolically healthy nonobese.

TABLE 4 | Odds ratios for metabolic health phenotypes according to liver health indicators.

Liver health indicator	**MUNO compared to MHNO**		**MHO compared to MHNO**		**MUO compared to MHNO**	
MeigsA	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
FLI	1.044 (1.037, 1.052)	**< 0.001**	1.108 (1.094, 1.121)	**< 0.001**	1.173 (1.155, 1.191)	**< 0.001**
ALT	1.042 (1.031, 1.054)	**< 0.001**	1.043 (1.029, 1.056)	**< 0.001**	1.053 (1.042, 1.064)	**< 0.001**
AST	1.017 (1.005, 1.029)	**< 0.001**	1.017 (1.001, 1.032)	**< 0.001**	1.022 (1.011, 1.034)	**< 0.001**
ALP	1.006 (1.002, 1.011)	**0.007**	1.006 (1.000, 1.012)	0.055	1.008 (1.003, 1.012)	**0.001**
GGT	1.016 (1.011, 1.021)	**< 0.001**	1.012 (1.006, 1.018)	**< 0.001**	1.016 (1.011, 1.021)	**< 0.001**
MeigsB						
FLI	1.052 (1.044, 1.060)	**< 0.001**	1.112 (1.098, 1.126)	**< 0.001**	1.172 (1.154, 1.191)	**< 0.001**
ALT	1.058 (1.046, 1.070)	**< 0.001**	1.045 (1.031, 1.059)	**< 0.001**	1.062 (1.050, 1.073)	**< 0.001**
AST	1.025 (1.012, 1.038)	**< 0.001**	1.019 (1.005, 1.034)	**0.008**	1.022 (1.010, 1.035)	**< 0.001**
ALP	1.005 (0.999, 1.010)	0.083	1.005 (0.999, 1.010)	0.104	1.006 (1.002, 1.011)	**0.006**
GGT	1.017 (1.012, 1.022)	**< 0.001**	1.011 (1.006, 1.017)	**< 0.001**	1.016 (1.011, 1.021)	**< 0.001**
Wildman						
FLI	1.040 (1.033, 1.047)	**< 0.001**	1.103 (1.089, 1.117)	**< 0.001**	1.169 (1.152, 1.186)	**< 0.001**
ALT	1.051 (1.039, 1.063)	**< 0.001**	1.049 (1.033, 1.065)	**< 0.001**	1.064 (1.051, 1.076)	**< 0.001**
AST	1.019 (1.008, 1.032)	**0.001**	1.016 (0.997, 1.035)	0.093	1.026 (1.014, 1.038)	**< 0.001**
ALP	1.008 (1.004, 1.013)	**0.001**	1.010 (1.003, 1.016)	**0.004**	1.009 (1.004, 1.013)	**0.001**
GGT	1.017 (1.012, 1.023)	**< 0.001**	1.012 (1.005, 1.020)	**0.001**	1.018 (1.012, 1.023)	**< 0.001**

Note: Adjusted for age, sex, education, smoking, alcohol use, dietary quality, physical activity and cardiovascular disease history. Multinomial logistic regression; models compare MUNO, MHO and MUO to MHNO for each phenotype definition. Odds ratios (OR) and 95% confidence intervals (CI) are shown. Significant *p* shown in bold.
Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FLI, Fatty liver index; GGT, Gamma-glutamyl transferase; MHO, Metabolically healthy obese; MUO, Metabolically unhealthy obese; MHNO, Metabolically healthy nonobese; MUNO, Metabolically unhealthy nonobese.

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relationships also withstood sensitivity analyses which excluded participants who were classified as having heavy alcohol use (Supporting Information S1: Table S6), those with a cardiovascular disease history (Supporting Information S1: Table S9), and participants with a previous diagnosis of type 2 diabetes (Supporting Information S1: Table S12).

3.3 | Sex-Stratified Regression Analyses

The results of sex-stratified analyses suggest sex-specific MHO associations. In sex-stratified models (Supporting Information S1: Table S13), among male study participants living with obesity, FLI scores were also significantly inversely associated with the MHO phenotype in crude, partially and fully adjusted models, consistently for each of the three MH definitions. Among obese female participants, FLI scores, ALT, AST, and GGT were significantly inversely associated with the MHO phenotype in both crude and adjusted models, across the three MH definitions, except for AST (Model 3, Wildman MH definition; $p = 0.059$) and GGT (Model 3, MeigsB MH definition; $p = 0.087$). In sex-stratified models which examined nonobese subjects (Supporting Information S1: Table S14), FLI scores, ALT and GGT were inversely associated with the MHNO phenotype in both crude and adjusted models, across the three MH definitions, among both male and female participants.

The results from sex-stratified multinomial logistic regression analyses which compared MUNO, MHO and MUO to MHNO for each phenotype definition are examined Supporting Information S1: Table S15. Consistent with the results of the nonstratified analyses, FLI scores demonstrated a higher OR for MUO across each MH definition, with ORs and 95% CIs for MUO with the FLI being 1.201 (1.171, 1.232) [MeigsA], 1.193 (1.164, 1.223) [MeigsB], and 1.203 (1.174, 1.233) [Wildman] (all $p < 0.001$) among male subjects, and 1.154 (1.133, 1.176) [MeigsA], 1157 (1.134, 1.181) [MeigsB] and 1.146, (1.126, 1.167) [Wildman] (all $p < 0.001$), among female participants. In addition, as seen in the nonstratified models, GGT demonstrated stronger associations with both the MUNO and MUO groups than the MHO group across all three MH definitions, in both sexes.

4 | Discussion

This study aimed to investigate the relationships between MH phenotypes, across a range of definitions (MeigsA, MeigsB, and Wildman) and measures of liver health, focusing on the FLI and liver function biomarkers. In fully adjusted models, higher FLI scores, a strong non-invasive predictor of both liver steatosis and MASLD [32], were inversely associated with MHO, which was consistent across all MH definitions (all $p < 0.001$). Lower likelihood of MHO was also observed with higher GGT concentrations. Higher ALT concentrations were additionally associated with decreased odds of MH among obese subjects for each MH definition. Among participants without obesity, FLI scores, ALT, AST, and GGT were inversely associated with the MHNO phenotype in both crude and adjusted models, across the three MH definitions. Higher ALP levels were also associated with a lower likelihood of being MHNO according to the MeigsA and Wildman definitions. These results were largely robust to sensitivity analyses which excluded participants with heavy alcohol use, those with a cardiovascular disease history, and participants with a previous diagnosis of type 2 diabetes. Collectively these findings suggest that liver function indicators are linked with MH status in middle- to older-aged adults. Nevertheless, the cross-sectional design limits the ability to infer causality and temporality. Consequently, it is not possible to determine whether liver dysfunction leads to poor MH or vice versa.

Bedogni et al. originally developed the FLI, using data from 2287 subjects, as a non-invasive measure to predict hepatic steatosis based on BMI, WC, TG, and GGT levels [33]. Subsequently, the FLI has been shown to accurately predict the presence of fatty liver disease, with a high diagnostic accuracy, in several studies and populations [10–12]. In our research study, FLI scores were strongly and positively correlated with BMI. However, it is important to note that liver health risks are not exclusive to individuals with a higher BMI. Even those with a BMI < 25 can be metabolically unhealthy and at risk of liver disease. Results from a systematic review and meta-analysis by Jarvis et al. underscore the critical need for addressing both obesity and MH as risk factors for liver disease [34].

Our novel examination of MH phenotypes among adults with and without obesity revealed that FLI scores were consistently higher among metabolically unhealthy groups, regardless of BMI, suggesting greater liver stress or damage associated with poor MH. Participants with higher FLI scores were generally older, male, had higher BP and TG levels, lower HDL-C concentrations and greater insulin resistance. Therefore, it is not surprising that they had a lower likelihood of being MHO or MHNO, in particular considering that the FLI calculation relies on variables (e.g., WC and TG levels) which are themselves components of the metabolic syndrome, and which are included in some MH definitions. Nevertheless, the FLI has been validated [11], and our findings demonstrated higher FLI scores to be associated with increased liver enzyme concentrations. Our research study also revealed independent associations between MH phenotypes and ALT, AST, ALP, and GGT levels. Consequently, our results suggest that the FLI is an indicator of liver health, and also of overall metabolic health. Previous research studies have shown the predictive ability of the FLI for metabolic syndrome in adults without fatty liver [35]. In a further validation of the FLI in an elderly population, Koehler et al. confirmed its association with metabolic syndrome components including increased BMI, WC and insulin resistance [36]. Collectively, this body of evidence underscores the importance of the FLI as a comprehensive marker for assessing liver health and metabolic risk and highlights the value of its novel examination in MH phenotypes.

In our sample, higher ALT and GGT concentrations were linked with a lower likelihood of MH, in both participants with and without obesity. In a study of 2197 Chinese subjects, Xie et al. reported that higher ALT and GGT concentrations were significantly associated with the MUO phenotype [37]. Having a BMI > 25 was an inclusion criterion for that study, so the MHNO phenotype was not examined. Fraser et al. conducted a prospective cohort study that utilized data from the British Women's Heart and Health Study which included a total of 4209

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women aged 60–79 years [38]. They also carried out a meta-analysis on the associations between liver enzymes and incident diabetes which revealed elevated baseline levels of ALT and GGT to be associated with an increased risk of type 2 diabetes, with GGT identified as a better predictor [38]. This evidence supports both ALT and GGT as markers of metabolic dysregulation and aligns with our finding of a lower likelihood of being metabolically healthy among middle- to older-aged men and women with higher ALT and GGT levels.

It should be noted, however, that effect sizes were relatively modest in our study. This may be partly explained by our examination of the FLI and liver enzymes as continuous variables in regression models. Other studies have used predefined thresholds [13, 39] or quartiles [37], despite a loss of statistical power to detect relationships associated with their use. Nevertheless, as previously mentioned, metabolically healthy participants demonstrated a more favorable hepatic health profile as demonstrated by the FLI and ALT and GGT concentrations compared to their unhealthy counterparts, across MH definitions. However, it has been suggested that the presence of MASLD may predict conversion from the metabolically healthy to the metabolically unhealthy phenotype, despite the fact that patients may have an apparently normal MH profile, and that significant liver fibrosis appears to be lower in MHO individuals compared to MUO subjects [40]. Research studies have shown that individuals with MHO and MASLD display an elevated 10-year cardiovascular risk and a three-fold increased risk of incident diabetes compared to MHO without MASLD [41, 42]. Consequently, it has been proposed that there are strong synergistic interactions between obesity and metabolic risk factors in defining MASLD outcomes [40].

Based on findings that subjects with MHO and liver dysfunction have excess risk of developing metabolic abnormalities, even in the absence of diabetes, hypertension or dyslipidaemia [40, 41], Koliaki et al. advocate the screening of all subjects with MHO for the presence of MASLD [40]. The presence of MASLD has also been identified as an independent predictor of failure to restore MH, and convert from the MUO to the MHO phenotype, in the setting of a weight loss intervention [40, 43], perhaps indicating a greater need for pharmacological treatments, in addition to weight loss interventions, among MUO subjects with MASLD. Therefore, it has been suggested that there is a requirement to incorporate hepatic health assessment into the MH concept, and that liver health should always be assessed to fully characterize MH [40]. This might be achieved by means of abdominal ultrasound and non-invasive fibrosis risk stratification scores [40]. Liver enzymes are included in the Edmonton Obesity Staging System [44], and recently adopted guidelines in Ireland now recommend assessing liver health to determine the severity of a patient's obesity and guide clinical decision making [45].

Although subgroup analyses result in a loss of statistical power to detect relationships, our sex-stratified analyses suggest sex-specific associations between MH phenotypes and hepatic health indicators, with only FLI scores demonstrating significant differences between MHO/MUO phenotypes in male participants. The study by Xie et al. also found MUO relationships with ALT and GGT to be more consistent, and stronger, among females than males [37]. In a longitudinal research study using a sample of 31,000 adults, Man et el. observed a stronger association between the MHO phenotype and advanced MASLD in females [46]. In a cohort study of 77,425 men and women, Chang et al. noted that a strong progressive association between BMI and MASLD was more pronounced in women, and in all BMI subgroups examined, including participants with low inflammation status [47].

As previously discussed, liver health risks are not exclusive to individuals with a higher BMI, as some subjects display metabolic abnormalities in the absence of obesity. Interestingly, our study found that GGT demonstrated stronger associations with the MUNO and the MUO groups, both of similar magnitude, than the MHO group (when compared to MHNO subjects) across all MH definitions, and this relationship was also seen in sensitivity analyses which excluded heavy drinkers, those with a cardiovascular disease history or previous diagnosis of type 2 diabetes, and in sex-stratified models. In a prospective study of 3045 subjects, Lee et al. [48] found that although when compared to MHNO individuals (reference), subjects in the MUO group demonstrated the highest risk of NAFLD development over 4 years of follow-up (OR = 2.501; 95% CI: 1.699, 3.681), and participants classified as MUNO demonstrated higher odds of NAFLD (OR = 1.877; 95% CI: 1.412, 2.494) compared to those of the MHO group (OR = 1.731; 95% CI: 1.239, 2.419). It should be emphasized that the recently derived term, MASLD, is defined as steatotic liver disease in the presence of at least one of five cardiometabolic risk factors that correspond to the components of metabolic syndrome, which include obesity [49]. Importantly, findings from Lee et al., and our study, suggest that being metabolically unhealthy might be a greater contributor to the development of NAFLD than simply being obese, as defined by BMI. Differences observed support the consideration of MH phenotypes by healthcare providers, rather than relying solely on BMI to predict and manage the risks associated with fatty liver disease, and that risk assessment should not be restricted to individuals living with obesity. The recent EASL-EASD-EASO Clinical Practice Guidelines on the management of MASLD advocates a structured stepwise approach for predicting liver-related outcomes [50]. Thus, MUNO patients should be considered for liver fibrosis assessment (starting with blood-based biomarkers, followed by imaging techniques) and aggressive risk factor control, including treatment for insulin resistance, dyslipidaemia, and hypertension.

4.1 | Strengths and Limitations

Although there are no well-established criteria for defining MH, a strength of our study is the comprehensive assessment of MH phenotypes using multiple definitions. This allowed for comparative analysis and testing of consistency and robustness of the identified associations, contributing to a nuanced understanding of how these phenotypes relate to liver health indicators. However, there are a number of limitations to consider. The cross-sectional design limits the ability to infer causality and temporality. Consequently, as previously mentioned, it is not possible to determine whether liver dysfunction leads to poor MH or vice versa. In addition, because measurements were taken at a single time point, our study cannot evaluate changes or trends in MH

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status or liver function indicators over time. It is therefore limited in its ability to predict the stability of phenotypes or long-term liver disease risk. In addition, the study population, consisting of a sample of middle- to older-aged Irish men and women, although relatively large, may limit the applicability of findings to other ethnicities, age groups or geographic regions. Thus, given that MH phenotypes and hepatic indicators may differ by age, sex, ethnicity, and genetic background, replication studies which examine phenotypes by sex in diverse ethnic and geographic age groups are warranted.

It should also be noted that liver heath was based on non-invasive indices and biomarkers, rather than using more definitive techniques such as imaging or biopsy. Notably, the FLI is highly dependent on TG and WC measurements, which are themselves components of the metabolic syndrome and MH definitions. Genetic factors may also affect the relationship between MH and MASLD, as certain genes are thought to predispose to MASLD and can be synergistically affected by concurrent obesity [40]. However, genetic testing data were not available in our sample. In addition, personal medical histories were based on self-administered questionnaires instead of medical records. Although no study participant reported treatment or medication use for liver disease, unmeasured factors (such as undiagnosed liver disease or genetic factors) may still influence results. Furthermore, the reliance on self-reported data may introduce reporting and social desirability biases. Nonetheless, the consistency of associations observed across MH definitions, after extensive adjustment, provides evidence of the robustness of our findings.

5 | Conclusions

In conclusion, the results from this study highlight novel associations between liver health indicators and MH phenotypes among middle- to older-aged adults living with and without obesity. Although effect sizes were modest, differences observed support the consideration of MH phenotypes, rather than relying solely on BMI, to predict and manage the risks associated with fatty liver disease, potentially through tailored and targeted interventions which may include liver fibrosis assessment and treatment for insulin resistance, dyslipidaemia, and hypertension. However, the cross-sectional design, precluding definitive conclusions regarding causality and temporality, and reliance on non-invasive liver assessment, highlight areas for future research, including longitudinal studies with direct liver imaging or biopsy. In addition, as MH phenotypes and hepatic indicators may differ by age, sex, ethnicity, and genetic background, future research should include diverse age, ethnic and geographical populations, as well as analyses stratified by sex, to determine the generalizability of liver health indicators as markers of MH.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The dataset used and analyzed for the purpose of this study is available from the corresponding author on reasonable request.

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