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Original Research

Fatty liver index and atherogenic risk determined by lipoprotein particle subclasses: A cross-sectional study of middle- to older-aged adults

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KEYWORDS

Fatty Liver Index;
Lipoproteins;
Particles;
Subclasses;
Cardiovascular Disease

BACKGROUND: The fatty liver index (FLI) provides a cost-effective way to screen for metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD is associated with preclinical atherosclerosis, with cardiovascular disease (CVD) mortality being the leading cause of death among MASLD patients.

OBJECTIVE: Lipoprotein particles can provide better CVD risk prediction than traditional lipid measures. Yet, FLI associations with intermediate disease markers remain under-researched. This study addressed this gap by investigating FLI relationships with lipoprotein particle subclass concentrations.

METHODS: This was a cross-sectional study of 1713 middle-aged to older-aged men and women randomly selected from a large primary care center. The FLI was calculated using triglyceride, body mass index, waist circumference, and gamma-glutamyl transferase levels. Lipoprotein particle subclass concentrations and size were determined using nuclear magnetic resonance spectroscopy. Linear regression analyses examined FLI associations with lipoprotein biomarkers.

RESULTS: In fully adjusted models, higher FLI scores were associated with larger very low-density lipoprotein (VLDL) and smaller low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particle size, more large and medium VLDL, small LDL, and less large HDL particle concentrations, and greater lipoprotein-related insulin resistance (all $P < .001$). In models that examined these variable associations across FLI quintiles, significant dose-response relationships were observed (P trend $< .001$ for all).

CONCLUSION: These findings support the clinical utility of the FLI as a marker of atherogenic risk and as a tool for identifying at-risk individuals. Incorporating the FLI into CVD risk assessment may help improve risk prediction in individuals with liver disease and guide targeted interventions.

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Introduction

Metabolic-dysfunction-associated steatotic liver disease (MASLD), formerly called nonalcoholic fatty liver disease

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(NAFLD), is the most common chronic liver condition globally, affecting 16.1% of the population.¹ In addition to being the leading cause of liver disease worldwide, MASLD is associated with preclinical atherosclerosis, with cardiovascular disease (CVD) mortality being the leading cause of death among MASLD patients.² Although the exact pathophysiological mechanisms underlying MASLD are not fully understood, fatty liver disease is associated with an atherogenic pattern in conventional lipid profiles characterized by high triglyceride and low high-density lipoprotein (HDL) concentrations.³

However, although routine plasma lipid measurements are clinically used to assess MASLD and CVD risk and guide lipid treatment,⁴ evidence suggests that chronic noncommunicable disease risk is also influenced by lipoprotein particle subclass concentrations and particle size.^{5–7} In particular, smaller low-density lipoprotein (LDL) and HDL particles and increased numbers of very low-density lipoprotein (VLDL) particles are associated with atherosclerosis and CVD.^{8–11} Consequently, it has been suggested that nuclear magnetic resonance (NMR) spectroscopy, which quantifies the number and size of lipoprotein particles, could help identify key biomarkers that may inform the development of new treatment strategies that reduce MASLD incidence and related CVD mortality.¹²

The fatty liver index (FLI) is a surrogate marker of hepatic steatosis and provides a cost-effective way to screen for MASLD in large populations.¹³ Developed by Bedogni et al. based on triglyceride, body mass index (BMI), waist circumference (WC), and gamma-glutamyl transferase (GGT) levels,¹⁴ it is particularly useful in epidemiological studies and clinical settings where liver biopsy, the gold standard for diagnosing fatty liver, is not feasible.^{15,16} The FLI has been shown to accurately predict the presence of fatty liver disease, with a high diagnostic accuracy, in several studies and populations.^{13,15,17} Importantly, in addition to being an indicator of hepatic steatosis, it has been suggested that the FLI could have other potential clinical applications, as it may be a marker of different biochemical parameters and physiological processes.¹³

Although a number of studies have evaluated the spectrum of lipoprotein abnormalities in MASLD, some of these have been limited by small sample sizes,¹⁸ and to date, only 1 study of 173 subjects has examined FLI relationships with a range of lipoprotein biomarkers determined by NMR spectroscopy.³ Consequently, information on the accuracy of the FLI in discriminating NMR-assessed lipoprotein abnormalities is lacking. Therefore, this study examined FLI associations with lipoprotein particle concentrations and size, using a random sample of 1713 middle- to older-aged men and women. We hypothesized that higher FLI scores (indicating a greater likelihood of fatty liver) would be associated with less favorable lipoprotein particle subclass concentrations and a more proatherogenic profile.

Materials and methods

Study population and setting

The Mitchelstown Cohort was a single-center, cross-sectional study conducted between 2010 and 2011. Full details regarding the study design have been previously described.¹⁹ In brief, the study population was patients who attended the Living Health Clinic in Mitchelstown, County Cork, Ireland. Participants were randomly selected from all registered middle-aged to older-aged (46–70 years) attending patients, and a stratified sample was recruited. Of 3807 potential participants, following the exclusion of duplicates, deaths, and subjects incapable of consenting or attending an appointment, 3051 were invited to take part in the study. Of these, 2047 (49% male) completed the questionnaire and physical examinations of the baseline assessment (response of 67%). Participants were broadly similar to the local background population in terms of proportional age representation, marital status, and education, representing a low risk of selection bias. Previous research has indicated that approximately 98% of Irish adults are registered with a General Practitioner (GP) and that, even in the absence of a universal patient registration system, it is possible to perform population-based epidemiological studies that are representative using this sampling method.²⁰ After excluding participants without data available for each FLI component and at least 1 lipoprotein biomarker, and those who indicated heavy alcohol use (> 14 drinks per week²¹), the current analysis includes 1713 participants.

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 provided written consent to use their data for research purposes.

Data collection

A general health and lifestyle questionnaire (GHLQ) assessed demographic variables, lifestyle behaviors, and morbidity. These included details on age, sex (male or female), education, smoking status, alcohol consumption, and use of prescription medications. Physical activity details, including frequency, duration, and intensity, were collected using the validated short-form International Physical Activity Questionnaire (IPAQ).²² Diet was evaluated using a modified version of the self-completed European Prospective Investigation into Cancer and Nutrition (EPIC) food frequency questionnaire (FFQ),²³ which has been validated extensively in several populations.²⁴ Adapted to reflect the Irish diet, the 150-item semiquantitative 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 sample²⁵ and incorporated into the

SLÁN Irish National Surveys of Lifestyle Attitudes and Nutrition 1998, 2002 and 2007.²⁶ 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 12 to 42. Lower scores represent poorer and higher scores represent better quality diet.²⁷

Clinical procedures

Clinical measurements were performed by trained researchers with reference to a standard operating procedures manual. Height was measured with a portable Seca Leicester height/length stadiometer (Seca), and weight was measured using a portable electronic Tanita WB-100MA weighing scale (Tanita Corp). The weighing scale was placed on a firm, flat surface and was calibrated weekly. BMI ($\text{BMI} = \text{weight}(\text{kg}) / \text{height}(\text{m})^2$) was calculated from measured weight and height. WC, defined as midway between the lowest rib and the iliac crest, was measured in centimeters to 1 decimal place using a Seca 200 measuring tape (Seca, Birmingham, UK). The average of 2 measurements was used for analyses.

Biochemical measurements

Study participants attended the clinic in the morning after an overnight fast (of at least 8 hours), and blood samples were taken on arrival. Fasting glucose and glycated hemoglobin A_{1c} (HbA_{1c}) concentrations were measured in fresh samples by Cork University Hospital Biochemistry Laboratory using standardized procedures. Glucose concentrations were determined using a glucose hexokinase assay (Olympus Life and Material Science Europa Ltd), and HbA_{1c} levels were measured in the hematology laboratory on an automated high-pressure liquid chromatography instrument, Tosoh G7 (Tosoh HLC-723 (G7), Tosoh Europe N.V., Tessenderlo). Triglyceride, total cholesterol, LDL cholesterol, and HDL cholesterol concentrations were measured by Cork University Hospital Biochemistry Laboratory on Olympus 5400 biochemistry analyzers with Olympus reagents using standardized procedures and fresh samples (Olympus Diagnostica GmbH). Non-HDL

cholesterol concentrations were computed by subtracting HDL cholesterol concentrations from total cholesterol concentrations. GGT levels were determined using a spectrophotometric enzymatic assay on a Beckman Coulter AU5832 analyzer (Beckman Coulter Diagnostics Ltd).

Lipoprotein subclass particle concentrations and average VLDL, LDL, and HDL particle diameters were measured on serum specimens by *NMR LipoProfile* analysis at LipoScience, Inc using the LP3 algorithm,²⁸ as previously described in detail.²⁹ Subclasses were quantified based on the amplitudes of their spectroscopically distinct lipid methyl group NMR signals. Weighted-average VLDL, LDL, and HDL particle sizes (in nanometer diameter units) were computed as the sum of the diameter of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its NMR signal. The following subclass categories were investigated: total triglyceride-rich lipoproteins (TRL) (VLDL and chylomicrons, if present), large VLDL (> 60 nm), medium VLDL (42-60 nm), small VLDL (29-42 nm), intermediate-density lipoprotein (IDL) (23-29 nm), large LDL (20.5-23 nm), small LDL (18-20.5 nm), large HDL (9.4-14 nm), medium HDL (8.2-9.4 nm) and small HDL (7.3-8.2 nm). Particle concentrations are expressed as nanomoles per liter (VLDL and LDL) and micromoles per liter (HDL). Total non-HDL concentrations were calculated to approximate apolipoprotein B100 particle concentrations by summing TRL, IDL, and LDL particle concentrations.³⁰ A lipoprotein-related insulin resistance (LP-IR) score, ranging from 0 (least) to 100 (most) insulin resistant, which is a weighted combination of the 6 lipoprotein subclass and size parameters most closely associated with insulin resistance, was calculated.³¹

FLI

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.¹³ The FLI was calculated using the following formula:

$$\text{FLI} = (e^{0.953 \cdot \ln(\text{Triglycerides})} + 0.139 \cdot \text{BMI} + 0.718 \cdot \ln(\text{GGT}) + 0.053 \cdot \text{WC} - 15.745) / (1 + e^{0.953 \cdot \ln(\text{Triglycerides})} + 0.139 \cdot \text{BMI} + 0.718 \cdot \ln(\text{GGT}) + 0.053 \cdot \text{WC} - 15.745) \cdot 100$$

FLI scores ranged from 2.48 to 99.92. For descriptive analyses, the scores were also categorized as FLI < 30, 30 to 59, and ≥60, indicating low, intermediate, and high likelihood of fatty liver.

Covariates

Education was defined as “primary level only” and “secondary or higher.” Living arrangement was classified as “married/cohabiting” or “other.” 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: (1) nondrinker, ie, < 1 drink per week; (2) moderate drinker, ie, between 1 and 14 drinks per week. The definition of “moderate drinker” aligns with criteria from the EPIC study.²¹ 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. Use of lipid-lowering medications was defined as a binary (yes/no) variable as determined from participants’ responses to questions in the GHLQ. Type 2 diabetes was determined as a fasting glucose level ≥ 7.0 mmol/L or HbA_{1c} level $\geq 6.5\%$ (≥ 48 mmol/mol)³² or by self-reported diagnosis. The presence of CVD was obtained by asking study participants if they had been diagnosed with any of the following 7 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 indicated a diagnosis of any one of these conditions were classified as having CVD.

Statistical analysis

Descriptive characteristics were examined according to FLI quintiles. Categorical features are presented as numbers (n) and percentages (%), and continuous variables are shown as a mean $\pm$ SD, or a median and IQR for skewed data. Differences between quintiles 5 and 1 were analyzed using Pearson’s chi-square, Student’s *t*-test, or a Mann–Whitney U. Correlations between FLI scores, individual FLI components, and lipoprotein biomarkers were further examined using Spearman’s rank-order correlation. Linear regression was used to investigate associations between FLI scores (independent variable) and lipoprotein particle subclasses (dependent variables). Three models were run to test relationships: Model 1 was age and sex-adjusted, while Model 2 additionally adjusted for education, smoking, alcohol use, physical activity, and dietary intake (DASH score). A third model also adjusted for lipid-lowering medication use, type 2 diabetes, and CVD history.

To correct for the multiple testing performed, we calculated family-wise error rate *P* values in final models via the Romano-Wolf (RW) multiple hypothesis correction method using the **rwolf** command in Stata.³³ Partial *R*² values were also calculated in final models using the **pcorr** command in Stata. The partial *R*² values indicate how much variance in each dependent variable is explained by the FLI, and which is not explained by other variables in the model. For lipoprotein biomarkers that demonstrated significant relationships with the FLI in final models, we additionally assessed linear relationships using FLI quintiles, with the first quintile set as the reference category. We also conducted sensitivity linear regression analyses, which excluded study participants who indicated lipid-lowering medication use and those with type 2 diabetes and a CVD history. Sex-stratified analyses were also performed. Data analysis was conducted using Stata SE Version 13 (Stata Corporation) for Windows. For all analyses, a *P* value (2-

tailed) of less than 0.05 was considered to indicate statistical significance.

Results

Descriptive characteristics

Table 1 presents characteristics of the study sample stratified by FLI quintiles. Participants with higher FLI scores (quintile 5 compared to quintile 1) were older, more likely to be male, and to have been educated to a primary level only, had lower levels of physical activity, and poorer diet quality as indicated by lower DASH scores. Subjects with higher FLI scores were also more likely to be on lipid-lowering medications and to have type 2 diabetes and a CVD history. Significant differences in lipoprotein biomarker concentrations between quintiles 5 and 1 were also observed, with total TRL, large, medium, and small VLDL, total LDL, IDL, small LDL, small HDL, total non-HDL concentrations, and the LP-IR score, increasing across FLI quintiles. Conversely, plasma LDL cholesterol, HDL cholesterol, and large LDL and HDL size decreased across quintiles. According to FLI diagnostic thresholds, 43.3% (*n* = 741) of study participants had FLI scores ≥ 60 , indicating a high likelihood of fatty liver, while 28.1% (*n* = 481) had intermediate scores (30–60) and 28.7% (*n* = 491) had scores < 30, suggesting a low likelihood of fatty liver.

Correlation analyses

In correlation analyses (Fig 1), significant positive correlations between the FLI and lipoprotein biomarkers were observed for non-HDL cholesterol, total TRL, large, medium, and small VDL, total LDL, IDL, small LDL, small HDL, total non-HDL, VLDL particle size, and the LP-IR score. Negative correlations between the FLI and biomarkers were observed for plasma LDL and HDL cholesterol, total and large HDL, and both LDL and HDL particle size. Relationships between the FLI and lipoprotein biomarkers were stronger for HDL size and plasma HDL cholesterol, with medium and large VLDL, and the LP-IR score, showing the highest correlative strengths.

Regarding individual FLI components, significant correlations were observed with each lipoprotein biomarker, with exceptions noted for total HDL with GGT and triglyceride concentrations. In general, however, triglyceride correlations with lipoprotein biomarkers were stronger when compared to other FLI components.

Linear regression

The results from linear regression analyses, which examined relationships between standardized FLI scores and lipoprotein biomarkers, are presented in Table 2. In models that adjusted for age and sex, significant associations were

Table 1. Characteristics of the study sample stratified by FLI quintiles.

FLI quintiles (N = 1713)					
Variable	Q1	Q2	Q3	Q4	Q5
General					
Age in years (median, IQR)	57.0 (54.0, 63.0)	59.0 (55.0, 63.0)	60.0 (55.0, 64.0)	60.0 (55.0, 54.0)	60.0 (55.0, 64.0)
Male (n, %)	61 (17.8)	128 (37.3)	157 (45.9)	198 (57.9)	220 (64.1)
Primary education only (n, %)	59 (17.2)	76 (22.2)	94 (27.5)	103 (30.1)	106 (30.9)
Current smoker (n, %)	57 (16.6)	51 (14.9)	41 (12.0)	30 (8.8)	51 (14.9)
Moderate drinker (n, %)	156 (45.5)	144 (42.0)	145 (42.4)	169 (49.4)	148 (43.1)
Low level physical activity (n, %)	145 (42.3)	144 (42.0)	155 (45.3)	154 (45.0)	187 (54.5)
DASH score (mean, SD)	28.1 ± 5.4	27.5 ± 5.7	26.9 ± 5.5	26.9 ± 5.1	25.7 ± 4.8
Lipid-lowering medication use (n, %)	86 (25.1)	97 (28.3)	129 (37.7)	131 (38.3)	151 (44.0)
Type 2 diabetes (n, %)	8 (2.3)	15 (4.4)	21 (6.1)	37 (10.8)	73 (21.3)
Cardiovascular disease (n, %)	25 (7.3)	13 (3.8)	34 (9.9)	48 (14.0)	48 (14.0)
FLI component					
Triglycerides, mmol/L (median, IQR)	0.8 (0.7, 1.0)	1.0 (0.8, 1.3)	1.2 (0.9, 1.6)	1.5 (1.2, 1.9)	1.9 (1.4, 2.4)
BMI, kg/m ² (mean, SD)	23.3 ± 2.2	26.2 ± 2.0	28.1 ± 2.1	30.4 ± 2.5	34.5 ± 4.4
WC, cm (mean, SD)	80.2 ± 6.7	90.0 ± 5.9	96.2 ± 5.7	102.4 ± 6.5	112.7 ± 9.6
GGT, U/L (median, IQR)	18.0 (14.0, 23.0)	22.0 (17.0, 28.0)	26.0 (20.0, 34.0)	31.0 (23.0, 42.0)	43.0 (30.0, 65.0)
Plasma lipoproteins					
LDL cholesterol, mmol/L (mean ± SD)	3.24 ± 0.8	3.35 ± 0.9	3.25 ± 0.8	3.15 ± 0.9	2.99 ± 1.0
HDL cholesterol, mmol/L (mean ± SD)	1.74 ± 0.4	1.55 ± 0.3	1.44 ± 0.3	1.33 ± 0.3	1.23 ± 0.3
Non-HDL cholesterol, mmol/L (mean ± SD)	3.64 ± 0.8	3.84 ± 0.9	3.84 ± 0.9	3.86 ± 0.9	3.93 ± 1.0
Lipoprotein particle concentration					
Total TRL, nmol/L (median, IQR)	34.10 (21.9, 51.5)	43.30 (28.8, 66.6)	62.50 (40.0, 86.9)	70.50 (46.1, 96.3)	88.30 (56.4, 119.1)
Large VLDL, nmol/L (median, IQR)	0.50 (0.3, 0.7)	0.60 (0.3, 1.1)	0.80 (0.4, 1.9)	1.90 (0.7, 4.2)	3.60 (1.5, 7.8)
Medium VLDL, nmol/L (median, IQR)	8.70 (4.6, 15.9)	15.90 (7.7, 25.3)	21.00 (11.2, 36.2)	27.45 (17.7, 42.4)	38.60 (23.4, 59.0)
Small VLDL, nmol/L (median, IQR)	22.50 (12.9, 36.5)	25.70 (14.0, 43.7)	36.90 (21.8, 52.5)	37.00 (20.0, 55.9)	37.00 (22.9, 55.7)
Total LDL, nmol/L (mean ± SD)	1123.23 ± 327.3	1257.26 ± 377.63	1275.98 ± 392.5	1303.05 ± 410.8	1337.51 ± 461.8
IDL, nmol/L (median, IQR)	77.00 (44.0, 121.0)	92.00 (53.0, 152.0)	90.50 (50.0, 156.5)	95.00 (52.0, 160.0)	100.50 (45.3, 169.0)
Large LDL, nmol/L (mean ± SD)	791.58 ± 264.9	710.24 ± 287.3	597.87 ± 262.0	510.05 ± 255.6	425.26 ± 253.6
Small LDL, nmol/L (mean ± SD)	241.99 ± 270.8	437.88 ± 349.5	567.01 ± 381.6	680.9 ± 374.8	798.9 ± 424.7
Total HDL, μmol/L (mean ± SD)	39.02 ± 5.6	38.54 ± 5.6	38.17 ± 5.8	37.68 ± 6.0	36.80 ± 6.3
Large HDL, μmol/L (median, IQR)	10.70 (8.1, 13.6)	7.20 (5.3, 10.3)	6.00 (3.8, 8.4)	4.95 (3.3, 6.9)	3.90 (2.5, 5.9)
Medium HDL, μmol/L (mean ± SD)	12.82 ± 5.8	13.82 ± 5.8	13.00 ± 5.8	13.29 ± 5.8	13.16 ± 6.3
Small HDL, μmol/L (mean ± SD)	15.28 ± 5.9	16.71 ± 5.7	18.73 ± 5.3	18.88 ± 5.5	19.17 ± 5.8
Total non-HDL, μmol/L (mean ± SD)	1252.7 ± 357.1	1417.6 ± 408.2	1455.5 ± 437.2	1496.7 ± 439.7	1552.4 ± 509.9

(continued on next page)

Table 1. (Continued)

FLI quintiles (N = 1713)					
Variable	Q1	Q2	Q3	Q4	Q5
Lipoprotein particle size					
VLDL size, nm (mean $\pm$ SD)	41.90 $\pm$ 3.8	42.54 $\pm$ 4.5	43.18 $\pm$ 4.5	45.90 $\pm$ 5.4	48.43 $\pm$ 6.7
LDL size, nm (mean $\pm$ SD)	21.24 $\pm$ 0.4	21.07 $\pm$ 0.4	20.88 $\pm$ 0.5	20.72 $\pm$ 0.5	20.53 $\pm$ 0.6
HDL size, nm (mean $\pm$ SD)	9.74 $\pm$ 0.4	9.41 $\pm$ 0.5	9.21 $\pm$ 0.5	9.12 $\pm$ 0.4	9.04 $\pm$ 0.4
LP-IR score (median, IQR)	9.00 (4.5, 19.5)	23.00 (12.0, 33.0)	32.0 (19.0, 46.8)	44.00 (30.0, 57.0)	54.0 (39.8, 67.3)

Abbreviations: BMI, body mass index; DASH, dietary approaches to stop hypertension; FLI, fatty liver index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LP-IR, lipoprotein-related insulin resistance; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein; WC, waist circumference.

Note: *P* values determined from Pearson's chi-square, Student's *t*-test, or Mann-Whitney *U*, and compare Q5 to Q1. Significant *P* shown in **bold**.

observed between the FLI and 18 biomarkers and the LP-IR score. In models that additionally adjusted for education, smoking, alcohol use, physical activity, dietary intake, lipid-lowering medication use, type 2 diabetes, and CVD history, and after a multiple hypothesis correction, significant associations remained, with exceptions noted for plasma LDL cholesterol and total HDL. The highest partial R^2 values were seen for plasma HDL cholesterol (14.2%), small LDL (16.3%), HDL size (17.3%), large HDL (17.9%), medium and large VLDL (21.8% and 23.8%), and the LP-IR score (27.7%). In fully adjusted linear regression models, which examined variable associations across FLI quintiles (Fig 2), significant dose-response relationships were observed (P trend $< .001$ for all).

In sensitivity analyses that excluded study participants who indicated lipid-lowering medication use (Supplementary Table S1) and those with type 2 diabetes and a CVD history (Supplementary Table S2), relationships were largely the same. In sex-stratified analyses (Supplementary Table S3), findings were also in keeping with the main results. As observed in nonstratified analyses, the highest partial R^2 values were seen for plasma HDL cholesterol, small LDL, HDL size, large HDL, medium and large VLDL, and the LP-IR score, in both sexes.

Discussion

In this study, we examined FLI associations with lipoprotein subclasses using a random sample of 1713 middle-to older-aged adults. Study participants with higher FLI scores displayed a distinct metabolic profile characterized by larger VLDL and smaller LDL and HDL particle size, more large and medium VLDL, small LDL, and less large HDL particle concentrations, and greater LP-IR. These associations were robust to a range of adjustments and corrections for multiple testing. The results from sensitivity analyses, which excluded participants on lipid-lowering medications, those with type 2 diabetes and a CVD history, and sex-stratified models, were also broadly similar. In fully adjusted linear regression models, which examined variable associations across FLI quintiles, significant dose-response relationships were observed. These results support our hypothesis that higher FLI scores (indicating a greater likelihood of fatty liver) would be associated with less favorable lipoprotein particle subclass concentrations and a more proatherogenic profile. Subsequently, these findings support the clinical utility of the FLI as a marker of atherogenic risk and as a tool for identifying at-risk individuals.

As previously discussed, the FLI is a validated, surrogate measure used to estimate the presence of hepatic steatosis, serving as a cost-effective alternative to liver ultrasound or liver biopsy. Importantly, in addition to its role as an indicator of fatty liver, a recent review suggested that the FLI

Variable	FLI	Triglycerides	BMI	WC	GGT
	rho	rho	rho	rho	rho
Plasma lipoproteins					
LDL cholesterol	−0.119***	0.013	−0.132***	−0.132***	−0.052*
HDL cholesterol	−0.501***	−0.459***	−0.369***	−0.484***	−0.220***
Non-HDL cholesterol	0.087***	0.324***	−0.021	−0.014	0.072**
Lipoprotein particle concentration					
Total TRL	0.475***	0.840***	0.240***	0.268***	0.252***
Large VLDL	0.546***	0.596***	0.379***	0.386***	0.361***
Medium VLDL	0.540***	0.829***	0.337***	0.317***	0.303***
Small VLDL	0.229***	0.522***	0.068**	0.112***	0.098***
Total LDL	0.159***	0.253***	0.074**	0.117***	0.086***
IDL	0.098***	0.197***	0.059*	0.006	0.093***
Large LDL	−0.453***	−0.430***	−0.321***	−0.394***	−0.251***
Small LDL	0.465***	0.503***	0.304***	0.403***	0.251***
Total HDL	−0.137***	−0.039	−0.117***	−0.216***	−0.008
Large HDL	−0.542***	−0.519***	−0.387***	−0.496***	−0.290***
Medium HDL	−0.002	0.095***	−0.003	−0.094***	0.056*
Small HDL	0.250***	0.230***	0.171***	0.233***	0.131***
Total non-HDL	0.210***	0.350***	0.102***	0.136***	0.120***
Lipoprotein particle size					
VLDL size	0.428***	0.386***	0.322***	0.308***	0.294***
LDL size	−0.459***	−0.467***	−0.285***	−0.413***	−0.267***
HDL size	−0.488***	−0.476***	−0.346***	−0.440***	−0.266***
LP-IR score	0.648***	0.672***	0.445***	0.529***	0.394***

Figure 1. Heatmap illustrating correlative strengths between the FLI, FLI components, and lipoprotein particle subclasses. Values are presented as Spearman correlation coefficients (rho) between the FLI, individual FLI components, and lipoprotein subclasses among the Mitchelstown Cohort (N = 1713). In each row, the color green denotes weaker and red indicates stronger correlations. * $P < .05$; ** $P < .01$; *** $P < .001$. Abbreviations: BMI, body mass index; FLI, fatty liver index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LP-IR, lipoprotein-related insulin resistance; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein; WC, waist circumference.

may also serve as a marker of a number of metabolic diseases, in particular CVD.¹³ A number of prospective studies have shown the FLI to be associated with CVD, CVD mortality, and all-cause mortality. Using data on 502,536 adults aged 40 to 69 years from the UK Biobank database, Zou et al. found a significant association between FLI and incident CVD, including in subgroups stratified by BMI.³⁴ In a Korean longitudinal study of 505,763 participants with type 2 diabetes, Kim et al. found the FLI to be associated with higher risk of CVD and all cause death.³⁵ In research which also utilized UK Biobank data (N = 502,128), Li et al.³⁶ found the FLI to be an independent risk factor for sudden cardiac arrest in CVD-free adults.³⁶ Huang et al.³⁷ found that hazard ratios for CVD and mortality increased in accordance with FLI grading in a large prospective study of participants with hypertension, which sourced data from 2

cohorts (N = 12,907 and N = 120,639).³⁷ Consequently, given these findings, it has been proposed that the FLI should be incorporated into clinical practice in order to enhance early risk stratification and inform timely interventions in patients at risk of CVD.³⁸

Conventional lipid/lipoprotein abnormalities associated with fatty liver disease are well known, with the characteristic pattern demonstrating an increase in triglycerides and a decrease in plasma HDL cholesterol concentrations.³ Elevated triglyceride and low HDL levels are recognized risk factors for CVD. In particular, HDL cholesterol has consistently emerged as a predictor of CVD risk, with lower levels linked to higher myocardial infarction rates and CVD mortality.⁴ In our study, examination of lipoprotein subclasses also revealed inverse associations between the FLI and HDL particle size. This aligns with existing studies on

Table 2. Linear regression analyses showing FLI associations with lipoprotein particle subclasses.

Variable	Model 1				Model 2				Model 3			
	β	95% CI	P		β	95% CI	P		β	95% CI	P	Partial R ²
Plasma lipoproteins												
LDL cholesterol	-0.083	-0.127, -0.040	<.001		-0.074	-0.121, -0.027	.002		-0.004	-0.050, 0.041	.856	0.000
HDL cholesterol	-0.136	-0.151, -0.122	<.001		-0.135	-0.150, -0.119	<.001		-0.129	-0.145, -0.113	<.001	0.142
Non-HDL cholesterol	0.110	0.063, 0.156	<.001		0.115	0.065, 0.164	<.001		0.181	0.132, 0.230	<.001	0.034
Lipoprotein particle concentration												
Total TRL	0.313	0.283, 0.343	<.001		0.317	0.285, 0.349	<.001		0.317	0.284, 0.350	<.001	0.186
Large VLDL	0.686	0.633, 0.740	<.001		0.667	0.610, 0.724	<.001		0.654	0.595, 0.713	<.001	0.238
Medium VLDL	0.529	0.483, 0.574	<.001		0.528	0.479, 0.578	<.001		0.532	0.481, 0.583	<.001	0.218
Small VLDL	0.174	0.130, 0.218	<.001		0.183	0.136, 0.231	<.001		0.179	0.130, 0.228	<.001	0.033
Total LDL	63.002	43.194, 82.811	<.001		67.128	45.880, 88.375	<.001		87.759	66.557, 108.960	<.001	0.041
IDL	0.047	0.030, 0.063	<.001		0.050	0.033, 0.068	<.001		0.070	0.052, 0.087	<.001	0.038
Large LDL	-107.812	-120.642, -94.983	<.001		-108.026	-121.720, -94.332	<.001		-95.264	-109.031, -81.496	<.001	0.107
Small LDL	160.823	143.310, 178.336	<.001		165.134	146.391, 183.877	<.001		169.705	150.535, 188.875	<.001	0.163
Total HDL	-0.071	-0.351, 0.209	.618		-0.086	-0.376, 0.204	.56		-0.123	-0.416, 0.169	.408	0.000
Large HDL	-0.274	-0.300, -0.247	<.001		-0.278	-0.307, -0.250	<.001		-0.277	-0.307, -0.247	<.001	0.179
Medium HDL	0.637	0.351, 0.923	<.001		0.592	0.289, 0.896	<.001		0.691	0.380, 1.002	<.001	0.012
Small HDL	1.082	0.802, 1.362	<.001		1.125	0.829, 1.421	<.001		0.984	0.684, 1.284	<.001	0.026
Total non-HDL	93.795	72.166, 115.423	<.001		97.852	74.646, 121.057	<.001		121.712	98.596, 144.829	<.001	0.065
Lipoprotein particle size												
VLDL size	2.508	2.214, 2.802	<.001		2.358	2.049, 2.667	<.001		2.233	1.916, 2.551	<.001	0.127
LDL size	-0.194	-0.217, -0.172	<.001		-0.198	-0.222, -0.174	<.001		-0.189	-0.213, -0.164	<.001	0.129
HDL size	-0.202	-0.222, -0.181	<.001		-0.204	-0.227, -0.182	<.001		-0.208	-0.231, -0.185	<.001	0.173
LP-IR score	0.519	0.482, 0.557	<.001		0.516	0.476, 0.557	<.001		0.515	0.473, 0.557	<.001	0.277

Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LP-IR, lipoprotein-related insulin resistance; RW, Romano-Wolf; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, education, smoking, alcohol use, physical activity, and dietary intake.

Model 3: additionally adjusted for lipid-lowering medication use, type 2 diabetes, and cardiovascular disease history.

Beta (β) coefficients and 95% CI are shown. Total TRL, large VLDL, medium VLDL, small VLDL, IDL, large HDL, and the LP-IR score are log-transformed.

Note: Significant *p* shown in **bold**.

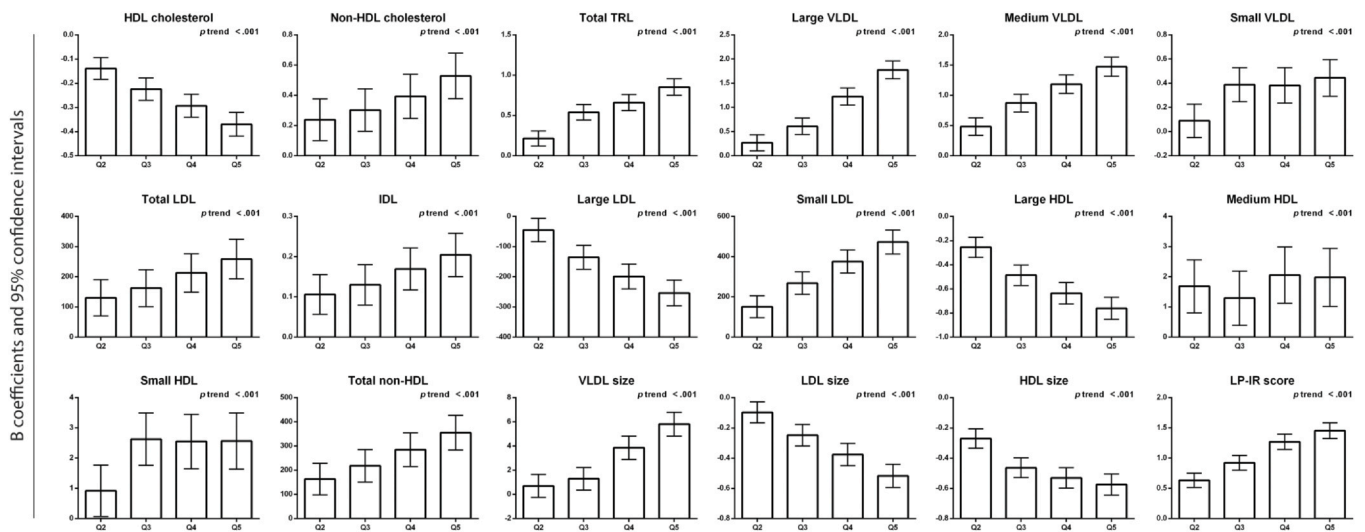


Figure 2. FLI quintile associations with lipoprotein particle subclasses. Quintile 1 is used as the reference category. All models adjusted for age, sex, education, smoking, alcohol use, physical activity, dietary intake, lipid-lowering medication use, type 2 diabetes, and cardiovascular disease history. Total TRL, large VLDL, medium VLDL, small VLDL, IDL, large HDL, and the LP-IR score are log-transformed. Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LP-IR, lipoprotein-related insulin resistance; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein.

HDL subclasses, which have demonstrated larger HDL particles to be inversely related to cardiovascular risk, as HDL cholesterol is primarily carried by large, buoyant, lipid-rich HDL particles.³⁹

Our study also found higher FLI scores to be related to larger VLDL and smaller LDL particle size and concentrations. Hepatic over-production of large triglyceride-rich VLDL may initiate diabetic dyslipidemia;^{40,41} large VLDL particles are elevated in those with insulin resistance and metabolic syndrome^{42,43} and have been found to be associated with atherosclerosis.¹¹ Large VLDL particles are also considered to be important in terms of CVD risk as they are associated with the proatherogenic small dense LDL phenotype.¹¹ Importantly, increased VLDL particle size and concentrations are believed to prevent lipoprotein lipase-mediated clearance of VLDL triglycerides, thereby producing triglyceride-rich lipoprotein remnants.⁴⁴ Hepatic lipases hydrolyze these remnant particles, producing small, dense lipoprotein particles.¹⁸ Small, dense LDL particles have been linked with angiographically defined coronary artery disease and a 3-fold increased risk of myocardial infarction, independent of age, sex, and weight.^{45,46} The European Society of Cardiology recommends considering LDL subclasses, such as small LDL particles, besides overall LDL cholesterol levels, for managing patients with CVD.⁴⁷ LDL subclasses may also serve as useful biomarkers to identify individuals at risk of CVD.⁴⁸

Interestingly, our study found the FLI to show the highest partial R^2 value for the LP-IR score, a relationship that was also observed in sex-stratified analyses. The LP-IR score is a weighted index of VLDL, LDL and HDL particle sizes and large VLDL, small LDL and large HDL particle concentrations that has been shown to be more strongly related to insulin resistance than each of its individual

subclasses.⁴⁹ This score has been found to be associated with mortality in heart failure patients.⁵⁰ In a study of 28,024 women, the LP-IR score showed the highest standardized risk for incident coronary heart disease (CHD) across most age groups (adjusted hazard ratio = 6.40; 95% CI: 3.14, 13.06) for CHD onset before age 55 (attenuating with age), surpassing LDL cholesterol levels, standard lipids, and inflammatory markers.⁵¹

Collectively, the results from this research further confirm that a greater likelihood of fatty liver disease, as characterized by the FLI, is associated with a more proatherogenic risk profile determined by NMR spectroscopy. These results are in agreement with findings from previous studies that have characterized fatty liver disease by the FLI,³ liver biopsy,^{18,52} and CT-diagnosed NAFLD,⁵³ and suggest that observed associations between the FLI and CVD risk and mortality are partially mediated through the lipoprotein particle subclass biomarkers examined. Fatty liver disease has historically been under-recognized as a major health concern as the condition is largely asymptomatic.^{54,55} Importantly, our finding of a graded, dose-response relationship between FLI scores and lipoprotein subclass biomarker concentrations suggests that incorporating the FLI into CVD risk assessment may help improve risk prediction in individuals with liver disease and guide targeted interventions. In Ireland, recently adopted guidelines now advocate assessing liver health to determine the severity of a patient's obesity in order to inform clinical decision-making.⁵⁶ This is in line with recommendations that liver health should always be assessed to fully characterize metabolic health.⁵⁷

This study has several strengths. With the elderly population growing, it is to be expected that the number of individuals with noncommunicable diseases will increase.⁵⁸

Research on risk indices, such as the FLI, is important for public health in terms of providing better insights into disease causation and for informing clinical decision-making. Our study is pioneering in its assessment of associations between the FLI and a comprehensive range of lipoprotein particle subclasses determined from NMR spectroscopy. Other strengths include the relatively large number of study participants and the use of validated questionnaires to collect data. Furthermore, to address the potential issue of multiple testing, we applied a stringent RW multiple hypothesis correction.³³

Our study's primary limitation is its cross-sectional nature. Because measurements were taken at a single time point, this research cannot evaluate changes in MASLD status and lipoprotein particle subclasses, or relationships between FLI scores and lipoprotein biomarkers, over time. In addition, the study population, consisting of a representative 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. Importantly, although previous research that has characterized fatty liver disease through hepatic biopsy lends substantial credibility to the current work,^{18,52} replication studies in diverse cohorts are needed to confirm our findings. It should also be noted that personal medical histories were based on self-administered questionnaires instead of medical records. While no study participant indicated treatment or medication use for liver disease, unmeasured factors may still influence results. Furthermore, the reliance on self-reported data may introduce reporting and social desirability biases. Nonetheless, the consistency of the associations observed, after extensive adjustment, provides evidence of the robustness of our findings.

In conclusion, the results from this research demonstrate that individuals with higher FLI scores display a distinct metabolic profile characterized by larger VLDL and smaller LDL and HDL particle size, more large and medium VLDL, small LDL, and less large HDL particle concentrations, and greater LP-IR. Significant dose-dependent associations were also observed. These findings support the clinical utility of the FLI as a marker of atherogenic risk and as a tool for identifying at-risk individuals in middle- to older-aged populations. Incorporating the FLI into CVD risk assessment may help improve risk prediction in individuals with liver disease and guide targeted interventions.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study was performed in compliance with relevant laws, regulatory frameworks, and guidelines where the research took place. This study was approved by the Clinical

Research Ethics Committee of University College Cork. (Approval No. ECM4(aa)02/02/10).

CRedit authorship contribution statement

Seán R. Millar: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Ivan J. Perry:** Funding acquisition. **Catherine M. Phillips:** Conceptualization.

Ethical approval

Ethics committee approval conforming to the Declaration of Helsinki was obtained from the Clinical Research Ethics Committee of University College Cork. All participants provided written consent to use their data for research purposes.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tool has been used in the writing process.

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Declaration of competing interest

No competing interests exist.

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Data availability

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

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jacl.2026.09.007.

References

- Kim S, Oh J, Shin JI, et al. Global burden of metabolic dysfunction-associated steatotic liver disease, 1990–2023, and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2023. *Lancet Gastroenterol Hepatol*. 2026;11:463–494.
- Shafiq A, Rashid AM, Shah SR, Chew NW, Haverkamp W. MASLD and cardiovascular disease: a state-of-the-art review. *Glob Cardiol*. 2026. Available: <https://www.globalcardiology.info/site/article/view/94/221>.
- Amor AJ, Pinyol M, Sola E, et al. Relationship between noninvasive scores of nonalcoholic fatty liver disease and nuclear magnetic resonance lipoprotein abnormalities: a focus on atherogenic dyslipidemia. *J Clin Lipidol*. 2017;11:551–561.e557.
- Dayimu A, Wang C, Li J, et al. Trajectories of lipids profile and incident cardiovascular disease risk: a longitudinal cohort study. *J Am Heart Assoc*. 2019;8:e013479.
- Kontush A. HDL particle number and size as predictors of cardiovascular disease. *Front Pharmacol*. 2015;6:218.
- Duparc T, Ruidavets J-B, Genoux A, et al. Serum level of HDL particles are independently associated with long-term prognosis in patients with coronary artery disease: the GENES study. *Sci Rep*. 2020;10:8138.
- Mora S, Szklo M, Otvos JD, et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211–217.
- Carmena R, Duriez P, Fruchart J-C. Atherogenic lipoprotein particles in atherosclerosis. *Circulation*. 2004;109:III2-7.
- Superko H, Garrett B. Small dense LDL: scientific background, clinical relevance, and recent evidence still a risk even with ‘normal’ LDL-C levels. *Biomedicines*. 2022;10:829.
- Arsenault BJ, Lemieux I, Després J-P, et al. HDL particle size and the risk of coronary heart disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Atherosclerosis*. 2009;206:276–281.
- Garvey WT, Kwon S, Zheng D, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003;52:453–462.
- Flores YN, Amoon AT, Su B, et al. Serum lipids are associated with nonalcoholic fatty liver disease: a pilot case-control study in Mexico. *Lipids Health Dis*. 2021;20:136.
- Kaneva AM, Bojko ER. Fatty liver index (FLI): more than a marker of hepatic steatosis. *J Physiol Biochem*. 2024;80:11–26.
- Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. 2006;6:1–7.
- Lonardo A, Ballestri S, Bedogni G, Bellentani S, Tiribelli C. The fatty liver index (FLI) 15 years later: a reappraisal. *Metab Target Organ Damage*. 2021;1:1–20.
- Dolan G, Millar SR, Perry IJ, Phillips CM. Metabolic health phenotypes among middle-to older-aged adults living with and without obesity: relationships with hepatic health indicators. *Hepatol Res*. 2026;56:302–313.
- Carli F, Sabatini S, Gaggini M, Sironi AM, Bedogni G, Gastaldelli A. Fatty liver index (FLI) identifies not only individuals with liver steatosis but also at high cardiometabolic risk. *Int J Mol Sci*. 2023;24:14651.
- Siddiqui MS, Fuchs M, Idowu MO, et al. Severity of nonalcoholic fatty liver disease and progression to cirrhosis are associated with atherogenic lipoprotein profile. *Clin Gastroenterol Hepatol*. 2015;13:1000–1008. e1003.
- Kearney PM, Harrington JM, Mc Carthy VJ, Fitzgerald AP, Perry IJ. Cohort profile: the Cork and Kerry diabetes and heart disease study. *Int J Epidemiol*. 2013;42:1253–1262.
- Hinchion R, Sheehan J, Perry I. Primary care research: patient registration. *Ir Med J*. 2002;95:249.
- Khaw K-T, Wareham N, Bingham S, et al. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med*. 2008;5:e12.
- Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381–1395.
- Riboli E, Elmståhl S, Saracci R, Gullberg B, Lindgärde F. The Malmö food study: validity of two dietary assessment methods for measuring nutrient intake. *Int J Epidemiol*. 1997;26:S161.
- Bingham SA, Gill C, Welch A, et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol*. 1997;26:S137.
- Harrington J. Validation of a food frequency questionnaire as a tool for assessing nutrient intake. *NUI Galway* 1997.
- Harrington J, Perry I, Lutonski J, et al. SLÁN 2007: Survey of Lifestyle, Attitudes and Nutrition in Ireland. Dietary Habits of the Irish Population. Department of Health and Children; 2008.
- Harrington JM, Fitzgerald AP, Kearney PM, et al. DASH diet score and distribution of blood pressure in middle-aged men and women. *Am J Hypertens*. 2013;26:1311–1320.
- Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clin Lab Med*. 2006;26:847–870.
- Elliott PS, Harrington JM, Millar SR, Otvos JD, Perry IJ, Phillips CM. Plant-based diet indices and lipoprotein particle subclass profiles: a cross-sectional analysis of middle- to older-aged adults. *Atherosclerosis*. 2023;380:117190.
- Delatour V, Clouet-Foraison N, Gaie-Levrel F, et al. Comparability of lipoprotein particle number concentrations across ES-DMA NMR, LC-MS/MS, immunonephelometry, and VAP: in search of a candidate reference measurement procedure for apoB and non-HDL-P standardization. *Clin Chem*. 2018;64:1485–1495.
- Shalaurova I, Connelly MA, Garvey WT, Otvos JD. Lipoprotein insulin resistance index: a lipoprotein particle-derived measure of insulin resistance. *Metab Syndr Relat Disord*. 2014;12:422–429.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36:S67–74.
- Clarke D., Romano J.P., Wolf M. The Romano-Wolf Multiple Hypothesis Correction in Stata. Available: <https://www.iza.org/publications/dp/12845/the-romano-wolf-multiple-hypothesis-correction-in-stata>.
- Zou B, Yeo YH, Cheung R, Ingelsson E, Nguyen MH. Fatty liver index and development of cardiovascular disease: findings from the UK biobank. *Dig Dis Sci*. 2021;66:2092–2100.
- Kim K-S, Hong S, Han K, Park C-Y. Association of non-alcoholic fatty liver disease with cardiovascular disease and all cause death in patients with type 2 diabetes mellitus: nationwide population based study. *BMJ*. 2024;384:e076388.
- Li L, Su S, Hu Z, et al. Fatty liver index increases the risk of sudden cardiac arrest in cardiovascular disease-free adults. *Heart Rhythm*. 2025;23:e1112–1121.
- Huang Y, Wan T, Hong Y, et al. Impact of NAFLD and fibrosis on adverse cardiovascular events in patients with hypertension. *Hypertension*. 2025;82:1012–1023.
- Kim BS, Kim H-J, Kim H, et al. Hepatic steatosis in cardiovascular-kidney-metabolic syndrome: fatty liver Index as a predictor of cardiovascular outcomes. *Eur J Prev Cardiol*. 2025;zwaf396.
- Kontush A. HDL particle number and size as predictors of cardiovascular disease. *Front Pharmacol*. 2015;6:218.

40. Klop B, Elte J, Cabezas M. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients*. 2013;5:1218–1240.
41. Gill J, Sattar N. Hepatic VLDL overproduction: is hyperinsulinemia or insulin resistance the culprit? *J Clin Endocrinol Metab*. 2011;96:2032–2034.
42. Goff Jr DC, D'Agostino Jr RB, Haffner SM, Otvos JD. Insulin resistance and adiposity influence lipoprotein size and subclass concentrations. Results from the insulin resistance atherosclerosis study. *Metabolism*. 2005;54:264–270.
43. Frazier-Wood AC, Glasser S, Garvey WT, et al. A clustering analysis of lipoprotein diameters in the metabolic syndrome. *Lipids Health Dis*. 2011;10:1–8.
44. Packard C. Triacylglycerol-rich lipoproteins and the generation of small, dense low-density lipoprotein. *Biochem Soc Trans*. 2003;31:1066–1069.
45. Hulthe J, Bokemark L, Wikstrand J, Fagerberg B. The metabolic syndrome, LDL particle size, and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2000;20:2140–2147.
46. Sacks FM, Campos H. Low-density lipoprotein size and cardiovascular disease: a reappraisal. *J Clin Endocrinol Metab*. 2003;88:4525–4532.
47. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
48. Chary A, Tohidi M, Hedayati M. Association of LDL-cholesterol subfractions with cardiovascular disorders: a systematic review. *BMC Cardiovasc Disord*. 2023;23:533.
49. Shalaurova I, Connelly MA, Garvey WT, Otvos JD. Lipoprotein insulin resistance index: a lipoprotein particle-derived measure of insulin resistance. *Metab Syndr Relat Disord*. 2014;12:422–429.
50. Turecamo S, Downie CG, Wolska A, et al. Lipoprotein insulin resistance score and mortality risk stratification in heart failure. *Am J Med*. 2024;137:640–648.
51. Dugani SB, Moorthy MV, Li C, et al. Association of lipid, inflammatory, and metabolic biomarkers with age at onset for incident coronary heart disease in women. *JAMA Cardiol*. 2021;6:437–447.
52. Sonmez A, Nikolic D, Dogru T, et al. Low-and high-density lipoprotein subclasses in subjects with nonalcoholic fatty liver disease. *J Clin Lipidol*. 2015;9:576–582.
53. DeFilippis AP, Blaha MJ, Martin SS, et al. Nonalcoholic fatty liver disease and serum lipoproteins: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2013;227:429–436.
54. Wissel S, Scharnagl H, Kleber ME, et al. Fatty liver-index, systemic inflammation and cardiovascular mortality. Results from the LURIC study. *Atherosclerosis* 2025;120557.
55. Mladenić K, Lenartić M, Marinović S, Polić B, Wensveen FM. The “Domino effect” in MASLD: the inflammatory cascade of steatohepatitis. *Eur J Immunol*. 2024;54:2149641.
56. Breen C, O'Connell J, Geoghegan J, et al. Obesity in adults: a 2022 adapted clinical practice guideline for Ireland. *Obes Facts*. 2022;15:736–752.
57. Koliaki C, Dalamaga M, Kakounis K, Liatis S. Metabolically healthy obesity and metabolic dysfunction-associated steatotic liver disease (MASLD): navigating the controversies in disease development and progression. *Curr Obes Rep*. 2025;14:1–13.
58. World Health Organization. Global Health and Aging. World Health Organization; 2011.