Research Article
NAFLD and Alcohol-Related Liver Diseases

JOURNAL OF HEPATOLOGY

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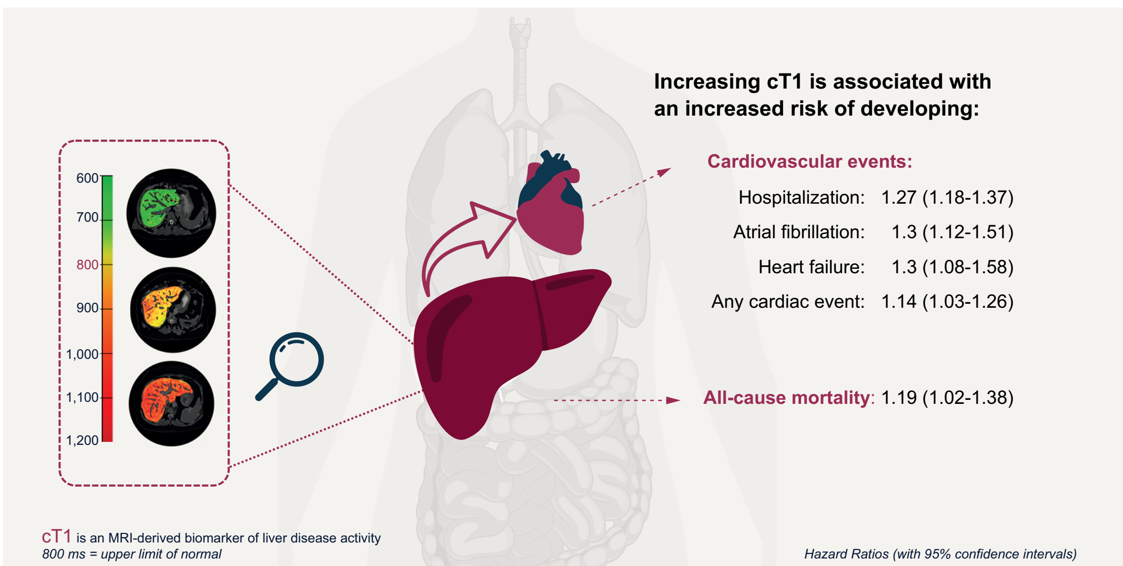
Graphical abstract



Highlights

- Liver disease on cT1 MRI is associated with a high risk of CVD events, CVD-related hospitalization, and all-cause mortality.
- The association between liver disease on cT1 and CVD is independent of liver function tests, fibrosis and metabolic risk.
- Risk of CVD events is increased even in the early stages of chronic liver disease.

Impact and implications

Chronic liver disease (CLD) is associated with a twofold greater incidence of cardiovascular disease. Our work shows that early liver disease on iron-corrected T1 mapping was associated with a higher risk of major cardiovascular disease (14%), cardiovascular disease hospitalisation (27%) and all-cause mortality (19%). These findings highlight the prognostic relevance of a comprehensive evaluation of liver health in populations at risk of CVD and/or CLD, even in the absence of clinical manifestations or metabolic syndrome, when there is an opportunity to modify/address risk factors and prevent disease progression. As such, they are relevant to patients, carers, clinicians, and policymakers.

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Liver disease is a significant risk factor for cardiovascular outcomes – A UK Biobank study

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Background & Aims: Chronic liver disease (CLD) is associated with increased cardiovascular disease (CVD) risk. We investigated whether early signs of liver disease (measured by iron-corrected T1-mapping [cT1]) were associated with an increased risk of major CVD events.

Methods: Liver disease activity (cT1) and fat (proton density fat fraction [PDFF]) were measured using LiverMultiScan® between January 2016 and February 2020 in the UK Biobank imaging sub-study. Using multivariable Cox regression, we explored associations between liver cT1 (MRI) and primary CVD (coronary artery disease, atrial fibrillation [AF], embolism/vascular events, heart failure [HF] and stroke), and CVD hospitalisation and all-cause mortality. Liver blood biomarkers, general metabolism biomarkers, and demographics were also included. Subgroup analysis was conducted in those without metabolic syndrome (defined as at least three of: a large waist, high triglycerides, low high-density lipoprotein cholesterol, increased systolic blood pressure, or elevated haemoglobin A1c).

Results: A total of 33,616 participants (mean age 65 years, mean BMI 26 kg/m^2, mean haemoglobin A1c 35 mmol/mol) had complete MRI liver data with linked clinical outcomes (median time to major CVD event onset: 1.4 years [range: 0.002-5.1]; follow-up: 2.5 years [range:1.1-5.2]). Liver disease activity (cT1), but not liver fat (PDFF), was associated with higher risk of any major CVD event (hazard ratio 1.14; 95% CI 1.03–1.26; p = 0.008), AF (1.30; 1.12–1.51; p <0.001); HF (1.30; 1.09–1.56; p = 0.004); CVD hospitalisation (1.27; 1.18-1.37; p <0.001) and all-cause mortality (1.19; 1.02–1.38; p = 0.026). FIB-4 index was associated with HF (1.06; 1.01–1.10; p = 0.007). Risk of CVD hospitalisation was independently associated with cT1 in individuals without metabolic syndrome (1.26; 1.13-1.4; p <0.001).

Conclusion: Liver disease activity, by cT1, was independently associated with a higher risk of incident CVD and all-cause mortality, independent of pre-existing metabolic syndrome, liver fibrosis or fat.

Introduction

Over the past decade, the incidence of chronic liver disease (CLD) related to non-alcoholic/metabolic dysfunction-associated fatty liver disease (NAFLD/MAFLD) has been increasing. NAFLD, affecting 25% of the population globally, is now the principal driver of cirrhosis, hepatocellular cancer and liver transplantation.[1,2] Multiple non-invasive biomarkers for both early and late stage CLD have been associated with liver-related outcomes[3,4] and adopted in drug efficacy trials[5–8] and clinical practice.[9–11] However, cardiovascular disease (CVD) is a leading cause of death in patients with NAFLD.[12,13] Coronary artery disease (CAD), arrhythmias, and stroke are more common in patients with CLD.[14] Guideline recommendations include CVD screening in CLD.[10,15,16] However, specific risk score-based treatment algorithms are lacking,[10] partly due to the unclear mechanisms behind the increased CVD risk in patients with NAFLD, which could be inflammatory,[17] metabolic or immune-mediated. A recent electronic health record study in over four million adults reported increased BMI ≥30, type 2 diabetes, hypertension, and chronic kidney disease, all associated with CVD risk across a range of liver diseases (NAFLD, alcohol-related liver disease, viral and autoimmune hepatitis), as well as serum/plasma-based markers of inflammation such as C-reactive protein. However, abnormalities in conventional liver biochemistry (*e.g.* bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST] and gamma-glutamyltransferase [GGT]), were not associated with CVD risk.[14] Various biochemistry-based risk scores have been incorporated into

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clinical assessment, such as AST/ALT ratio (commonly used to differentiate causes of liver damage), fibrosis-4 index (FIB-4) (for initial screening for liver fibrosis)[9,10,18,19] and NAFLD fibrosis score; all these biomarkers predict liver-related outcomes (such as cirrhosis, liver transplant and hepatocellular carcinoma).[20] These biomarkers are independent predictors,[21] or associated[22] with major adverse CVD events, but have only been tested in populations with established liver disease. Risk stratification for early, asymptomatic liver disease and CVD outcomes still requires further investigation.[23]

Quantitative medical imaging biomarkers have gathered momentum in both CVD and CLD, as they are non-invasive, allow for whole organ assessment and are inherently organ-related. MRI-derived cardiac T1-mapping has been associated with cardiomyopathies (including diffuse fibrosis[24] and myocarditis[25]), resulting in inclusion in clinical guidelines.[26] In the liver, iron-corrected T1 mapping (cT1) is a marker of CLD activity, which has been shown to correlate with parenchymal ballooning, inflammation and fibrosis[27] and has been associated with histological disease activity in steatohepatitis,[28] and in viral[29] and autoimmune hepatitis.[30] cT1 has been shown to predict liver-related outcomes in CLD.[4] cT1 has since been recognised by gastroenterology and endocrinology guidelines as a tool for the assessment of NAFLD.[10,31] Recently, cT1 has been used to elucidate mechanisms of liver inflammation, namely clonal haematopoiesis.[32] Proton density fat fraction (PDFF) is a biomarker of liver fat that can stratify all grades of liver steatosis; used clinically for patient screening and as a clinical trial endpoint,[7,9,33] but not reported to be associated with clinical events.

The UK Biobank is a large-scale UK biomedical database investigating development of disease, exploring both genetic predisposition, and environmental exposure.[34] We sought to explore associations between the liver and cardiovascular clinical outcomes using this resource. We investigated: i) associations between established non-invasive (blood and imaging) CLD biomarkers and CVD outcomes, ii) how these associations related to CLD characteristics and iii) whether associations with CVD events were independent from associated metabolic disease.

Patients and methods

The UK Biobank imaging sub-study is an ongoing investigation to scan the brains, hearts, bones and abdomens of 100,000 of the 502,506 UK Biobank participants.[35] A retrospective analysis of all available data, acquired between January 2016 and February 2020 was performed. UK Biobank has approval from the Northwest Multi-Centre Research Ethics Committee (MREC) and obtained written informed consent from all participants prior to the study. Data were extracted under access application 9914. Some of the authors (AR-F, RB, CM, and AD) had access to all data through this application and take responsibility for the content of this manuscript. Patients and the public were involved at every stage of the conception and design of the UK Biobank. Patients with CLD contributed to this article and the patient impact of this research.

Study population

Inclusion criteria were complete liver image-derived phenotypes for liver fat (PDFF, %) and disease activity (cT1, milliseconds) from the abdominal imaging protocol. The CONSORT diagram is shown in Fig. 1.

There were no exclusion criteria. Patient meta-data including demographic information at the time of the scan were available. Cardiometabolic risk factors and metabolic blood biomarkers associated with CLD were collected at baseline assessment.

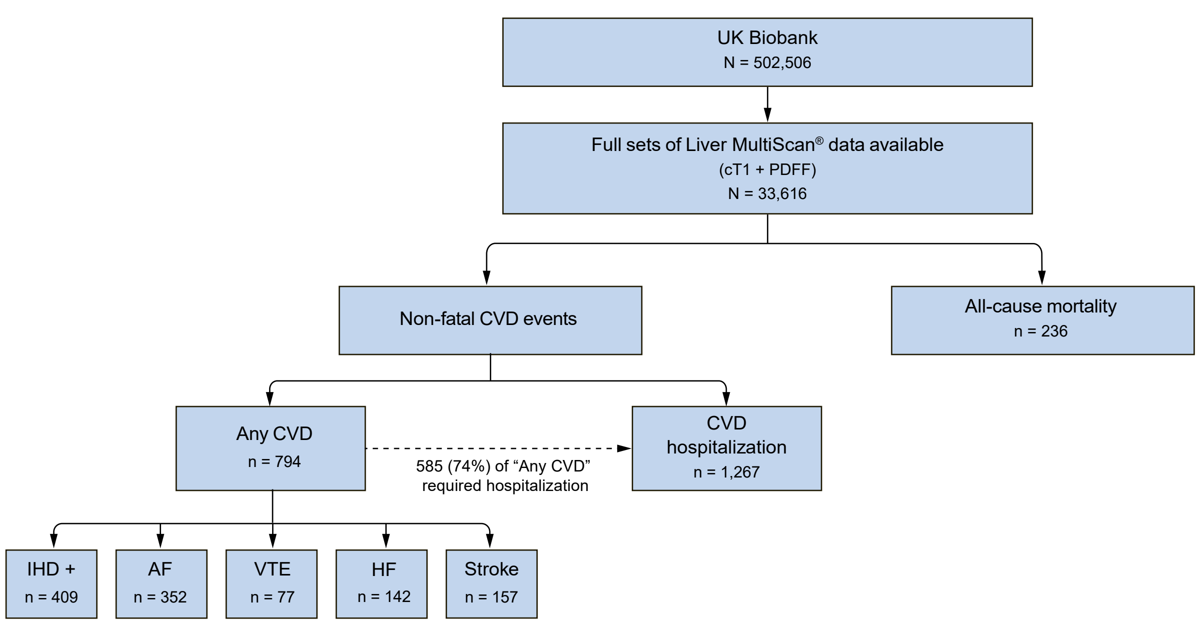

Fig. 1. Consort diagram. AF, atrial fibrillation; CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; IHD, ischemic heart disease; NIC, non-ischemic cardiomyopathy; PDFF, proton density fat fraction; VTE, embolism/vascular event (see Tables S1 and S2 for more details). +Includes 160 cases of acute myocardial infarction.

Independent variables and outcomes

New-onset CVD events were the outcomes of interest; specifically CAD, atrial fibrillation (AF), embolism/vascular events (VTE), heart failure (HF), and stroke. ICD-10 codes to define events were agreed by consensus cardiologists (BR, SN, RB) based on Bosco *et al.*.[36] Hospitalisation due to a primary cardiovascular event and all-cause mortality were also recorded. To ensure capture of the most severe events they were defined as first event for each patient following their UK Biobank imaging visit (Table S1). Inpatients were defined as individuals admitted to hospital and occupying a hospital bed, including both admissions where an overnight stay was planned and day cases. Liver events were defined as ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma and liver transplantation[4] following ICD-10 codes.

Liver measurements derived from the LiverMultiScan® software and standard liver function tests (AST/ALT ratio, ALT, AST, and FIB-4 index [(Age*AST)/(platelet count*sqrt(ALT)]) were assessed as predictors of CVD events. Additional blood biomarkers (high-density lipoprotein, low-density lipoprotein, haemoglobin A1c [HbA1C], triglycerides, total cholesterol, and C-reactive protein) were also evaluated. Previously reported risk factors which included being male, age, BMI, systolic blood pressure and smoking, were also explored.[37,38]

Imaging protocol and analysis

Participants were scanned at one of four UK Biobank imaging centres on Siemens Aera 1.5 T scanners (Syngo MR D13) using the LiverMultiScan® protocol from Perspectum Ltd (UK) which forms part of the UK Biobank abdominal imaging protocol. Liver MRI data was analysed automatically using LiverMultiScan® software, and every case was manually reviewed by trained analysts, blinded to any subject variables.

Statistical analysis

Statistical analysis was performed using R software (version 4.0.4) with a p value <0.05 considered statistically significant. Descriptive statistics were used to summarize baseline characteristics. Mean and SD were used to describe normally distributed-continuous variables, median (IQR) for non-normally distributed, and frequency and percentage for categorical variables. For group-wise comparisons of continuous parametric and non-parametric, and categorical variables, t test, Wilcoxon rank sum and Fisher's exact tests, respectively, were used.

Analyses into associations between CVD events (CAD, AF, VTE, HF, stroke, hospitalisation, and all-cause mortality) and imaging and blood biomarkers, comorbidities, and demographics were by Cox proportional hazard regression analysis. Initially, a univariate analysis was performed to study the contribution of an individual variable on the occurrence of each specific clinical event. Significant variables were included in a multivariable Cox proportional hazard regression model to assess which variables were independent predictors of CVD. This process was performed: i) with all biomarkers treated as continuous variables following transformation into Z-scores, ii) using pre-defined clinically used thresholds, and iii) in individuals without comorbid metabolic syndrome. Sensitivity analyses were performed in: i) individuals without prior history of CVD, ii) individuals without prior history of CLD, iii) all male individuals, and iv) using Z-scores based on imputed blood biomarker values. This imputation to individual values was corrected for the difference in time of collection for blood and imaging data by addition of an "annualised change" calculated from a subset with paired blood data (Table S3). A clinical threshold cT1 value of ≥800 ms was used, as it is considered the upper limit of normal and is the recommended threshold to identify those in transition from simple steatosis to non-alcoholic steatohepatitis (NASH),[28] to predict failure to maintain remission in autoimmune hepatitis[39] and to identify those with mild fibrosis in a mixed CLD[40,41] cohort. Metabolic syndrome was defined as having three or more of: a large waist (≥89 cm waist circumference in women and ≥102 cm in men), high triglycerides (≥1.7 mmol/L), low high-density lipoprotein cholesterol (<1.04 mmol/L in men and <1.3 mmol/L in women), increased systolic blood pressure (≥130/85 mmHg) or elevated HbA1c (≥32 mmol/mol).[42]

Results

Data from 41,994 participants were extracted from the UK Biobank imaging showcase, with full liver imaging and biochemistry measurements available for 33,616. In the time following the MRI scan, 794 participants (2.4%) experienced a CVD event requiring hospitalisation. Looking at the specific CVD categories, 409 participants experienced CAD events (including 160 acute myocardial infarctions), 352 AF events, 77 VTE events, 142 HF events and 157 stroke events. In addition, 1,267 individuals required hospitalisation due to any CVD event and 236 individuals died (Fig. 1).

Median time to event was 1.4 years (0.002–5.1) and median follow-up time was 2.5 (1.1- 5.2) years based on imaging, and 10.6 (5.7–14.6) years based on blood data collection. Comparing those with and without any major CVD post-MRI, participants experiencing events were older (p <0.001), had higher BMI (p <0.001) and were more likely to be male (64%, p <0.001). Participant characteristics for the whole population and relevant subgroups are reported in Table 1. Associations between the liver biomarkers investigated are shown in Table S4.

Association between CVD and biomarkers (continuous variables)

Elevation in liver cT1 was associated with higher risk of all CVD events investigated and all-cause mortality, in all cases independently of other liver biomarkers, including FIB-4 and AST/ALT ratio (Table 2). FIB-4 was selected over NAFLD fibrosis score to avoid collinearity effects (univariable results for NAFLD fibrosis score are provided in Table S5). Smoking and alcohol intake were not significant in univariable analyses and therefore, were not included in multivariable models (characteristics of the population with any major CVD events are provided in Table S6). All conclusions were maintained when blood values were corrected by imputation to account for the time interval between imaging and blood data collection (Table S7).

Cases where liver IDPs were not significantly associated with clinical outcomes (VTE, stroke, myocardial infarction, and CAD) are described in Table S8. Increasing liver cT1 was associated with a higher risk of any CVD outcomes (hazard ratio [HR] 1.14; 95% CI 1.03-1.26; p = 0.008) alongside waist

Table 1. Demographics, baseline characteristics and clinical outcomes in the whole cohort and according to liver cT1.

	N	Whole cohort (N = 33,616)	cT1 <800 ms (n = 31,840)	cT1 ≥800 ms (n = 1,776)	*p* value cT1 <800 ms *vs.* cT1 ≥800 ms
Demographics					
Age [mean (SD)]	33,616	64.2 (7.6)	64.3 (7.6)	63.7 (7.6)	0.001
Sex (Male) [n (%)]	33,616	15,938 (47%)	14,908 (47%)	1,030 (58%)	<0.001
Race (White British) [n (%)]	33,606	30,571 (91%)	28,956 (91%)	1,615 (91%)	>0.9
Smoking [n (%)]	33,615	1,066 (3%)	993 (3%)	73 (4%)	0.025
Alcohol intake frequency	33,608				
More than once a week		25,704 (76.5%)	24,550 (77.1%)	1,154 (65%)	<0.001
Less than once a week		6,343 (18.9%)	5,852 (18.4%)	491 (27.6%)	<0.001
Never		1,551 (4.6%)	1,421 (4.5)	130 (7.4%)	<0.001
Metabolic comorbidities					
BMI at MRI [mean (SD)]	33,614	26.4 (4.2)	26.1 (4.0)	31.4 (5.1)	<0.001
Categories [n (%)]	33,614				<0.001
Lean (BMI <25 kg/m^2)		13,956 (42%)	13,819 (43%)	137 (7.7%)	
Overweight (BMI ≥25-<30 kg/m^2)		13,841 (41%)	13,233 (42%)	608 (34%)	
Obese (BMI ≥30 kg/m^2)		5,817 (17%)	4,786 (15%)	1,031 (58%)	
SBP, mmHg [mean (SD)]	31,340	137[19]	136[19]	140[18]	<0.001
Categories [n (%)]	31,340				<0.001
SBP ≤130 mmHg		12,546 (40%)	12,048 (41%)	498 (30%)	
SBP >130 mmHg		18,794 (60%)	17,621 (59%)	1,173 (70%)	
HbA1c, mmol/mol [mean (SD)]	31,216	35.0 (5.2)	34.9 (5.1)	37.4 (7.1)	<0.001
Categories [n (%)]	31,216				<0.001
≤42 mmol/mol		29,830 (96%)	28,395 (96%)	1,435 (87%)	
42 mmol & <48 mmol/mol		805 (2.6%)	688 (2.3%)	117 (7.1%)	
≥48 mmol/mol		581 (1.9%)	484 (1.6%)	97 (5.9%)	
LDL, mmol/L [mean (SD)]	31,393	3.58 (0.83)	3.58 (0.83)	3.59 (0.89)	0.8
Categories [n (%)]	31,393				0.006
≤4.1 mmol/L		23,333 (74%)	22,146 (74%)	1,187 (71%)	
>4.1 mmol/L		8,060 (26%)	7,586 (26%)	474 (29%)	
HDL, mmol/L [mean (SD)]	28,725	1.48 (0.38)	1.49 (0.38)	1.23 (0.29)	<0.001
Categories [n (%)]	28,725				<0.001
≥1.04 mmol/L [men] & 1.3 mmol/L [women]		23,449 (82%)	22,544 (83%)	905 (59%)	
<1.04 mmol/L [men] & 1.3 mmol/L [women]		5,276 (18%)	4,638 (17%)	638 (41%)	
Triglycerides [mean (SD)]	31,440	1.64 (0.95)	1.60 (0.92)	2.24 (1.18)	<0.001
Categories [n (%)]	31,440				<0.001
≤1.7 mmol/L		20,301 (65%)	19,664 (66%)	627 (38%)	
>1.7 mmol/L		11,139 (35%)	10,115 (34%)	1,034 (62%)	
Total cholesterol, mmol/L [mean (SD)]	31,462	5.73 (1.08)	5.74 (1.08)	5.60 (1.17)	<0.001
Categories [n (%)]	31,462				<0.001
≤5.2 mmol/L		10,077 (32%)	9,440 (32%)	637 (38%)	
>5.2 mmol/L		21,385 (68%)	20,356 (68%)	1,029 (62%)	
Any previous major CVD event [n (%)]	33,610	4,111 (12%)	3,782 (12%)	329 (19%)	<0.001
Any previous major CLD event [n (%)]	33,615	1,162 (3.5%)	1,020 (3.2%)	142 (12.1%)	<0.001
Metabolic syndrome [n (%)]	25,440	8,877 (35%)	7,906 (33%)	971 (70%)	<0.001
Liver biomarkers					
ALT [mean (SD)]	31,458	23 (14)	22 (13)	33 (20)	<0.001
Categories [n (%)]	31,458				<0.001
≤45 U/L		30,299 (96%)	28,877 (97%)	1,422 (85%)	
>45 U/L		1,159 (3.7%)	917 (3.1%)	242 (15%)	
AST [mean (SD)]	31,333	26 (10)	25 (9)	29 (12)	<0.001
Categories [n (%)]	31,333				<0.001
≤40 U/L		30,080 (96%)	28,607 (96%)	1,473 (89%)	
>40 U/L		1,253 (4.0%)	1,070 (3.6%)	183 (11%)	
FIB-4 [mean (SD)]	30,564	1.3 (0.58)	1.3 (0.59)	1.2 (0.53)	<0.001
Categories [n (%)]	30,564				<0.001
FIB-4 <1.3		17,962 (59%)	16,875 (53%)	1,087 (61%)	
FIB-4 ≥1.3 & <2.67		12,107 (40%)	11,597 (40%)	510 (31%)	
FIB-4 ≥2.67		495 (2%)	472 (1.6%)	23 (1.4%)	
cT1, ms [mean (SD)]	33,616	700 (55)	693 (44)	840 (38)	<0.001
Categories [n (%)]	33,616				—
<800 ms		31,840 (95%)	—	—	
≥800 ms		1,776 (5.3%)	—	—	
PDFF (%) [mean (SD)]	33,616	4.9 (4.7)	4.3 (3.6)	15.9 (8.3)	<0.001
Categories [n (%)]	33,616				<0.001
<5%		24,503 (73%)	24,269 (76%)	234 (13%)	
≥5%		9,113 (27%)	7,571 (24%)	1,542 (87%)	

(*continued on next page*)

Table 1. (*continued*)

	N	Whole cohort (N = 33,616)	cT1 <800 ms (n = 31,840)	cT1 ≥800 ms (n = 1,776)	*p* value cT1 <800 ms *vs.* cT1 ≥800 ms
Cardiac biomarkers					
CRP (mg/ml) [mean (SD)]	31,387	2.01 (3.48)	1.93 (3.41)	3.51 (4.25)	<0.001
Categories [n (%)]	31,387				<0.001
≤10 mg/L		30,586 (97%)	29,038 (98%)	1,548 (93%)	
>10 mg/L		801 (2.6%)	690 (2.3%)	111 (6.7%)	
New-onset outcomes [n (%)]					
Any CVD event	29,499	794 (2.7%)	734 (2.6%)	60 (4.1%)	<0.001
CAD	31,582	409 (1.3%)	380 (1.3%)	29 (1.8%)	0.066
MI	32,781	160 (0.5%)	147 (0.5%)	13 (0.8%)	0.094
AF	32,536	352 (1.1%)	321 (1.0%)	31 (1.8%)	0.002
VTE	32,787	77 (0.2%)	73 (0.2%)	4 (0.2%)	>0.9
HF	33,411	142 (0.4%)	128 (0.4%)	14 (0.8%)	0.013
Stroke	32,936	157 (0.5%)	146 (0.5%)	11 (0.6%)	0.3
CVD hospitalisation	33,610	1,267 (3.8%)	1,145 (3.6%)	122 (6.9%)	<0.001
All-cause mortality	33,610	236 (0.7%)	210 (0.7%)	26 (1.5%)	<0.001
Liver-related events	32,453	318 (0.9%)	280 (0.9%)	38 (2%)	<0.001

AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; CRP, c-reactive protein; cT1, iron-corrected T1 relaxation time; CVD, cardiovascular disease; HbA1C, glycated haemoglobin; HDL, high-density lipoprotein; HF, heart failure; LDL, low-density lipoprotein; MI, myocardial infarction; PDFF, proton density fat fraction; VTE, embolism/vascular event.

Age was at MRI visit; bloods were taken at baseline visit. Group-wise comparisons of continuous parametric and non-parametric, and categorical variables was performed with *t* test, Wilcoxon rank sum and Fisher's exact tests, respectively, with a *p* value <0.05 considered statistically significant.

circumference (*p* = 0.003), systolic blood pressure (SBP) (*p* = 0.017), age (*p* <0.001) and male sex (*p* <0.001) (Table 2, Fig. 2). These effects persisted even without prior history of CVD or CLD, or in all males (Tables S9-11). Associations with specific CVD are described in Table 2 and Table S8).

Atrial fibrillation

AF was significantly associated with increasing liver cT1 (HR 1.30; 95% CI 1.12-1.51; *p* <0.001), age (*p* <0.001) and male sex (*p* <0.001). Characteristics of those with AF events are provided in Table S12. Effects were maintained regardless of sex or prior history of CVD/CLD (Tables S9-11).

Heart failure

HF was associated with increasing liver cT1 (HR 1.30; 95% CI 1.09-1.56; *p* = 0.004) alongside waist circumference (*p* = 0.005), FIB-4 (*p* = 0.007) and age (*p* <0.001), while total cholesterol was negatively associated (*p* = 0.017). Characteristics of those with HF are provided in Table S13. These effects were consistent, regardless of prior history of CLD events, or sex (Tables S10-11).

Hospitalisation due to cardiovascular events

Higher risk of hospitalisation from CVD causes was associated with increasing liver cT1 (HR 1.27; 95% CI 1.18-1.37; *p* <0.001) and higher HbA1c (HR 1.06; 95% CI 1.01-1.12; *p* = 0.011), as well as waist circumference (*p* = 0.001), SBP (*p* = 0.004), age (*p* <0.001) and male sex (*p* <0.001). Characteristics of those hospitalised due to CVD events are provided in Table S14. These effects were consistent, regardless of prior history of CVD or CLD events, or sex (Tables S9-11).

All-cause mortality

Higher liver cT1 (HR 1.19; 95% CI 1.02-1.38; *p* = 0.026), and age (*p* <0.001) were significantly associated with all-cause mortality. Characteristics of deceased individuals after MRI scan are provided in Table S15. Effects were maintained regardless of prior history of CLD (Tables S10-11).

Association between CVD outcomes and biomarkers with clinical thresholds

Associations with CVD were assessed using validated clinical biomarker thresholds and demographic categories. The cT1 threshold was ≥800 ms as this is considered the upper limit of normal and the recommended threshold to identify those in transition from simple steatosis to NASH.[28] The threshold for elevated liver fat was PDFF ≥5% and for elevated fibrosis was FIB-4 index >1.3 and ≥2.67 (based on established guidelines,[11,28,33,43] respectively).

A total of 1,776 individuals had cT1 ≥800 ms (Table 1); of whom 70% had metabolic syndrome and 87% clinically significant liver steatosis (PDFF ≥5%). Participants with cT1 ≥800 ms experienced a twofold higher prevalence of cardiovascular events (n = 122, 7%) compared to those with cT1 <800 ms (n = 1,145, 4%).

In the multivariable models, cT1 ≥800 ms was significantly associated with the risk of hospitalisation due to CVD (HR 1.38; 95% CI 1.11-1.75; *p* = 0.005). Other liver biomarkers were not: PDFF ≥5% (*p* = 0.5), ALT >45 U/L in the presence of diabetes and >50 U/L the absence of diabetes (*p* = 0.64); AST >40 U/L (*p* = 0.43); AST/ALT ratio (*p* = 0.87) and FIB-4 (≥1.3 <2.67, *p* = 0.69; ≥2.67 points, *p* = 0.87). Other exposures associated with CVD hospitalisation were BMI ≥25 kg/m^2 (*p* = 0.016) or BMI ≥30 kg/m^2 (*p* <0.001), diabetes (HbA1c ≥48 mmol/mol) (*p* = 0.028), older age (*p* <0.001) and male sex (*p* <0.001). Other known CVD risk factors such as total cholesterol ≥5.2 mmol/L (*p* = 0.275) and hypertension (*p* = 0.065) were not significantly associated with CVD hospitalisation in this subgroup (Fig. 3).

CVD hospitalisation risk in individuals without metabolic disease

In this group of 16,563 individuals, characterised by lower age (mean 64 (7.6) years, *p* <0.001), lower BMI (mean 25 (3.8) kg/

Table 2. Multivariate analysis Cox proportional HRs with 95% CIs of cardiovascular outcomes, based on Z-scores to enable comparisons across different unit scales.

Outcome	HR	*p* value
cT1 (ms)		
CVD hospitalisation	1.27 (1.18–1.37)	<0.001
Atrial fibrillation	1.3 (1.12–1.51)	<0.001
Heart failure	1.3 (1.08–1.58)	0.004
All-cause mortality	1.19 (1.02–1.38)	0.026
Any CVD event	1.14 (1.03–1.26)	0.008
PDFF (%)		
CVD hospitalisation	0.87 (0.8–0.95)	0.001
Atrial fibrillation	0.91 (0.78–1.05)	0.229
Heart failure	n.s.	n.s.
All-cause mortality	n.s.	n.s.
Any CVD event	0.96 (0.87–1.06)	0.402
BMI (kg/m^2)		
CVD hospitalisation	1.05 (0.95–1.16)	0.309
Atrial fibrillation	1.14 (0.94–1.38)	0.167
Heart failure	0.87 (0.65–1.17)	0.267
All-cause mortality	1.03 (0.81–1.29)	0.825
Any CVD event	1.05 (0.92–1.19)	0.47
HbA1c (mmol/mol)		
CVD hospitalisation	1.06 (1.01–1.12)	0.011
Atrial fibrillation	0.96 (0.86–1.08)	0.554
Heart failure	1.1 (0.97–1.25)	0.086
All-cause mortality	1.06 (0.94–1.2)	0.326
Any CVD event	1.04 (0.97–1.12)	0.211
Waist circumference (cm)		
CVD hospitalisation	1.19 (1.07–1.33)	0.001
Atrial fibrillation	1.17 (0.95–1.45)	0.107
Heart failure	1.43 (1.07–1.92)	0.005
All-cause mortality	1.18 (0.92–1.53)	0.182
Any CVD event	1.22 (1.06–1.4)	0.003
Total cholesterol		
CVD hospitalisation	0.94 (0.89–1.01)	0.079
Atrial fibrillation	0.94 (0.83–1.06)	0.28
Heart failure	0.81 (0.67–0.98)	0.017
All-cause mortality	n.s.	n.s.
Any CVD event	n.s.	n.s.
AST		
CVD hospitalisation	1.02 (0.91–1.15)	0.616
Atrial fibrillation	0.89 (0.68–1.16)	0.347
Heart failure	0.92 (0.73–1.16)	0.483
All-cause mortality	0.98 (0.82–1.19)	0.825
Any CVD event	0.94 (0.77–1.15)	0.544
ALT		
CVD hospitalisation	0.99 (0.87–1.13)	0.87
Atrial fibrillation	1.03 (0.83–1.28)	0.788
Heart failure	n.s.	n.s.
All-cause mortality	n.s.	n.s.
Any CVD event	1.03 (0.85–1.24)	0.779
AST/ALT ratio		
CVD hospitalisation	1.01 (0.91–1.12)	0.782
Atrial fibrillation	n.s.	n.s.
Heart failure	n.s.	n.s.
All-cause mortality	n.s.	n.s.
Any CVD event	0.99 (0.86–1.14)	0.882
C-reactive protein		
CVD hospitalisation	1.02 (0.96–1.08)	0.419
Atrial fibrillation	0.99 (0.88–1.11)	0.76
Heart failure	1.1 (0.97–1.23)	0.136
All-cause mortality	n.s.	n.s.
Any CVD event	1.03 (0.96–1.11)	0.358
FIB-4		
CVD hospitalisation	0.97 (0.9–1.06)	0.438
Atrial fibrillation	1.01 (0.9–1.14)	0.783
Heart failure	1.06 (1.01–1.10)	0.007
All-cause mortality	0.96 (0.8–1.15)	0.56
Any CVD event	0.99 (0.9–1.09)	0.788
Systolic blood pressure		
CVD hospitalisation	1.1 (1.03–1.17)	0.004
Atrial fibrillation	1.04 (0.92–1.17)	0.573
Heart failure	1.08 (0.89–1.3)	0.432
All-cause mortality	0.94 (0.81–1.1)	0.432
Any CVD event	1.1 (1.02–1.2)	0.017
Age at MRI		
CVD hospitalisation	1.58 (1.46–1.71)	<0.001
Atrial fibrillation	1.95 (1.67–2.27)	<0.001
Heart failure	2.04 (1.61–2.59)	<0.001
All-cause mortality	2.09 (1.72–2.54)	<0.001
Any CVD event	1.69 (1.53–1.86)	<0.001
Sex (male)		
CVD hospitalisation	1.65 (1.39–1.95)	<0.001
Atrial fibrillation	1.79 (1.29–2.48)	<0.001
Heart failure	1.46 (0.89–2.4)	0.125
All-cause mortality	1.33 (0.92–1.95)	0.096
Any CVD event	1.62 (1.31–1.99)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, c-reactive protein; cT1, iron-corrected T1 relaxation time; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HR, hazard ratio; PDFF, proton density fat fraction.
This table shows only HR from multivariable models, variables with "ns" were not included in these models. Multivariable Cox regression analysis with a *p* value <0.05 considered statistically significant. n.s., variables not significant in the univariate analysis that were not included in the multivariate analysis.

m^2, p <0.001) and lower prevalence of clinically significant liver fat (17%, p <0.001), liver cT1 was associated with CVD hospitalisation (HR 1.26; 95% CI 1.13-1.4; p <0.001). No other liver biomarkers showed any associations. These effects persisted regardless of prior history of CVD or CLD events, or sex (Tables S9-11). Age and male sex were associated with all CVD events, SBP with any major CVD event and HbA1c with CVD hospitalisations (Table S16). All-cause mortality was associated with age only.

Discussion

In this large-scale, longitudinal study of CVD incidence in a mainly healthy older population, we have identified specific associations between individual liver biomarkers and CVD. We found that, firstly, elevation of liver cT1, a liver-specific marker of disease activity, was associated with increased risk of new onset CVD, and specifically AF, HF, CVD hospitalisation and all-cause mortality. In contrast, the commonly used liver risk score FIB-4 had less predictive value, being associated with HF only, while the AST/ALT ratio was not predictive of any adverse events. Secondly, we identified that for clinical events of higher prevalence (such as CVD hospitalisation), only cT1 at or above the clinically defined threshold that is used to diagnose CLD activity remained associated; non-invasive blood screening tests for liver fibrosis were not. Thirdly, in those with pre-existing metabolic syndrome, the independent association between elevated cT1 and increased incident CVD hospitalisation remained, indicating that the association between CLD activity is independent of traditional cardiovascular risk factors such as obesity, hypertension, and type 2 diabetes. These conclusions remained when prior history of CVD or liver disease were excluded, highlighting the prognostic relevance of a comprehensive evaluation of liver health in populations at risk of CVD and/or CLD, even in the absence of clinical

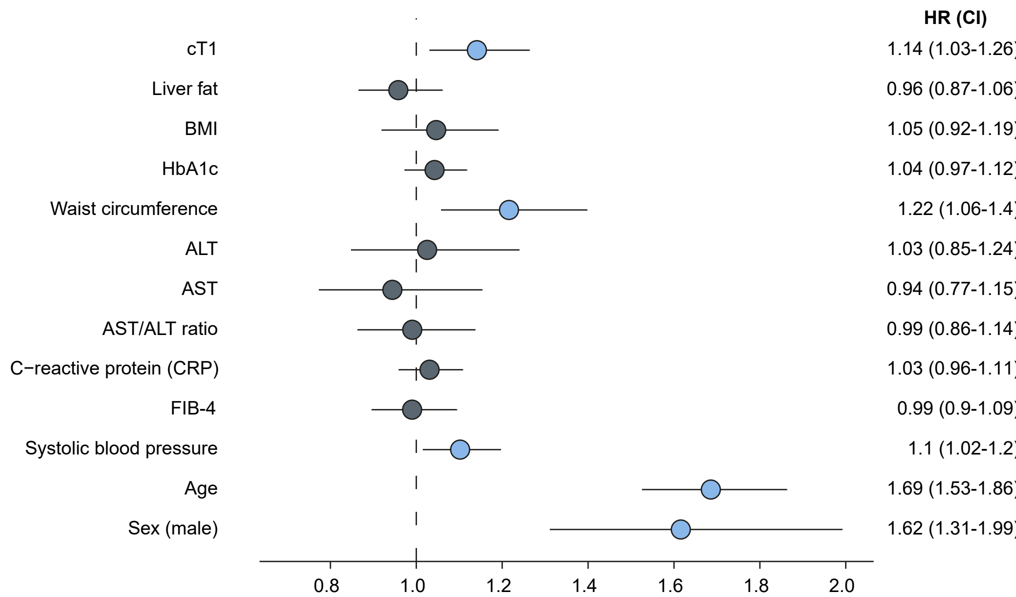

Fig. 2. Multivariable model HRs of associations for risk of any major CVD event in the whole cohort. Variables treated as continuous based on Z-scores to enable comparisons across different unit scales. Significant associations shown in red. Multivariable cox regression analysis was used with a *p* value <0.05 considered statistically significant. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; cT1, iron-corrected T1 relaxation time; FIB-4, fibrosis-4; HbA1c, glycated haemoglobin; HR, hazard ratio.

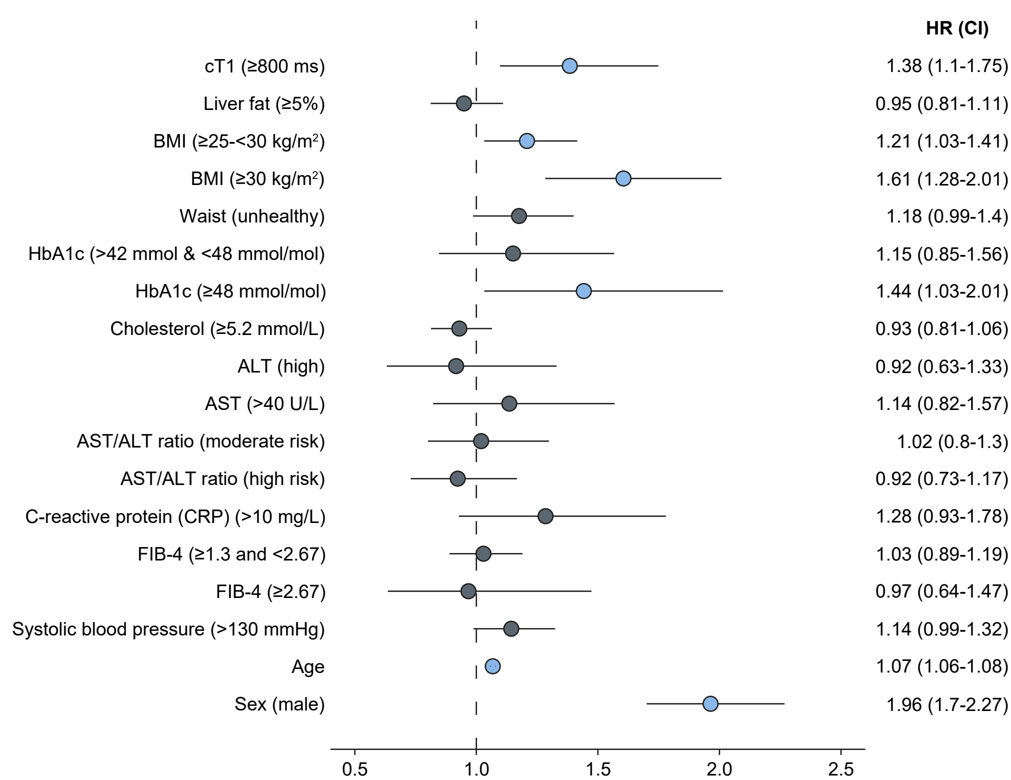

Fig. 3. HRs of associations for risk of CVD hospitalisation in the whole cohort. Variables treated as binary based on pre-specified clinical thresholds. 95% CI for age effect is too small to be appreciated in the plot. Significant associations shown in red. Multivariable cox regression analysis was used with a *p* value <0.05 considered statistically significant. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; cT1, iron-corrected T1 relaxation time; FIB-4, fibrosis-4; HbA1c, glycated haemoglobin; HR, hazard ratio.

manifestations or metabolic syndrome, when there is an opportunity to modify/address risk factors and prevent disease progression. Given the recognition of T1 mapping in clinical guidelines for cardiac health as well as liver health, there may be an opportunity for quantitative imaging-based measurements to play a key role in shared cardiometabolic pathways.

Prior studies have observed liver-related clinical events in NAFLD linked to the stage/severity of fibrosis, as measured from the blood-based enhanced liver fibrosis test[44] or using other imaging techniques, *e.g*. liver stiffness by magnetic resonance elastography[45] or transient elastography from ultrasound. Using the current MR-based technique, cT1 has also been associated with all-cause mortality and event-free survival in patients with CLD.[4] Whilst prognostic (fibrosis-based) assessment of risk in those with CLD may be of use in the liver clinic, it may be argued that this is late in the disease course. Measurements of liver health that allow for risk stratification across the spectrum of disease stages have the potential to be transformative in terms of personalised care. Our results showed a robust link between evidence of measurable CLD activity change from cT1 and a variety of cardiovascular events, and validate associations observed between cT1 and MR features of cardiac structure and function in this UK general population cohort[46] that reflect common pathophysiological drivers and disease mechanisms associated with ageing and obesity.[47] Of clinical relevance is the link between cT1 ≥800 ms and hospitalisation for CVD. Previous literature has reported that cT1 ≥800 ms has excellent diagnostic accuracy for identifying patients with early-stage fibrosis (*vs.* no fibrosis) in a cohort of patients with CLD,[40] and those with NAFLD (*vs.* healthy) in a fatty liver disease cohort.[28] Distinguishing patients with clinically significant steatohepatitis (at an early and modifiable stage) from those with more benign simple steatosis is a clinical opportunity.

Significantly, another defining feature of NAFLD, the accumulation of liver fat (steatosis), although univariately associated with various CVD outcomes, was not independently associated with any of the clinical outcomes in multivariable analyses. On one occasion, lower PDFF appeared to be significantly associated with CVD hospitalisation, which, given the linear relationship observed when included as a univariate analysis, suggests multicollinearity observed between PDFF and other variables. It should be noted, however, that lower PDFF is a common feature of advanced CLD and cirrhosis and therefore is not a biomarker that can reliably be used for risk stratification. There was also no association between the blood-based algorithm for cirrhosis risk, the AST/ALT ratio, and CVD outcomes, and the FIB-4 index was only observed to be associated with higher incidence of HF in our analysis. Advanced fibrosis by MR elastography has been associated with elevated coronary artery calcium, a biomarker of atherosclerosis, in a small cohort of patients with type 2 diabetes.[48] While previous work in the Rotterdam general population cohort study has shown that liver fibrosis, evaluated by transient elastography, has been associated with a prevalence of AF of 7%, no association between incident AF and fibrosis was described[49] and no independent association with FIB-4 was observed in a CAD cohort.[50] This, together with our findings, suggests that the association between CVD risk in the general population and liver health is likely related to underlying disease activity and not to fibrosis, thus supporting previous hypotheses of underlying mechanisms related to tissue inflammation and metabolic processes.

Whilst there are no approved therapeutic agents yet in NAFLD, agents such as semaglutide and other glucagon-like peptide-1 receptor agonists have been incorporated into clinical guidelines in those with type 2 diabetes as a treatment for NASH, the aggressive form of NAFLD.[10,51] In addition, tirzepatide (a dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist), which has been approved for weight loss in those with type 2 diabetes, has also recently been shown to achieve meaningful and sustained weight reduction in non-diabetic obese patients,[52] and reductions in liver fat.[53] These positive effects on metabolic health may also improve liver-related health, thus potentially having a profound modifiable effect on CVD risk. Markers for early-stage liver disease, such as cT1, may be considered as non-invasive alternatives to biopsy to monitor response and personalise treatments. cT1 has already been shown to be an effective pharmacodynamic biomarker in NASH trials,[7,8] and being inherently non-invasive, is an attractive tool for assessing early response in drug development. The current results showing a robust link to clinical outcomes, coupled with response to therapy, are suggestive of a place for cT1 in future NASH trials as a surrogate endpoint.

Many CVD risk scores exist, including the QRISK score, Framingham score and ASCVD score, which are already employed clinically. However, considering these results, and the momentum towards appreciating multi-system disease and multi-speciality care, our results highlight an opportunity to improve on these risk scores by incorporating the degree of liver-related disease activity. In relation to the FIB-4 index, whilst we did not observe a robust association with CVD risk, it should be acknowledged that the currently adopted thresholds to rule out or rule in significant liver fibrosis are designed for patients being specifically evaluated for CLD[10,54] and may be inappropriate in 'healthier' populations[55] where CLD is underdiagnosed or at an earlier, potentially more modifiable, stage.[56] Of course, the fact that we did not observe an association with the FIB-4 index is being attributed to the likely absence of fibrosis, but a notable limitation of the UK Biobank imaging study is that there is a delay of approximately 10 years between the blood tests and imaging, which may prevent meaningful interpretation of blood test results, although correction for this by imputation of annualised change did not alter our main findings. Other notable limitations are the lack of confirmatory biopsy, although in following the guiding medical principal of *primum non nocere* this is not surprising in a study of the general population. The study cohort was also homogenous with a predominant white ethnicity and was slightly older compared to the whole UK Biobank cohort but had no clinically significant differences in the mean BMI or proportion of males. Low numbers in this imaging cohort or collinearity effects may have prevented full investigation of known CVD risk factors, such as smoking, cholesterol, BMI, or diabetes. Our analyses had short duration of follow-up for imaging and relied on ICD-10 codes for outcome collection. Despite these limitations, the results of our study reinforce the utility of cT1 in evaluating cardiometabolic risk in patients, highlighting cT1 as a prognostic non-invasive imaging biomarker that can stratify patients for therapy.

In a population-based study we observed CVD events in 4% of people which were independently associated with evidence of CLD. These results suggest the MRI-derived biomarker cT1 has a promising role to play in risk stratification of those at greatest risk of CVD morbidity and mortality.

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Abbreviations

AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; CLD, chronic liver disease; cT1, iron-corrected T1-mapping; CVD, cardiovascular disease; FIB-4, fibrosis-4; HF, heart failure; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PDFF, proton density fat fraction; SBP, systolic blood pressure; VTE, embolism/vascular events.

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Conflict of interest

ARF, HTB, AD are shareholders and employees at Perspectum Ltd, which developed LiverMultiScan™. AT is employee at Perspectum Ltd. RB is employee, founder, shareholder, and former board member of Perspectum Ltd. AS receives grants or contracts from Conatus, Gilead, Malinckrodt, Boehringer Ingelheim, Novartis, Bristol Myers, Merck, Lilly, Novo Nordisk, Fractyl, Madrigal, Inventiva, Covance, Gilead, Malinckrodt, Salix, Novartis, Galectin, Bristol Myers, Sequana and Conatus. Receives royaltis or licenses from Elsevier and UpToDate. Receives consulting fees from Genfit, Gilead, Malinckrodt, Pfizer, Salix, Boehringer Ingelhiem, Novartis, Bristol Myers Squibb, Merck, Hemoshear, Lilly, Novo Nordisk, Terns, Albireo, Jansen, Poxel, 89 Bio, Siemens, NGM Bio, Amgen, Regeneron, Genetech, Alnylam, Roche, Madrigal, Inventiva, Covance, Prosciento, Histoindex, Path AI, Intercept, Sequana, Fractyl, AstraZeneca. Dr Sanyal participates on a Data Safety Monitoring Board or Advisory Board at Immuron. Has a leadership or fiduciary role at Sanyal Bio. Has stock or stock options at Sanyal Bio, Genfit, Exhalenz, Hemoshear, Durect, Indalo, Northsea, Tiziana, Rivus. Received equipment from Echosense-Sandhill. Is employed by Sanyal Bio. Works with non-financial interests with Echosense-Sandhill, Owl, Second Genome and Siemens. SN receives funds from Oxford National Institute for Health and Care Research (NIHR) Biomedical Research Centre, is a founder, shareholder, and former board member of Perspectum Ltd. TEN receives statistical consulting fees from Perspectum Ltd. BR receives grants from BHF oxford CRE; and payment or honoraria from Axcella Therapeutics. CM receives funding in the form of salary from the NIHR Oxford Biomedical Research Centre. SEP receives consulting fees from Circle Cardiovascular Imaging, Inc., Calgary, Canada. SEP is President European Association of Cardiovascular Imaging and Board member European Society of Cardiology. NABN: receives payments or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Servier and Novo Nordisk. Has a leadership or fiduciary role at University of Cape Town Council, Ikamva Labantu Board Trustee and University of Cape Town United Kingdom Board Trustee. DJC has received support to travel to and attend scientific meetings for unrelated collaborative research funded from Novo Nordisk, Astra Zeneca and Perspectum Ltd. This relates to work using drugs or imaging to assess NAFLD in people living with obesity and type 2 diabetes. ML has no conflicts of interest. AB has no relevant conflicts of interest. cT1 has been developed by Perspectum.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

The authors confirm contribution to the paper as follows: Study conception and design: ARF, RB, AS, DJC, AB.Data collection: ARF, CM. Analysis and interpretation of results: ARF, AT, CM, AD, HTB, TEN, ML, NABN, BR, SEP, SN, AS, DJC, AB. Draft manuscript preparation: ARF, HTB, AB. All authors reviewed the results and approved the final version of the manuscript.

Data availability statement

The data analysed in this study is subject to the following licenses/restrictions: Data belongs to UK Biobank. Requests to access these datasets should be directed to access@ukbiobank.ac.uk.

Ethics statement

The studies involving human participants were reviewed and approved by 11/NW/0382. The patients/participants provided their written informed consent to participate in this study.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.05.046.

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