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Steatotic liver disease is a marker of multimorbidity, not underlying cirrhosis, in older adults

O. Oduwole[1,8], C. Ding[1,2,8], N. Bitar[1], D. Nair[2], S. Salter[2,3], M. Silverman[4], R. Allen[4], L. Ng Fat[5], E. Tsochatzis[1], S. Bell[6,7], G. Mehta[1,9] ✉ & A. Britton[5,9] ✉

Steatotic liver disease (SLD) prevalence in adults is estimated at 30%, but older populations are understudied. Here, SLD prevalence and associated risk factors were assessed 1,021 Whitehall II study participants (mean age 72.5) using transient elastography (FibroScan). SLD was present in 33.3% (CAP ≥ 275 dB/m), with most classified as metabolic dysfunction-associated SLD. Only 2.4% had significant fibrosis (≥ 7.9 kPa). Adjusted for age and sex, SLD was associated with low physical activity (OR 1.60, 95% CI 1.13-2.27), poorer motor function (SF-36 PCS OR 1.21, 95% CI 1.05-1.40), difficulties in activities of daily living (OR 3.19, 95% CI 1.17-8.64), and multimorbidity (OR 1.45, 95% CI 1.22-1.73). These associations persisted after adjustment for socioeconomic, behavioural, and cardiometabolic risk factors. Frailty was associated with SLD at higher CAP thresholds (≥ 290 dB/m). In this older adult sample, SLD is common and appears more as a marker of multimorbidity and low physical activity than significant fibrosis.

The global burden of liver disease is rising annually, with nearly 2 million deaths worldwide each year—representing 1 in 25 of all fatalities[1]. While liver disease has traditionally been associated with younger, working-age individuals, its prevalence among older adults is increasingly recognised[2].

Liver disease due to cardiometabolic risk factors, termed metabolic dysfunction-associated steatotic liver disease (MASLD), is the most common liver disease worldwide affecting over 30% of the global adult population[3]. The disease encompasses a spectrum of conditions, ranging from simple steatosis (5% or more fat accumulation in hepatocytes) to steatohepatitis and liver scarring[4,5]. The increased burden of liver disease has been exacerbated by the rising prevalence of obesity and type 2 diabetes, which are major risk factors for MASLD[6,7]. This carries significant healthcare resource implications, since patients with MASLD are at high risk of developing cirrhosis, liver failure, hepatocellular carcinoma, and requiring future liver transplantation[8,9].

The nomenclature for liver disease related to obesity or cardiometabolic factors was updated in 2023. Steatotic liver disease (SLD) was introduced as the umbrella term for hepatic steatosis of any cause[10]. MASLD has replaced the term 'non-alcoholic fatty liver disease' and describes patients with hepatic steatosis and at least one of five cardiometabolic risk factors; overweight/obese, hyperglycaemia, high blood pressure, increased plasma triglycerides or reduced plasma high-density lipoprotein cholesterol (HDL-c). Additionally, metabolic dysfunction and alcohol-associated liver disease (Met-ALD), describes individuals with MASLD and associated heavy alcohol consumption (> 20 g/day for women and >30 g/day for men)[10].

MASLD and Met-ALD are common, but to our knowledge the prevalence of MASLD in older adults has not yet been studied in a UK population. Recently, Clayton-Chubb et al. found that MASLD was associated with social disadvantage and frailty in older Australian adults (mean age 75 years), a relatively new area of investigation[11]. Further work is needed to accurately assess the health burden of MASLD in older adults, particularly in view of the potential association with frailty and other markers of ageing.

Here, we describe the prevalence of SLD, assessed by transient elastography, in a nested study of older adults within the Whitehall II cohort. Additionally, we examine associations between SLD and frailty, multimorbidity, motor function, and disability in this older population.

[1]Institute for Liver and Digestive Health, University College London, London, UK. [2]Department of Clinical Biochemistry, Royal Free Hospital, London, UK. [3]Health Services Laboratories, London, UK. [4]Patient and public involvement and engagement (PPIE) representative, London, UK. [5]Research Department of Epidemiology and Public Health, University College London, London, UK. [6]Precision Breast Cancer Institute, Department of Oncology, University of Cambridge, Cambridge, UK. [7]Cancer Research UK Cambridge Centre, Li Ka Shing Centre, University of Cambridge, Cambridge, UK. [8]These authors contributed equally: O. Oduwole, C. Ding.[9]These authors jointly supervised this work: G. Mehta, A Britton. ✉e-mail: gautam.mehta@ucl.ac.uk; a.britton@ucl.ac.uk

Results

Participant characteristics

A total of 1021 participants attended the FibroScan clinic. Characteristics of these participants are shown in Table 1. The population had a mean age of 72.5 years (SD = 2.7), comprised 775 (75.9%) men and 246 (24.1%) women, and 94.7% were white.

Prevalence of SLD in the Whitehall II cohort

Valid CAP results were available in 983 participants; the overall prevalence of SLD (CAP ≥ 275 dB/m) was 33.3% (n = 327; Fig. 1). On analysis of the subclasses of SLD, one participant was excluded due to missing data on alcohol intake. Of the 326 SLD cases, 311 (95.4%) had at least one cardiometabolic risk factor and only 15 presented with none. Of these, 249 had a low alcohol intake and met the MASLD criteria, 55 had an excessive alcohol intake matching the Met-ALD criteria. The remaining 11 participants with SLD met the criteria for ALD.

When comparing the SLD subclasses (Table S1), the ALD-only group was slightly older than the other groups, with the ALD+ group having the highest representation of men. The median number of cardiometabolic risk factors was 2 (IQR = 2-4) in the Met-ALD group, compared with 3 (IQR = 2-4) in both the MASLD and ALD+ groups. Liver fibrosis by LSM was similar among the subclasses with cardiometabolic risk factors (MASLD, Met-ALD, and ALD +), but lower in the group with ALD-only.

Associations of SLD with age, sex, and risk factors: Fig. 2 shows the characteristics of participants in association with CAP as a continuous variable. In univariate analysis, higher CAP was associated with male sex, the presence of cardiometabolic risk factors, low physical activity, limitations in ADLs, lower motor function, and an increasing multimorbidity score. Higher liver enzymes and liver stiffness were also significantly associated with higher CAP.

Similar associations were observed when comparing participants with and without SLD (CAP < 248 dB/m, equivalent to S0), after adjusting for age and sex (Table 2). Specifically, low physical activity was associated with a 1.6-fold increased odds of SLD (95% confidence interval [CI] = 1.13–2.27). Among cardiometabolic risk factors, overweight/obesity showed the strongest association with SLD (odds ratio [OR] = 3.91, 95% CI = 2.81–5.43), followed by low HDL-c (OR = 3.23, 95%CI = 1.95–5.37) and diabetes (OR = 1.84, 95%CI = 1.38–2.45).

Adverse health conditions, such as worse motor function indicated by lower SF-36 PCS score (OR = 1.21, 95%CI = 1.05–1.40), more limitations in basic ALDs (OR = 3.19, 95%CI = 1.17–8.64), and increasing multimorbidity (OR = 1.45, 95%CI = 1.22–1.73), were also associated with higher odds of SLD, independent of age and sex. Association of multimorbidity with SLD remained significant (OR = 1.31, 95%CI = 1.05–1.64; p = 0.018) after adjusting for additional socioeconomic factors (marital status, education, household income), as well as smoking, physical activity, alcohol consumption, and all other cardiometabolic risk factors except diabetes.

Applying a higher CAP threshold for SLD (≥ 290 dB/m) resulted in minimal changes to our findings (Table S2), with the exception of a significant association with frailty (age-sex-adjusted OR = 4.63, 95% CI = 1.12–19.07; p = 0.034). Associations with each component of the Fried frailty scale are presented in Table S3.

Among 974 participants with valid LSM, only 23 (2.4%) had significant fibrosis (F2-F4; ≥7.9 kPa). Associations with liver fibrosis are presented in Table 3, with LSM as a continuous variable in Fig. 3. No associations were found between liver stiffness and low physical activity, motor function or limitations in ADLs. Low HDL-c (OR = 3.03, 95%CI = 1.09–8.45), diabetes (OR = 2.62, 95%CI = 1.06–6.45) and increasing multimorbidity (OR = 1.58, 95%CI = 1.01-2.47) was associated with significant fibrosis (F2-F4) in analysis adjusted for age and sex. Significant liver fibrosis was associated with elevated liver enzymes (AST, ALT, and GGT) independent of age and sex.

Table 1 | Participant characteristics

	All clinic attendees (n = 1021)
Age, years	72.5 (2.7)
Male	775 (75.9%)
White ethnicity	965 (94.7%)
Married/cohabiting	784 (76.9%)
University degree or higher	401 (43.5%)
Annual household income ≥£50,000	378 (38.6%)
Current smoker	32 (3.2%)
Physical activity below recommended levels[a]	664 (73.4%)
Alcohol intake, g/day	12.6 (4.6–24.0)
Hazardous drinking (AUDIT-C score ≥5)	33 (3.3%)
Cardiometabolic risk factors	
Overweight/obese	645 (63.2%)
Diabetes	497 (48.7%)
High blood pressure	553 (54.2%)
High triglycerides	472 (46.2%)
Low HDL-c	86 (8.4%)
Motor function and disability	
SF-36 PCS score	52.2 (48.2–55.0)
≥2 limitations in basic ADLs	23 (2.3%)
≥2 limitations in basic or instrumental ADLs	37 (3.6%)
Frailty	9 (0.9%)
Chronic conditions	
Cancer	139 (13.6%)
Arthritis	114 (11.2%)
Coronary heart disease	98 (9.6%)
Depression	37 (3.6%)
Stroke	14 (1.4%)
Chronic obstructive pulmonary disease	14 (1.4%)
Parkinson's disease	5 (0.5%)
Dementia	0 (0.0%)
Multimorbidity score ≥2[b]	214 (21.0%)
Liver stiffness by transient elastography (LSM), kPa	4.0 (3.3–5.0)
Controlled attenuation parameter (CAP), dB/m	248.7 (60.2)

Data are n (% of available data), mean (SD), or median (IQR).
AUDIT-C Alcohol Use Disorders Identification Test for Consumption; SF-36 PCS Score=Physical Component Summary score of Short Form 36 General Health Survey; *ADLs* activities of daily living.
Missing data: ethnicity, n = 2; marital status, n = 2; education, n = 100; income, n = 41; smoking, n = 20; physical activity, n = 116; alcohol intake, n = 8; AUDIT-C, n = 24; SF-36 PCS score, n = 34; frailty, n = 2; basic ADLs, n = 2; instrumental ADLs, n = 4; liver stiffness, n = 47; CAP, n = 38.
[a]Moderate and vigorous physical activity less than 2.5 h per week.
[b]Score defined as the count of chronic conditions listed above plus diabetes.

Discussion

In this nested study within the Whitehall II cohort, one in three older adults had SLD, and one in 40 had significant liver fibrosis. The frequency of SLD and significant fibrosis was higher in older men than in older women. The prevalence of SLD in this study is comparable to unselected cohorts of younger adults, but the prevalence of significant liver fibrosis is slightly lower[12–14]. Although prior data have demonstrated an association of MASLD-related cirrhosis with frailty in younger adults[15,16], the data presented here demonstrate a novel association of SLD, independent of fibrosis, with multimorbidity in older adults. Additionally, these demonstrate a novel association of SLD, at a higher CAP threshold ≥290 dB/m, with frailty. In the context of an ageing population, with an increasing global prevalence of

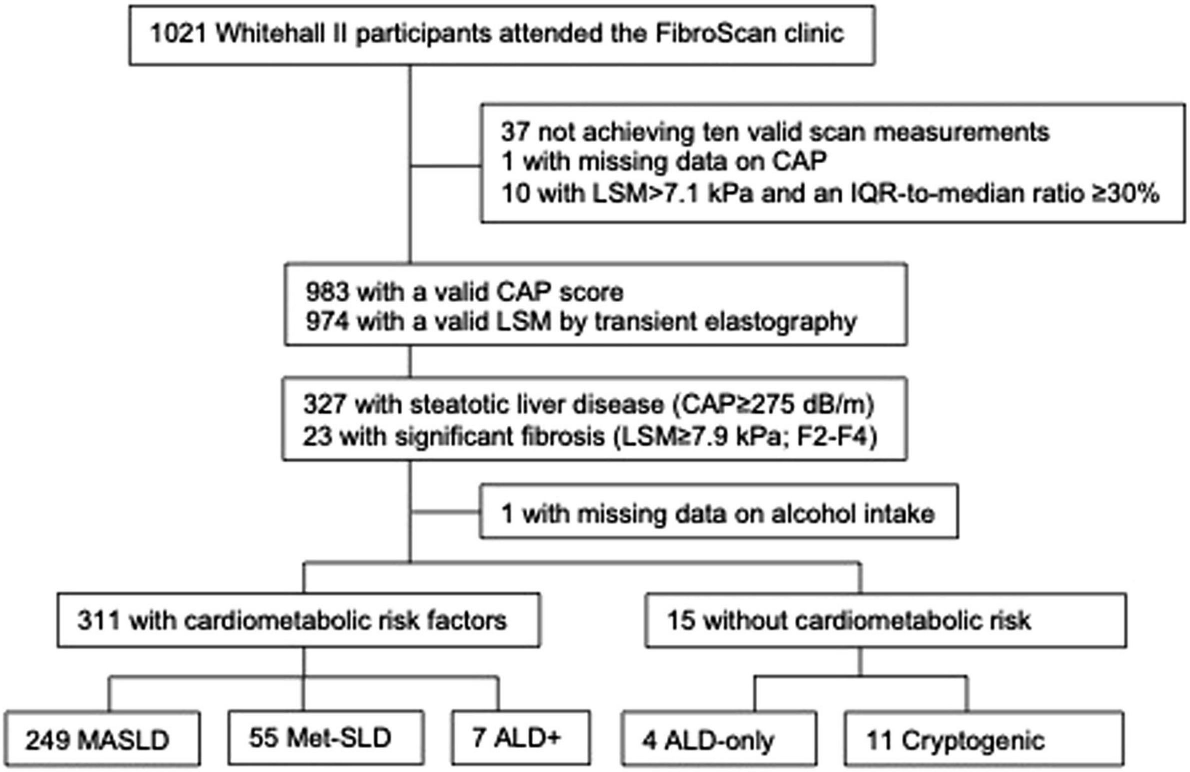

Fig. 1 | Participant flow chart. Participant flow chart.

SLD, these data are important for planning healthcare provision for older patients with SLD and highlight the need for future studies to determine causality between SLD and physical function in older adults.

Relatively few population-based studies have reported a prevalence of SLD, measured by CAP or ultrasound, alongside liver stiffness measures. Petta et al. demonstrated a prevalence of 48.1% in an unselected population from Palermo, Italy (mean age 53 years), albeit with a lower CAP threshold for SLD of 248 dB/m[13]. Advanced fibrosis (F3 or above) was present in 6.5% of those with SLD, and 1.6% of those without SLD. Similarly, amongst an adult population with at least one cardiometabolic risk factor (mean age 58 years), Fabrellas et al. found a prevalence of 43% for SLD, applying a CAP threshold off 280 dB/m, and an overall prevalence of significant fibrosis of 4% in this group[14]. Finally, in the Rotterdam population-based study of adults aged 45 and over, Koehler et al. report a prevalence of SLD of 35.5%, from abdominal ultrasound imaging, and significant liver fibrosis in 5.6%[12].

The data from this study demonstrate a similar prevalence of SLD, although rates of significant liver fibrosis are slightly lower than reported in younger adults. This likely represents a degree of survivorship bias; deaths from liver disease are highest in the sixth and seventh decades, and consequently, it is likely that individuals with more advanced liver fibrosis may have died prematurely from liver-related or other causes. Additionally, younger generations have the additional risk factor of increased consumption of sugar and processed foods, and consequently may have experienced fibrosis at an earlier age[17]. Nevertheless, these data are unique in describing steatosis and liver fibrosis, using TE, in a population of older adults. The only similar published cohort, from Clayton-Chubb et al., demonstrated a prevalence of SLD of 33% in older Australian adults (mean age 75 years), although steatosis was assessed indirectly using the fatty liver index (FLI)[11]. Liver fibrosis was not reliably studied in this cohort.

The data presented here also demonstrate an association of SLD with limited motor function, frailty and increasing multimorbidity. Again, Clayton-Chubb et al. previously demonstrated an association of frailty, as assessed by the Deficit-Accumulation Frailty Index (DAFI), with MASLD (assessed by FLI)[11]. Here, we extend this observation by characterising SLD using TE with a CAP threshold of 290 dB/m, and demonstrating an association with the Fried Frailty Score which, unlike the DAFI, is focussed on physical measures of frailty. Additionally, the presence of SLD was associated with motor dysfunction and disability, and limitations in basic ADLs. Sarcopenia is a potential underpinning mechanism for these observations. In particular, insulin resistance inhibits the growth hormone/insulin-like growth factor-1 axis, leading to promotion of gluconeogenesis and muscle loss, and altered triglyceride metabolism leading to ectopic deposition of TGs in liver and muscle[18,19]. SLD is also a chronic inflammatory state, which exacerbates sarcopenia in older adults[20]. Future study of frailty phenotypes in SLD, with a longitudinal study design, would provide valuable data to confirm our findings and determine if therapies directed at SLD in older adults may provide functional benefits aside from reducing the risk of advanced liver disease.

In terms of an association of SLD with multimorbidity, it is well established that cardiovascular disease[21], renal disease[22], and extra-hepatic cancer are linked to SLD. However, our findings reinforce the need to consider SLD from a multi-organ perspective in older adults. We demonstrate that SLD in older adults is associated with cardiometabolic factors (diabetes, overweight/ obese BMI, high blood pressure, high triglycerides, low HDL-c) as well as a multimorbidity score incorporating nine chronic conditions that are the most common causes of death in high-income countries. Several of these, including arthritis and dementia, have not been well studied in association with SLD. Longitudinal cohorts including older individuals would also clarify relationships between SLD and other chronic conditions, further informing public health strategies.

Perhaps surprisingly, alcohol consumption was not associated with SLD in this cohort. However, overall levels of alcohol use were low and, again, this may be influenced by factors including survivorship bias, the limitation of using alcohol consumption recorded at one visit only, and the possibility that due to the sample size there was an inability to detect a significance difference. Among the 194 non-drinkers in our study, only 61 had information on past drinking. The OR for former drinkers versus lifetime abstainers was 1.15 (95%CI = 0.34–3.86) for SLD, making it difficult

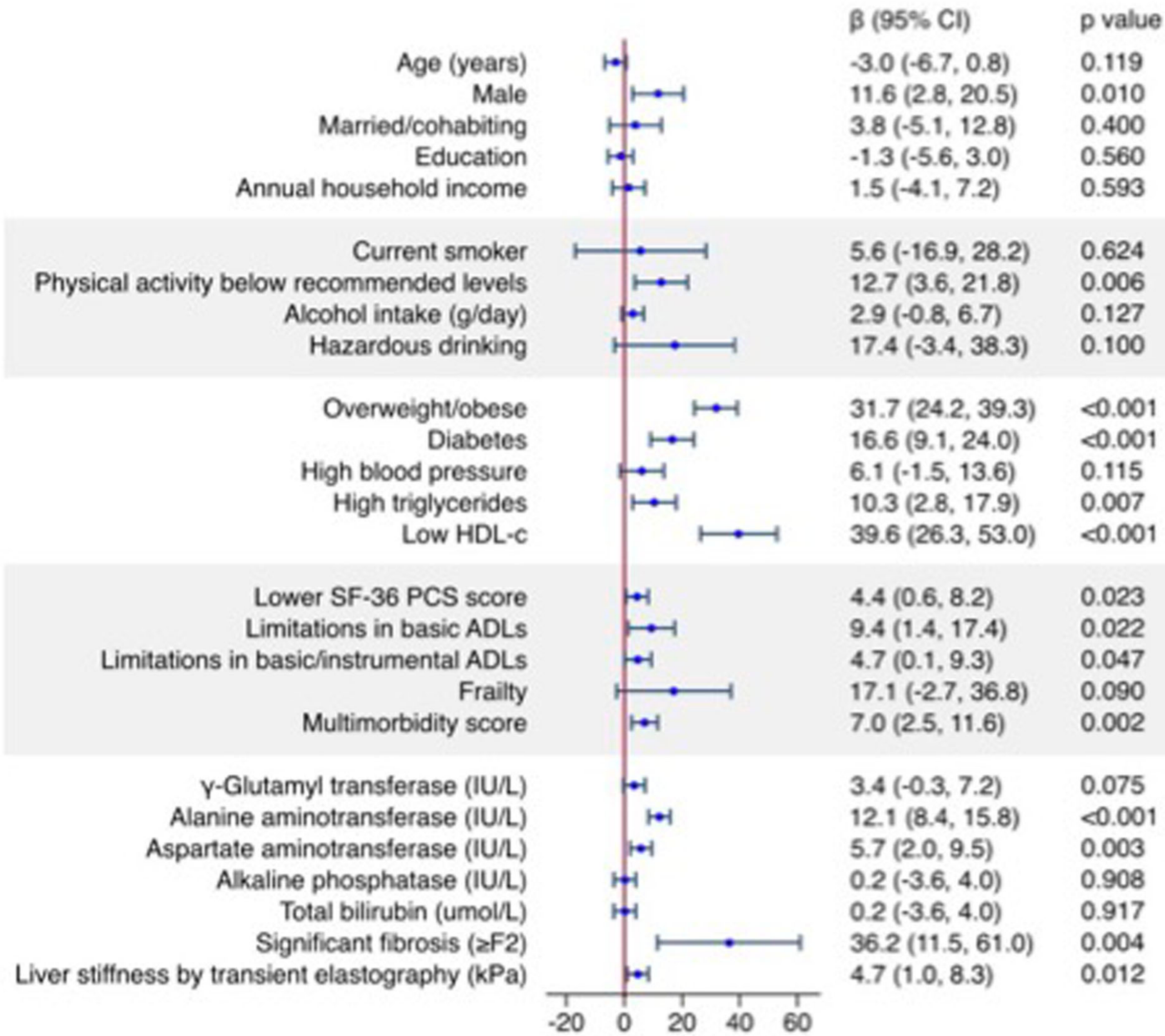

Fig. 2 | Association of risk factors and adverse health conditions with controlled attenuation parameter (CAP). Association of risk factors and adverse health conditions with controlled attenuation parameter (CAP) in analysed participants ($n = 983$). The β coefficients from univariate regression indicated the change in CAP (dB/m) for a one-SD increase in continuous variables, one additional limitation in activities of daily living (ADLs), or a one-category change or increase in dichotomous or ordinal categorical variables. One SD corresponds to 2.7 years for age, 17.8 g/day for alcohol intake, 7.0 for the SF-36 PCS score, 40.9 IU/L for γ-Glutamyl transferase, 11.3 IU/L for alanine aminotransferase, 6.6 IU/L for aspartate aminotransferase, 19.0 IU/L for alkaline phosphatase, 5.9 umol/L for total bilirubin, and 3.5 kPa for liver stiffness. Education was categorized as no or lower primary school, lower secondary school, higher secondary school, university degree or higher, and annual household income as less than £25,000, £25,000 to 50,000, and £50,000 or greater.

to draw firm conclusions on sick quitter bias. Of note, in the Australian cohort of older adults described by Clayton-Chubb et al., no association between alcohol use and elevated FLI was found[13].

This study has several strengths, including a sample size of nearly 1000 participants, comprehensive evaluation of biological and lifestyle factors, and application of the recently defined classification of SLD which has been used for the presented analyses. However, there are several limitations which should be acknowledged. First, the study population is not fully representative, since it is drawn from the Whitehall II cohort which predominantly consists of male and Caucasian participants, restricting the generalizability of our prevalence findings to the wider population. It is increasingly recognised that certain non-Causasian populations may have an increased risk of SLD[23], and data collected from more diverse cohorts may show increased SLD prevalence. Nevertheless, the associations of cardiometabolic risk factors observed in the Whitehall II cohort are generally consistent with those in nationally representative studies[24]. Additionally, this study did not have data on platelet count, which precluded the calculation of the fibrosis-4 (FIB-4) score. While FIB-4 is widely used to assess fibrosis in clinical practice, it has been found to be less accurate in older adults (aged ≥65 years)[25]. Clinical characteristics were measured, on average, 4 years before TE and may have varied over time. Finally, as a prevalence study, the observed associations may be subject to residual confounding. The scope of this paper, however, is to identify potential associations of SLD with a broad range of risk factors, notably markers of ageing and frailty, rather than to establish causality.

Nevertheless, this large study provides the first data demonstrating an association between SLD, assessed by TE, with frailty and multimorbidity in older adults. There are several important public health implications; firstly, these data reaffirm that SLD in older adults is associated with cardiometabolic risk factors, but the prevalence of advanced liver disease is relatively low. Secondly, as population-based screening efforts for MASLD and liver fibrosis are initiated, these data will help inform upper age limits for screening and detection of advanced liver disease. Thirdly, these data suggest that conventional advice for SLD in younger adults, in terms of cardiovascular exercise, may need to be modified for older adults with different levels of physical performance. In particular, these data suggest caution in

Table 2 | Characteristics of participants based on the presence of steatotic liver disease (controlled attenuation parameter ≥275 dB/m)

	SLD (n = 327)	No SLD (S0; n = 482)	Age-sex-adjusted OR (95%CI)	p value
Age, years	72.4 (2.7)	72.6 (2.8)	0.95 (0.82–1.10)*	0.489
Male	271 (82.9%)	355 (73.7%)	1.72 (1.21–2.45)	**0.002**
Married/cohabiting	255 (78.2%)	363 (75.5%)	1.04 (0.74–1.47)	0.824
Education				
No or lower primary school	12 (4.0%)	17 (4.0%)	0.92 (0.78–1.09) †	0.354
Lower secondary school	67 (22.4%)	101 (23.5%)		
Higher secondary school	100 (33.4%)	118 (27.5%)		
University degree or higher	120 (40.1%)	193 (45.0%)		
Annual household income				
<£25,000	38 (12.1%)	68 (14.6%)	1.07 (0.86–1.33) [b]	0.538
£25,000 to <50,000	146 (46.6%)	218 (46.9%)		
≥£50,000	129 (41.2%)	179 (38.5%)		
Current smoker	10 (3.1%)	13 (2.7%)	1.11 (0.48–2.56)	0.816
Physical activity below recommended levels	230 (78.2%)	291 (69.5%)	1.60 (1.13–2.27)	**0.008**
Alcohol intake, g/day	12.6 (2.3-25.1)	11.4 (3.4-22.9)	1.05 (0.91–1.21)[a]	0.488
Hazardous drinking (AUDIT-C score ≥5)	14 (4.4%)	13 (2.8%)	1.45 (0.67–3.14)	0.350
Cardiometabolic risk factors				
Overweight/obese	264 (80.7%)	250 (51.9%)	3.91 (2.81–5.43)	**<0.001**
Diabetes	187 (57.2%)	205 (42.5%)	1.84 (1.38–2.45)	**<0.001**
High blood pressure	200 (61.2%)	247 (51.2%)	1.49 (1.12–1.99)	**0.006**
High triglycerides	172 (52.6%)	204 (42.3%)	1.46 (1.10–1.94)	**0.009**
Low HDL-c	49 (15.0%)	25 (5.2%)	3.23 (1.95–5.37)	**<0.001**
Motor function and disability				
SF-36 PCS score	49.7 (7.1)	50.9 (7.0)	1.21 (1.05–1.40) [a]	**0.008**
≥2 limitations in basic ADLs	12 (3.7%)	6 (1.2%)	3.19 (1.17–8.64)	**0.023**
≥2 limitations in basic/instrumental ADLs	16 (4.9%)	11 (2.3%)	2.28 (1.04–5.01)	**0.040**
Frailty	6 (1.8%)	3 (0.6%)	3.29 (0.80–13.45)	0.098
Multimorbidity score	1.0 (0.9)	0.8 (0.8)	1.45 (1.22–1.73)	**<0.001**
Liver parameters				
γ-Glutamyl transferase, IU/L	27 (20–36)	21 (15–30)	1.25 (1.03-1.52)*	**0.021**
Alanine aminotransferase, IU/L	28.3 (12.8)	23.6 (10.0)	1.54 (1.30-1.83)*	**<0.001**
Aspartate aminotransferase, IU/L	23.0 (6.9)	21.7 (6.7)	1.19 (1.04-1.38)*	**0.015**
Alkaline phosphatase, IU/L	66.4 (20.3)	66.1 (17.6)	1.07 (0.92-1.24)*	0.387
Total bilirubin, umol/L	10.9 (5.4)	10.8 (5.5)	0.98 (0.83-1.14)*	0.772

Data are n (% of available data), mean (SD), or median (IQR).
SLD teatotic liver disease, *AUDIT-C* Alcohol Use Disorders Identification Test for Consumption, *SF-36 PCS score* Physical Component Summary score of Short Form 36 General Health Survey; *ADLs* activities of daily living.
[a]Association with a one-SD increase using the scale from Fig. 2.
[b]Association with a one-category higher level in the ordinal education or household income variable.

older adults with the use of newer agents that are associated with muscle loss, such as GLP1-agonists[26]. Finally, longitudinal studies in this patient group are warranted to see if SLD is a modifiable risk factor for frailty and multimorbidity in older adults, particularly in view of the rising global prevalence of SLD and the healthcare burden of an ageing, multimorbid population.

Methods

Study design and participants

Participants were prospectively recruited within the Whitehall II study, an ongoing cohort study of 10,308 participants recruited from the British Civil Service between 1985-1988. All participants completed a comprehensive questionnaire and underwent a uniform, structured, clinical evaluation at baseline, and approximately every 5 years thereafter. Participant consent and research ethics approval were renewed at each contact; the most recent approval was granted by the NHS London-Harrow Research Ethics Committee (reference number 85/0938).

Transient elastography (TE; FibroScan) was introduced in March 2019 as part of a nested study within the Whitehall II cohort (PB-PG-0418-20038). This analysis includes participants who underwent TE before clinic closures due to the COVID-19 pandemic. Data on cardiometabolic risk factors, health behaviours, socioeconomic factors, and adverse health conditions were drawn from phase 12, the most recently completed phase prior to the time of TE, with a median interval of 4.1 years.

Assessment of steatosis and fibrosis

TE with controlled attenuation parameter (CAP) was used to assess liver fibrosis and steatosis respectively. Participants were required to have at least

Table 3 | Characteristics of participants based on the presence of significant fibrosis (F2-F4)

	F0-F1 (*n* = 951)	F2-F4 (*n* = 23)	Age-sex-adjusted OR (95%CI)	*p* value
Age, years	72.5 (2.8)	71.9 (1.6)	0.74 (0.43–1.27)[a]	0.277
Male	723 (76.0%)	22 (95.7%)	6.76 (0.91–50.49)	0.062
Married/cohabiting	730 (76.9%)	21 (91.3%)	2.55 (0.59–11.07)	0.212
Education				
No or lower primary school	38 (4.4%)	0 (0.0%)	0.69 (0.43–1.12) [b]	0.132
Lower secondary school	185 (21.6%)	8 (40.0%)		
Higher secondary school	252 (29.4%)	6 (30.0%)		
University degree or higher	382 (44.6%)	6 (30.0%)		
Annual household income				
<£25,000	123 (13.5%)	3 (13.0%)	1.11 (0.58–2.12)[b]	0.751
£25,000 to <50,000	431 (47.3%)	9 (39.1%)		
≥£50,000	358 (39.3%)	11 (47.8%)		
Physical activity below recommended levels	619 (73.5%)	16 (80.0%)	1.47 (0.49–4.47)	0.494
Alcohol intake, g/day	12.6 (4.6-24.0)	15.4 (9.1-26.3)	1.09 (0.74–1.62)[a]	0.649
Cardiometabolic risk factors				
Diabetes	454 (47.7%)	16 (69.6%)	2.62 (1.06–6.45)	**0.036**
Overweight/obese	595 (62.6%)	12 (52.2%)	0.64 (0.28–1.46)	0.287
High blood pressure	512 (53.8%)	13 (56.5%)	1.11 (0.48–2.58)	0.803
High triglycerides	431 (45.3%)	13 (56.5%)	1.47 (0.64–3.41)	0.366
Low HDL-c	76 (8.0%)	5 (21.7%)	3.03 (1.09–8.45)	**0.034**
Motor function and disability				
SF-36 PCS score	50.5 (7.0)	52.0 (3.9)	0.82 (0.49–1.39)[a]	0.470
≥2 limitations in basic/instrumental ADLs	30 (3.2%)	2 (9.1%)	3.26 (0.72–14.81)	0.126
Multimorbidity score	0.9 (0.8)	1.2 (0.9)	1.58 (1.01–2.47)	**0.044**
Liver parameters				
γ-Glutamyl transferase, IU/L	23 (17–33)	44 (35–56)	1.33 (1.11–1.59)[a]	**0.002**
Alanine aminotransferase, IU/L	25.1 (11.0)	36.5 (19.9)	1.59 (1.26–2.01)[a]	**<0.001**
Aspartate aminotransferase, IU/L	21.9 (6.4)	28.0 (13.8)	1.53 (1.21–1.94)[a]	**<0.001**
Alkaline phosphatase, IU/L	66.1 (18.1)	72.7 (43.4)	1.34 (1.01–1.78)[a]	**0.040**
Total bilirubin, umol/L	11.0 (5.9)	12.2 (6.8)	1.09 (0.76–1.55) [a]	0.637

Data are n (% of available data), mean (SD), or median (IQR); association was not estimated for current smoking, hazardous drinking, two or more limitations in basic ADLs, and frailty due to the absence of cases with these characteristics in the fibrosis (F2-F4) group.
AUDIT-C Alcohol Use Disorders Identification Test for Consumption, *SF-36 PCS score* Physical Component Summary score of Short Form 36 General Health Survey; *ADLs* activities of daily living.
[a]Association with a one-SD increase using the scale from Fig. 2.
[b]Association with a one-category higher level in the ordinal education or household income variable.

ten valid CAP readings within the range of 100-400 dB/m to be eligible for analysis[27]. SLD was defined as a CAP ≥ 275 dB/m[28]. For inclusion in the analysis of liver fibrosis, participants needed at least ten valid liver stiffness measurements (LSM). If a participant's median LSM was greater than 7.1 kPa, the interquartile range (IQR) to median ratio had to be less than 30% to be considered valid[29]. Significant fibrosis was defined by an LSM of ≥7.9 kPa (comparable to fibrosis histological stage F2-F4).

Participants with SLD were further subclassified according to the new nomenclature into the following categories: 1) MASLD, defined as the presence of at least one cardiometabolic risk factor (as described below) and no other discernible cause, this has replaced the previous term non-alcoholic fatty liver disease (NAFLD); 2) Met-ALD, defined as the presence of at least one cardiometabolic risk factor and an average alcohol intake of 20–50 g/day for women and 30–60 g/day for men; 3) ALD + , defined as the presence of at least one cardiometabolic risk factor and an alcohol intake of >50 g/day for women and >60 g/day for men; 4) ALD-only, defined as no cardiometabolic risk factors and an alcohol intake of ≥20 g/day for women and ≥30 g/day for men, ALD+ and ALD-only were combined and referred to as ALD; Cryptogenic SLD, defined as the absence of cardiometabolic risk factors and an alcohol intake of <20 g/day for women and <30 g/day for men[10].

Cardiometabolic risk factors

Cardiometabolic risk factors used for the classification of SLD were as follows: overweight/obese (body mass index; BMI) ≥ 25 kg/m², or waist circumference>80 cm for women and >94 cm for men), diabetes (fasting glucose≥5.6 mmol/L, HbA1c ≥ 5.7%, reported doctor-diagnosed diabetes, ICD-10 codes E10-14, or use of diabetes medication), high blood pressure (systolic/diastolic blood pressure≥130/85 mmHg or use of antihypertensive drug), high triglycerides (triglycerides≥1.70 mmol/L or use of lipid-lowering drug), low HDL-c (HDL-c ≤ 1.3 mmol/L for women and ≤1.0 mmol/L for men).

Health behaviours and socioeconomic factors

Participants were asked to report the number of alcoholic drinks they had consumed in the last 7 days for beer/cider (pints), wine (glasses), and spirits (measures) separately. Drinks were converted into UK units of alcohol (where one unit is equivalent to 8 grams of ethanol), using a conservative estimate: one UK unit for each measure of spirits, and two UK units for each glass of wine or pint of beer[30]. These converted measurements were then summed to determine the average daily consumption of alcohol in grams.

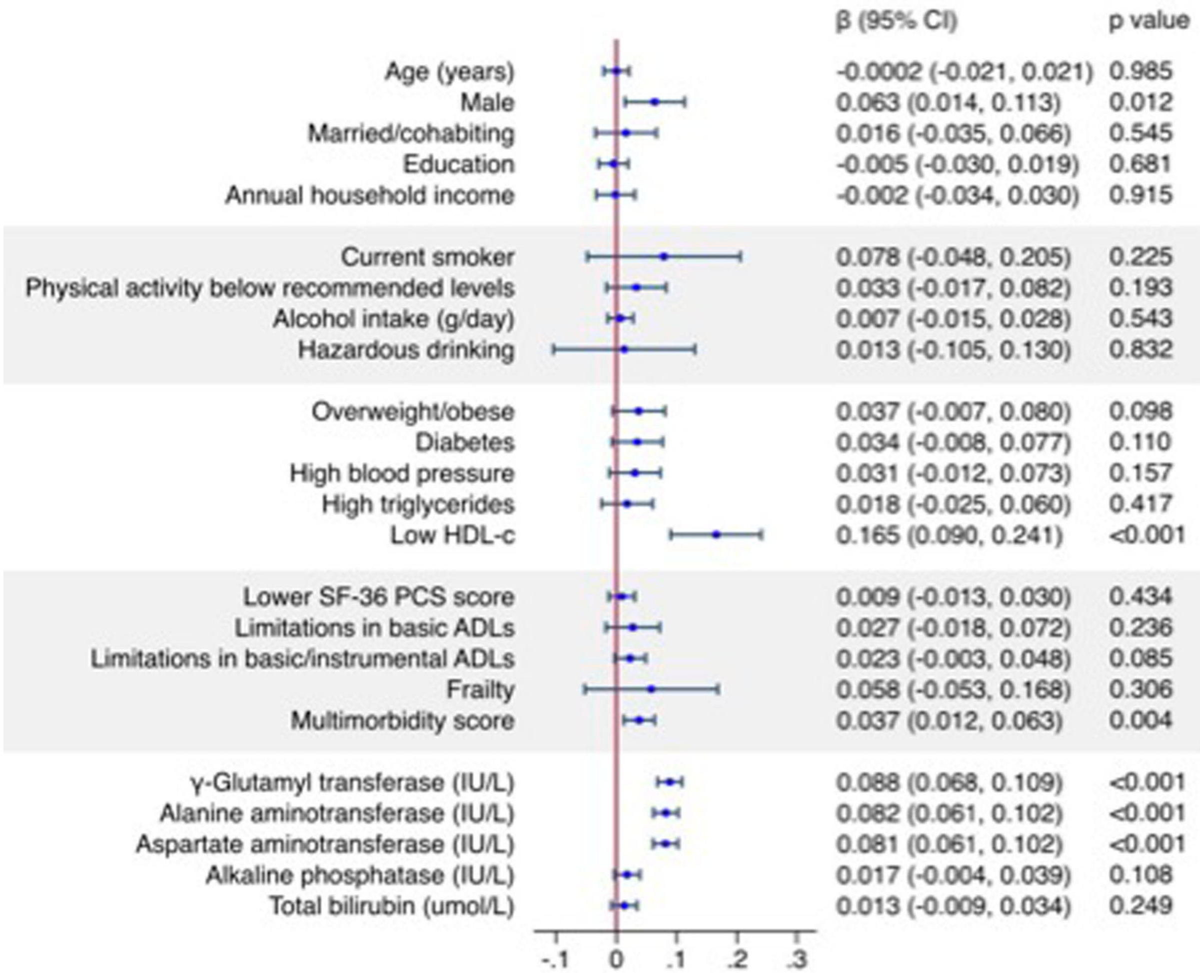

Fig. 3 | Association of risk factors and adverse health conditions with liver stiffness. Association of risk factors and adverse health conditions with liver stiffness by transient elastography in analysed participants ($n = 974$). When multiplied by 100, the β coefficients from univariate regression indicate the percentage difference in liver stiffness (kPa) for a one-SD increase in continuous variables, one additional limitation in activities of daily living (ADLs), or a one-category change or increase in dichotomous or ordinal categorical variables. The scale for one-SD increments and for categories of education and household income is the same as in Fig. 2.

Additional information was collected on the Alcohol Use Disorder Identification Test for Consumption (AUDIT-C) score[31], using a cut-off of 5 for hazardous drinking. Other health behaviours and socioeconomic factors included smoking status (current or non-smoker), physical activity (less than or at least the recommended 2.5 h per week of moderate-to-vigorous physical activity), marital status (married/cohabiting, others), education (no or lower primary school, lower secondary school, higher secondary school, university degree or higher), and annual household income (less than £25,000, £25,000-50,000, £50,000 or greater).

Adverse health conditions

Disability was assessed by difficulties in activities of daily living (ADLs), using a modified version of the Katz Index of Independence in ADLs[32]. Basic ADLs included dressing, walking, bathing, eating, getting in bed, and using the toilet, and the instrumental ADLs were cooking, shopping for groceries, making telephone calls, taking medication, doing housework, and managing money. In addition, motor functioning was measured using the physical component summary score of the Short Form 36 General Health Survey (SF-36 PCS score)[33]. A low SF-36 PCS score indicates limitations in self-care and daily activities, experiencing severe pain, and poor general health.

Frailty was measured using the Fried frailty scale, with the threshold for each criterion based on the original[34] and detailed in Table S3. Variables within the scale are low physical activity, slow walking speed, poor grip strength, weight loss, and exhaustion. Of note, low physical activity in the Fried frailty scale is defined as energy expenditure <383 kcal/week in men or <270 kcal/week in women, which is different to the definition of low physical activity used for other analyses (above). Participants were classified as frail if they met at least three of the frailty criteria.

A multimorbidity score was constructed by counting the presence of nine specific chronic conditions, which are the leading causes of death in high-income countries[35]. We ascertained chronic diseases by using data from multiple sources, including clinical examinations in the study and linkage to electronic health records. We used three national databases: the national hospital episode statistics (HES) database with inpatient and outpatient data, the Mental Health Services Data Set (which in addition to inpatient and outpatient data also has data on care in the community), and the cancer registry. The nine chronic conditions considered were: diabetes (as defined above in cardiometabolic risk factors), coronary heart disease (ICD-10 codes I20-I25), stroke (ICD-10 codes I60-I64), chronic obstructive pulmonary disease (ICD-10 codes J41-J44), arthritis (ICD-10 codes M15-M19), depression (use of antidepressants or ICD-10 codes F32-F33), cancer (ICD-10 codes C00-C97 to include colorectal, lung, breast, prostate, smoking related, and melanoma skin cancers), Parkinson's disease (ICD-10 code G20), and dementia (ICD-10 codes F00-F03, F05.1, G30, G31).

Statistical analysis

Univariate linear regression models were used to examine the associations of continuous CAP and LSM with different characteristics/risk factors, adverse health conditions, and liver parameters. Continuous data on these factors were standardized using SD scaling to facilitate interpretation and comparison. A nature log-transformation was applied to LSM to achieve normal distribution. When multiplied by 100, the β coefficients from the linear regression analyses of log-transformed LSM can be interpreted as the percentage change associated with a one-SD change in continuous variables or as the percentage difference relative to the reference group[36]. After categorising individuals as having or not having SLD and significant liver fibrosis, we used logistic regression models to examine associations, adjusting for age and sex. Additionally, a sensitivity analysis was conducted using a higher CAP threshold of 290 dB/m to define SLD[37]. All analyses were performed using Stata 17. A two-sided p value of <0.05 was considered statistically significant.

Data availability

These Whitehall II data are available to researchers for research purposes or replication. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing.

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Author contributions

Study concept and design: G.M., A.B.; acquisition of data: O.O., C.D., N.B., D.N., S.S., L.N.F., E.T., S.B., G.M., A.B.; analysis and interpretation of data: O.O., C.D., S.B., G.M., A.B.; drafting of the manuscript: O.O., C.D., G.M., A.B.; statistical analysis: O.O., C.D.; critical revision and approval of the manuscript: O.O., C.D., N.B., D.N., S.S., M.S., R.A., L.N.F., E.T., S.B., G.M., A.B.; study supervision: G.M., A.B.

Competing interests

GM has shares in Hepyx Limited and Yaqrit Limited, which are involved in liver disease therapeutics. GM is an inventor of 'Treatment of Pyroptosis in Liver Disease' (Patent filing: US20210069296A1; EP19721333.3A). The remaining authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to G. Mehta or A. Britton.