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Unequal mortality risks in steatotic liver disease beyond liver: influence of disease subtypes and fibrosis

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Abstract

Background and aims: To examine mortality risks associated with steatotic liver disease (SLD), focusing on how disease subtypes (MASLD, MetALD, ALD), and fibrosis severity shape cause-specific mortality across a broad spectrum of diseases.

Methods: We analysed 486156 UK Biobank participants. Causes of death were summarised by SLD subtypes. Multivariable Cox models estimated associations between SLD, its subtypes, and fibrosis severity (FIB4 score), with cause-specific mortality outcomes across ICD10 disease categories.

Results: Among 178336 participants with SLD, 20766 died over a median follow up of 13.8 years. The leading causes of deaths were neoplasm (46.4%), circulatory disease (24.2%), respiratory disease (7.0%), and digestive disease (4.8%). Compared to participants without SLD (n=307820), those with SLD had significantly higher mortality from neoplasm (HR 1.24 (1.20, 1.28)), circulatory (1.57 (1.50, 1.64)), and digestive diseases (1.85 (1.67, 2.05)), as well as from metabolic, and genitourinary diseases, across all FIB4 score levels. Elevated risks were also observed for mortality from diabetes (3.40 (2.59, 4.46))), Covid-19 (1.97 (1.76, 2.21)), myocardial infarction (1.69 (1.53, 1.86)), stroke (1.24 (1.04, 1.48)), and several cancers, such as breast (1.50 (1.35, 1.68)),

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colorectal (1.22 (1.11, 1.34)), and prostate cancer (1.22 (1.09, 1.37)). Importantly, SLD subtypes exhibited distinct and unequal patterns of cause-specific mortality, with further stratification by fibrosis severity revealing graded risk differentials.

Conclusion: SLD is associated with unequal mortality risks across a wide range of disease categories, driven by substantial heterogeneity across subtypes, fibrosis severity and outcomes. Extrahepatic cancers and circulatory diseases contribute most to overall mortality, but the magnitude of risk varies markedly. These findings highlight the need for risk-stratified, multidisciplinary management strategies that account for both subtypes and fibrosis stage, targeting liver progression, cardiometabolic burden, and cancer prevention.

Keywords: steatotic liver disease; mortality; fibrosis; cardiometabolic disease.

1. Introduction

Steatotic liver disease (SLD) affects one in three adults globally [1]. It encompasses three subtypes: metabolic dysfunction associated steatotic liver disease (MASLD), alcohol related liver disease (ALD), and metabolic dysfunction and alcohol-related steatotic liver disease (MetALD). MASLD is linked to increased risk of various extrahepatic conditions, including cardiovascular disease (CVD), and extrahepatic cancers [2,3].

The impact of SLD on mortality remains incompletely understood. Most studies concentrated on all-cause mortality, liver related mortality, CVD and cancer mortality [4], with mixed results. A systematic review reported that MASLD increased mortality overall and from liver-related diseases[5], in contrast to the null associations found in another review [6]. These discrepancies may be due to variations in study populations, disease definition, and more importantly, disease subtypes and severity.

Emerging evidence suggests that mortality risk may differ substantially across subtypes and fibrosis severity in SLD. However, this heterogeneity remains poorly characterised. First, most existing research has focused on a few causes of death [4], leaving many other causes underexplored. Second, comparative evidence on mortality risk across disease subtypes and fibrosis severity is limited. A more granular, stratified approach is therefore needed to uncover mortality variation across disease phenotypes and severity. To address these limitations, this study aimed to provide a comprehensive assessment of mortality patterns in individuals with SLD.

2. Methods

2.1 Data and participants

This study utilised the UK Biobank data, a prospective cohort comprising half million UK residents aged 40 - 70 years, recruited 2006 -2010. Baseline assessment included socioeconomic status, lifestyle, environmental exposure, medical history, and physical

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measures. Participants were followed up via linkage to national death registries, and hospital records.

SLD was defined as fatty liver index (FLI) ≥ 60. FLI is an indicator for liver steatosis [7]. The cutoff value of 60 to define liver steatosis has been used extensively and validated [8]. In a sensitivity analysis, we replaced FLI with hepatic steatosis index (HSI), another measure for liver steatosis [9]. SLD subtypes (MASLD, MetALD, and ALD) were defined based on alcohol consumption and presence of cardiometabolic risk factors (CMRFs), using the definition recommended by the latest SLD guideline [10]. The daily alcohol consumption cutoff values for MASLD, MetALD and ALD were < 20/30 (females/males), 20-50/30-60, and > 50/60 g/day, respectively. We excluded women who were pregnant at baseline, and people who had missing data for calculating FLI.

Participants with presence of liver steatosis were classified as having MASLD, MetALD or ALD, and as Others if they had viral hepatitis, hemochromatosis, Wilson's disease, biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, drug-induced liver injuries or Budd-Chiari syndrome. These chronic liver diseases were ascertained via hospital records; the code lists for these conditions are presented in supplementary methods.

Participants with SLD were further categorised into three groups based on FIB4 score, a non-invasive marker for fibrosis status. We used the cutoff values 1.30 and 2.67 to categorise low, intermediate and high levels of FIB-4 score for people < 65 years, and 2.00 and 2.67 for people ≥ 65 years [11].

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2.2 Covariates

Ethnicity was classified into White, and mixed/others. The Townsend Deprivation Index was used to assess socioeconomic status. Lifestyle factors included smoking status (current, previous and never smoker), alcohol intake, and physical activity level. Alcohol intake was assessed via self-reported consumptions of various alcoholic drinks summed up to derive the average alcohol consumption (g/day). Physical activity level was categorized into low, moderate and high levels, based on the frequency, duration and intensity of their physical activities. Systolic and diastolic blood pressure (BP) were measured twice and the averages were used in analyses. Blood biochemistry markers were measured at the central laboratory, including triglycerides (TG), high density lipoprotein (HDL), and glycated haemoglobin (HbA1c). Aligning with the SLD guideline, we considered five CMRFs: Overweight/obesity was defined as body mass index (BMI) ≥ 25 kg/m ² or waist circumference (WC) >94 cm (male) or >90 cm (female). Prediabetes/diabetes was defined as HbA1c ≥ 48mmol/mol or diagnosis of type 2 diabetes or on treatment for type 2 diabetes. Hypertension was defined as systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or on antihypertensive drug treatment or diagnosis of hypertension. High TG was defined as plasma TG ≥ 1.70 mmol/L or on lipid lowering treatment. Low HDL was defined as HDL-cholesterol ≤1.0 mmol/L (male) or ≤1.3 mmol/L (female) or on lipid lowering treatment [10].

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2.3 Outcomes

We examined causes of death by ICD10 disease category, including infectious/parasitic (ICD10 codes: A00-B99), neoplasms (C00-D48), haematological (D50-D89), endocrine/ metabolic (E00-E99), mental/behavioral (F00-F99), nervous system (G00-G99), eye/adnexa (H00-H59), ear/mastoid (H60-H69), circulatory (I00-I99), respiratory (J00-J99), digestive (K00-K99), skin/subcutaneous (L00-L99), musculoskeletal (M00-M99), genitourinary (N00-N99), pregnancy/childbirth (O00-O99), congenital (Q00-Q99), symptoms/signs (R00-R99), injury/poisoning (S00-T98), external causes (V01-Y98), special purpose codes (U00-U99) and health services (Z00-Z99). We additionally evaluated the associations with common disease-specific causes in this cohort. Participants were censored at the date of death or the last date of follow-up (30 November 2022), whichever occurred first.

2.4 Statistical analysis

We summarised the number of deaths from each ICD10 disease category, and identified the top 10 most common ICD10 codes in each category. Cox models were used to assess the association between SLD, subtypes, FIB4 score and mortality, expressed as hazard ratio (HR) and 95% confidence interval (CI), using individuals without SLD as reference. Models were stratified by region and age group (< vs. ≥ 65 years old), and adjusted for sex, ethnicity, education, Townsend Deprivation Index (in fifths), physical activity, smoking, and daily alcohol consumption. Cox models were not fitted for outcomes with < 50 deaths. The proportional hazard assumption was examined by scaled Schoenfeld residuals, and no evidence was observed for violation.

We conducted several sensitivity analyses. First, we additionally adjusted for the CMRFs to examine the association robustness and whether the associations were independent of these risk factors. We did not include them in the primary analyses, because cardiometabolic risk factors form part of the diagnostic definition of SLD subtypes, and may also lie on the pathway between SLD and mortality. Second, we excluded the first two years of follow-up to allow for reverse causation bias. Third, alternative to FLI, we used HSI as a surrogate for liver steatosis, with HSI > 36 indicating presence of liver steatosis. Although a subset of UK Biobank participants underwent liver MRI scans, which was a more accurate measure for liver fat, we could not conduct a similar sensitivity analysis, because FIB4 data were not available at the time of the MRI scans. Fourth, we fitted Fine-Gray model to examine the associations, to account for competing risks to cause-specific death. We also conducted sex-specific analyses.

3. Results

Among 486156 eligible participants, 178836 were identified as having SLD (age 57.3 years, 36.3% females). Among people with SLD, 73.5% had MASLD, 19.0% MetALD, and 6.4% ALD (figure 1). Individuals with SLD were more likely to be older, male, more socioeconomically deprived, less educated, less physically active, and to have higher

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alcohol consumption, BMI, waist circumference, BP, TG, HbA1c, and to have lower HDL, compared to those without SLD. (table 1; supplementary Table 1)

FIB4 scores were not available for 4625 (2.6%) participants with SLD. Among those with available FIB4 scores, 68.7% had low FIB4 scores, while 28.7% and 2.6% had intermediate and high scores, respectively.

3.1 Causes of death

During a median follow-up of 13.8 years, 42520 deaths were recorded: 20766 (48.8%) in participants with SLD. Overall, six ICD10 disease categories accounted for 90% of all deaths: neoplasms (49.3%), circulatory (21.0%), respiratory (7.2%), nervous (6.0%), digestive (3.9%) diseases and special purpose codes (3.3%). Compared to individuals without SLD, those with SLD had a higher proportion of deaths from circulatory (24.2% vs. 17.9%), special purpose codes (4.1% vs. 2.5%), endocrine/metabolic (1.5% vs. 0.9%) and digestive (4.8% vs. 3.1%) diseases. (figure 2, supplementary table 2)

Among neoplasms-related deaths, the most common cancers were lung (C34, 16.9%), pancreatic (C25, 7.5%), breast (C50, 7.3%), prostate (C61, 6.0%) and colon (C18, 5.3%) (supplementary table 3). Liver cancer (C22) accounted for 3.4% of neoplasm-related death (2.6% and 4.1% in people without and with SLD, respectively). Leading causes of circulatory mortality were ischemic heart disease (I25, 30.3%), myocardial infarction (I21, 20.4%), and stroke (I64, 6.4%). For respiratory disease, the top contributor was COPD (J44, 37.2%). Alzheimer's disease (G30, 31.6%) and Parkinson's disease (G20, 21.6%) were the top causes of nervous system deaths. Nearly all deaths in the special purpose codes chapter were attributed to Covid-19 (U07, 97.3%). In digestive disease category, ALD (K70, 20.1%), vascular disorders of intestine (K55, 11.2%) and hepatic fibrosis/cirrhosis (K74, 9.1%) were the most common; overall 66.6% were liver-related (K70-K77). Dementia (F03, 66.0%; F01, 28.7%) and diabetes (E11, 30.6%; E14, 23.5%) were the most common mental/behavioral and metabolic causes, respectively. Chronic kidney disease (N18) contributed 19.4% of the genitourinary deaths.

3.2 Associations with mortality outcomes

Overall mortality was higher in people with SLD compared to those without, with an absolute mortality rate difference of 3.53/1000 person-years (pys) (8.78 vs. 5.25 /1000 person-years), corresponding to a 28% higher mortality (HR (95%CI): 1.28 (1.26, 1.31)). Progressively higher mortality rate was observed with higher FIB4 score: compared to those without SLD, participants with SLD with low, intermediate and high FIB4 scores also had higher mortality by 11%, 63%, and 162%, respectively.

By ICD10 disease categories, SLD was significantly associated with mortality from neoplasms (SLD vs non-SLD: mortality rate 4.05 vs. 2.71 /1000pys, HR 1.24 (1.20, 1.28)), circulatory diseases (2.11 vs. 0.93 /1000pys, 1.57 (1.50, 1.64)), digestive diseases (0.42

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vs. 0.16 /1000pys, 1.85 (1.67, 2.05)), special purpose codes (0.35 vs. 0.13 /1000pys, 1.92 (1.71, 2.15); mainly Covid-19 infection), endocrine/metabolic disease (0.13 vs. 0.04 /1000pys, 2.22 (1.83, 2.69)), genitourinary disease (0.08 vs. 0.03 /1000pys, 2.09 (1.63, 2.67)) and skin/subcutaneous diseases (0.02 vs. 0.01 /1000pys, 3.11 (1.83, 5.19)) (table 2). Furthermore, for intermediate and high FIB4 scores were also associated with increased mortality from respiratory diseases, respectively. We found no evidence for increased mortality from infectious/parasitic, mental/behavioural, musculoskeletal, nervous system diseases or external causes.

3.3 Associations by SLD subtypes

All three SLD subtypes were consistently associated with mortality from neoplasms, circulatory, digestive diseases and special purpose codes, although effect sizes varied. (figure 3)

MASLD was associated with the highest HR for endocrine/metabolic disease mortality (2.31 (1.88, 2.84)), higher than MetALD and ALD. MASLD also showed highest HR with circulatory disease mortality (1.64 (1.57, 1.72)), higher than MetALD and ALD. It also showed the highest risk for Covid-19-dominated special purpose related mortality (1.97 (1.74, 2.22)).

ALD had the strongest association with digestive disease mortality (3.65 (3.03, 4.39)), higher than MASLD and MetALD. ALD also showed a similarly elevated cancer mortality risk to MASLD, higher than MetALD.

MetALD was associated with increased mortality across these categories, but typically with lower HR than MASLD or ALD, suggesting an intermediate risk profile.

FIB4 score levels showed a consistent dose-response relationship with each cause-specific mortality. Genitourinary disease mortality was associated with MASLD (2.26 (1.74, 2.93)), but not with MetALD or ALD.

3.4 Sensitivity analyses

Sensitivity analyses adjusting for CMRFs and excluding the first two years of follow-up showed similar results to the primary analysis. Sensitivity analysis replacing FLI with HSI for liver steatosis also yielded consistent findings. Among all participants with available data on FLI and HSI, the FLI definition identified 178336 participants with SLD, while the HSI definition identified 211097 SLD cases, including 163467 (77.4%) MASLD, 35850 MetALD (17.0%) and 9359 (4.4%) SLD. The findings closely mirror the primary results using FLI, reinforcing the robustness of our conclusion across different case definitions. (supplementary table 4).

To account for competing risk, we fitted Fine-Gray models to assess the associations between SLD subtypes and cause-specific mortality, showing overall consistent results

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with the primary analysis. For mortality from neoplasm, the HR estimates were 1.26 (1.22, 1.30), 1.16 (1.10, 1.22) and 1.30 (1.21, 1.39) for MASLD, MetALD and ALD, respectively. For mortality from circulatory diseases, the according HR estimates were 1.64 (1.57, 1.72), 1.41 (1.31, 1.51) and 1.48 (1.33, 1.66) (Supplementary table 5). For other outcomes with smaller number of events, the direct of the associations remained although the 95%CI turned out to be wide, which is a common problem in Fine-Gray model.

Positive associations between SLD subtypes and mortality from neoplasms, endocrine/metabolic, circulatory, digestive and respiratory diseases were observed in both females and males (Supplementary table 6). However, the associations for MASLD were generally stronger in females than in males, particularly for mortality from neoplasm, endocrine/metabolic, circulatory, digestive, respiratory diseases and Covid-19.

3.5 Associations with mortality from specific diseases

We observed positive associations of SLD with mortality from female breast cancer (C50, HR 1.50 (1.35, 1.68)), male prostate cancer (C61, 1.22 (1.09, 1.37)), colorectal cancer (C18-C21, 1.22 (1.11, 1.34)), pancreatic cancer (C25, 1.33 (1.20, 1.48)), ischemic heart disease (I25, 1.73 (1.59, 1.87)), myocardial infarction (I21, 1.69 (1.53, 1.86)), stroke (I64, 1.24 (1.04, 1.48)), diabetes (E10-E14, 3.40 (2.59, 4.46)), and Covid-19 (U07, 1.97 (1.76, 2.21)). There was a marginal association between MASLD and lung cancer mortality . We observed negative associations with mortality of COPD, Alzheimer's disease, and Parkinson's disease. (table 3)

4. Discussion

In this UK-based cohort, neoplasm and circulatory diseases were the predominant causes of death, jointly representing over 70% of all deaths, whereas deaths from digestive disease accounted for a small proportion (4.8%), and 66.6% of these deaths (3.2% of total deaths) were due to liver diseases.

Although neoplasm and circulatory disease were the leading causes of death across all SLD subtypes[12,13], SLD subtypes demonstrated distinct cause-specific mortality patterns. Particularly, individuals with ALD showed a substantially higher proportion of deaths from digestive diseases than MASLD and MetALD. Among all digestive disease related death, liver-related conditions, including ALD itself and fibrosis/cirrhosis, accounted for the majority across all subtypes: 58.2%, 86.1% and 79.1% for MASLD, MetALD and ALD, respectively, corresponding to the overall liver related mortality of 2.3%, 3.5% and 7.8%. These findings highlighted the disproportionate burden of liver-related mortality in ALD.

SLD showed elevated mortality from several major disease categories, including neoplasm, circulatory disease, digestive disease, and endocrine/metabolic disease, consistent with previous evidence[14 15]. We found that ALD had strongest associations with digestive-related mortality (mainly liver-related deaths), consistent with a Swedish

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study [16]. This may be partly explained by the higher prevalence of advanced fibrosis among people with ALD [17]. In contrast, MASLD exhibited stronger associations with mortality from circulatory and endocrine/metabolic diseases, reflecting the higher cardiometabolic burdens in MASLD [18]. These findings suggest that, rather than treating SLD as a single entity, risk assessment should be individualised according to SLD subtypes. All SLD subtypes would benefit from cardiometabolic and cancer risk management, whereas individuals with ALD also require close surveillance for liver progression.

Beyond these commonly investigated outcomes, we also found evidence linking SLD and mortality from skin/subcutaneous, genitourinary and respiratory diseases. Due to the low number of skin/subcutaneous disease related deaths, we were unable to assess associations with specific ICD10 codes in this category. In the genitourinary category, MASLD showed strong associations with chronic kidney disease, the predominant diagnosis in this category[19]. For overall respiratory disease mortality, only intermediate and high FIB4 scores were linked to higher risk[20]. However, both MASLD and MetALD were associated with lower mortality of COPD, the most frequent respiratory cause of death. Although MASLD has been reported as an independent risk factor for COPD incidence[21], its association with COPD-specific mortality has not been well established, and future investigations are warranted.

Interestingly, we observed inverse associations between SLD and mortality of Alzheimer's disease and Parkinson's disease, which should be interpreted with caution. They may reflect competing risks, whereby individuals with SLD die earlier from CVD, cancer or liver-related complications before developing or dying from these conditions. Cause-of-death misclassification may also contribute, as we only studied primary underlying cause recorded on death certificates, rather than all contributing causes, potentially underestimating mortality attributable to neurodegenerative diseases. Residual confounding may also have influenced these associations. Consequently, these findings should not be interpreted as evidence of a protective effect of SLD, and further studies are needed to determine whether they reflect true biological mechanisms or methodological artefacts.

We also found that SLD was associated with Covid-19 mortality, and MASLD showed the strongest associations, suggesting that the cardiometabolic burdens may exacerbate outcomes in covid-19 infection. A previous review of 5198 individuals found that NAFLD was associated with 67% higher risk of severe Covid-19, but did not significantly affect Covid-19 mortality [22]. Our study provided evidence for such an association with a much larger sample size. Hoffmann et al. reported a bidirectional positive association between Covid-19 infection and NAFLD [23].

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Our findings were generally consistent with a Swedish nationwide cohort [20] of 13000 clinically diagnosed MASLD individuals reporting increased mortality from cancers, circulatory, digestive, respiratory, mental health and endocrine disorders. However, several important differences distinguish our work. First, the Swedish cohort identified MASLD cases via ICD10 codes, which preferentially identified severe cases. Second, their adjustment for confounding was limited to age, sex, education, region and the Charlson comorbidity index, whereas our study additionally adjusted for lifestyle factors. Third, they did not explore specific diseases in each mortality category. Most importantly, their analysis was restricted to MASLD, whereas our study investigated the full spectrum of SLD subtypes.

Although SLD is traditionally viewed as a liver disorder, liver-related deaths accounted for only a small proportion of overall mortality, which reinforces the growing recognition of SLD as a multisystem disease with prognosis largely driven by extrahepatic complications. Given the broader range of disease-specific mortality seen in this study, coordinated multidisciplinary care is required to address the complex needs of people living with SLD. Since extrahepatic cancer and circulatory disease are the predominating causes of mortality in SLD population, particularly in those with low fibrosis stage, clinical management should prioritise prevention and treatment of these conditions alongside efforts to halt fibrosis progression. Some SLD-related extrahepatic cancers (e.g., colorectal cancer, breast cancer, prostate cancer) could be identified by screening programmes [24]; however, it remains unclear whether enhanced cancer screening would be cost-effective in this population and how best to implement them. CVD risk assessment is also a critical component of SLD care, as both steatosis and fibrosis are independent risk factors for CVD incidence and mortality [10,25].

We also found generally stronger associations between SLD and several mortality outcomes in females than in males. Although the underlying mechanisms remain uncertain, several explanations may contribute, such as sex hormones, sex chromosomes, gut microbiota, body fat distribution, insulin resistance, and inflammatory responses [26]. In addition, differences in clinical management of MASLD may also contribute. These findings highlight the importance of considering sex-specific risk assessment and warrant further investigation into mechanisms for the sex differences in SLD outcomes.

This study offers several strengths, notably its long follow-up period, large cohort size, and a comprehensive examination of mortality outcomes across ICD10 categories. Nonetheless, there are some limitations. First, liver steatosis and fibrosis were assessed using non-invasive biomarkers of FLI and FIB4, rather than more accurate imaging or biopsy-based methods. MRI-measured liver fat measurements were not available for the majority of participants and were acquired several years after baseline, whereas our study required baseline classification of both steatosis and fibrosis in the full cohort. While this

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may have introduced misclassification bias, these scores are widely validated and used in previous research and outperformed liver biopsy in certain populations [27]. A sensitivity analysis of using HSI replacing FLI generated consistent results, reinforcing the robustness of the main findings. Nevertheless, FIB4 is an indirect marker that estimates fibrosis risk rather than histologically confirmed fibrosis. Therefore, our findings should be interpreted as associations across FIB4 defined fibrosis risk categories rather than confirmed fibrosis stages.

Second, FLI incorporates BMI, WC, TG and GGT, which are themselves associated with mortality. Consequently, the observed association may partly reflect the prognostic information carried by these metabolic components rather than hepatic steatosis alone. Therefore, our findings should be interpreted as associations with FLI-defined SLD rather than the isolated effect of liver fat. Similar findings using HSI also suggest that the observed associations are not unique to one specific surrogate index. Third, the progressive increase in mortality across FIB4 categories supports the importance of fibrosis severity for risk stratification. However, FIB4 incorporates age as one of its components, and although we applied age-specific cutoffs and stratified analysis by age group, residual prognostic effects of age still cannot be completely excluded. The findings should be interpreted as the prognostic value of increasing FIB4 categories rather than fibrosis severity alone. Fourth, UK Biobank is not fully representative of the wider UK population regarding demography, ethnicity, socioeconomic status and disease prevalence [28], which may affect the generalisability of our findings. Fifth, we conducted complete case analysis to handle missing data. Although the proportion of missing data was low (2.8%), complete case analysis may introduce selection bias if missing is related to the exposures or outcome (i.e., missing not at random). Sixth, our primary models adjusted for lifestyle factors, some of which may act not only as confounders but also as mediators on the causal pathway between SLD and mortality. Adjustment for such variables may have resulted in overadjustment, potentially attenuating the observed associations.

To conclude, in this large UK study, SLD was linked to elevated mortality from neoplasm, CVD, digestive disease, chronic kidney disease, diabetes and Covid-19. Among these, CVD and neoplasms were the leading contributors to excess mortality. These findings highlight the wide-ranging systemic impact of SLD beyond liver-related complications, and emphasize the importance of a comprehensive multidisciplinary management strategy that integrates cardiometabolic burden management, cancer prevention, optimisation of metabolic health and fibrosis mitigation.

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Declarations

Ethical approval and consent to participate

UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. This approval means that researchers do not require separate ethical clearance and can operate under the RTB approval.

Consent for publication

Not applicable.

Availability of data and material

UK Biobank data are available to registered researchers at https://www.ukbiobank.ac.uk/.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose.

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Author contribution

QF conceived the research idea and conducted data analysis. MW provided data access. QF, MW, PM and CI interpreted results. QF drafted the manuscript. QF, MW, PM and CI critically reviewed and revised the manuscript. QF is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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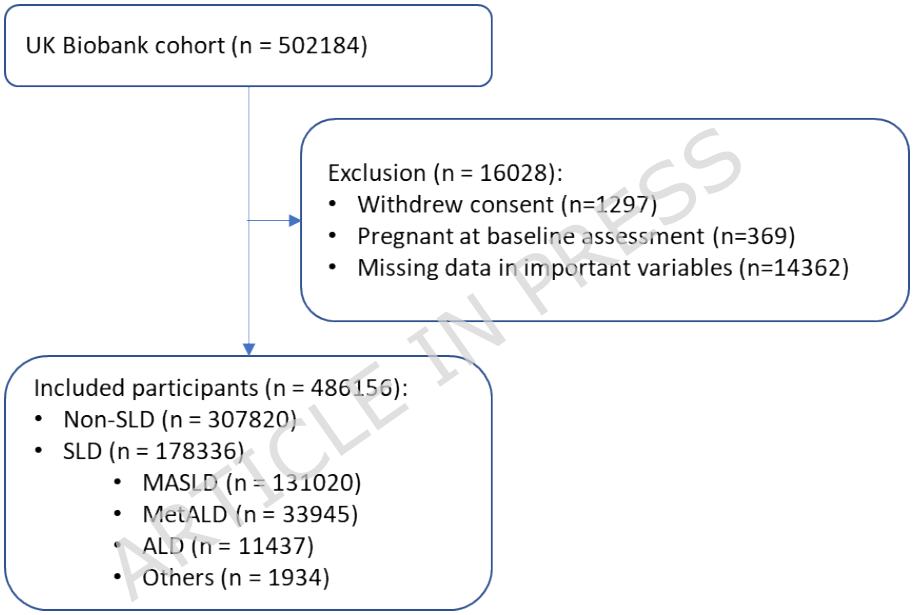


Figure 1: flowchart of participant selection.

SLD: steatotic liver disease. MASLD: metabolic dysfunction associated steatotic liver disease. MetALD: metabolic dysfunction and alcohol related liver disease. ALD: alcohol related liver disease.

Table 1: Baseline characteristics of people with and without SLD in the UK Biobank

		SLD		
	Non-SLD	All SLD	MASLD	MetALD
	n = 307820	n = 178336	n = 131020	n = 33945
Sex, male	108955 (35.4%)	113587 (63.7%)	76275 (58.2%)	25701 (75.7%)
Age, years	56.1 (8.2)	57.3 (7.8)	57.4 (7.9)	57.0 (7.7)
Townsend deprivation index				
1st fifth (least deprived)	65121 (21.2%)	32462 (18.2%)	23791 (18.2%)	6619 (19.5%)

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5th fifth (most deprived)	56140 (18.2%)	40870 (22.9%)	30641 (23.4%)	6584 (19.4%)	2
Education, higher education	109872 (35.7%)	47346 (26.5%)	34208 (26.1%)	9794 (28.9%)	2
Ethnicity, White	290659 (94.4%)	168183 (94.3%)	121919 (93.1%)	33225 (97.9%)	11
Smoking, never	179488 (58.3%)	85523 (48%)	69146 (52.8%)	12397 (36.5%)	3
Alcohol drinking, g/d*	9.7 (0.7, 20.0)	11.9 (0.0, 28.6)	5.7 (0.0, 14.8)	37.9 (32.2, 45.9)	75.4
Physical activity, high	106203 (34.5%)	47835 (26.8%)	33406 (25.5%)	10236 (30.2%)	3
Hypertension	188397 (61.2%)	145417 (81.5%)	105177 (80.3%)	28663 (84.4%)	10
Overweight/obesity	172114 (55.9%)	175794 (98.6%)	129553 (98.9%)	33341 (98.2%)	11
Prediabetes/diabetes	38433 (12.5%)	51762 (29.0%)	40909 (31.2%)	7641 (22.5%)	2
High triglycerides	77920 (25.3%)	128292 (71.9%)	95116 (72.6%)	23904 (70.4%)	8
Low HDL-cholesterol	92556 (30.1%)	73177 (41.0%)	61157 (46.7%)	9109 (26.8%)	2
FIB4 score level					
Low	NA	119362 (66.9%)	90035 (68.7%)	21825 (64.3%)	6
Intermediate	NA	49888 (28.0%)	34669 (26.5%)	10465 (30.8%)	4
High	NA	4461 (2.5%)	2766 (2.1%)	861 (2.5%)	
Unknown	NA	4625 (2.6%)	3550 (2.7%)	794 (2.3%)	

SLD: steatotic liver disease. MASLD: metabolic dysfunction associated steatotic liver disease. MetALD: metabolic dysfunction and alcohol related liver disease. ALD: alcohol related liver disease. HDL: high density lipoprotein. The cutoff values for low, intermediate and high FIB4 scores were 1.30 and 2.67 for people < 65 years old, and 2.00 and 2.67 for people >= 65 years old. *: showing median(interquartile interval)

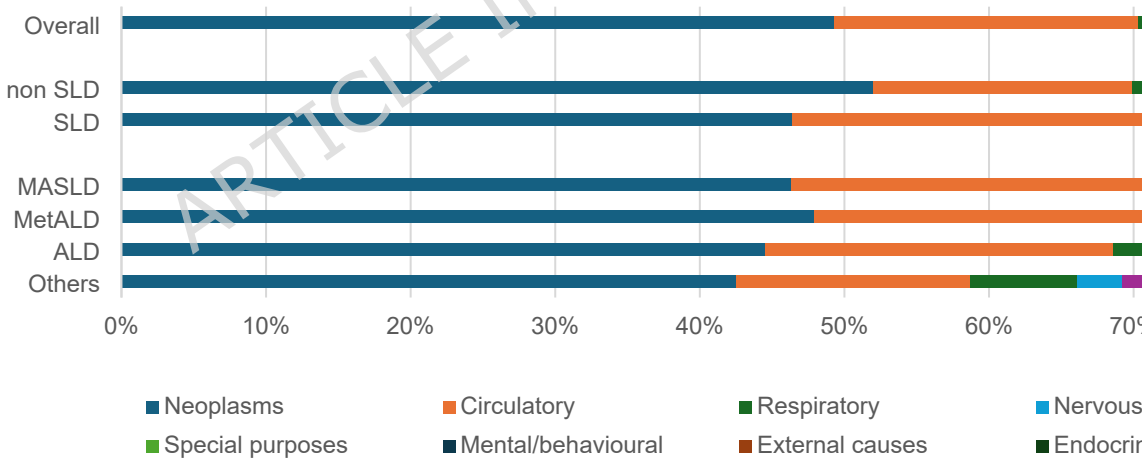


Figure 2: Causes of death in people with and without SLD

The numbers show the percentage. The cutoff values for low, intermediate and high FIB4 scores were 1.30 and 2.67 for people < 65 years old, and 2.00 and 2.67 for people >= 65 years old. SLD: steatotic liver disease. MASLD: metabolic dysfunction associated steatotic liver disease. MetALD: metabolic dysfunction and alcohol related liver disease. ALD: alcohol related liver disease. The ICD10 chapters were defined using the following ICD10 codes: neoplasms (C00-D48), circulatory (I00-I99),

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respiratory (J00-J99), nervous system (G00-G99), digestive (K00-K99), special purpose codes (U00-U99) mental/behavioral (F00-F99), external causes (V01-Y98), endocrine/ metabolic (E00-E99).

Table 2: Adjusted associations between SLD, FIB4 scores and cause-specific mortality.

		SLD		
	Non-SLD	All SLD	Low FIB4	Intermediate FIB4
	n = 307820	n = 178336	n = 119362	n = 49888
Neoplasms (C00-D48)				
Death, n	11239	9564	5981	2819
Mortality rate, /1000py	2.71	4.05	3.75	4.3
HR (95%CI)	Reference	1.24 (1.20, 1.28)	1.11 (1.08, 1.15)	1.50 (1.44, 1.57)
Circulatory (I00-I99)				
Death, n	3860	4997	2977	1575
Mortality rate, /1000py	0.93	2.11	1.87	2.4
HR (95%CI)	Reference	1.57 (1.50, 1.64)	1.34 (1.28, 1.41)	2.08 (1.96, 2.22)
Digestive (K00-K99)				
Death, n	676	988	417	325
Mortality rate, /1000py	0.16	0.42	0.26	0.5
HR (95%CI)	Reference	1.85 (1.67, 2.05)	1.15 (1.01, 1.30)	2.55 (2.21, 2.93)
Special purpose codes (U00-U99)				
Death, n	549	837	509	269
Mortality rate, /1000py	0.13	0.35	0.32	0.41
HR (95%CI)	Reference	1.92 (1.71, 2.15)	1.66 (1.46, 1.88)	2.65 (2.27, 3.09)
Endocrine/metabolic (E00-E99)				
Death, n	179	315	180	99
Mortality rate, /1000py	0.04	0.13	0.11	0.15
HR (95%CI)	Reference	2.22 (1.83, 2.69)	1.82 (1.47, 2.26)	2.92 (2.26, 3.79)
Genitourinary (N00-N99)				
Death, n	111	188	103	54
Mortality rate, /1000py	0.03	0.08	0.06	0.08
HR (95%CI)	Reference	2.09 (1.63, 2.67)	1.61 (1.22, 2.12)	2.78 (1.97, 3.92)
Skin/subcutaneous (L00-L99)				
Death, n	22	48	23	17
Mortality rate, /1000py	0.01	0.02	0.01	0.03
HR (95%CI)	Reference	3.11 (1.83, 5.29)	2.05 (1.12, 3.76)	6.07 (3.09, 11.93)
Respiratory (J00-J99)				
Death, n	1611	1438	908	406
Mortality rate, /1000py	0.39	0.61	0.57	0.62
HR (95%CI)	Reference	1.01 (0.94, 1.09)	0.89 (0.82, 0.97)	1.27 (1.14, 1.43)

HR (95%CI): hazard ratio (95% confidence interval). py: person-years. SLD: steatotic liver disease. Model was stratified by region and age group (<65 vs. >=65) and adjusted

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for sex, ethnicity, education, Townsend Deprivation Index, physical activity level, smoking, and drinking. The cutoff values for low, intermediate and high FIB4 scores were 1.30 and 2.67 for people < 65 years old, and 2.00 and 2.67 for people >= 65 years old.

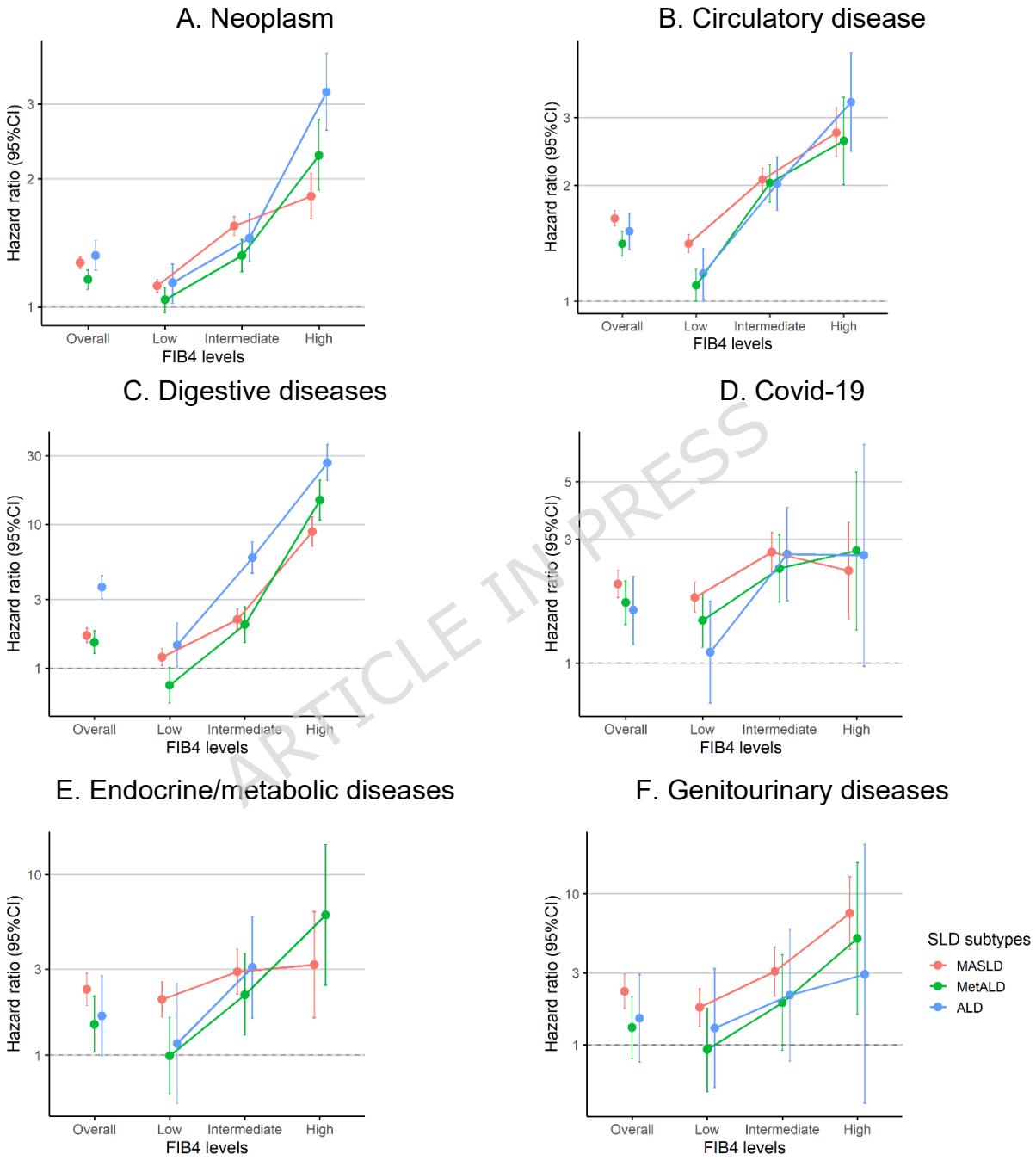


Figure 3: Associations between SLD subtypes, FIB4 score levels and mortality of neoplasm, circulatory diseases, digestive diseases, Covid-19, endocrine diseases and genitourinary diseases.

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The figure shows hazard ratio (95% confidence interval), compared to non-SLD population. Model was stratified by region and age group (<65 vs. >=65) and adjusted for sex, ethnicity, education, Townsend Deprivation Index, physical activity level, smoking, and drinking. MASLD: metabolic-dysfunction associated steatotic liver disease. MetALD: metabolic and alcohol associated steatotic liver disease. ALD: alcohol related liver disease. The cutoff values for low, intermediate and high FIB4 scores were 1.30 and 2.67 for people < 65 years old, and 2.00 and 2.67 for people >= 65 years old.

Table 3: Adjusted associations between SLD, SLD subtypes and selected disease-specific mortality.

			SLD		
		Non-SLD	All SLD	MASLD	MetALI
		n = 307820	n = 178336	n = 131020	n = 3394
Colorectal cancer	Events	1095	919	620	19
(C18-C21)	HR (95%CI)	Reference	1.22 (1.11, 1.34)	1.19 (1.07, 1.32)	1.32 (1.12, 1.54
Pancreatic cancer	Events	834	725	505	14
(C25)	HR (95%CI)	Reference	1.33 (1.20, 1.48)	1.32 (1.17, 1.48)	1.36 (1.12, 1.64
Lung cancer	Events	1928	1583	1097	31
(C34)	HR (95%CI)	Reference	1.07 (1.01, 1.15)	1.09 (1.01, 1.17)	1.01 (0.89, 1.14
Breast cancer (females)	Events	1005	502	421	6
(C50)	HR (95%CI)	Reference	1.50 (1.35, 1.68)	1.55 (1.37, 1.75)	1.63 (1.27, 2.10
Prostate cancer (males)	Events	535	708	473	15
(C61)	HR (95%CI)	Reference	1.22 (1.09, 1.37)	1.23 (1.08, 1.40)	1.19 (0.99, 1.44
Diabetes	Events	76	214	176	2
(E10-E14)	HR (95%CI)	Reference	3.40 (2.59, 4.46)	3.64 (2.74, 4.84)	1.81 (1.10, 2.98
Myocardial infarction	Events	724	1082	813	18
(I21)	HR (95%CI)	Reference	1.69 (1.53, 1.86)	1.86 (1.68, 2.07)	1.38 (1.17, 1.63
Ischemic heart disease	Events	1008	1674	1158	32
(I25)	HR (95%CI)	Reference	1.73 (1.59, 1.87)	1.77 (1.62, 1.94)	1.61 (1.42, 1.83
Stroke	Events	286	277	213	4
(I64)	HR (95%CI)	Reference	1.24 (1.04, 1.48)	1.34 (1.11, 1.61)	0.92 (0.65, 1.29
Chronic kidney disease	Events	23	35	34	
(N18)	HR (95%CI)	Reference	1.15 (0.59, 2.24)	2.22 (1.26, 3.89)	NA
COPD	Events	661	474	320	8
(J44)	HR (95%CI)	Reference	0.76 (0.67, 0.86)	0.75 (0.65, 0.87)	0.67 (0.53, 0.85
Parkinson disease	Events	348	200	157	3
(G20)	HR (95%CI)	Reference	0.73 (0.61, 0.87)	0.78 (0.64, 0.95)	0.58 (0.40, 0.84
Alzheimer's disease	Events	548	254	206	3
(G30)	HR (95%CI)	Reference	0.72 (0.61, 0.84)	0.78 (0.66, 0.92)	0.54 (0.38, 0.78

HR (95%CI): hazard ratio (95% confidence interval). py: person-years. SLD: steatotic liver disease. Model was stratified by region and age group (<65 vs. >=65) and adjusted for sex, ethnicity, education, Townsend Deprivation Index, physical activity level, smoking, and drinking. The cutoff values for low, intermediate and high FIB4 scores

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were 1.30 and 2.67 for people < 65 years old, and 2.00 and 2.67 for people >= 65 years old.

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