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Effects of social determinants of health on mortality and incident liver-related events and cardiovascular disease in steatotic liver disease

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Summary

Background: Social determinants of health (SDOH) are becoming increasingly recognised as mediators of human health. In the setting of metabolic dysfunction-associated steatotic liver disease (MASLD), most of the literature on SDOH relates to individual-level risk factors. However, there are very limited data on neighbourhood-level SDOH in MASLD.

Aim: To assess whether SDOH impact fibrosis progression in patients who already have MASLD.

Methods: This was a retrospective cohort study of patients with MASLD seen at Michigan Medicine. The primary predictors were two neighbourhood-level SDOH, ‘disadvantage’ and ‘affluence’. The primary outcomes were mortality, incident liver-related events (LREs) and incident cardiovascular disease (CVD). We modelled these outcomes using Kaplan–Meier statistics for mortality and competing risk analyses for LREs and CVD, using a 1-year landmark.

Results: We included 15,904 patients with MASLD with median follow-up of 63 months. Higher affluence was associated with lower risk of overall mortality (hazard ratio 0.49 [0.37–0.66], $p < 0.0001$ for higher vs. lower quartile), LREs (subhazard ratio 0.60 [0.39–0.91], $p = 0.02$) and CVD (subhazard ratio 0.71 [0.57–0.88], $p = 0.0018$). Disadvantage was associated with higher mortality (hazard ratio 2.08 [95% confidence interval 1.54–2.81], $p < 0.0001$ for the highest vs.

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AUTHOR CONTRIBUTIONS

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AUTHORSHIP

Guarantor of the article: Vincent Chen. All authors approved the final version of the manuscript.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

lowest quartile) and incident CVD (subhazard ratio 1.36 [95% confidence interval 1.10–1.68], $p < 0.0001$). These findings were robust across several sensitivity analyses.

Discussion: Neighbourhood-level SDOH are associated with mortality, incidence of LREs and incident CVD in patients with steatotic liver disease. Interventions aimed at disadvantaged neighbourhoods may improve clinical outcomes.

1 | INTRODUCTION

Steatotic liver disease (SLD) is characterised by hepatic steatosis in the presence of metabolic dysfunction (metabolic dysfunction-associated steatotic liver disease, MASLD) or the absence of secondary causes. SLD is a leading cause of end-stage liver disease in the United States and is associated with increased mortality and cardiovascular disease burden.[1–3] Conventional risk factors for adverse outcomes include fibrosis stage and metabolic comorbidities such as diabetes and obesity.[4] The cornerstone is therapy is lifestyle intervention including weight loss of 7%–10% total body weight, high-quality diet and regular physical activity.[5,6]

There is increasing recognition that social determinants of health (SDOH) are important potentially modifiable risk factors for adverse health-related outcomes.[7] In one commonly used framework, disparities in living conditions and environment (neighbourhood) subsequently lead to risk behaviours including poor nutrition, low physical activity and increased alcohol intake.[8] Most of the research in impact of SDOHs on longitudinal outcomes in SLD have focused on SDOH at the level of the individual or household.[9] For example, one study found that lower socioeconomic status is linked with increased probability of having SLD and advanced fibrosis,[10] and in another study, food insecurity was associated with increased mortality in patients with SLD.[11]

SDOH at a more upstream neighbourhood level may also influence liver-related health outcomes by, for example, impairing the ability of patients to enact the lifestyle changes recommended for optimal treatment of SLD such as weight loss and improvements in diet quality. However, whether neighbourhood-level SDOH are independently associated with increased risk of adverse health-related outcomes such as development of LREs or cardiovascular disease among people who already have SLD is not well-established. In this study, we were interested in evaluating effects of neighbourhood-level SDOH on health outcomes in patients with SLD.

2 | METHODS

2.1 | Ethics

This study was deemed exempt from regulation by the Institutional Review Board of the University of Michigan. All study procedures complied with the Declarations of Helsinki and Istanbul.

2.2 | Cohort

The cohort included patients seen at Michigan Medicine, an integrated healthcare system based in southeast Michigan. We included consecutive patients with MASLD diagnosed between 2010 and 2020. MASLD was defined as hepatic steatosis on imaging identified based on a validated natural language processing algorithm,[12] plus *either* type 2 diabetes, overweight (BMI ≥25 kg/m^2) or two of dyslipidaemia, hypertension and prediabetes (Table S1).[13,14] We also excluded patients with a diagnosis code for baseline malignancy other than non-melanoma skin cancer because at our medical centre malignancy is a common indication for imaging diagnoses of hepatic steatosis and is associated with high short-term mortality.[15] The index date was defined as the first date of imaging showing hepatic steatosis. Follow-up time was defined as time between the index date and development of a clinical event (as detailed in 'Outcomes' below), the last encounter with a medical provider at Michigan Medicine or the end of the study period (31 December 2021).

2.3 | Predictors

The predictors of interest were two composite neighbourhood-level SDOH measures from the National Neighbourhood Data Archive at the census tract geographic level[16] (Table S2). The primary predictors were 'disadvantage' and 'affluence' as previously reported. 'Disadvantage' is a composite measure of percentage of households within each census tract who were led by a single mother, receiving public assistance income, under the poverty level or not employed. 'Affluence' is a composite measure of percentage of people with annual income >$75,000, who completed high school and who were employed in a managerial or professional occupation. In brief, disadvantage and affluence scores were derived using a factor analysis of all census tracts within the United States, in which it was found that the four components of the affluence score were strongly associated with one another, and three components of disadvantage with one another, but the components of affluence were only weakly associated with those of disadvantage. Thus, disadvantage and affluence were designed to be orthogonal measures of neighbourhood-level SDOH.[16] For these analyses, both scores were divided into quartiles (Q) for simplicity of interpretation. Disadvantage and affluence data were available for the 2007–2012 and 2013–2017 time periods; we used the data of whichever time period was closest to the index date.

2.4 | Outcomes

The primary outcomes were overall mortality, incident liver-related events (LREs, defined as hepatic decompensation or hepatocellular carcinoma) and new diagnosis of cardiovascular disease (CVD) (Table S1). Mortality was modelled based on Cox proportional hazards analyses, whereas LREs/CVD were modelled as Fine-Grey competing risk analyses with death as a competing risk and censoring at loss to follow-up or end of the study period. Mortality data were obtained via the Michigan Department of Vital and Health Records database, to which all deaths occurring in the state of Michigan must be reported. LRE and CVD outcomes were defined based on validated International Classification of Diseases codes (Table S1).[17–19] For all outcomes, we used a landmark of 365 days to reduce immortal time bias and (for the LRE and CVD outcomes) account for delays in diagnosis which might result in incorrect classification as incident LRE/CVD when the patient actually had

prevalent disease. We generated multivariable models adjusted for age, sex, race, diabetes, body mass index, hypertension and dyslipidaemia based on causal inference since these variables differed significantly between affluence and disadvantage (Table 1); we did not adjust for laboratory values because of high levels of missingness.

2.5 | Covariates

Demographic data were obtained from patient self-report. Laboratory values and body mass index values were obtained from the medical record; we used the median of outpatient values within a ±12-month period from the index date. Diagnoses were made using International Classification of Diseases-9 and -10 codes (Table S1), with the first date of the code used as the diagnosis date.

2.6 | Statistics

Descriptive statistics were reported as median (interquartile range) or %. Analyses were conducted in R version 4.2.1. A two-tailed p-value < 0.05 was used for statistical significance. Missing data were excluded in analyses.

3 | RESULTS

3.1 | Cohort

After excluding patients with baseline malignancy, <1 year follow-up, and missing SDOH data, the final cohort included 15,904 patients with MASLD (Figure S1). Figure 1 shows the distribution of disadvantage and affluence scores among the subset of the cohort living in Michigan (n = 15,773). Most patients (65%) lived in the four counties closest to Ann Arbor, MI where Michigan Medicine is based.

Median follow-up was 63.3 months with total follow-up 99,877 person-years. 2921 (18%) had prevalent CVD, and 342 (2.2%) had prevalent LREs. The cohort had median age 53 years; 48% were female, 50% had diabetes, and 49% had obesity (Table 1). Patients with the highest disadvantage scores (Q4) were younger (51 vs. 55 years), more often female (53% vs. 43%), and less often white (64% vs. 80%) compared to those with the lowest disadvantage scores (Q1); p < 0.001 for all. In addition, higher disadvantage was associated with higher prevalence of diabetes (59% vs. 44%), higher triglycerides (223 vs 194 mg/dL), and higher haemoglobin A1c (7.0% vs. 6.5%), but slightly lower prevalence of obesity (47% vs. 50%); p < 0.001 for all. Conversely, lower affluence score (Q1) was associated with similar patterns (Table S3).

3.2 | Associations between disadvantage or affluence and clinical outcomes

The disadvantage score was associated with increased overall mortality with unadjusted hazard ratio 1.77 (95% confidence interval 1.39–2.26, p < 0.0001) for the highest vs. lowest quartiles (Table S4) and adjusted hazard ratio (aHR) 2.08 (1.54–2.81, p < 0.0001) (Table 2, Figure 2). Disadvantage was also associated with incident CVD with adjusted subhazard ratio (asHR) 1.36 (1.10–1.68, p = 0.0048) (Table 2), though not with LREs (asHR 1.24 [0.80–1.92], p = 0.33).

Conversely, the highest quartile of affluence score was associated on multivariable regression with decreased overall mortality (aHR 0.49 [0.37–0.66], $p < 0.0001$), incident LREs (asHR 0.62 [0.39–0.98], $p = 0.04$) and CVD (asHR 0.71 [0.57–0.88], $p = 0.0018$) compared with the lowest quartile (Table 2, Figure 3). Unadjusted results are shown in Table S4 and were overall similar to the adjusted results.

Multivariable associations between all covariates and primary outcomes are shown in Table S5.

3.3 | Sensitivity analyses

We conducted several sensitivity analyses to address the possibility of reverse causation, specifically, that severe medical comorbidities may lead to poverty, and therefore it may be that underlying comorbidities rather than affluence and disadvantage scores that are driving adverse health outcomes. First, we excluded patients with severe comorbidities (Charlson comorbidity index >3) (Table S6). Next, we excluded patients with any hospitalisation or emergency department visit within 2 years before the index date (Table S7). Finally, because private medical insurance is often connected to employment in the United States, we conducted an analysis including only persons with private health insurance (Table S8). In these analyses, there were overall no meaningful changes in the associations between disadvantage or affluence scores and mortality, CVD and LREs, though statistical significance was generally lower due to smaller number of patients.

Next, we accounted for the possibility of delays in MASLD diagnosis based on disadvantage/affluence scores by stratifying by FIB4 score <1.3, 1.3–2.67 and >2.67 as a proxy for fibrosis stage (Table S9). Associations between both disadvantage and affluence scores and mortality remained significant in the FIB4 <1.3 and 1.3–2.67 groups. Higher affluence was associated with lower incidence of LREs and CVD in the FIB4 <1.3 group, and higher disadvantage with higher incidence of CVD in the FIB4 >2.67 group. Other associations were overall similar to the primary analysis, though differences were not statistically significant likely due to smaller sample size.

We then conducted a sensitivity analysis excluding patients with documented chronic liver diseases other than MASLD or self-reported excess alcohol use as previously described (Table S1).[18] While the effects of disadvantage and affluence were consistent with the primary analysis, there was no longer a significant association between either score and risk of LREs (Table S10). In a model additionally adjusting for individual-level behaviours including self-reported alcohol and tobacco use, the effects of disadvantage and affluence on mortality, LREs and CVD were similarly significant (Table S11).

Finally, we evaluated the disadvantage and affluence scores modelled in slightly different ways. First, we included both affluence and disadvantage in the same model (Table S12) and in this model the pattern of associations between disadvantage/affluence and mortality or LREs was similar to the primary analysis, and the highest quartile of affluence had a borderline significant association with lower risk of incident CVD ($p = 0.082$). Finally, we treated both disadvantage and affluence as continuous variables (Table S13). The effects of all scores were more statistically significant when analysed in this way: each 10% absolute

increase in disadvantage was associated with aHR 1.42 (1.25–1.62) for mortality, asHR 1.23 (1.01–1.49) for LREs, and asHR 1.12 (1.01–1.24) for CVD, while the corresponding values for a 10% absolute increase in affluence were 0.83 (0.79–0.88), 0.88 (0.81–0.96) and 0.93 (0.89–0.97) ($p < 0.05$ for all).

4 | DISCUSSION

We found that neighbourhood-level SDOH were associated with overall mortality and incidence of LREs and CVD in MASLD. This finding was robust across several sensitivity analyses. This is the first study to our knowledge showing that among patients who already have MASLD, neighbourhood-level SDOH are associated with increased risk of LREs, though the effect was seen only with affluence, not with disadvantage. Notably, the disadvantage and affluence scores are orthogonal SDOH measures and different interventions may be needed to mitigate them. For example, disadvantage is primarily a measure of poverty, and its effects may be best addressed via outreach and financial assistance programmes. Affluence includes education and employment in relatively high-paying industries and measures to improve early education may be more beneficial in low-affluence neighbourhoods.

Impact of SDOH on SLD and related metabolic factors such as diabetes and obesity have been well-studied.[20,21] Prevalence of hepatic steatosis differs markedly across racial, ethnic and gender groups and is also more common in people experiencing food insecurity.[22,23] Lower socioeconomic status has also been associated with higher risk of having SLD.[10] SDOH may also influence hospitalisation-related outcomes in people with SLD: one study of the National Inpatient Sample also found disparities among admissions with SLD, with higher lengths of stay and/or cost in Black, Hispanic and Asian people compared with White people and increased mortality and longer length of stays in uninsured patients.[24] Finally, food insecurity is associated with increased mortality in the general population,[25] and food insecurity and fast food intake are associated with increased risk of SLD.[11,26] However, there is a relative paucity of literature on neighbourhood-level SDOH in SLD. Neighbourhood- and individual-level SDOH should be considered complementary in that neighbourhood-level factors are relevant to health-related outcomes even when individual-level factors are accounted for. In one state-wide study in Colorado, among persons with low income (<$25,000/year), greater neighbourhood affluence was associated with lower risk of diabetes and greater fruit/vegetable intake.[27] Another study found that while unemployed, non-college-educated people in the United States had higher mortality than employed people, this pattern did not hold in Germany.[28] These findings suggest that while individual-level SDOH are important, they exist within a broader context that influences their impact on morbidity and mortality. Our cohort adds to the literature by (1) focusing on neighbourhood rather than individual-level SDOH and (2) including granular data on health-related events and demonstrating associations between SDOH and specific outcomes most notably LREs.

While medical professionals may not be able to directly change neighbourhood-level affluence and disadvantage, understanding the potential impact of these SDOH may allow us to focus interventions or solutions at the neighbourhood level to help overcome disparities in

health outcomes. Investment by health systems in high-risk neighbourhoods or populations has been shown to be beneficial in other diseases and may offer a roadmap for how this may be applied to SLD. First, health promotion by barbers combined with medication management by pharmacists in Black-owned barbershops markedly improved hypertension control compared to an active control in Black men,[29] a group historically underrepresented in clinical trials and with comparatively high prevalence of cardiovascular risk factors and disease burden. Second, in one study in the Cincinnati, Ohio region, investigators developed a multi-level programme designed to reduce paediatric hospitalisations in two neighbourhoods with disproportionately high levels of hospital admissions among children, with a special focus on asthma which was the leading reason for hospitalisation.[30] After implementation of these measures, hospitalisations from the two neighbourhoods decreased by 20%.[30] Of note, the effects of SDOH may go beyond the initial diagnosis of decompensated cirrhosis and influence the types of treatment received after decompensation has developed, for example in disparities in use of non-selective beta-blockers, albumin and dietary counselling,[31–33] and outreach programmes among these populations may improve clinical outcomes. Outreach programmes aimed at a higher intensity of treatment of SLD in neighbourhoods that are underserved or with high health-related morbidity may include outpatient management of metabolic comorbidities such as diabetes and obesity, programmes to encourage reduction in alcohol intake or integration of lifestyle modification programmes within community spaces which may improve access to care and treatment. While it would likely take many years to observe differences in ‘hard’ LREs with such programmes, such programmes may in the relatively short-term result in differences in risk surrogate endpoints such as liver enzymes or non-invasive tests such as vibration-controlled transient elastography, or improvements in management of associated diseases, for example improved glycaemic control and weight loss. In addition, policy changes to improve neighbourhood conditions and advocacy by medical providers may help mitigate disparities as outlined in a recent report by the National Academies of Sciences, Engineering and Medicine.[34]

This study has several limitations. First, our cohort was derived from a medical centre, and our findings may not apply to individuals without access to healthcare. While Michigan Medicine includes the entire spectrum of primary through tertiary care, it is nonetheless a referral centre, and whether our findings hold in a truly community-based setting remains to be seen. We conducted sensitivity analyses excluding patients with documented excess alcohol intake or alcohol-related liver disease, but alcohol intake was determined primarily by patient self-report rather than validated tools such as AUDIT-C. Because we focused on neighbourhood-level SDOH, we were not able to identify mechanisms by which the disadvantage and affluence scores may have resulted in adverse outcomes, and we were unable to account for important individual-level factors such as household income or education level. Finally, this was a single-centre study with a primarily White population, though our cohort was geographically diverse in that it included patients across Michigan and neighbouring states. Strengths include large sample size of consecutive patients with MASLD, not only those seen in subspecialty clinics and access to the electronic medical record allowing us to capture the spectrum of health-related events rather than only mortality.

In conclusion, neighbourhood-level affluence and disadvantage were linked to mortality and risk for LREs and CVD in patients with MASLD. Further research to identify the root causes by which neighbourhood-level SDOH result in morbidity and mortality may inform policy-based interventions such as community outreach to mitigate socioeconomic disparities between neighbourhoods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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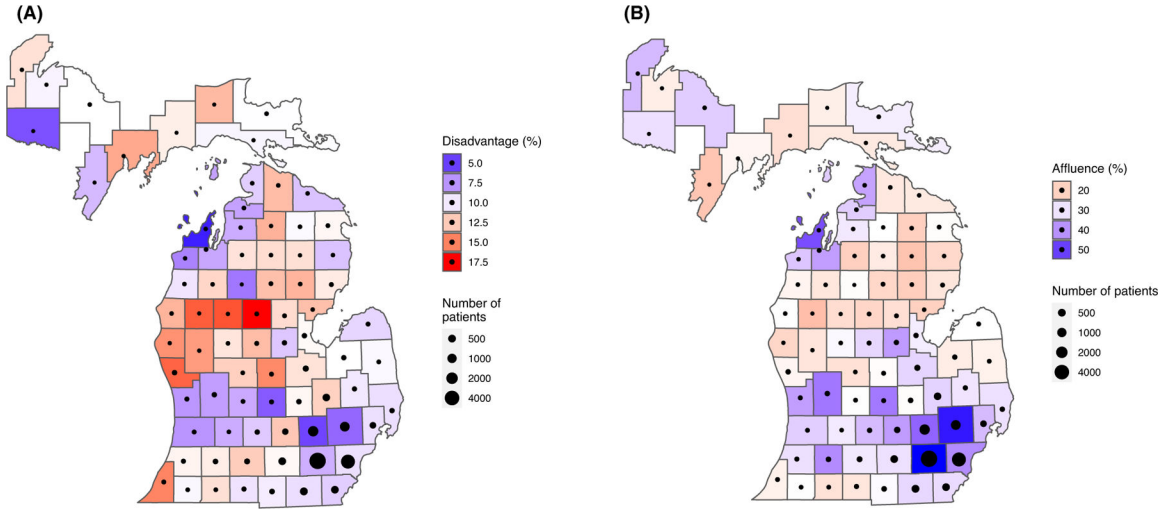

FIGURE 1.

Map showing the counties in which the patients in our cohort resided. For simplicity, we included only patients living in Michigan (n = 15,773). Colour represents disadvantage or affluence score, with red representing higher disadvantage or lower affluence, and blue representing lower disadvantage or higher affluence. Note that the graphed scores are raw values, not quartiles. Size of the circle represents the number of patients in our cohort living within that county. (A) Distribution of disadvantage scores. (B) Distribution of affluence scores.

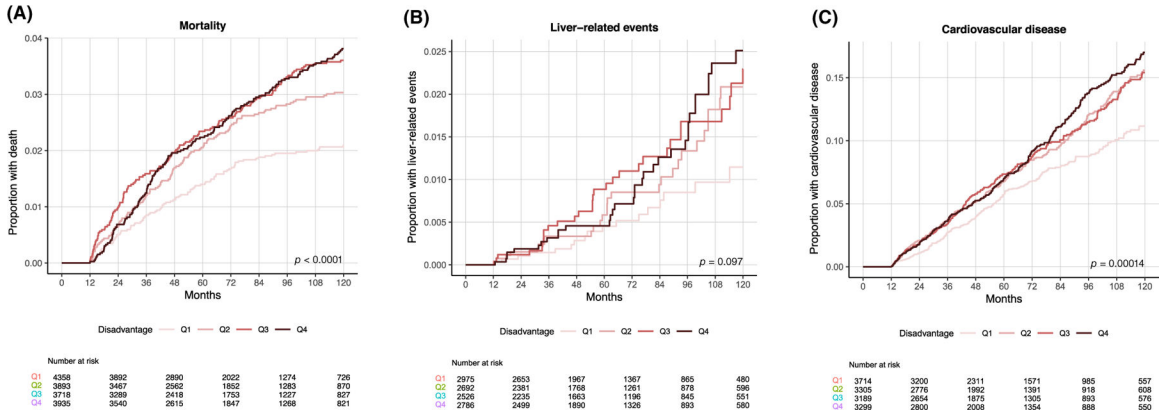

FIGURE 2.

Association between disadvantage score quartile and (A) mortality, (B) incident liver-related events and (C) cardiovascular disease. Quartile 4 indicates highest disadvantage or affluence score. *p*-values for mortality are based on Cox proportional hazard models, while *p*-values for liver-related events and cardiovascular disease are based on Fine-Grey competing risk models with death without that income as a competing risk.

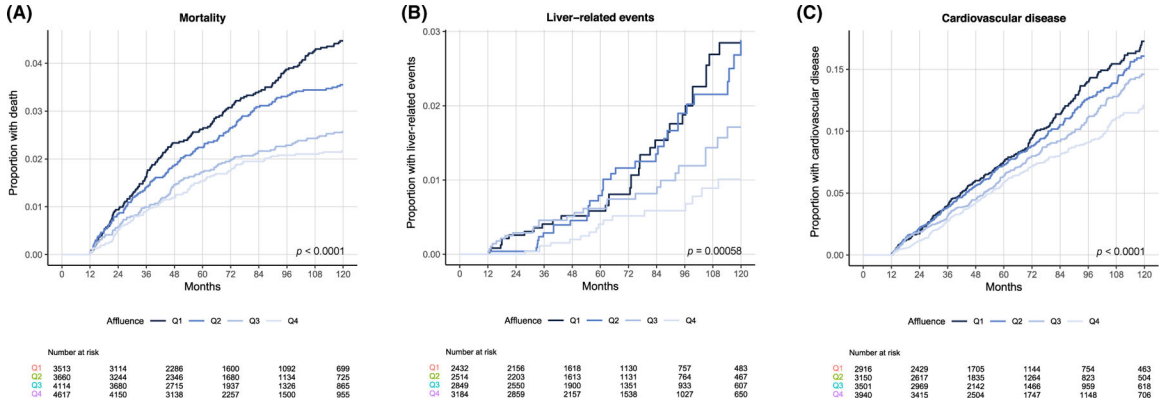

FIGURE 3.

Association between affluence score quartile and (A) mortality, (B) incident liver-related events, and (C) cardiovascular disease. Quartile 4 indicates highest disadvantage or affluence score. *p*-values for mortality are based on Cox proportional hazard models, while *p*-values for liver-related events and cardiovascular disease are based on Fine-Grey competing risk models with death without that income as a competing risk.

TABLE 1

Baseline characteristics based on disadvantage score quartile.

Characteristic	Overall	Disadvantage quartile 1 (lowest)	Disadvantage quartile 4 (highest)	*p*-value
Age	53.7 (43.8–62.6)	55.3 (45.8–64.1)	51.8 (40.8–60.6)	<0.0001
Male	51.4%	56.9%	46.3%	<0.0001
Race				
Asian	6.3%	9.3%	4.7%	<0.0001
Black	9.1%	3.8%	22.1%	
Hispanic	4.0%	3.0%	5.9%	
White	77.3%	80.9%	63.5%	
Other	3.3%	3.0%	3.8%	
Body mass index (kg/m^2) (n = 13,255)				
<25	6.3%	6.0%	6.7%	<0.0001
≥25 to <30	42.9%	47.3%	38.8%	
≥30 to <35	20.6%	21.6%	20.4%	
≥35 to <40	14.7%	13.4%	14.9%	
≥40	15.1%	11.5%	18.7%	
Diabetes	51.3%	44.0%	60.0%	<0.0001
Pre-diabetes	72.4%	69.4%	76.7%	<0.0001
Dyslipidaemia	64.4%	68.2%	59.7%	<0.0001
Hypertension	70.1%	69.2%	71.1%	<0.0001
Chronic hepatitis C	3.0%	1.4%	5.3%	<0.0001
Chronic hepatitis B	1.4%	1.7%	1.3%	<0.0001
Baseline cirrhosis	4.7%	3.5%	5.3%	<0.0001
Charlson comorbidity index	2 (1–4)	1 (0–3)	2 (1–4)	<0.0001
Excess alcohol use	8.2%	7.4%	9.7%	<0.0001
Prior tobacco use	22.0%	24.5%	19.7%	<0.0001
Active tobacco use	9.5%	6.9%	12.9%	<0.0001
Insurance type (n = 14,723)				
Private	82.0%	91.1%	68.7%	<0.0001
Medicare	3.8%	3.1%	3.8%	

Characteristic	Overall	Disadvantage quartile 1 (lowest)	Disadvantage quartile 4 (highest)	*p*-value
Medicaid	7.5%	3.5%	13.9%	
Multiple	6.7%	2.4%	13.6%	
Laboratory values				
Platelet count (K/μL) (*n* = 12,967)	236 (192–285)	230 (192–278)	242 (194–293)	<0.0001
Total bilirubin (mg/dL) (*n* = 13,592)	0.5 (0.4–0.8)	0.6 (0.4–0.8)	0.5 (0.3–0.7)	0.91
Alkaline phosphatase (U/L) (*n* = 13,603)	85 (69–109)	81 (67–103)	88 (701–114)	<0.0001
Aspartate aminotransferase (U/L) (*n* = 13,655)	31 (24–44)	31 (24–43)	31 (23–46)	0.22
Alanine aminotransferase (U/L) (*n* = 13,711)	38 (25–60)	38 (26–59)	36 (23–60)	0.66
Albumin (mg/dL) (*n* = 13,727)	4.3 (4.1–4.5)	4.4 (4.2–4.6)	4.3 (4.0–4.5)	<0.0001
Triglycerides (mg/dL) (*n* = 8158)	164 (115–241)	160 (112–227)	164 (114–248)	0.00043
High-density lipoprotein (mg/dL) (*n* = 7898)	43 (36–52)	44 (38–53)	42 (36–52)	<0.0001
Low-density lipoprotein (mg/dL) (*n* = 7433)	98 (74–125)	100 (76–125)	95 (71–121)	0.0036
Haemoglobin A1c (%) (*n* = 6869)	6.2 (5.7–7.3)	6.0 (5.6–6.9)	6.4 (5.8–7.8)	<0.0001

Note: Baseline characteristics are compared between the lowest and highest quartiles of disadvantage. Values are shown as median (interquartile range) or percentage.

TABLE 2

Associations between social determinants of health and mortality, incident liver-related events and incident cardiovascular disease.

	Mortality		Liver-related events		Cardiovascular disease	
Predictor	**Adjusted hazard ratio**	***p* value**	**Adjusted subhazard ratio**	***p* value**	**Adjusted subhazard ratio**	***p* value**
Disadvantage						
Quartile 1	(Referent)		(Referent)		(Referent)	
Quartile 2	1.55 (1.14–2.09)	0.0046	1.13 (0.74–1.71)	0.57	1.18 (0.96–1.45)	0.12
Quartile 3	2.18 (1.64–2.92)	<0.0001	1.32 (0.87–1.99)	0.19	1.32 (1.07–1.62)	0.01
Quartile 4	2.08 (1.54–2.81)	<0.0001	1.36 (0.90–2.07)	0.15	1.36 (1.10–1.68)	0.0048
Affluence						
Quartile 1	(Referent)		(Referent)		(Referent)	
Quartile 2	0.85 (0.66–1.10)	0.21	1.06 (0.72–1.56)	0.75	0.95 (0.76–1.17)	0.61
Quartile 3	0.58 (0.44–0.77)	0.00015	0.80 (0.53–1.21)	0.29	0.81 (0.65–1.00)	0.049
Quartile 4	0.49 (0.37–0.66)	<0.0001	0.60 (0.39–0.92)	0.020	0.71 (0.57–0.88)	0.0018

Note: Quartile 4 indicates highest disadvantage or affluence score. Hazard ratios and *p*-values for mortality are based on Cox proportional hazard models, while subhazard ratios for liver-related events and cardiovascular disease are based on Fine-Grey competing risk models with death without that outcome as a competing risk. All models were adjusted for age, sex, race, diabetes, body mass index, hypertension and dyslipidaemia.

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