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Targeting population groups with heavier burden of hepatocellular carcinoma incidence: A nationwide descriptive epidemiological study in Sweden

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Abstract

Contemporary European studies examining associations between socioeconomic status and hepatocellular carcinoma (HCC) incidence are scarce. We aimed to target population groups with a heavier burden of HCC by assessing associations of individual-level sociodemographic variables and neighbourhood deprivation with all-stage and stage-specific HCC incidence rates (IR). Patient and population data stratified by calendar year (2012-2018), sex, age (5-year groups), household income (low, medium and high), country of birth (Nordic, non-Nordic) and neighbourhood deprivation (national quintiles Q1-Q5) were retrieved from Swedish registers. HCC stages were defined by Barcelona Clinic Liver Cancer stages 0 to A (early-stage) and B to D (late-stage). IR (per 100 000 person-years) were estimated by Poisson regression models. Men had four times higher IR than women. IRs increased markedly with lower household income as well as with neighbourhood deprivation. Seven times higher IR was observed among people with a low household income living in the most deprived neighbourhoods (IR 3.90, 95% confidence interval [CI] 3.28-4.64) compared to people with a high household income living in the least deprived neighbourhoods (IR 0.58, 95% CI 0.46-0.74). The gradient across income categories was more pronounced for late-stage than early-stage HCC. IR reached 30 (per 100 000 person-years) for people in the age span 60 to 79 years with low income and 20 for 60 to 79 year old people living in the most deprived neighbourhoods (regardless of income). Men with low household income and/or living in the most deprived neighbourhoods might be considered as primary targets in studies evaluating the cost-effectiveness of screening for early-stage HCC detection.

KEYWORDS
epidemiology, hepatocellular carcinoma, income, neighbourhood, surveillance

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; DeSO, [Demografiska StatistikOmråden]—in Swedish; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IMD, index of multiple deprivation; IR, incidence rate; IRR, incidence rate ratio; RCT, randomised controlled trial; SES, socioeconomic status; SweLiv, Swedish registry for cancers found in the liver, gallbladder and bile ducts.

What's new?

Contemporary European studies examining the impact of socioeconomic status on liver cancer incidence are scarce. No other European study using nationwide data has included sociodemographic data at the individual and neighbourhood levels. This epidemiological study covering the 2012-2018 period in Sweden found that men with a low household income and/or living in the most deprived areas had the heaviest burdens of liver cancer and incurable disease at diagnosis. These populations should be considered as primary targets for future studies examining the benefit of screening to detect liver cancer at an earlier stage.

1 | INTRODUCTION

Primary liver cancer is the third leading cause of cancer related deaths.[1] Its global incidence remains rising, which implies an urgent need for preventive measures, such as hepatitis B virus screening and immunisation, environmental and behavioural risk factor reduction and early liver cancer screening among at risk populations.[2] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and accounts for 75% to 85% of cases globally.[1]

Socioeconomic status (SES) is a major contributor to health disparities.[3] The impact of SES on inequities in health differs substantially across Europe.[4] Comparisons between nations can also be challenging as SES is measured by varying indicators.[5] Education, occupational social class and income are commonly used in descriptive and analytical epidemiology for the study of associations between individual SES and risk for cancer.[5] These SES indicators are not fully interchangeable but they are frequently related to each other.[6]

Neighbourhood-level, or contextual, SES indicators are regularly used in descriptive epidemiology, often in order to overcome lack of individual-level SES data.[5] Indices of multiple deprivation (IMD) are useful as they can serve as proxies for unavailable individual data.[7] IMDs are most commonly used in the UK but other countries have developed their own IMDs as well.[8-10] Contextual-level SES indicators might also be useful for geographically targeted and contextualised interventions, for example, cancer screening programs in high-risk areas.[11] Social inequities in cancer should preferably be measured using both individual and neighbourhood-level SES indicators.[5]

In the United States, SES and ethnicity are associated with liver cancer incidence and stage at diagnosis.[12] Late-stage diagnosis is more frequent in low SES groups.[12,13] Low education and low income are associated with both late-stage and early-stage cancer at diagnosis in immigrants.[13] Associations between low SES, or being an immigrant from a non-western country and increased risk for liver cancer have previously been reported in European populations.[14,15] Contemporary studies are scarce though and, to date, no prior nationwide European study includes both individual-level and contextual-level SES data.[16-23]

The aim of this descriptive epidemiological study was to target population groups with a heavier burden of HCC in Sweden with consideration for (a) both individual-level and neighbourhood-level (contextual) sociodemographic variables and (b) all-stage incidence as well as stage-specific incidences of HCC. In particular, our interest lies in providing new information to be considered for rational targeting of population groups to be included in future studies and randomised controlled trials (RCTs) evaluating the cost-effectiveness of screening to detect liver cancer at an early stage.

2 | MATERIALS AND METHODS

The Swedish registry for cancers found in the liver, gallbladder and bile ducts (SweLiv) was established in 2008. A comprehensive description of SweLiv has been provided elsewhere.[24] SweLiv currently includes >95% of all known HCC cases registered in Sweden.[24] The registry consists of four different modules: (a) diagnosis, staging and treatment recommendations; (b) interventions; (c) complications and pathology and (d) follow-up.[24]

We included all patients aged 18 years and older, registered in SweLiv with a diagnosis of HCC (International Classification of Diseases 10th Revision—Swedish Edition, code C22.0) between 1 January 2012 and 31 December 2018.

Patient data were retrieved from the different modules in SweLiv. The beginning of the study period was chosen as 1 January 2012, because the Swedish national program for the treatment of patients with HCC was launched in 2012.[24]

The Swedish treatment algorithm for HCC is provided as Figure S1. Based on this algorithm, patients were regarded as early-stage if diagnosed with a single tumour (disregarding of tumour size) or multiple up to three tumours (all <3 cm), had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 and Child-Pugh score ≤7 (not relevant for liver transplant candidates). All patients with multinodular tumours, portal invasion, extrahepatic spread, end-stage liver function or ECOG performance status ≥2 were regarded as late-stage. This classification, although not identical, is based on the Barcelona Clinic Liver Cancer (BCLC) staging system.[25] Early-stage correlates roughly to BCLC stages 0 to A, and late-stage represents BCLC stages B to D.

Unlike most nations worldwide, the Scandinavian countries have access to individual-level SES data. Registry holders in Sweden use the unique Swedish personal numbers for data linkage.[26] The entire population of Sweden (10.2 million, year 2020) has equal access to universal, tax-financed healthcare services.

In 2018, Statistics Sweden launched a new geographic division referred to as DeSO ("Demografiska StatistikOmråden"—in

TABLE 1 Baseline characteristics of adult patients diagnosed with HCC in Sweden (2012-2018)

	Neighbourhood deprivation, n (%)						
	Q1	Q2	Q3	Q4	Q5	Total	*P*-value
Total, n (%)	432 (12)	598 (17)	663 (19)	790 (23)	990 (29)	3473 (100)	
Male	326 (76)	466 (78)	500 (75)	596 (75)	748 (76)	2636 (76)	.804
Age group (years)							
<60	59 (14)	96 (16)	113 (17)	145 (18)	231 (23)	644 (19)	<.0001
60-69	132 (30)	203 (34)	213 (32)	245 (31)	337 (34)	1130 (32)	
70-79	184 (43)	219 (37)	224 (34)	282 (36)	280 (29)	1189 (34)	
80+	57 (13)	80 (13)	113 (17)	118 (15)	142 (14)	510 (15)	
Country of birth							
Nordic	395 (91)	550 (92)	593 (89)	702 (89)	737 (74)	2977 (86)	<.0001
Non-Nordic	37 (9)	48 (8)	70 (11)	88 (11)	253 (26)	496 (14)	
Household income							
High	121 (28)	110 (18)	80 (12)	69 (9)	56 (6)	436 (13)	<.0001
Medium	207 (48)	286 (48)	300 (45)	326 (41)	320 (32)	1439 (41)	
Low	104 (24)	202 (34)	283 (43)	395 (50)	614 (62)	1598 (46)	

Note: Neighbourhood deprivation according to the index for multiple deprivation for Sweden, presented as quintiles, from least deprived (Q1) through most deprived (Q5).[8] Nordic country of birth: Sweden, Denmark, Finland, Iceland and Norway. Household income defined as disposable income per household per consumption unit.
Abbreviation: HCC, hepatocellular carcinoma.

TABLE 2 Age- and calendar-year-adjusted incidence rate ratios of HCC in Sweden (2012–2018)

		Incidence rate ratio (95% CI)		
		All-stage	Early-stage	Late-stage
Model 1				
Sex	Female	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Male	3.45 (3.19-3.73)	2.94 (2.56-3.38)	3.73 (3.39-4.10)
Model 2				
Country of birth	Nordic	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Non-Nordic	1.57 (1.43-1.73)	1.98 (1.69-2.33)	1.42 (1.25-1.60)
Model 3				
Household income	High	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Medium	2.13 (1.91-2.38)	1.95 (1.63-2.34)	2.22 (1.94-2.55)
	Low	4.61 (4.13-5.14)	3.55 (2.94-4.29)	5.19 (4.52-5.97)
Model 4				
Neighbourhood deprivation	Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Q2	1.24 (1.09-1.40)	1.29 (1.04-1.61)	1.20 (1.03-1.39)
	Q3	1.33 (1.17-1.50)	1.17 (0.94-1.46)	1.40 (1.21-1.62)
	Q4	1.54 (1.37-1.74)	1.32 (1.06-1.64)	1.60 (1.39-1.85)
	Q5	2.19 (1.95-2.45)	2.17 (1.77-2.66)	2.15 (1.87-2.47)
Model 5				
Sex	Female	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Male	3.44 (3.18-3.72)	2.93 (2.55-3.37)	3.72 (3.38-4.10)
Country of birth	Nordic	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Non-Nordic	1.56 (1.41-1.71)	1.97 (1.68-2.32)	1.40 (1.24-1.59)

(Continues)

TABLE 2 (Continued)

		Incidence rate ratio (95% CI)		
		All-stage	Early-stage	Late-stage
Model 6				
Sex	Female	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Male	3.83 (3.55-4.15)	3.13 (2.72-3.61)	4.24 (3.85-4.67)
Country of birth	Nordic	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Non-Nordic	1.09 (0.99-1.21)	1.49 (1.26-1.76)	0.97 (0.85-1.09)
Household income	High	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Medium	2.15 (1.93-2.40)	1.93 (1.61-2.31)	2.25 (1.96-2.59)
	Low	5.13 (4.59-5.73)	3.57 (2.94-4.33)	6.00 (5.22-6.90)
Model 7				
Sex	Female	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Male	3.50 (3.24-3.78)	2.97 (2.58-3.41)	3.80 (3.45-4.18)
Country of birth	Nordic	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Non-Nordic	1.34 (1.21-1.48)	1.69 (1.43-2.01)	1.21 (1.07-1.37)
Neighbourhood deprivation	Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Q2	1.24 (1.10-1.41)	1.30 (1.04-1.62)	1.21 (1.03-1.40)
	Q3	1.34 (1.18-1.51)	1.17 (0.94-1.47)	1.42 (1.23-1.64)
	Q4	1.58 (1.41-1.78)	1.32 (1.06–.164)	1.65 (1.43-1.91)
	Q5	2.18 (1.95–2.45)	2.03 (1.65-2.49)	2.21 (1.92-2.54)
Model 8				
Sex	Female	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Male	3.85 (3.56-4.17)	3.14 (2.73-3.62)	4.26 (3.87-4.70)
Country of birth	Nordic	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Non-Nordic	1.01 (0.92-1.12)	1.36 (1.15-1.62)	0.90 (0.79-1.02)
Household income	High	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Medium	2.06 (1.85-2.30)	1.86 (1.55-2.24)	2.16 (1.88-2.49)
	Low	4.71 (4.20-5.28)	3.30 (2.71-4.03)	5.51 (4.78-6.36)
Neighbourhood deprivation	Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Q2	1.07 (0.94-1.21)	1.15 (0.93-1.44)	1.02 (0.87-1.18)
	Q3	1.06 (0.94-1.20)	0.98 (0.78-1.23)	1.10 (0.95-1.27)
	Q4	1.19 (1.06-1.35)	1.06 (0.85-1.32)	1.22 (1.05-1.40)
	Q5	1.48 (1.31-1.66)	1.48 (1.20-1.84)	1.44 (1.25-1.67)

Note: HCC stage defined according to a modified Barcelona Clinic Liver Cancer (BCLC) staging system, which accepted Child-Pugh ≤7, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 for patients with BCLC 0 to A (early-stage). Late-stage was defined as BCLC stages B-D. Among 3473 cases of HCC, 1007 (29%) were regarded as early-stage, 2372 (68%) as late-stage and HCC stage could not be defined for 94 of cases (3%). Nordic country of birth: Sweden, Denmark, Finland, Iceland and Norway. Household income defined as disposable income per household per consumption unit. Neighbourhood deprivation according to the index for multiple deprivation for Sweden, presented as quintiles, from least deprived (Q1) through most deprived (Q5).[8] Incidence rate ratios estimates obtained from age and calendar year adjusted multivariable Poisson regression models.
Abbreviation: HCC, hepatocellular carcinoma.

Swedish).[27] At the end of 2018, the population size across the 5985 DeSOs in Sweden varied between 653 and 4253. It has been demonstrated that these small areas can be used for monitoring influence of neighbourhood deprivation in public health; a novel IMD for Sweden was constructed that took into account economic standards, educational level, employment status and type of housing in each DeSO.[9]

Statistics Sweden carried out linkage to national population registries and provided data regarding *country of birth*, *household income* (disposable income per household per consumption unit [Statistics Sweden applies the following weights: 1.0 for single or living alone, 1.51 for cohabiting couple, 0.6 for each additional adult, 0.52 for first child 0-19 years and 0.42 for each additional child 0-19 years]) and *residential neighbourhood* (DeSO) at year of diagnosis for each HCC patient registered in SweLiv. Population size data for the incidence estimations (see Section 2.1) were also delivered by Statistics Sweden. Country of birth was classified as "Nordic" if born in Sweden, Norway, Denmark,

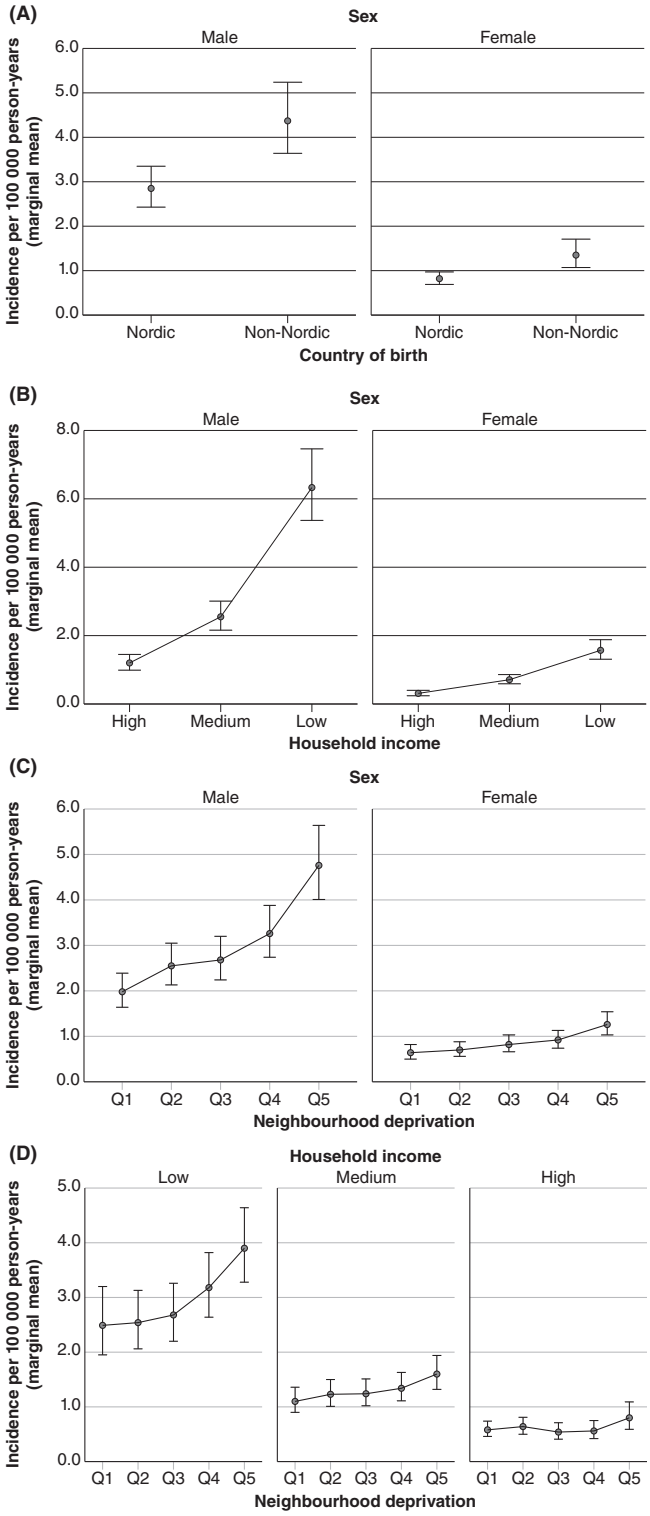

FIGURE 1 Age- and calendar year adjusted incidence of all-stage hepatocellular carcinoma in Sweden (2012-2018) by: sex and country of birth (A), sex and household income (B), sex and neighbourhood deprivation (C) and household income and neighbourhood deprivation (D). Nordic country of birth: Sweden, Denmark, Finland, Iceland and Norway. Household income defined as disposable income per household per consumption unit. Neighbourhood deprivation according to the index for multiple deprivation for Sweden, presented as quintiles, from least deprived (Q1) through most deprived (Q5)

Finland or Iceland; and as "non-Nordic" otherwise. Patients' household income was used as the individual-level SES measure.[28] Data on household income were available for each study subject (this would not be the case for the alternative individual-level SES measures *educational level* and *occupational social class*, because such data are frequently missing for immigrants). Household income was categorised as low, medium or high, according to the distribution of household income across all household in Sweden (low = in first quartile [poorest], medium = in second or third quartile, high = in fourth quartile [wealthiest]). Regarding neighbourhood deprivation, each HCC case was assigned to an IMD quintile (Q1 = least deprived, Q5 = most deprived) based on his/her residential DeSO at the time of HCC diagnosis. More details about the variables included are presented as Table S1.

2.1 | Statistical analysis

For comparing data between different patient groups, the χ^2 test or Fisher's test was employed for categorical variables and the *t*-test or, when comparing >2 groups, one-way ANOVA for continuous variables. We were able to stratify the underlying (at risk) population size data for the total, early-stage and late-stage numbers of incident HCC cases by: (a) neighbourhood (DeSO), (b) calendar year (2012-2018), (c) sex, (d) age group (15-19, 20-24, …, 85-89, 90+), (e) household income (low, medium, high) and (f) country of birth (Nordic, non-Nordic). Multivariable Poisson regression models were employed for estimating HCC incidence variations with regard to IMD (Q1 = least deprived to Q5 = most deprived) assigned to each neighbourhood and the explanatory variables (b) to (f). The natural logarithm of the population size in each group (ie, each combination of strata) was included as an off-set term.

We estimated incidence rates (IR; newly diagnosed HCC cases per 100 000 person-years) with 95% confidence intervals (CIs) for various population groups by corresponding marginal means. Estimated incidence rate ratios (IRR) with 95% CIs were used for group comparisons. Analogous Poisson regression analyses were performed for a number of incident HCC at early- and late-stage, respectively.

3 | RESULTS

3.1 | HCC cases

This descriptive epidemiologic study included 3473 patients (Figure S2, Tables S2 and S3). The mean age at diagnosis was 69 ± 10 years and 76% of the patients were male. The overall IR of HCC in Sweden was unchanged between 2012 and 2018 (data not shown). The distribution of household income among patients is presented as Figure S3. In the most deprived neighbourhoods, not only the proportion of cases with low household income was higher, but also the proportions of cases aged <60 years and born in a non-Nordic country, respectively (Table 1). Patients born in a non-Nordic country had a lower mean age at HCC diagnosis (64 vs 69 years; Table S2).

3.2 | All-stage HCC incidence trends across population groups defined by sex, country of birth, household income and neighbourhood deprivation

Table 2 presents adjusted IRR estimates based on various multivariable models. Age and calendar year were included as covariates in each model; hence, each IRR estimate was basically adjusted for age and calendar year. Both low household income and male sex were associated with pronouncedly elevated incidences of HCC, independent of other covariates. In population groups defined by country of birth, household income or neighbourhood deprivation, men had generally four times higher all-stage IR than women (Figure 1, Table 2).

Sex did not noticeably affect the estimated IRR for country of birth, or vice versa. The all-stage incidence was higher for people born outside the Nordic countries than for people with a Nordic origin (Figure 1A). However, this association was confounded by household

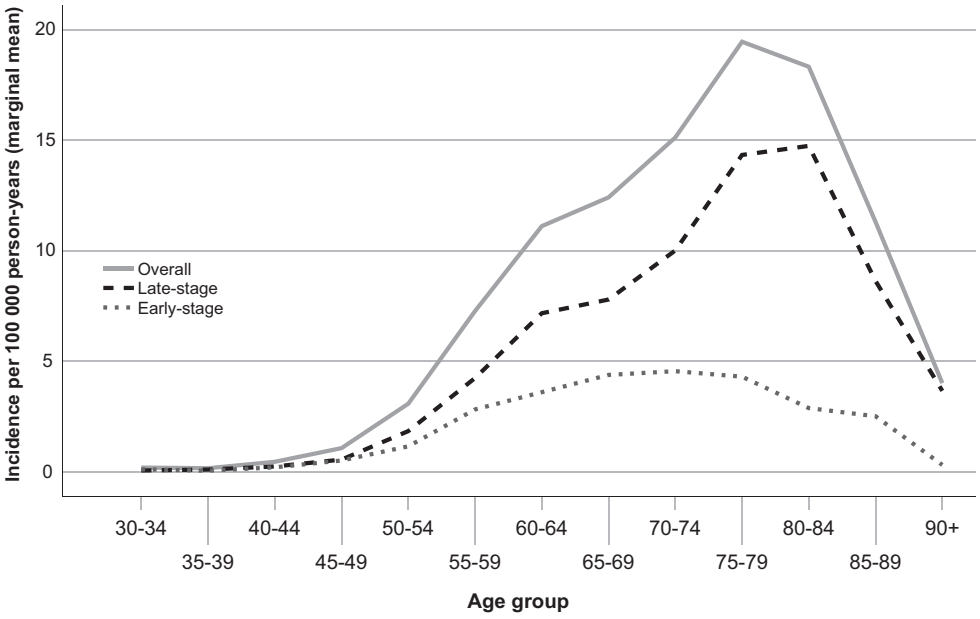

FIGURE 2 Incidence of hepatocellular carcinoma in Sweden (2012-2018) by age group and stage at diagnosis

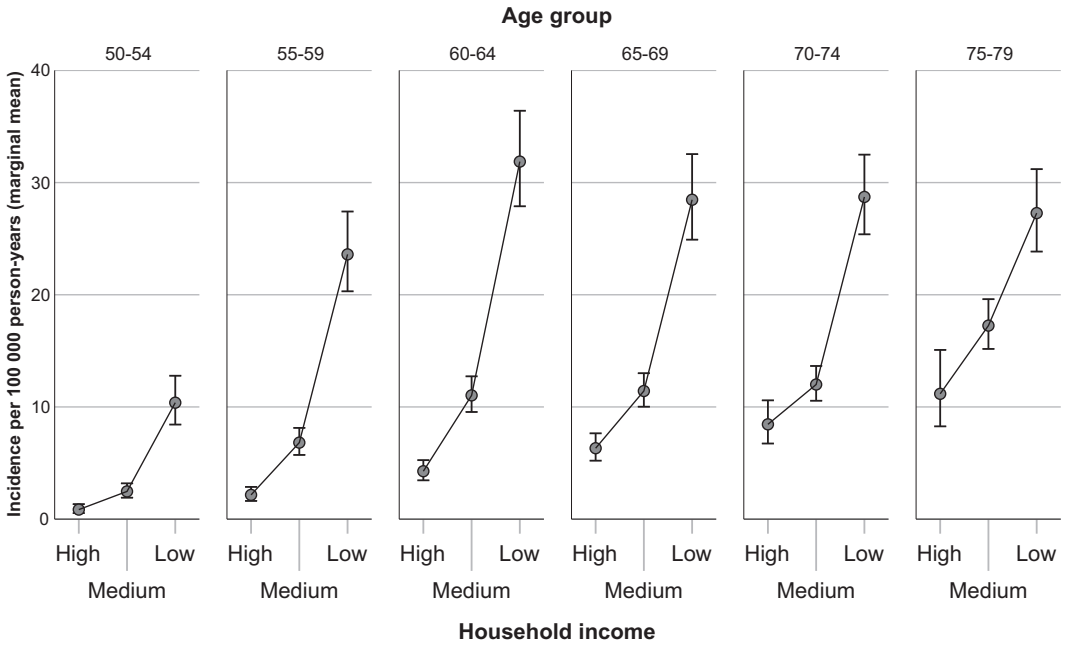

FIGURE 3 Sex and calendar year adjusted incidence of all-stage hepatocellular carcinoma (HCC) in Sweden (2012-2018) for different age groups. Shown for all-stage HCC by household income. Household income defined as disposable income per household per consumption unit

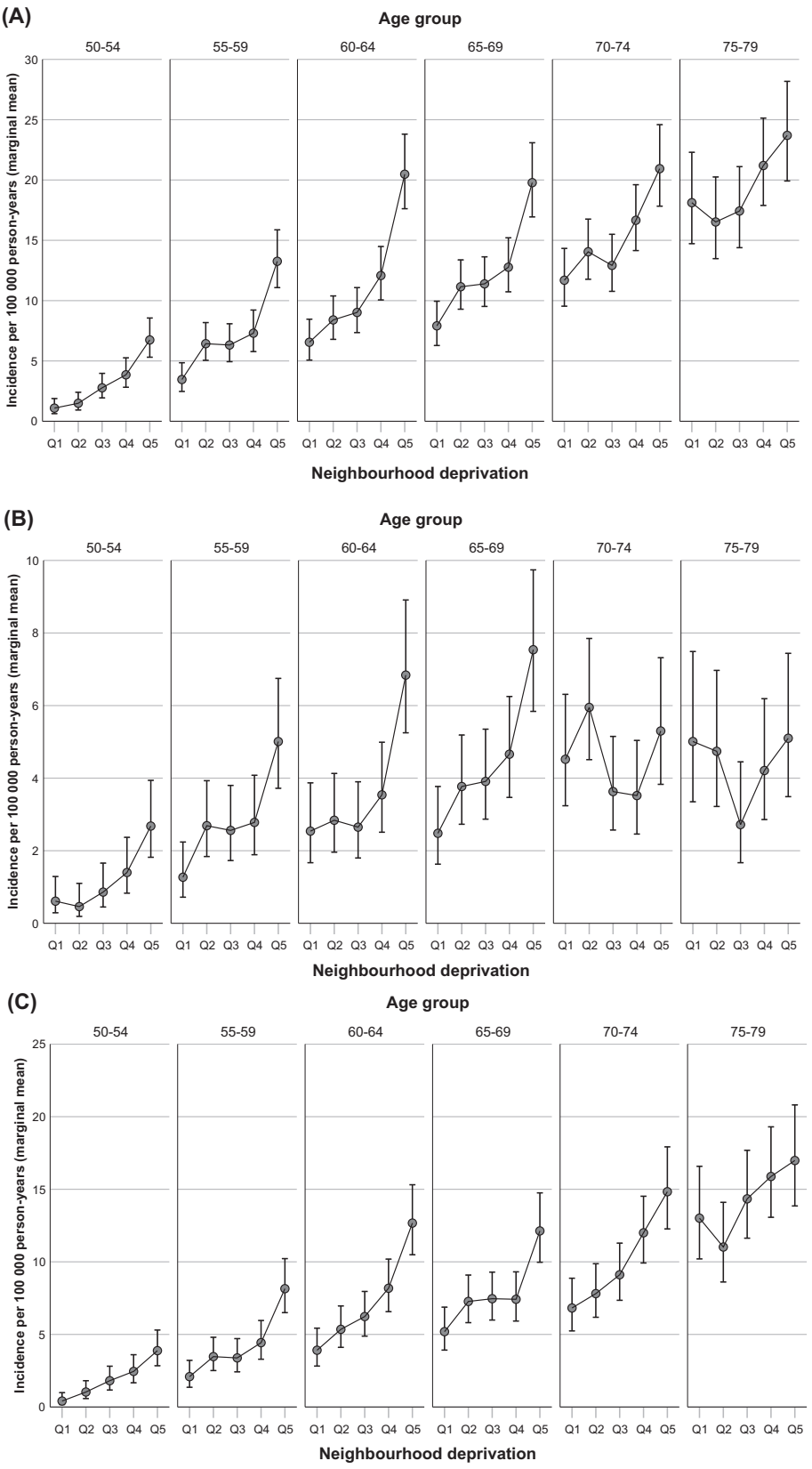

FIGURE 4 Sex and calendar year adjusted incidence of hepatocellular carcinoma (HCC) in Sweden (2012-2018) for different age groups. Shown for all-stage HCC by neighbourhood deprivation (A). Stage-specific incidences by neighbourhood deprivation and early-stage (B), respectively late-stage (C) HCC are also shown. Neighbourhood deprivation according to the index for multiple deprivation for Sweden, presented as quintiles, from least deprived (Q1) through most deprived (Q5). HCC-stage defined according to a modified Barcelona Clinic Liver Cancer (BCLC) staging system, which accepted Child-Pugh ≤7, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 for patients with BCLC 0 to A (early-stage). Late-stage was defined as BCLC-stages B to D

income and, although to a lesser extent, neighbourhood deprivation (Table 2; Figure S4). Household income also influenced associations with other variables. Adjustments for household income somewhat increased the IRR of male sex. Furthermore, as expected, incorporation of household income reduced the IRRs related to neighbourhood deprivation.

We also observed markedly increasing trends with lower household income (Figure 1B, Table 2) and more disadvantageous neighbourhood deprivation (Figure 1C, Table 2).

Among people with low household income, the all-stage incidence increased with more disadvantageous neighbourhood deprivation (Figure 1D). For example, seven times higher IR was estimated for people with a low household income living in the most deprived neighbourhoods (IR 3.90, 95% CI 3.28-4.64), as compared to people with a high household income living in the least deprived neighbourhoods (IR 0.58, 95% CI 0.46-0.74). The estimated IRs are summarised in Tables S4 and S5.

3.3 | Early- and late-stage HCC incidence trends across population groups defined by sex, country of birth, household income and neighbourhood deprivation

A total of 1007 patients (29%) were regarded as early-stage. In 90 cases (3%) staging was not possible due to missing data. The characteristics of patients classified as early-stage and late-stage, respectively, are provided as Table S6.

Compared to IRRs for early-stage HCC, the corresponding IRRs for late-stage HCC were higher for men vs women and more markedly increasing over household income categories (Table 2). Being born in a non-Nordic country was associated with higher IRR for early-stage HCC, but not for late-stage HCC (Tables 2, S7 and S8).

3.4 | Incidence patterns with regard to age

Incidence rates for early- and late-stage peaked in people aged 65 to 74 and 75 to 84 years, respectively (Figure 2). Increasing age was associated with an increased incidence of HCC, independent of sex or country of birth (Figure S5). IR reached 30 (per 100 000 person-years) for people in the age span 60 to 79 years with low household income (Figure 3) and 20 for 60 to 79 years old people living in the most deprived neighbourhoods (regardless of household income) (Figure 4A). Late-stage IR associations with neighbourhood deprivation were apparent in the whole age span 50 to 79 years (Figure 4C), while early-stage IR associations with deprivation dissipated in patients older than 70 years (Figure 4B).

4 | DISCUSSION

In the present study, we investigated the associations of individual-level sociodemographic variables and neighbourhood deprivation with HCC incidence in Sweden. Men had four times higher incidences of HCC than women. We found strong incidence increments with lower household income as well as high degree of neighbourhood deprivation, in both men and women. Immigrants from the non-Nordic countries had increased IRs compared to people born in the Nordic countries. The association of Nordic/non-Nordic origin with HCC incidence was largely confounded by the individual-level SES measure (household income). However, the incidence of *early-stage* HCC remained statistically significantly higher in immigrants from a non-Nordic country, compared to people born in a Nordic country, in the fully adjusted model.

Less favourable contextual deprivation and low education have been associated with up to two times increased risk for liver cancer in Europe.[16-23] To our knowledge, no other nationwide study using European data has included SES data at individual- and contextual-level. The analysis of the link between household income and risk for HCC in a European nation is also a unique feature of the present study. The IRRs for HCC across the household income categories in Sweden estimated from the present study are by far the highest reported yet.[15]

Low social class is a strong predictor of intravenous drug use, which is the main transmission route of hepatitis C (HCV) in Sweden.[29,30] Socioeconomic inequalities have also been associated with increased risk HCV.[31] HCV is the second common cause of cirrhosis, and the foremost cause of HCC in Sweden.[24,32] Historically, low education and occupations with risk for harmful alcohol consumption and/or high prevalence of smoking, have been linked to higher risk for liver cancer in Sweden.[21,22] As educational level, occupational complexity, and income level are intrinsically related to each other in Sweden, our results support prior observations.[32]

Neighbourhood deprivation level was directly associated with HCC incidence, which was in line with studies from England, France and Germany.[16-18] The inclusion of IMD in regression models considerably reduced the effect of individual-level SES indicators and vice versa. The interplay between these variables motivates the use of both individual-level (if possible) and neighbourhood-level SES indicators in descriptive epidemiology of cancer burden.[5] Our study demonstrated that both low household income and living in a deprived neighbourhood could identify population groups with particularly high risk for HCC.

In line with prior studies from Sweden and Norway, patients born in a non-Nordic country were younger at HCC diagnosis than patients with a Nordic origin.[33,34] Also consistent with observations from Norway,[34] we found that the patients born in a non-Nordic country were more frequently diagnosed at early-stage. The following explanations have been suggested: higher awareness of liver cancer in some immigrant groups and physicians being more attentive to liver cancer diagnosis in specific ethnical minorities.[34]

The results of our descriptive epidemiological study could be considered for rational targeting of high-risk population groups. To achieve progress in practice, however, further intervention studies will be essential.

The European Association for the Study of the Liver (EASL)-Lancet Liver Commission has recently published 10 recommendations to counteract liver disease complications and premature mortality in Europe.[35] Liver disease (including HCC) prevention in high-risk groups may be the most cost-effective strategy in a country such as Sweden.

Most of the recommendations made by the EASL-Lancet Liver Commission aim to provide guidance for primary prevention.[35] Several of these recommendations have already been established in Sweden.[30,36]

In line with the EASL recommendations, as well as the recommendations by the American Association for the Study of Liver Diseases and the American Diabetes Association, we advise the creation and implementation of active liver disease screening programmes into current follow-up guidelines for type 2 diabetes.[37] Furthermore, we advocate RCTs to evaluate the effect of analogous screening programmes, including the early identification of hazardous alcohol consumption, in disadvantaged/high-risk population groups with other non-communicable metabolic diseases.[35] Our results provide a useful basis for targeting population groups who could benefit most by future screening interventions. The cost-effectiveness of such interventions needs to be demonstrated. Hence, RCTs with consideration to health equity aspects could be pursued for evaluating the cost-effectiveness of screening to detect liver cancer at an early stage.[38]

We have shown that patients diagnosed at late-stage HCC were generally older and neighbourhood-level SES differences dissipated in patients aged 70+ years. The contextual-level SES associations with early-stage HCC diagnosis were most prominent for people on the age span 55 to 69 years. Preferably, this age span should be at focus for targeted interventions against late-stage diagnosis in high-risk population groups.

Causal factors, such as cirrhosis, underlying comorbidity (eg, diabetes, obesity, arterial hypertension), alcohol consumption and tobacco use,[39] were not regarded as confounders in the present study; because our aim was to target population groups with a high burden of HCC. In Sweden, most cirrhosis patients are diagnosed at the age of 60 to 66 years, and alcoholic liver disease, HCV and non-alcoholic fatty liver disease are the main aetiologies.[32,40] Susceptibility to alcohol-related harm, HCV incidence and obesity prevalence are all increased in low SES groups.[41-43] In cirrhosis, low individual-SES has been associated with a 3.4 times (95% CI 1.9-6.2) higher risk for mortality, compared to high individual-SES.[32] High prevalence of HCC at cirrhosis diagnosis (12.5%) have been described, and HCC is the second leading cause of death in patients with cirrhosis in Sweden.[32,40]

Cirrhosis diagnosis delay might be common, and roughly 50% of the patients are already decompensated at the time of cirrhosis diagnosis.[32,40] Decompensated cirrhosis patients with HCC seldom receive curative treatment.[39] In a quarter of cirrhosis patients, cirrhosis might also be unrecognised prior HCC diagnosis.[44] These patients are more often diagnosed at a late-stage HCC.[44]

The results of our study should be considered with some limitations in mind. First, patients were regarded as either early- or late-stage and stage-specific analyses for all the different stages defined by BCLC were not possible. Second, our definition of country of birth does not allow comparison among different nationalities. Third, as most prior studies use education or occupational social class, a direct comparison with household income might not be straightforward. Forth, our study design does not allow for causal inferences; for example, we could not sort out whether the elevated early- and late-stage incidences of HCC observed among the immigrants from the non-Nordic counties were mainly due to migration-related aetiological factors or other causes linked to a low SES in Sweden.

The most important strengths of our study were: (a) inclusion of high-quality nationwide data retrieved from validated registries; (b) absence of missing data regarding SES and only 3% missing data regarding HCC staging; (c) use of well-defined variables and statistical methods and (d) inclusion of ethnicity, individual- and contextual-level SES indicators.

5 | CONCLUSIONS

Men with a low household income and/or living in the most deprived neighbourhoods are at the highest risk of HCC in Sweden. This population group might be considered as a primary target in future studies evaluating the cost-effectiveness of screening for early-stage HCC detection.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

AUTHOR CONTRIBUTION

Guarantor of the article: Juan Vaz. Specific author contributions: Juan Vaz: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualisation, Funding acquisition, Writing—Original Draft. Patrik Midlöv: Conceptualization, Writing—Review and Editing, Supervision. Malin Sternby Eilard: Conceptualization, Writing—Review and Editing. Berne Eriksson: Writing—Review and Editing. David Buchebner: Writing—Review and Editing. Ulf Strömberg: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualisation, Funding acquisition, Writing—Original Draft, Main supervision. The work reported in the article has been performed by the authors, unless clearly specified in the text.

DATA AVAILABILITY STATEMENT

Anonymised datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The present study was approved by the Central Ethical Review Board in Sweden (Decision Number 2020-04430). For this kind of study, no patient consent was required.

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