Genetic and healthy lifestyle factors in relation to the incidence and prognosis of severe liver disease in the Chinese population

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Abstract

Background: Severe liver disease (SLD), including cirrhosis and liver cancer, constitutes a major disease burden in China. We aimed to examine the association of genetic and healthy lifestyle factors with the incidence and prognosis of SLD.

Methods: The study population included 504,009 participants from the prospective China Kadoorie Biobank aged 30–79 years. The individuals were from 10 diverse areas in China without a history of cancer or liver disease at baseline. Cox regression was used to estimate adjusted hazard ratios (HRs) for incident SLD and death after SLD diagnosis associated with healthy lifestyle factors (smoking, alcohol, physical activity, and central adiposity). Additionally, the contribution of genetic risk for hepatitis B virus (HBV, assessed by genetic variants in major histocompatibility complex, class II, DP/DQ [*HLA-DP/DQ*] genes) was also estimated.

Results: Compared with those with 0–1 healthy lifestyle factor, participants with 2, 3, and 4 factors had 12% (HR 0.88 [95% confidence interval [CI] 0.85, 0.92]), 26% (HR 0.74 [95%CI: 0.69, 0.79]), and 44% (HR 0.56 [95%CI: 0.48, 0.65]) lower risks of SLD, respectively. Inverse associations were observed among participants with both low and high genetic risks (HR per 1-point increase 0.83 [95%CI: 0.74, 0.94] and 0.91 [95%CI: 0.82, 1.02], respectively; $P_{interaction} = 0.51$), although with a non-significant trend among those with a high genetic risk. Inverse associations were also observed between healthy lifestyle factors and liver biomarkers regardless of the genetic risk. Despite the limited power, healthy lifestyle factors were associated with a lower risk of death after incident SLD among participants with a low genetic risk (HR 0.59 [95%CI: 0.37, 0.96]).

Conclusions: Lifestyle modification may be beneficial in terms of lowering the risk of SLD regardless of the genetic risk. Moreover, it is also important for improving the prognosis of SLD in individuals with a low genetic risk. Future studies are warranted to examine the impact of healthy lifestyles on SLD prognosis, particularly among individuals with a high genetic risk.

Keywords: Healthy lifestyle; Gene–environment interaction; Liver cancer; Cirrhosis; Prognosis; China

Introduction

Severe liver disease (SLD), including cirrhosis and liver cancer, constitutes a major disease burden in China.[1] Globally, cirrhosis caused more than 1.32 million deaths in 2017, of which 12% occurred in China.[2] Liver cancer caused 8.19 million deaths in 2017, with 3 million deaths reported from China.[2] Despite the increasing number of SLD deaths from 1990 to 2017, age-standardized death rates have been decreasing.[3] While alcohol, non-alcoholic fatty liver disease (NAFLD), and hepatitis C virus account for the majority of SLD in western countries,[3] hepatitis B virus (HBV) is the leading cause of SLD in China, accounting for 50% of SLD cases in 1990 and 40% in 2013.[4]

Previous prospective studies in western countries and China have reported lifestyle and genetic risk factors for SLD.[5–16] For individual lifestyle factors, smoking, alcohol

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consumption, physical inactivity, and adiposity are associated with a high risk of SLD.[5–12] When combining these factors into a lifestyle score, adherence to a healthy lifestyle has been shown to be associated with lower risk of liver cancer.[13] For genetic factors, previous studies have focused on the human leukocyte antigen (HLA) class II region at 6p21. Genetic variations in *HLA-DQ* and *HLA-DP* genes are associated with the risk of HBV infection and hepatocellular carcinoma.[14–16]

Despite the evidence on genetic and lifestyle risk factors for SLD, there is limited evidence on whether genetic factors could interact with lifestyle factors to increase the risk of SLD. The evaluation of gene–environment interactions can help identify the groups that would benefit the most from lifestyle interventions. Apart from clinical outcomes, non-invasive biomarkers for liver diseases have the potential to screen for subclinical liver diseases and inform risk stratification at the early stage of diseases. However, these have been rarely examined in gene–environment interaction analyses. In addition, there is little evidence on the genetic and lifestyle factors related to prognosis after SLD. Previous studies have mainly used medical records and reported clinical characteristics (e.g., blood biochemistry and prognostic scores) associated with SLD prognosis.[17,18] Assessing the associations between lifestyle and SLD prognosis may provide crucial information for designing secondary prevention strategies.

Therefore, this study examined the following: the association of genetic (i.e., HBV) and healthy lifestyle factors with the incidence of SLD and liver biomarkers; whether genetic factors could interact with healthy lifestyle and liver biomarkers and play a role in the incidence of SLD; and the association of genetic and healthy lifestyle factors with the prognosis of SLD.

Methods

Study population

The China Kadoorie Biobank (CKB) study was approved by the Ethical Committee and Research Council of the Chinese Center for Disease Control and Prevention (Beijing, China, 005/2004) and the Oxford Tropical Research Ethics Committee at the University of Oxford (UK, 025-04). All participants provided written informed consent for the study. Details of the CKB design, survey methods, and population characteristics have been described elsewhere.[19] Briefly, 512,726 participants (210,204 men and 302,522 women) aged 30–79 years were recruited into the study from 10 (5 urban, 5 rural) geographically defined localities in China during 2004–2008. The study areas were selected to provide diversity in risk exposure and disease patterns, while considering population stability, quality of mortality and morbidity registries, capacity, and long-term commitment within the areas. At the local study assessment clinics, participants completed an interviewer-administered laptop-based questionnaire on sociodemographic characteristics, smoking, alcohol consumption, diet, physical activity, personal and family medical history, and current medication. Trained technicians recorded a range of physical measurements, including height, weight, hip and waist circumference, bio-impedance, lung function, blood pressure, and heart rate, using calibrated instruments with standard protocols. Details of the data collection on lifestyle factors are described in Supplementary Material, http://links.lww.com/CM9/B685.

Follow-up for and ascertainment of disease cases

The vital status of each participant was determined periodically through the China Center for Disease Control and Prevention's Disease Surveillance Points (DSP) system, supplemented by regular checks against local residential and administrative records, and by annual active confirmation through street committees or village administrators.[20] In addition, information about major diseases and any episodes of hospitalization were collected through linkages, via each participant's unique national identification number, with disease registries (for cancer, ischemic heart disease, stroke, and diabetes) and national health insurance claims databases. All disease events were coded using the International Classification of Diseases, 10th Revision (ICD-10). This was done by trained DSP staff (for death) or medical professionals (for hospitalized events) who were blinded to the baseline information. Here, SLD was defined using ICD-10 codes K74 (cirrhosis) and C22 (liver cancer). In CKB, C22 was used only for primary liver cancer and secondary cancer was coded as "C78.7." By January 1, 2017, 44,066 (9%) participants had died and 4751 (<1%) were lost to follow-up. The prognosis analysis was restricted to participants with incident SLD during follow-up, and all-cause mortality was used as the outcome.

Genotyping and biochemistry measurements

Three variants of *HLA-DQ* (rs2856718, rs7453920, and rs2647050) and two variants of *HLA-DP* (rs3077 and rs9277535) were selected based on previously reported associations with HBV infection in East Asians.[16,21] Genotyping was conducted in 151,217 individuals by using a 384-single nucleotide polymorphism (SNP) array (GoldenGate; Illumina; San Diego, California; USA) or a custom-designed 800 K-SNP array (Axiom; Affymetrix; Santa Clara, California; USA) (overall call rate >99.97% across all variants). Genotyping consisted of a population-based sample of 134,790 participants included in analyses of all disease outcomes. An additional 13,000 participants with an incident cardiovascular disease (CVD) event and control participants were included in analyses of specified CVD outcomes. Also, additional 3427 participants with an incident chronic obstructive pulmonary disease (COPD) event were included in analyses of COPD. After quality control, 99,500 participants had available dosage variables for all five SNPs. A subset of the genotyped population (17,567 selected for CVD case-control studies) underwent assessment of plasma concentrations of liver function biomarkers (alanine aminotransferase [ALT], aspartate transaminase [AST], and γ-glutamyl transferase [GGT]) using a clinical chemistry analyzer (AU680; Beckman Coulter; Brea, Cali-

fornia; USA). The details of the study design are described in the Supplementary Material, http://links.lww.com/CM9/B685(eMethods and Supplementary Figure 1, http://links.lww.com/CM9/B685).

Liver function was assessed by measuring ALT, AST, and GGT levels. Steatosis was measured using the fatty liver index (FLI) with the following formula:[22]

$$\left(e^{0.953\times log_e TG+0.139\times BMI+0.718\times log_e GGT+0.052\times WC-15.745}\right)/\left(1+e^{0.953\times log_e TG+0.139\times BMI+0.718\times log_e GGT+0.052\times WC-15.745}\right)\times 100.$$

TG indicates triglyceride, and WC indicates waist circumstance.

Fibrosis was measured using the BMI, AST/ALT ratio, and diabetes (BARD) score calculated as the weighted sum of body mass index (BMI) >28 kg/m^2 (1 point), AST/ALT ratio >0.8 (2 points), and diabetes (1 point).[23] The FLI is a noninvasive diagnostic biomarker for NAFLD and provides a quantitative assessment of steatosis.[23] The BARD score is a noninvasive model for detecting liver fibrosis caused by various etiologies and has been shown to predict advanced fibrosis with good sensitivity and specificity.[23]

Definition of healthy lifestyle factors

We selected smoking, alcohol consumption, physical activity, and central adiposity to construct a combined healthy lifestyle score. These lifestyle factors have been shown to be associated with risk of chronic liver disease in the Chinese population.[9,10,12] To investigate the combined effects of a healthy lifestyle, we grouped each participant into one of the four categories according to the number of healthy lifestyle factors (0–3), encompassing smoking (non-smokers, occasional smokers, or former smokers who quitted for reasons other than illness), alcohol consumption (occasional/monthly drinkers or consumers of <30 g/day of pure alcohol), physical inactivity (total physical activity ≥17.47 metabolic equivalent of task (MET) -h/day [the top 50%]), and central obesity measurement (WC <90 cm [men] or <80 cm [women]). The cut-off points were selected for each metabolic factor based on *a priori* knowledge of the risk factors for chronic liver disease and were considered achievable at the population level.

Definition of genetic risk factors

To investigate whether the association of the combined healthy lifestyle factors and risk of SLD differed by genetic predisposition, we constructed an unweighted genetic risk score (GRS) for HBV (HBV-GRS) by summing the risk alleles of five HBV-related variants identified in a previous genome-wide association studies (GWAS) in East Asians (0–10 copies of risk alleles across five SNPs).[16,21] Participants were divided into two groups according to their genetic predisposition: low genetic risk (HBV-GRS <5 risk alleles) and high genetic risk (HBV-GRS ≥5 risk alleles).

Statistical analysis

The present study excluded individuals with a history of cancer ($n = 2578$) and cirrhosis or hepatitis ($n = 6139$), leaving 504,009 individuals for the main analysis. The primary outcome was SLDs (composite SLD, cirrhosis, and liver cancer), and the secondary outcomes were liver biomarkers (ALT, AST, GGT, FLI, and BARD). In the analysis of individual lifestyle factors, Cox proportional hazards regression models were used to estimate adjusted hazard ratios (HRs) for SLD, adjusted for age at baseline, sex, study area (10 regions), education (four groups: no formal school, primary school, middle/high school, or college/university), BMI, hepatitis B surface antigen (HBsAg), and self-rated health, with additional adjustment for other lifestyle factors. The time since birth was used as the underlying time scale, and participants entered the study at their baseline age.

In the combined analyses, healthy lifestyle factors were modeled as categorical variables (0–4 points) and ordinal variables (per 1-point increase in number; linear trend). The same variables were adjusted for in the analysis of individual risk factors, and each lifestyle factor was weighted equally. Adjusted HRs were reported for individuals with 2, 3, and 4 healthy lifestyle factors compared with those with 0–1 healthy lifestyle factor. Combined analyses were also performed separately for the patients with cirrhosis and liver cancer. For analyses involving more than two categories, all HRs are presented with 95% confidence intervals (CIs) calculated using "floating" standard errors to facilitate comparisons between any two groups rather than just with the reference group.[24] Instead of selecting one level of the risk factor as the reference group, a "floated" variance was assigned to each level. This described the uncertainty in risk without reference to another level.

To investigate the potential influence of genetic risk factors on the association between healthy lifestyle and risk of SLD, we performed analyses stratified by HBV-GRS. In addition, we examined the associations of the combination of genetic and healthy lifestyle categories (six categories, with high genetic risk and 0–1 healthy lifestyle factor as reference) with the risk of SLD. Besides, we tested the interaction between healthy lifestyle and genetic factors using the likelihood ratio test. In a parallel analysis, we examined the association between healthy lifestyle factors and SLD stratified by family history of cancer.

In the analysis of prognosis after incident SLD, Cox proportional hazards regression models were used to estimate the adjusted HRs associated with lifestyle and genetic factors for any incidence of death among participants who developed SLD during follow-up. This was done with the same statistical models used in the analysis of incident SLD. Lifestyle factors from the baseline interview were used whose data were collected 10 years prior to disease onset. This was done to avoid reverse causality caused by lifestyle changes after disease diagnosis.

Results

Baseline characteristics of study participants

Of the 504,009 participants, the mean age was 52 years, and 59.2% were women. During 10 years of follow-up, there were 4590 incident cases of SLD, including 2298 cirrhosis and 2803 liver cancer cases. Participants with SLD were more likely to be male, older, living in rural areas, and have lower household incomes [Table 1]. Additionally, participants with SLD, particularly men, were more likely to smoke and consume alcohol. No differences in anthropometric factors were observed between participants with and without SLD. Participants with SLD were more likely to have prevalent diabetes and family history of cancer.

Table 1: Baseline characteristics of participants with and without incident SLD.

Variables*	Incident SLD (n = 4590)	No incident SLD (n = 499,419)
Age (years)	57.5 ± 10.2	52.0 ± 10.7
Female	1905 (41.5)	296,477 (59.4)
Socioeconomic and lifestyle factors		
Urban region	1852 (40.3)	220,261 (44.1)
≥9 years of education	708 (20.9)	104,678 (18.6)
Household income ≥35,000 RMB/year	632 (15.5)	89,783 (18.0)
Ever regular smoking		
Male	1716 (67.4)	124,345 (61.2)
Female	78 (2.8)	6958 (2.4)
Weekly drinking		
Male	952 (36.6)	67,928 (33.4)
Female	39 (1.9)	6130 (2.1)
Total physical activity (MET-h/day)	20.1 ± 13.5	21.1 ± 13.8
Sedentary leisure time (h/day)	3.1 ± 1.6	3.0 ± 1.5
Blood pressure and anthropometry		
SBP (mmHg)	131.7 ± 21.9	131.1 ± 21.3
RPG (mmol/L)	6.4 ± 3.0	6.1 ± 2.3
BMI (kg/m^2)	23.6 ± 3.5	23.7 ± 3.4
WC (cm)	80.3 ± 10.2	80.3 ± 9.7
HC (cm)	90.6 ± 7.4	90.9 ± 6.9
Waist-to-hip ratio	0.90 ± 0.07	0.90 ± 0.07
Percent body fat (%)	27.4 ± 8.9	28.0 ± 8.4
Height (cm)	158.4 ± 8.5	158.7 ± 8.3
Prior disease history		
Diabetes	466 (9.0)	29,150 (5.8)
CHD	163 (2.8)	14,937 (3.0)
Stroke or TIA	98 (1.5)	8606 (1.7)
Family history of cancer	623 (15.2)	69,498 (13.9)

Data are shown as n (%) or mean ± SD. BMI: Body mass index; CHD: Coronary heart disease; HC: Hip circumference; MET: Metabolic equivalent of task; RPG: Random plasma glucose; SBP: Systolic blood pressure; SD: Standard deviation; SLD: Severe liver disease; TIA: Transient ischemic attack; WC: Waist circumference. *Results were standardized by age, sex, and region (where appropriate). Values are means unless otherwise stated.

Associations of healthy lifestyle factors with SLD incidence

In the analysis of individual lifestyle factors, each of the four factors was associated with the risk of SLD [Table 2]. The HR (95% confidence interval [CI]) for healthy lifestyle factors was 0.80 (0.74, 0.87) for no current smoking, 0.77 (0.72, 0.82) for low to moderate alcohol intake, 0.90 (0.82, 0.98) for no central obesity, and 0.94 (0.88, 1.01) for physical activity. Additional adjustments for the other three lifestyle factors did not alter the association with each individual factor.

In the analysis of healthy lifestyles, participants with more healthy lifestyle factors had a lower risk of SLD [Supplementary Table 1, http://links.lww.com/CM9/B685]. Compared with those with 0–1 healthy lifestyle factor, participants with 2, 3, and 4 factors had 12% (HR 0.88 [95%CI: 0.85, 0.92]), 26% (HR 0.74 [95%CI: 0.69, 0.79]), and 44% (HR 0.56 [95% CI: 0.48, 0.65]) lower risks of SLD, respectively. Each 1-point increase in the number of healthy lifestyle factors was associated with a 15% lower risk of SLD (HR 0.85 [95%CI: 0.82, 0.88]). Similar associations were observed when the analysis was restricted to participants with available genetic data [Supplementary Table 1, http://links.lww.com/CM9/B685].

Associations of healthy lifestyle factors with SLD incidence by genetic factors

Among 97,851 participants with available genetic data, each risk allele in HLA genes was associated with a 7% (HR 1.07 [95%CI: 1.03, 1.10]) higher risk of SLD, whereas a high GRS was associated with a 30% (HR 1.30 [95%CI: 1.14, 1.48]) higher risk. For HBV-GRS, participants with more healthy lifestyle factors had a lower risk of SLD among those with a low GRS (HR for 4 *vs*. 0–1 factors 0.60 [95% CI: 0.36, 0.99], Figure 1). Similarly, there were inverse associations among participants with a high GRS (HR for 4 *vs*. 0–1 healthy lifestyle factors: 0.67 [95%CI: 0.43, 1.05]), although the trend was not statistically significant. The P value for gene–environment interaction was not significant (P value for interaction 0.51). When examining the HR per 1-point increase in the number of healthy lifestyle factors, the HR (95%CI) was 0.83 (0.74, 0.94) among participants with a low GRS. This score was 0.91 (0.82, 1.02) among participants with a high GRS. The associations between healthy lifestyle factors and HBV-GRS were similar [Supplementary Table 2, http://links.lww.com/CM9/B685].

Compared with participants with a low GRS and 0–1 healthy lifestyle factor, the HRs (95%CIs) among participants with a low GRS and 2, 3, and 4 healthy lifestyle factors were 0.96 (0.83, 1.11), 0.70 (0.57, 0.87), and 0.63 (0.38, 1.03), respectively [Supplementary Table 3, http://links.lww.com/CM9/B685]. Concurrently, the HRs (95%CIs) among participants with a high GRS and 0–1, 2, 3, and 4 healthy lifestyle factors were 1.27 (1.08, 1.49), 1.02 (0.88, 1.17), 1.04 (0.87, 1.25), and 0.82 (0.52, 1.28), respectively.

Table 2: Associations of individual lifestyle factors with risk of SLD.

Healthy lifestyle factor	Description	*N* cases/*N* total	HR (95% CI)*	HR (95% CI)†
No current smoking	Never, occasional and former smokers‡	2358/341,411	0.80 (0.74, 0.87)	0.82 (0.75, 0.89)
	Reference	2232/162,598	1.00	1.00
Low to moderate alcohol intake	Occasional/monthly drinkers, or <30 g/day of pure alcohol	1868/219,828	0.77 (0.72, 0.82)	0.77 (0.72, 0.82)
	Reference	3372/292,898	1.00	1.00
No central obesity	WC <90 cm (men), WC <80 cm (women)	3100/325,626	0.90 (0.82, 0.98)	0.91 (0.83, 0.99)
	Reference	1490/178,383	1.00	1.00
Physical activity	Total physical activity ≥17.47 MET-h/day	1983/252,912	0.94 (0.88, 1.01)	0.94 (0.88, 1.01)
	Reference (the top 50%)	2607/251,097	1.00	1.00

CI: Confidence interval; HBV: Hepatitis B virus; HR: Hazard ratio; MET: Metabolic equivalent of task; SLD: Severe liver disease; WC: Waist circumference. *The model was adjusted for age, sex, region, HBV, education, and self-rated health. †The model was additionally adjusted for the other three lifestyle factors. ‡Former smokers who quitted for reasons other than illness.

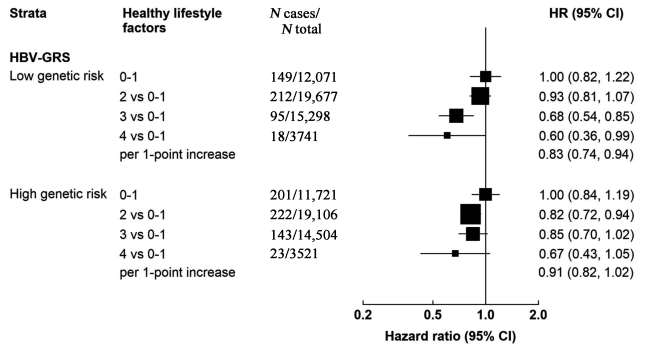

Figure 1: HRs of incident SLD according to healthy lifestyle categories within each genetic risk category. Boxes represent the HRs of SLD associated with healthy lifestyle factors in participants by strata of HBV-GRS, with the size of the box inversely proportional to the variance of the logHR. Cox proportional hazards regression models were used in the analysis. The model was adjusted for age, sex, region, HBV, education, self-rated health, and 12 national principal components (PCs). *P* values for interaction were obtained from the likelihood ratio test. *P* value for interaction was 0.51. HBV: Hepatitis B virus; HBV-GRS; Hepatitis B virus genetic risk score; CI: Confidence interval; HRs: Hazard ratios; SLD: Severe liver disease.

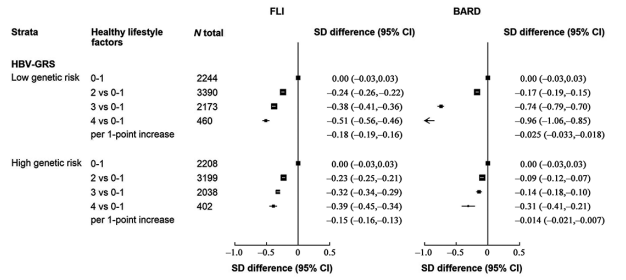

Figure 2: HRs of liver biomarkers according to healthy lifestyle categories within each genetic risk category. Boxes represent the SD differences of liver biomarkers associated with healthy lifestyle factors in participants by strata of HBV-GRS, with the size of the box inversely proportional to the variance of the SD difference. Linear regression models were used in the analysis. The model was adjusted for age, sex, region, HBV, education, self-rated health, 12 national PCs, and fasting hours. *P* values for interaction were obtained from the likelihood ratio test. *P* value for interaction was 0.20 for FLI and <0.001 for BARD (BMI, diabetes, and AST/ALT ratio). Both FLI and BARD were associated with a higher risk of SLD (HR per 1-SD [95%CI]: 1.25 [1.08, 1.45] for FLI and 1.25 [0.96, 1.63] for BARD). CI: Confidence interval; FLI: Fatty liver index; HBV: Hepatitis B virus; HBV-GRS: Hepatitis B virus genetic risk score; HRs: Hazard ratios; SD: Standard deviation; SLD: Severe liver disease.

Associations of healthy lifestyle factors with liver biomarkers by genetic factors

Of the 16,638 participants with available liver biomarker measurements, both FLI and BARD scores were associated with a higher risk of SLD (HR per 1-SD [95%CI]: 1.25 [1.08, 1.45] for FLI and 1.25 [0.96, 1.63] for BARD). For BARD, healthy lifestyle factors were associated with greater reduction among participants with a low GRS than among those with a high GRS (unit difference [95%CI] for 4 *vs*. 0–1 healthy lifestyle factors: –0.96 [–1.06, –0.85] and –0.31 [–0.41, –0.21], *P* value for interaction <0.001, Figure 2). For FLI, healthy lifestyle factors were associated with a similar reduction among participants with low and high GRS (unit difference for 4 *vs*. 0–1 healthy lifestyle factors: –0.51 [–0.56, –0.46] and 0.39 [–0.45, –0.34], *P*-value for interaction 0.20, Figure 2). For AST and ALT, there were similar associations for the number of healthy lifestyle factors among participants with both low and high GRS (*P* values for interaction, 0.34 and 0.90, Supplementary Table 4, http://links.lww.com/CM9/B685). For GGT, the inverse associations were stronger among participants with a low GRS (*P* value for interaction <0.001).

Associations of healthy lifestyle and genetic risk factors with SLD prognosis

Of the 4590 cases of incident SLD that occurred during follow-up, baseline healthy lifestyle factors were associated with all-cause mortality, while there was no clear association for HBV-GRS (high *vs*. low, HR [95%CI] 1.09 [0.91, 1.31]) [Table 3]. The HR (95%CI) was 0.89 (0.79, 0.99) for no current smoking, 0.97 (0.89, 1.06) for low to moderate alcohol intake, 0.92 (0.84, 0.99) for physical activity, and 0.86 (0.76, 0.97) for no central obesity. When stratified by HBV-GRS [Figure 3], a healthy lifestyle was associated with a lower risk of death after SLD diagnosis among those with a low GRS (4 *vs*. 0–1 healthy lifestyle factors: 0.59 [0.37, 0.96]), but there were no clear associations among those with a high GRS (1.07 [0.89, 1.29], *P* value for interaction, 0.049).

Table 3: Associations of genetic and lifestyle factors with risk of any death after diagnosis of SLD.

Prognostic factor	*N* deaths/*N* cases	HR (95% CI)*
Genetic factor		
High HBV-GRS	337/589	1.09 (0.91, 1.31)
Healthy lifestyle†		
No current smoking	1417/2626	0.89 (0.80, 0.99)
Low to moderate alcohol intake	2402/4161	0.97 (0.89, 1.06)
No central obesity	2149/3597	0.86 (0.75, 0.97)
Physical activity	1210/2205	0.92 (0.84, 0.99)
Healthy lifestyle category		
0–1	199/328	1.00 (0.93, 1.08)
2 *vs*. 0–1	1246/2050	0.92 (0.78, 1.09)
3 *vs*. 0–1	1270/2211	0.81 (0.68, 0.98)
4 *vs*. 0–1	330/652	0.74 (0.60, 0.92)
Per 1 unit	–	0.90 (0.85, 0.95)

HBV: Hepatitis B virus; HBV-GRS: Hepatitis B virus genetic risk score; HR: Hazard ratio; SLD: Severe liver disease; –: Not available. *The model was adjusted for age, sex, region, HBV, education, and self-rated health. †For smoking, alcohol, physical activity, and central adiposity, the model additionally included the other three factors.

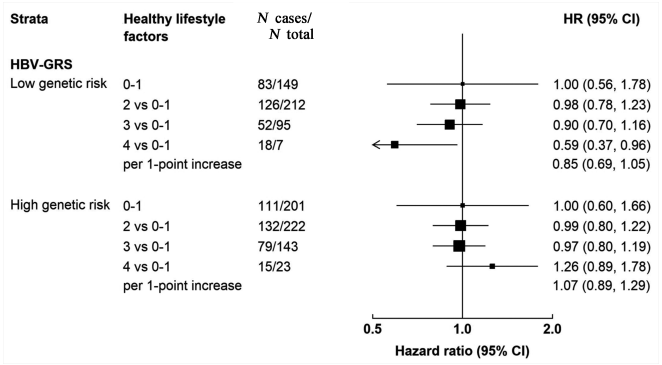

Figure 3: HRs of any death after diagnosis of SLD according to healthy lifestyle categories within each genetic risk category. Boxes represent the HRs of SLD associated with healthy lifestyle factors in participants by strata of HBV-GRS, with the size of the box inversely proportional to the variance of the logHR. Cox proportional hazards regression models were used in the analysis. The model was adjusted for age, sex, region, HBV, education, self-rated health, and 12 national principal components (PCs). *P* values for interaction were obtained from the likelihood ratio test. *P* value for interaction was 0.049. CI: Confidence interval; HBV-GRS: Hepatitis B virus genetic risk score; HRs: Hazard ratios; SLD: Severe liver disease.

Discussion

In the studied Chinese population, a healthy lifestyle was associated with lower risk of SLD, particularly among individuals with low genetic risk. Lifestyle factors were associated with lower levels of liver biomarkers, regardless of the genetic risk. However, the magnitude of inverse association for the BARD (a marker for liver fibrosis) was higher among individuals with low genetic risk. Healthy lifestyle factors were associated with a lower risk of death after SLD among individuals with a low genetic risk. Lifestyle modification is beneficial in terms of lowering the incidence of SLD regardless of the genetic risk. Besides, it also contributes to improving the prognosis of SLD among adults with low genetic risk. More evidence is needed to quantify the impact of healthy lifestyles on SLD prognosis among individuals with high genetic risk.

Previous prospective studies in western countries and China have shown that individual lifestyle factors, including smoking, alcohol consumption, physical inactivity, and adiposity, are risk factors for SLD.[5–12] A recent meta-analysis has reported that a healthy lifestyle, consisting of smoking, alcohol consumption, physical activity, BMI, and diet, is associated with a lower risk of liver cancer mortality.[13] That meta-analysis included 408,330 European adults and showed that the HR (95%CI) comparing individuals with the most *vs*. the least healthy lifestyles was 0.68 (0.48, 0.97). In CKB, the HR (95%CI) comparing individuals with 4 *vs*. 0 healthy lifestyle factors was 0.69 (0.62, 0.75). This is generally consistent with the results of the meta-analysis. We extended the findings of previous studies by showing that there were inverse associations between healthy lifestyle factors and SLD risk regardless of the genetic risk.

Despite the different definitions of healthy lifestyle, our findings for healthy lifestyle factors and liver biomarkers were generally consistent with those of a cross-sectional study of 12,368 Finnish adults. The latter study showed that an unfavorable combination of lifestyle risk factors, including smoking, alcohol consumption, coffee consumption, and physical inactivity, was associated with higher levels of FLI.[25] In addition to FLI, we showed that a healthy lifestyle is associated with other liver biomarkers, including AST, ALT, GGT, and BARD. It must be noted that FLI is a marker of liver steatosis,[22] while BARD is a marker of liver fibrosis.[23] Therefore, BARD is more specific to SLD. The analysis of biomarkers strengthened the findings of the main analysis for SLD and showed a stronger association between healthy lifestyle and BARD among individuals with low genetic risk.

Previous studies on the prognosis of SLD have reported on the clinical characteristics associated with prognosis, including age, sex, adiposity, diabetes, platelet count, and albumin level.[17,18] A Chinese study reported the role of *FNDC3B* gene in the prognosis of liver cancer, but there have been no studies on the *HLA-DP/DQ* genes.[26] In CKB, smoking, physical inactivity, and central adiposity were associated with death after SLD. This is consistent with the findings of previous studies in western countries that showed the association of smoking and physical inactivity with disease progression in patients with chronic liver disease.[17,18] Although clinical characteristics are non-modifiable, lifestyle factors can be modified through lifestyle intervention in the secondary prevention of SLD, particularly among individuals with low genetic risk.

Among individuals with a high GRS, the associations of a healthy lifestyle with FLI and BARD were somewhat

weaker than those with low GRS. Although FLI and BARD reflect NAFLD and NAFLD-related fibrosis, previous studies have suggested the impact of HBV on liver steatosis and fibrosis.[27] Our findings indicate that HBV may weaken the association between healthy lifestyle and fibrosis, a key determinant of SLD. Despite the different magnitudes of associations among those with low and high genetic risks, we found that healthy lifestyle factors showed a graded inverse association with FLI and BARD. Given the positive associations between these liver biomarkers and incident SLD, the said biomarkers may serve as targets for primary prevention. This necessitates close monitoring of these markers in individuals with high genetic risk.

The strengths of the CKB include its prospective design, a large and diverse study population, detailed assessment of risk factors for SLD, and validity of the genetic score developed for SLD. In particular, we measured a range of liver biomarkers in a nested case-control study, which allowed us to validate the associations identified for SLD. Our study also had several limitations. First, SLD was ascertained through linkages to death and disease registries as well as health insurance databases, without proactive assessment of the liver using ultrasound or noninvasive measures of assessing fibrosis (e.g., Fibrosis score 4, AST-platelet ratio index). However, using biomarker data for CKB, we showed that the main results for SLD were generally consistent with those for BARD, a marker of liver fibrosis.[23] Second, analyses of genetic and healthy lifestyle factors were conducted in ~100,000 participants with genetic data, with a much smaller sample size than the overall associations for healthy lifestyle factors. However, when we compared the associations between healthy lifestyle factors and SLD risk in all participants and those with genetic data, consistent associations were observed [Supplementary Table 1, http://links.lww.com/CM9/B685]. Third, the current study included variants of *HLA-DP/DQ* to assess the genetic predisposition to SLD. Therefore, it is possible that other components of genetic predisposition were not included. Fourth, the analysis of SLD prognosis only included a small number of participants. Therefore, the potential to explore gene–environment interactions might be limited. Finally, residual confounding due to unmeasured or unknown variables (e.g., subclinical infections) cannot be ruled out.

In conclusion, a healthy lifestyle, consisting of smoking, alcohol consumption, physical activity, and central adiposity, was associated with a lower risk of SLD in Chinese participants with both low and high genetic risks. A healthy lifestyle was associated with lower levels of liver biomarkers regardless of genetic risk. In most cases, a greater reduction in BARD was observed among individuals with low genetic risk than among those with high genetic risk. Healthy lifestyle factors were also associated with the prognosis of SLD among individuals with low genetic risk. Our study findings add to the available evidence base on gene–environment interactions in SLD and may contribute to the primary and secondary prevention of SLD. Lifestyle modifications may be beneficial in terms of lowering the risk of SLD regardless of the genetic risk. Besides, they would also improve the prognosis of SLD in individuals with low genetic risk.

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Conflicts of interest

None.

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