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Hepatitis B virus infection and risk of non-alcoholic fatty liver disease (NAFLD): a population-based cohort study

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Abstract

Background & aims: Although non-alcoholic fatty liver disease (NAFLD) has been studied extensively, the potential risk factors for NAFLD among chronic hepatitis B (CHB) patients have not been fully known.

Methods: A population-based cohort of adult CHB patients without a history of alcohol drinking or NAFLD were recruited and followed up from October 2012 to January 2015 in Jiangsu province, China. Using Cox proportional hazards regression model, potential risk factors including viral and metabolic factors for NAFLD were evaluated.

Results: 2,393 adult CHB patients (mean age 50.7±13.2 years) were included in the cohort. With 4,429 person-years of follow up, 283 individuals progressed to NAFLD with an incidence rate of 63.89/1,000 person-years. Overweight and obese CHB patients had an increased risk of NAFLD (overweight adjusted hazard ratio [HR], 3.10; 95% CI, 2.29-4.18; obese HR, 8.52; 95%CI, 5.93-12.25) compared to normal weight carriers. The incidence of NAFLD was associated with concurrent type 2 diabetes mellitus (DM) (HR, 1.88; 95%CI, 1.15-3.08). However, no associations between viral factors with NAFLD incidence rate were identified. In a subgroup of participants with concurrent type 2 DM, detectable HBV DNA levels were negatively associated with the

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development of NAFLD (HR, 0.37; 95%CI, 0.14-0.98). There was super-multiplicative interaction between BMI and gender with respect to incidence of NAFLD, with an ROR of 2.08 (95%CI, 1.02-4.23).

Conclusion: Metabolic factors play an important role in presence of NAFLD among Chinese CHB patients. However, viral replication factors are not related to NAFLD except among those with concurrent type 2 DM.

Keywords

NAFLD; HBsAg carriers; BMI; Diabetes mellitus

INTRODUCTION

Although Hepatitis B virus (HBV) infection has experienced an epidemiological shift in recent decades with a steep decrease in the prevalence of HBsAg from 9.8% to 7.2%, it is still a major public health problem in China. [1] Patients with HBV often progress to other debilitating chronic liver diseases, including cirrhosis and hepatocellular carcinoma. [2] Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide [3,4] with a global prevalence of 25.24% (95% CI: 22.10-28.65). [5] The increasing rate of NAFLD among HBV infected patients is alarming; it is estimated that as many as 29.6% of HBV infected patients worldwide have NAFLD.[6] A study of liver histopathology in Thailand found that steatohepatitis, a type of NAFLD, was independently correlated with significant liver fibrosis (OR,10.0; 95%CI, 2.08-48.5) and advanced liver fibrosis (OR, 3.45; 95%CI, 1.11-10.7) in chronic hepatitis B (CHB) patients. [7] Moreover, a retrospective cohort study found that fatty liver disease in HBV-infected patients can independently increase HBV-associated HCC development by 7.3-fold (95%CI, 1.52-34.76). [4] Conversely, a recent study indicated that HBsAg positivity was significantly associated with lower risk of incident NAFLD with an adjusted hazard ratio (95% CI) of 0.83(0.73-0.94). [8] Even though a clear understanding of the determinants of NAFLD among HBV infected patients is crucial to managing the public health impacts of this disease in a vulnerable population, the underlying mechanism through which HBV influences NAFLD development is still not well understood. [9–11] A meta analysis comprising of 4100 HBV infected patients found evidence that male sex, BMI, obesity, moderate alcohol consumption, diabetes mellitus, glycemia, serum triglycerides, HBV viral load were risk factors of NAFLD in HBV infected patients. [6] However, the authors did not find a clear association between HBV replication status (HBV DNA levels, hepatitis B e antigen (HBeAg) status) and incidence rate of NAFLD among chronic HBV carriers. [8,12,13] A better understanding of the epidemiology of NAFLD etiology among HBV carriers is critical for the implementation of effective preventive strategies among individuals with chronic HBV infection. In this study, we hypothesize that metabolic factors such as over-weight/obesity and diabetes mellitus are associated with increased risk of NAFLD among adult chronic HBV carriers. Our aim was to investigate the association between viral factors and the risk of NAFLD in a population-based prospective cohort of adult chronic HBV carriers without a history of drinking. We tested our hypothesis longitudinally and evaluated association between viral/metabolic factors and NAFLD controlling for potential confounders, including age and gender.

PATIENTS AND METHODS

Study populations

From September 2009 to March 2010, 149,172 inhabitants at least 1 year of age and residing in Jiangsu province, China, agreed to participate in a community based study as a part of National Major S&T Projects. [14] A total of 11,474 participants were HBsAg seropositive after sera-screening. From September to November 2010, 8,006 individuals (69.8%, 8,006/11,474) had their hepatitis serum markers re-evaluated and agreed to be regularly followed up annually from October 2012 to January 2015. A subset of individuals from this study were enrolled in 2012 into a community-based cohort if they met the inclusion criteria: 20 years or older, ALT lower than 40U/L, no history of antiviral therapy, HBsAg positive, and negative for antibodies against hepatitis C virus (anti-HCV) as of 2012. [15] Patients who had a history of alcohol drinking, or concomitant NAFLD at baseline were excluded. The study was approved by Institutional Review Board of Jiangsu CDC. All participants provided written informed consent for an interview, as well as follow-up interviews and blood sample collection.

Investigation and Laboratory Methods

All participants were interviewed in person with a structured questionnaire administered by trained physicians, nurses, and village doctors at study entry, which sought information about the participants' demographic characteristics, lifestyle habits (history of alcohol drinking and cigarette smoking), chronic disease history (hypertension, type 2 diabetes mellitus), dietary consumption habit (high-fat, non-high fat), workload, and antiviral therapy information (i.e. interferon therapy, oral nucleos(t)ide analogue therapy). NAFLD was diagnosed through abdominal ultrasound performed in the township hospital with the presence of fatty liver and no alcohol use.

By using standard sterile techniques, an overnight fasting 5-mL blood sample was collected at study entry and during follow-up examinations. Anti-HCV serostatus was ascertained at study entry. Alanine aminotransferase [ALT] levels, aspartate aminotransferase [AST] levels, albumin, globulin, total bilirubin, HBsAg, HBeAg, HBV DNA were tested at study entry and during follow-up examinations. HBsAg was measured by an enzyme-linked immunosorbent assay (ELISA) with the use of a commercial kit (KeHua Bioengineering Co., Ltd., Shanghai, China) with a lower detection limit of 0.2 IU/ml. ALT level was classified as elevated when ALT > 40 U/L for both men and women. [16,17]HBV DNA was measured by RT-PCR with a detection limit of 100 IU/mL. Hyperproteinemia was defined by total serum protein over 80 g/L or globulin over 35g/L. BMI was calculated using weight divided by height squared (kg/m^2). According to the adults' overweight and obesity screening standards in China, BMI can be classified into three levels: normal weight (<24 kg/m^2), overweight (24~28 kg/m^2) and obesity (≥28 kg/m^2). A health report was sent to participants in a sealed envelope privately within two months of study completion, and appropriate medical care suggestions were provided according to participants' infection status.

Statistical analysis

Follow-up began in 2012 at the time of enrollment, and the end-point was either the last visit before January 2015 or development of the outcome, NAFLD. Incidence was calculated using the number of incident cases of NAFLD divided by person-years of follow-up. Differences in demographics and baseline characteristics between normal weight, overweight, and obese patients were calculated using one-way analysis of variance (for continuous variables) and a $\chi 2$ test (for categorical variables). Kaplan-Meier curves and log-rank tests were calculated for categorical variables of NAFLD incidence. The association between participants' demographics, lifestyle habits, liver function, metabolic factors, HBeAg status, and HBV DNA level at baseline with incidence rate of NAFLD was estimated by computing hazard ratios (HRs) from univariate and multiple Cox regression analyses. The additive and multiplicative interactions of HBV replication status and other covariates with the incidence rate of NAFLD were estimated by computing RERI (relative excess risk for interaction) and ROR (the ratio of odds ratio) from Cox regression analyses. All statistical analyses were performed with Stata software version 14.0. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the population-based cohort at baseline

A total of 4,069 individuals met the inclusion criteria and were enrolled in 2012. We excluded 995 HBsAg carriers with a history of alcohol drinking, 15 with insufficient serum for testing ALT, 546 with concomitant NAFLD at baseline, and 120 carriers without BMI measurement. In total there were 2,393 adult HBsAg carriers (mean age 50.7±13.2 years) included in this cohort. The demographic data, behavior characteristics and serum virus status of all subjects are shown in Table 1. Among the population of adult chronic HBV carriers, 1,767 (73.8%) were female, 275 (11.5%) had a history of smoking, 1020 (45.3%) had a baseline level of HBV DNA lower than the detect limit (100IU/mL), 192 (8.0%) were HBeAg positive, 930 (38.9%) had a BMI over 24 kg/m^2 at baseline, 70 (3.3%) had concurrent type 2 diabetes mellitus, 355 (16.7%) had concurrent hypertension.

Rate and predictors of NAFLD in the whole cohort

After two years of follow-up, 283 (11.8%) adult chronic HBV carriers developed NAFLD. Over 4,429.2 person-years of follow-up, the incidence rate of NAFLD was 63.89/1000 person-years (Table 1). HBV DNA levels and HBeAg status at baseline were not associated with a difference in NAFLD incidence rates. The incidence rate of NAFLD significantly increased with higher BMI, type 2 diabetes mellitus, hypertension, hyperproteinemia and consumption of a high-fat diet (Table 1). The log-rank test and Kaplan-Meier failure estimate curves showed that overweight/obesity and type 2 diabetes mellitus at baseline might be risk factors for NAFLD in adult chronic HBV carriers (Figure 1). There was no significant difference between antiviral therapy status during the follow-up period and incident NAFLD (HR, 0.97; 95%CI, 0.69-1.37).

In the multivariate analysis, compared to carriers with BMI<24, overweight (HR, 3.10; 95% CI, 2.29-4.18) and obese (HR, 8.52; 95%CI, 5.93-12.25) HBV carriers had an increased risk

of NAFLD. Similarly, HBV carriers had an increased risk of NAFLD for a one unit increase in baseline BMI (HR, 1.32; 95%CI, 1.27-1.37) (Table 3). Incident NAFLD rate was also associated with concurrent type 2 diabetes mellitus (HR, 1.88; 95%CI, 1.15-3.08). However, there was no significant association among chronic HBV carriers with detectable levels of HBV DNA or by baseline HBeAg status (Table 1).

Predictors of NAFLD in the cohort stratified by BMI levels

HBV carriers with BMI >24 kg/m^2 at baseline had a higher mean age and proportion of concurrent type 2 diabetes mellitus, but a lower proportion of undetectable HBV DNA relative to those with a BMI less than 24 kg/m^2 ($P<0.05$). However, the male to female ratio, rate of cigarette smoking history, and HBeAg positive rate were not significantly different among these subgroups (Table 2).

In the multivariate analysis, male gender (HR, 0.53; 95%CI, 0.28-0.99) and concurrent type 2 diabetes mellitus (HR, 2.68; 95%CI, 1.05-6.86) were significantly related to development of NAFLD in the subgroup of participants with BMI<24 kg/m^2. However, in overweight/obese individuals, age, gender, concurrent type 2 diabetes mellitus, viral load, and HBeAg status at baseline did not have a significant effect on the development of NAFLD (Table 4).

Development of NAFLD according to HBV replication status in relevant subgroups

Table 5 shows that the associations between HBV DNA levels and NAFLD incidence rate were not observed across different subgroups except for participants with concurrent type 2 diabetes mellitus. Among patients with concurrent type 2 diabetes mellitus, detectable HBV DNA was significantly and negatively associated with development of NAFLD (HR, 0.37; 95%CI, 0.14-0.98). There was no significant heterogeneity of the association between HBV DNA levels and NAFLD incidence rate between subgroups. Meanwhile, no association was found between HBeAg status at baseline and NAFLD incidence rate across different subgroups.

Interactions of the factors for development of NAFLD

Table 6 showed the joint effects of BMI, concurrent type 2 diabetes mellitus and other covariates in relationship to incidence rate of NAFLD. We observed that there was super-multiplicative interaction between BMI and gender, with an ROR of 2.08 (95%CI, 1.02-4.23). The relative excess risk due to interaction between BMI and gender was 0.80(95%CI, −0.60-2.18), suggesting that the joint effect was multiplicative. No obvious multiplicative and additive interactions between viral factors and metabolic factors at baseline with development of NAFLD were observed.

DISCUSSION

This prospective study examined the association between incident NAFLD and potential risk factors including HBV replication status and metabolic factors in a cohort of Chinese adult HBV carriers without a history of drinking and without NAFLD at baseline. This is the first prospective cohort study in China to investigate incident NAFLD in adult HBV carriers thus far. The results of our study indicated that HBV DNA level and HBeAg status among

HBsAg carriers have no significant risk of progressing of NAFLD. However, we confirmed the hypothesis that overweight and obese chronic HBV carriers and those with concurrent type 2 diabetes mellitus had significantly increased risk of fatty liver disease. Our findings indicated that there was no synergistic interaction between metabolic factors and HBV replication status with the risk of incident NAFLD, however, there was a super multiplicative interaction between BMI and gender in relationship to incidence rate of NAFLD in adult chronic HBV carriers.

A total of 283 adult HBV carriers developed NAFLD during follow-up, with an incidence rate of 63.89/1,000 person-years. These findings are much higher than the results from a study in South Korea (40.6/1,000 person-years), in which HBV carriers were younger (mean age of 38.5 years) and more likely to have had a history of alcohol drinking (18.9%). [8] The NAFLD incidence rate in our cohort was similar to the pooled NAFLD incidence rate of 52.34 per 1,000 person-years (95%CI, 28.31-96.77) in the general Asian population. [5] Our finding that overweight/obesity was a risk factor for NAFLD among adult HBV carriers was consistent with earlier studies, [7,18] and similar with findings from the general population. [19] Male HBV carriers in a cohort study showed that the adjusted ORs increased to 2.91 (95%CI, 2.33-3.63) and 9.72 (95%CI, 2.96-31.97) for fatty liver disease among overweight and obese HBV carriers; however, the subjects included alcohol drinkers. [18] In the Korean general population, [19] obesity is an independent risk factor for liver steatosis (OR=5.32; P<0.001). Diabetes was shown to be a risk factor of presence of NAFLD among patients with CHB [6] and in the general population. [20] Consistent with previous studies, [6,21] our HBV cohort study confirmed that incident NAFLD rate was significantly associated with concurrent type 2 diabetes mellitus. There is an increasing trend between age and NAFLD, however this trend was not significant. When age was categorized as binary variable, we found that participants over 40 had a higher risk of NAFLD (HR, 1.65; 95%CI, 1.16-2.35) compared to those under 40 in the univariate analyses, but not in the adjusted analyses.

The impact of HCV on the development of NAFLD is well established, [22] however, the underlying mechanism by which HBV mediates hepatic steatosis has not been clearly studied. Currently, studies have shown that the risk of NAFLD was significantly lower in HBV-infected patients than in uninfected controls. [8,23] Moreover, some case-control and cross-sectional studies revealed an inverse relationship between HBV DNA levels and the risk of NAFLD. [24,25] In contrast to these reports, our cohort study revealed that HBsAg carriers with detectable HBV DNA had no significant increase in hazard rate compared to those with undetectable HBV DNA. Additionally, HBeAg positive and HBeAg negative subjects had a similar level of risk for incident NAFLD. The difference in results between our study and previous studies may be due to study design. In our prospective cohort study we can test the temporal relationship between HBV DNA levels and presence of NAFLD, in which different levels of viral load at baseline preceded the presence of NAFLD. However, in the case-control and cross-sectional studies, different levels of viral load were likely obtained from past records or concurrently with NAFLD, in which case the temporal relationship may be imprecise. Previous studies showed that Hepatitis B virus X protein induced lipid accumulation in hepatic cells via transcriptional activation of SREBP1 and PPAR gamma [26] and by enhancing the expression of liver fatty acid binding protein. [27] In our study, two hepatitis B virus indexes (HBV DNA level and HBeAg status) may not reflect

the levels of HBx of the patients with CHB, so we did not observe the relationship between hepatitis B virus replication levels and development of NAFLD by a community-based cohort study. Interestingly, we found that antiviral treatment during the follow-up period was not related with incident NAFLD rate, which indicated that antiviral therapy didn't affect development of fatty liver disease. We postulate that viral load itself and antiviral therapy-related may not affect the presence of NAFLD among Chinese adult HBsAg carriers.

Among HBV patients with concurrent type 2 diabetes mellitus, detectable HBV DNA levels were significantly negatively associated with development of NAFLD (HR, 0.37; 95%CI, 0.14-0.98), in contrast to the majority of HBV patients. However, these results were likely impacted by the small number of patients in the type 2 diabetes mellitus subgroup. A recent study revealed that diabetes mellitus had a large effect on HCC risk in patients with low viral loads. [28] The mechanism of how HBV DNA levels affect NAFLD incidence in patients with concurrent type 2 diabetes mellitus and low viral loads warrants further investigation.

No obvious additive or multiplicative interactions between HBV DNA/HBeAg at baseline and metabolic factors on the incidence of NAFLD were observed. These findings were similar to previous clinical studies, which indicated that HBV infection and NAFLD were two independent diseases without underlying pathological interactions. [29, 30] However, our study indicated that the joint effect between BMI and gender exceeded multiplicative interaction, which suggested that these two factors played synergistic roles. In participants with BMI <24 kg/m^2, male gender was significantly negatively related with development of NAFLD (p=0.046), however, in overweight and obese participants, male gender can potentiate development of NAFLD by 3.8-fold (95%CI,2.58-5.69). In China, HBsAg-positive adults are more likely to be male, therefore weight control could be an effective approach to lower NAFLD incidence risk for male chronic HBV adults.

This study has some limitations. Firstly, 30.2% of HBsAg seropositive participants could not be enrolled in this cohort, which may induce selection bias. Additionally, in this study, the proportion of individuals lost to follow-up was 14.5% which may induce selection bias. However the distribution of age, gender and BMI between subjects who were followed up and those lost to follow-up were comparable (P>0.05), mitigating the likelihood of selection bias. In addition, HBsAg negative participants from the community-based study were not followed up due to lack of resources. Therefore, we cannot verify whether hepatitis B infection was indeed protective against the development of NAFLD by matching our cohort to a control group of HBsAg negative subjects. NAFLD detection methods in this study were mainly based on B ultrasonography, which was known to underestimate the prevalence of NAFLD.[20] Diabetes mellitus status was obtained by participants self-report, which may induce misclassification. Despite these limitations, this is the first large prospective cohort study in Chinese population on the association between HBV replication factors and metabolic factors on the risk of development of NAFLD.

In conclusion, findings from our large-scale population-based prospective cohort study revealed an increased risk of NAFLD due to higher BMI and concurrent type 2 diabetes mellitus among adult non-alcohol drinking HBV carriers. The findings of this study suggested that metabolic factors, as opposed to viral factors, may play an important role in

the development of NAFLD among chronic HBV carriers in Chinese population. The joint effects indicated that it was important to monitor BMI status among adults, especially male adults with chronic HBV infection and to implement intervention strategies among overweight/obese HBsAg carriers to reduce risk of NAFLD.

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List of abbreviations:

NAFLD	non-alcoholic fatty liver disease
HBV	hepatitis B virus
CHB	chronic hepatitis B
HBsAg	hepatitis B surface antigen
HBeAg	hepatitis B e antigen
BMI	body mass index
AST	aspartate aminotransferase
ALT	alanine aminotransferase
anti-HCV	antibodies against hepatitis C virus
HR	hazard ration
RERI	relative excess risk for interaction
ROR	the ratio of odds ratio

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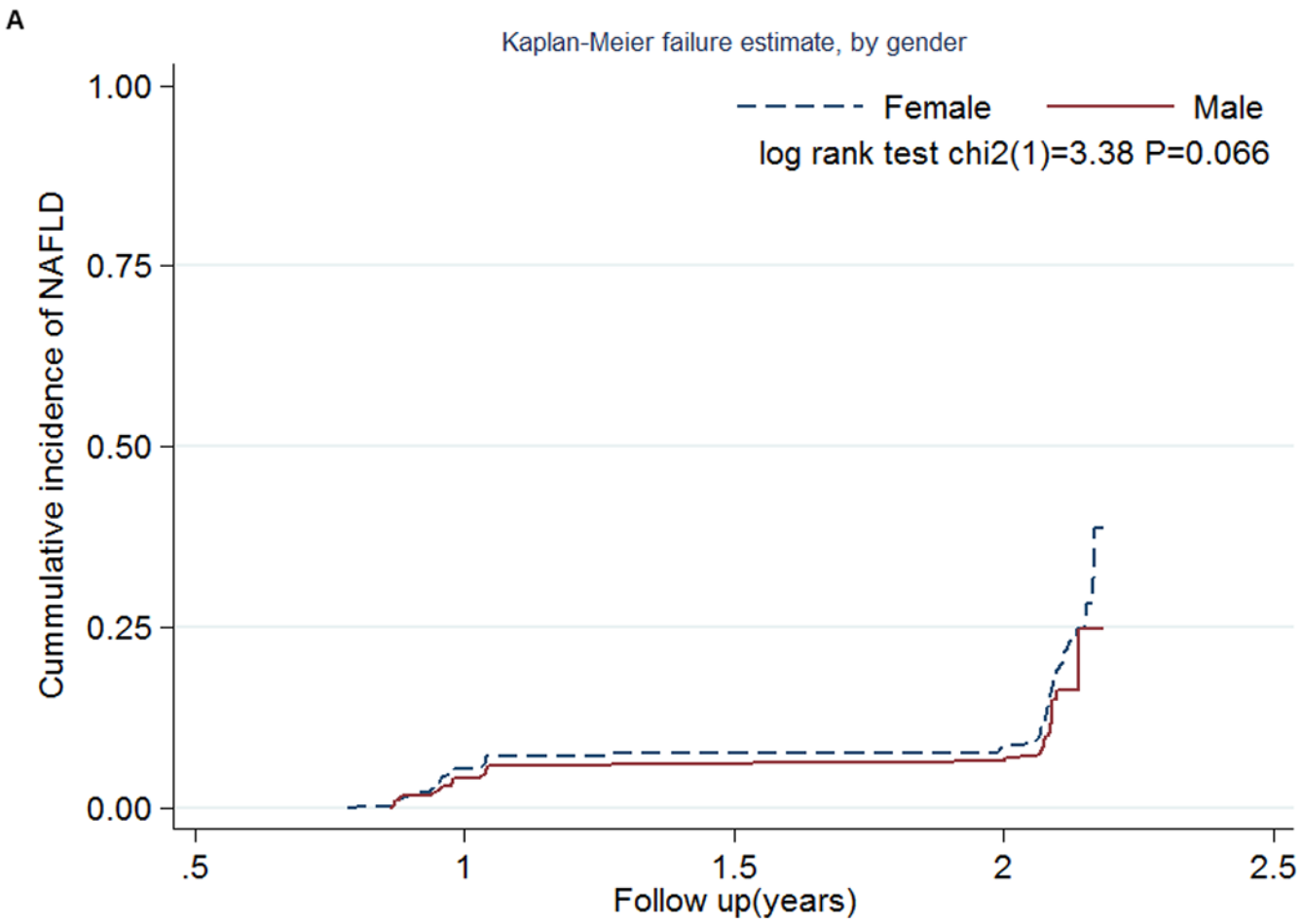
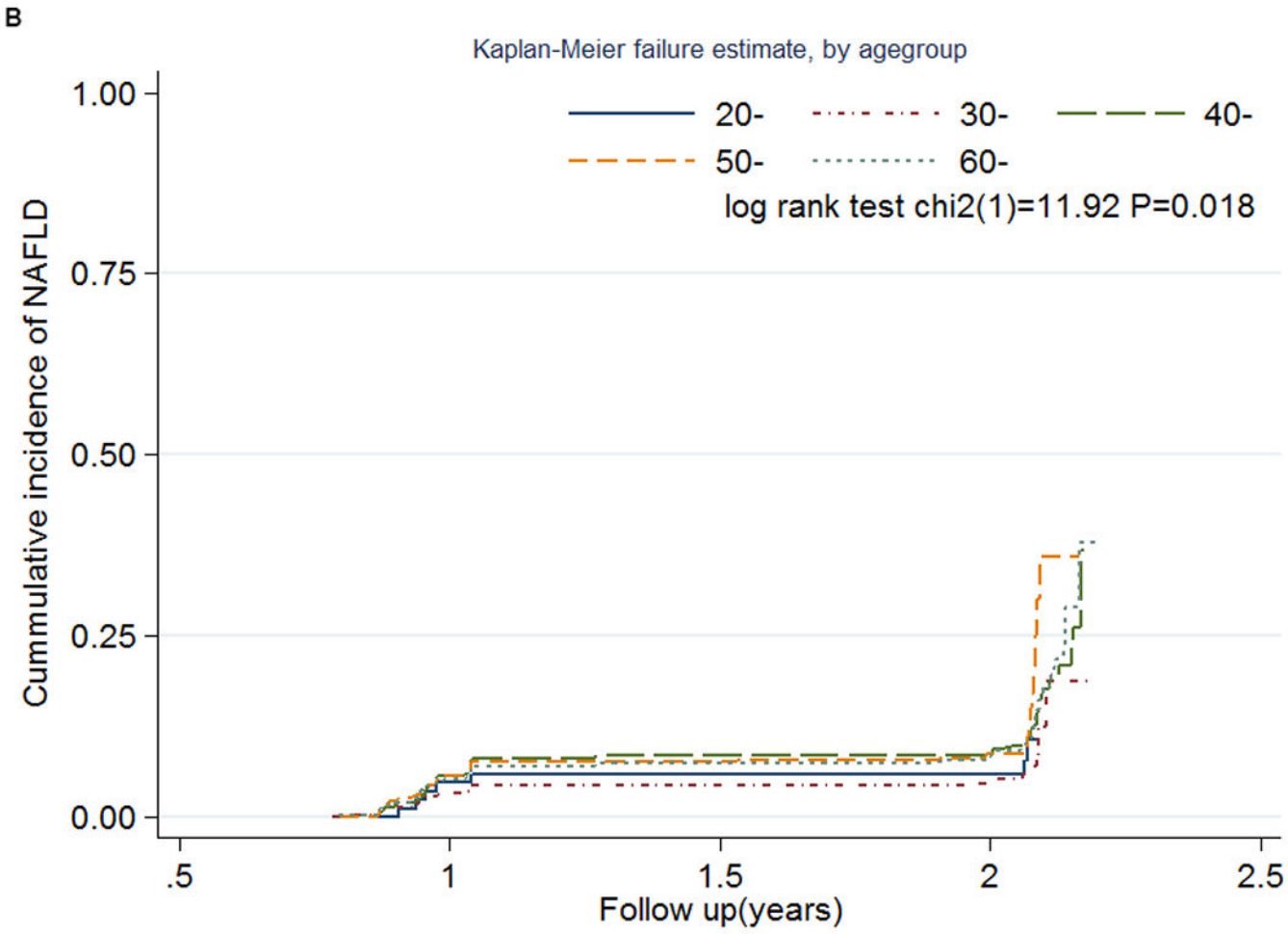
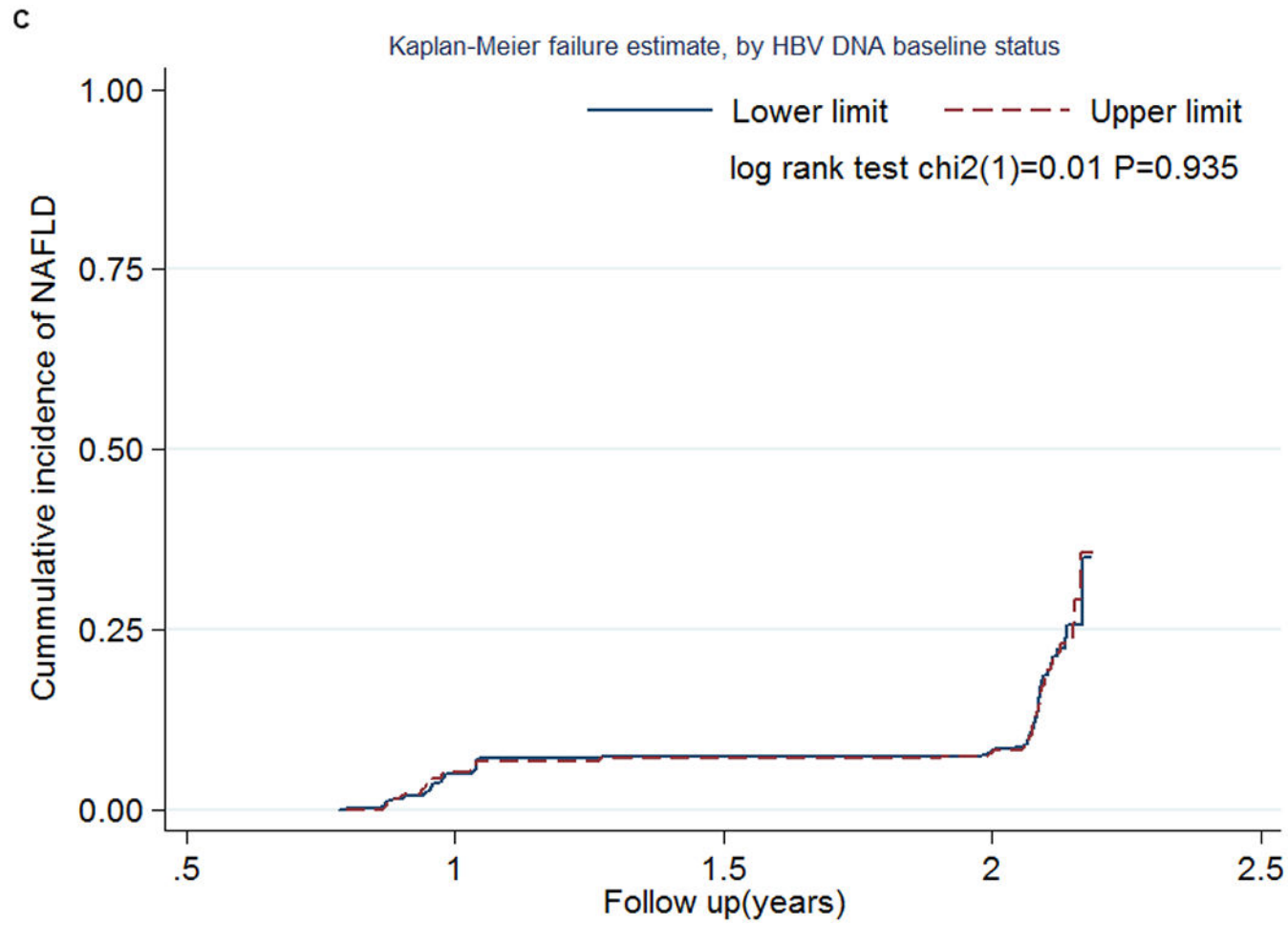
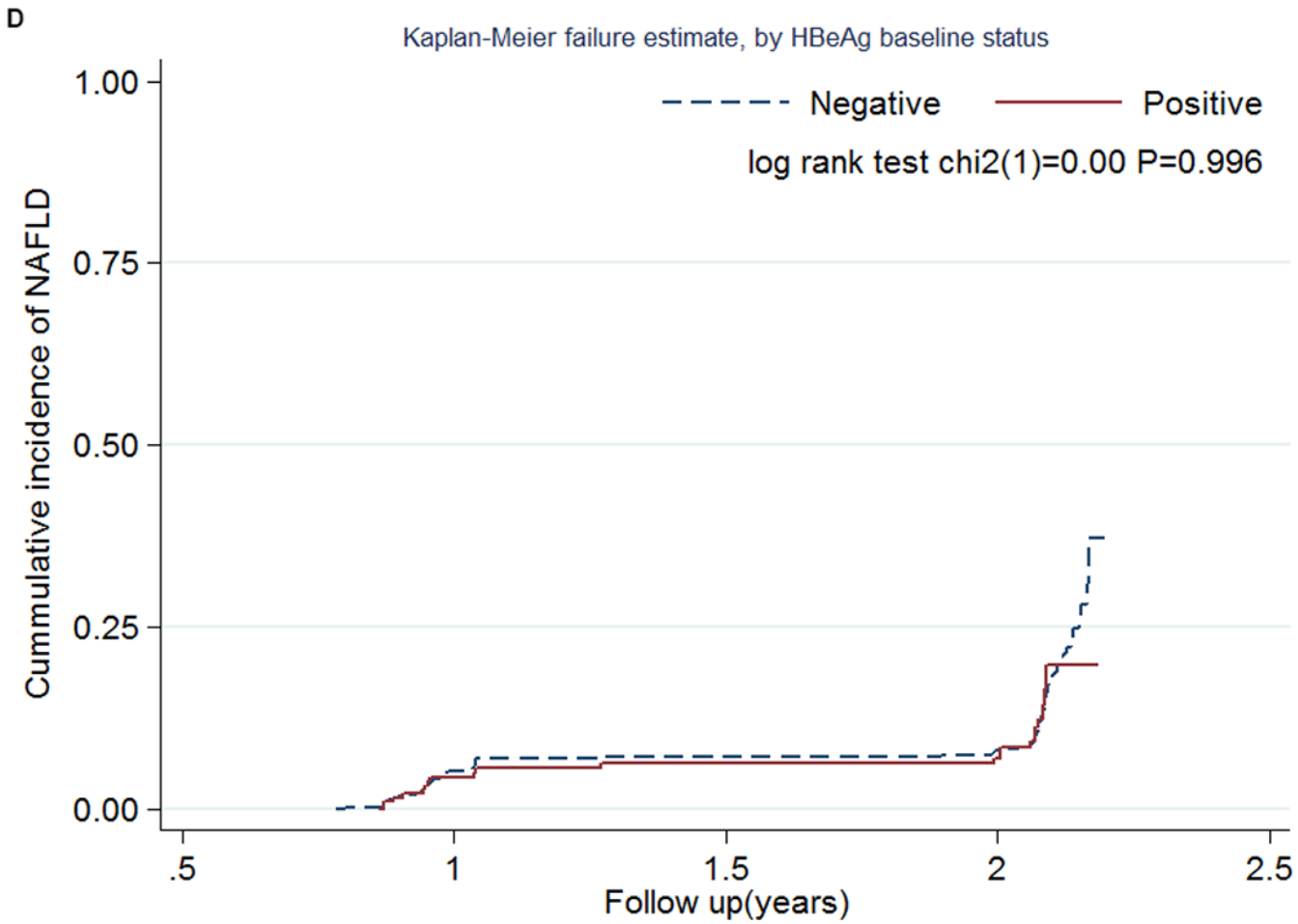
Key points

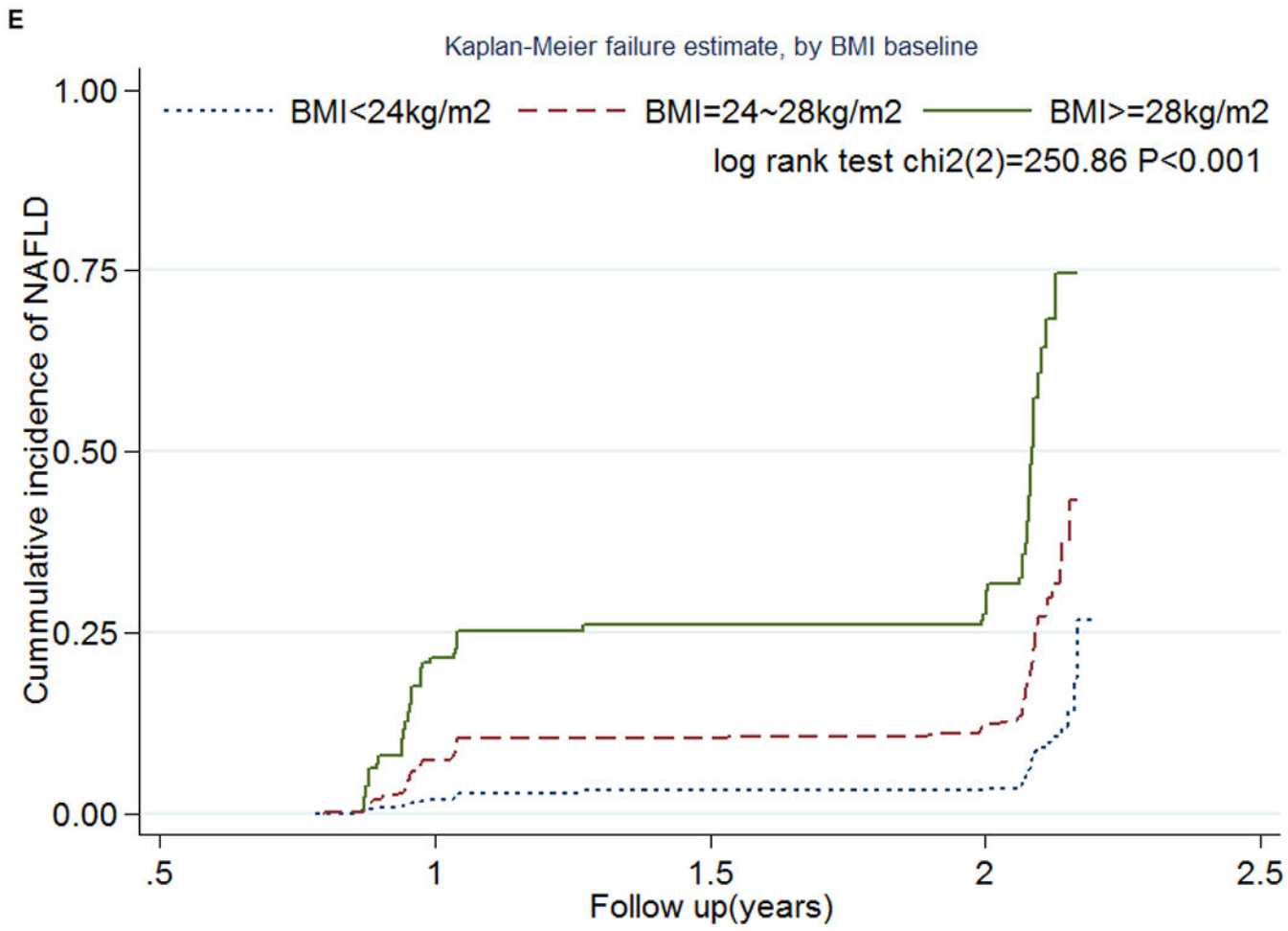
1. The incidence rate of NAFLD in a Chinese community-based cohort of adult HBsAg carriers was 63.89/1,000 person-years.
2. HBV carriers had an increased risk of NAFLD for those overweight and obese, and with concurrent type 2 diabetes mellitus.
3. In the subgroup of participants with concurrent type 2 diabetes mellitus, detectable HBV DNA levels were negatively associated with the development of NAFLD.
4. There was super-multiplicative interaction between BMI and gender, which was in relationship with incidence rate of NAFLD, indicating that it is important to monitor overweight/obese male adults with chronic HBV infection.











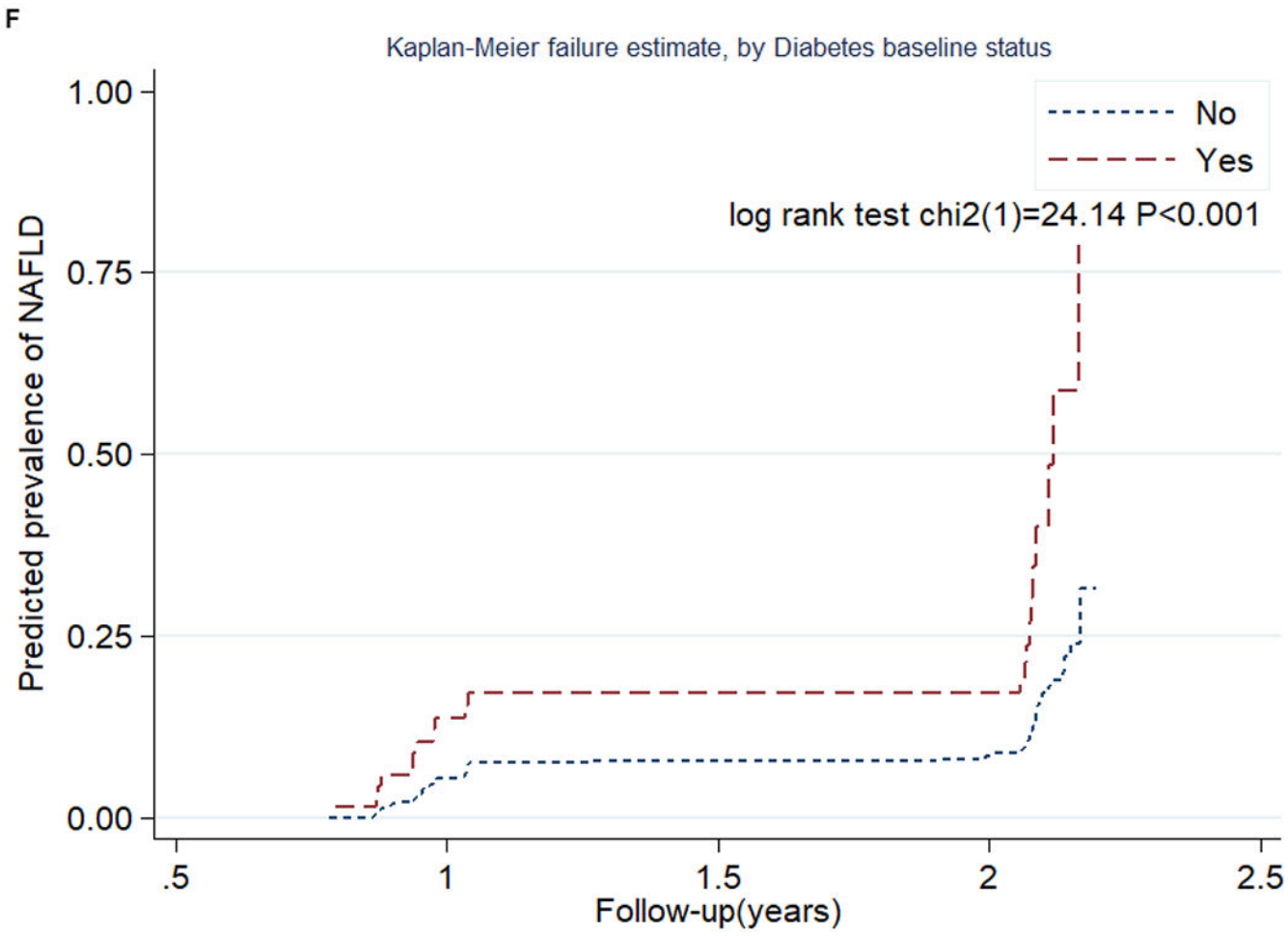


Figure 1.

Log rank test and Kaplan-Meier failure estimates by gender(A), age group (B), HBV DNA at baseline (C), HBeAg status at baseline (D), BMI at baseline(E), and Diabetes status at baseline(F) with NAFLD incident rate among HBsAg carriers

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Table 1.

Crude and adjusted measure effects of variables and incidence rate of NAFLD by Cox regression.

Variable [a]	Observed number (N)	Observed person-time (PY)	Incidence num. of NAFLD	Incidence Rate (/ 1000 person-year)	Cox regression			
					cHR (95%CI)	*P*	aHR* (95%CI)	*P*
Total	2393	4429.2	283	63.89				
Age(years)								
20-	92	166.9	7	41.94	1.00		1.00	
30-	421	776.7	29	37.34	0.71(0.31-1.62)	0.416	0.81(0.31-2.13)	0.676
40-	730	1359.4	94	69.15	1.14(0.53-2.47)	0.736	0.90(0.36-2.26)	0.830
50-	497	912.6	66	72.32	1.50(0.69-3.28)	0.305	1.05(0.42-2.67)	0.913
60-	653	1213.6	87	71.69	1.18(0.55-2.57)	0.670	0.87(0.34-2.20)	0.769
Gender								
female	1767	3256.9	222	68.16	1.00		1.00	
male	626	1172.4	61	52.03	0.77(0.58-1.02)	0.067	0.85(0.62-1.16)	0.310
Smoking status								
Ever	275	511.1	29	56.74	1.00			
Never	2118	3918.1	254	64.83	1.14(0.78-1.67)	0.506		
HBV DNA								
Undetectable	1020	1896.0	125	65.93	1.00		1.00	
Detectable	1230	2268.6	146	64.36	0.99(0.78-1.26)	0.935	0.94(0.72-1.21)	0.616
HBeAg								
Negative	2201	4078.6	262	64.24	1.00		1.00	
Positive	192	350.6	21	59.90	1.00(0.64-1.56)	0.996	0.97(0.57-1.63)	0.896
BMI(kg/m^2)								
<24	1463	2766.5	83	30.00	1.00		1.00	
24~	755	1375.9	132	95.94	3.38(2.57-4.45)	**<0.001**	3.10(2.29-4.18)	**<0.001**
≥28	175	286.9	68	237.06	9.49(6.88-13.1)	**<0.001**	8.52(5.93-12.25)	**<0.001**
Baseline ALT (U/L) [b]								
<14	554	1031.6	57	55.25	1.00			
14~	560	1034.9	73	70.54	1.32(0.93-1.87)	0.117		
18~	670	1236.5	77	62.27	1.21(0.86-1.71)	0.268		

Variable [a]	Observed number (N)	Observed person-time (PY)	Incidence num. of NAFLD	Incidence Rate (/ 1000 person-year)	Cox regression			
					cHR (95%CI)	*P*	aHR* (95%CI)	*P*
≥24	609	1126.2	76	67.48	1.29(0.92-1.82)	0.144		
Baseline AST (U/L)								
<40	2093	3878.6	259	66.78	1.00			
≥40	300	550.6	24	43.59	0.7(0.46-1.07)	0.098		
Baseline total serum protein (g/L)								
normal	1939	3594.2	215	59.82	1.00		1.00	
hyperproteinemia	443	816.9	68	83.24	1.32(1.00-1.72)	**0.049**	1.22(0.91-1.63)	0.189
Baseline total bilirubin (μmol/L)								
<17.1	2142	3954.7	262	66.25	1.00			
≥17.1	251	474.5	21	44.26	0.68(0.44-1.06)	0.092		
Hypertension								
No	1774	3281.8	189	57.59	1.00		1.00	
Yes	355	629.6	68	108.00	1.90(1.44-2.5)	**<0.001**	1.35(0.99-1.84)	0.061
Type 2 diabetes mellitus								
No	2059	3791.2	236	62.25	1.00		1.00	
Yes	70	120.2	21	174.70	2.91(1.86-4.54)	**<0.001**	1.88(1.15-3.08)	**0.012**
Work time (hours/day)								
≥8	973	1796.9	117	65.11	1.00			
4~	669	1219.2	74	60.70	0.89(0.66-1.19)	0.432		
<4	433	796.5	61	76.59	1.11(0.82-1.52)	0.494		
Diet consumption								
Non-high fat	1974	3636.8	231	63.52	1.00		1.00	
High fat	106	187.8	20	106.52	1.83(1.16-2.89)	0.010	1.53(0.96-2.44)	0.074
Antiviral therapy during the follow up period								
Never	2071	3804.3	244	64.14	1.00			
Ever	322	625.0	39	62.40	0.97(0.69-1.37)	0.876		

Note:

*Adjusted for age, gender, HBV DNA levels, HBeAg status, BMI, total serum protein, hypertension, type 2 diabetes mellitus, and diet at baseline

[a]143 missing HBV DNA level baseline data; 264 missing hypertension, type 2 diabetes mellitus, diet consumption; 318 missing work time data; 11 missing total serum protein baseline data

[b] Cutpoints defined by quartiles of ALT at baseline among participants

Table 2.

Distribution of selected variables in adult HBsAg carriers stratified by BMI level at baseline

	Total population (2393)	**Participants with BMI<24 kg/m^2 (Normal Weight) (1463)**	**Participants with 24≤BMI<28 kg/m^2 (Overweight) (755)**	**Participants with BMI≥28 kg/m^2 (Obese) (175)**	***P***
Age(continuous)	50.7±13.2	49.8±13.8	52.3±11.9	51.7±12.5	**<0.001**
Category					**<0.001**
20-	92(3.8)	73(5.0)	13(1.7)	6(3.4)	
30-	421(17.6)	311(21.2)	95(12.6)	15(8.6)	
40-	730(30.5)	422(28.8)	237(31.4)	71(40.6)	
50-	497(20.8)	269(18.4)	201(26.6)	27(15.4)	
60-	653(27.3)	388(26.6)	209(27.7)	56(32.0)	
Gender					0.099
Female	1767(73.8)	1061(72.5)	579(76.7)	127(72.6)	
Male	626(26.2)	402(27.5)	176(23.3)	48(27.4)	
Smoking status					0.283
Ever	275(11.5)	180(12.3)	76(10.1)	19(10.9)	
Never	2118(88.5)	1283(87.7)	679(89.9)	156(89.1)	
HBV DNA					**0.042**
Undetectable	1020(45.3)	659(47.4)	292(42.0)	69(41.8)	
Detectable	1230(54.7)	731(52.6)	403(58.0)	96(58.2)	
HBeAg					0.373
Negative	2201(92.0)	1352(92.4)	686(90.9)	163(93.1)	
Positive	192(8.0)	111(7.6)	69(9.1)	12(6.9)	
Type 2 diabetes mellitus					**<0.001**
No	2059(96.7)	1286(97.9)	637(95.5)	136(91.9)	
Yes	70(3.3)	28(2.1)	30(4.5)	12(8.1)	

Note: 264 missing type 2 diabetes mellitus data; 163 missing HBV DNA levels baseline data

Table 3.

Adjusted measure effects of variables and incidence rate of NAFLD by Cox Multivariate regression.

	aHR*(95%CI)	***P***
Age		
20-	1.00	
30-	0.93(0.36-2.42)	0.885
40-	0.97(0.39-2.41)	0.945
50-	1.22(0.49-3.05)	0.669
60-	1.01(0.40-2.52)	0.985
Gender		
Female	1.00	
Male	0.92(0.68-1.26)	0.617
HBV DNA		
Undetectable	1.00	
Detectable	0.89(0.69-1.15)	0.386
HBeAg		
Negative	1.00	
Positive	0.99(0.59-1.66)	0.959
Type 2 diabetes mellitus		
No	1.00	
Yes	1.89(1.17-3.05)	**0.009**
BMI	1.32(1.27-1.37)	**<0.001**

Note:

*Adjusted for age, gender, HBV DNA, HBeAg status, type 2 diabetes mellitus and baseline BMI (as continuous variable)

Table 4.

Adjusted measure effects of variables and incidence rate of NAFLD stratified by BMI level at baseline by Cox multivariate regression.

	Participants with BMI<24 kg/m^2 Normal Weight (1250)		Participants with 24≤BMI<28 kg/m^2 Overweight (615)		Participants with BMI≥28 kg/m^2 Obese (140)	
	aHR*(95%CI)	*P*	aHR*(95%CI)	*P*	aHR*(95%CI)	*P*
Age						
20-	1.00		1.00		1.00	
30-	0.93(0.20-4.27)	0.927	0.50(0.11-2.24)	0.366	1.05(0.12-9.53)	0.966
40-	1.18(0.27-5.14)	0.826	0.47(0.11-1.97)	0.300	1.48(0.20-11.14)	0.702
50-	1.39(0.31-6.28)	0.669	0.60(0.14-2.50)	0.479	2.12(0.27-16.59)	0.474
60-	1.34(0.31-5.82)	0.698	0.51(0.12-2.17)	0.363	1.41(0.18-10.90)	0.742
Gender						
Female	1.00		1.00		1.00	
Male	0.53(0.28-0.99)	**0.046**	1.15(0.75-1.77)	0.517	0.86(0.46-1.62)	0.640
HBV DNA						
Undetectable	1.00		1.00		1.00	
Detectable	1.26(0.79-1.99)	0.330	0.78(0.54-1.14)	0.199	0.86(0.50-1.48)	0.588
HBeAg						
Negative	1.00		1.00		1.00	
Positive	1.03(0.40-2.62)	0.952	0.93(0.42-2.03)	0.846	0.95(0.33-2.77)	0.929
Type 2 diabetes mellitus						
No	1.00		1.00		1.00	
Yes	2.68(1.05-6.86)	**0.040**	1.69(0.82-3.51)	0.156	2.24(0.93-5.34)	0.074

Note:

*Adjusted for age, gender, smoke, HBV DNA levels, HBeAg status, and type 2 diabetes mellitus at baseline 264 missing type 2 diabetes mellitus data; 163 missing HBV DNA levels baseline data

Table 5.

Development of NAFLD according to HBV replication status in relevant subgroups

Subgroups	Participants with HBV DNA undetectable	Participants with HBV DNA detectable	aHR*(95%CI)	P for heterogeneity	Participants with HBeAg negative	Participants with HBeAg positive	aHR*(95%CI)	P for heterogeneity
	Incidence Rate (/ 1000 person-year)	Incidence Rate (/ 1000 person-year)			Incidence Rate (/ 1000 person-year)	Incidence Rate (/ 1000 person-year)		
Age(years)				0.414				0.986
20-39	32.3	46.1	1.22(0.59-2.56)		37.5	41.7	0.96(0.35-2.59)	
≥40	75.0	69.5	0.88(0.67-1.16)		70.8	72.5	0.95(0.51-1.75)	
Gender				0.786				0.638
Female	69.8	67.1	0.90(0.68-1.21)		68.5	63.8	0.92(0.50-1.67)	
Male	55.4	56.1	0.98(0.57-1.69)		52.4	47.5	1.23(0.43-3.49)	
BMI(kg/m^2)				0.252				0.969
<24	27.8	32.9	1.25(0.79-1.99)		30.4	24.6	1.04(0.41-2.62)	
24~	118.9	87.4	0.76(0.53-1.11)		97.7	79.0	0.94(0.43-2.07)	
≥28	244.8	227.5	0.87(0.51-1.50)		232.7	293.1	0.87(0.35-2.92)	
Type 2 diabetes mellitus				0.064				-
No	62.3	64.1	0.96(0.73-1.25)		61.9	66.9	0.96(0.57-1.62)	
Yes	222.1	131.8	0.37(0.14-0.98)		179.1	0.0	-	

Note

*Adjusted for age, gender, smoke, HBV DNA levels, HBeAg status, and type 2 diabetes mellitus at baseline

Table 6.

Multiplicative and additive analysis models of demographic, HBV replication variables and BMI status at baseline with incidence rate of NAFLD.

One variable	Another variable	aHR	ROR	RERI
BMI(kg/m^2)	Gender			
<24	Female	1.00	2.08(1.02,4.23)	0.80(−0.60,2.18)
<24	Male	0.53(0.28,0.97)		
≥24	Female	3.55(2.62,4.82)		
≥24	Male	3.88(2.62,5.76)		
BMI(kg/m^2)	Age(years)			
<24	20-39	1.00	0.77(0.36-1.64)	−0.07(−2.61-2.48)
<24	≥40	1.39(0.76-2.52)		
≥24	20-39	5.17(2.57-10.40)		
≥24	≥40	5.49(3.10-9.71)		
BMI(kg/m^2)	HBV DNA		0.64(0.37-1.11)	−1.41(−3.12-0.31)
<24	Undetectable	1.00		
<24	Detectable	1.26(0.80-1.99)		
≥24	Undetectable	5.31(3.53-8.00)		
≥24	Detectable	4.17(2.77-6.26)		
BMI(kg/m^2)	HBeAg		0.87(0.29-2.58)	−0.27(−2.95-2.41)
<24	Negative	1.00		
<24	Positive	1.11(0.45-2.78)		
≥24	Negative	4.17(3.14-5.55)		
≥24	Positive	4.01(2.11,7.65)		
BMI(kg/m^2)	Type 2 diabetes mellitus		0.59(0.20-1.70)	1.50(−3.56-6.55)
<24	No	1.00		
<24	Yes	3.16(1.27-7.85)		
≥24	No	4.27(3.21-5.69)		
≥24	Yes	7.93(4.43-14.18)		
Type 2 diabetes mellitus	Gender		1.52(0.47-4.88)	0.72(−1.97-3.41)
No	Female	1.00		
No	Male	0.85(0.62-1.17)		
Yes	Female	1.93(1.13-3.29)		
Yes	Male	2.50(0.92-6.84)		
Type 2 diabetes mellitus	HBV DNA		0.50(0.19-1.28)	−1.52(−3.60-0.56)
No	Undetectable	1.00		
No	Detectable	0.96(0.74-1.25)		
Yes	Undetectable	2.97(1.59-5.56)		
Yes	Detectable	1.41(0.68-2.92)		

Note:

*Adjusted for age, gender, HBV DNA levels, HBeAg status, BMI, and type 2 diabetes mellitus at baseline