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Research Letter

Seroepidemiology of hepatitis B virus infection in apparently healthy adults in China: a nationwide study based on 17 million check-up adults

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Hepatitis B virus (HBV) infection remains a major public health challenge worldwide. China bears the world's highest HBV burden, with one-third of the global infected population.[1] In China, remarkable progress has been made in HBV prevention and control, particularly among infants and children.[2,3] However, HBV remains highly prevalent among adults, with an estimated prevalence of 7% between 2013 and 2017.[4] A detailed seroepidemiological profile of HBV infection in apparently healthy adults, who constitute the backbone of national workforce, is still lacking. To address this gap, this study based on a nationwide check-up population in China, aimed to provide a comprehensive analysis of the prevalence and incidence rate of HBV infection in apparently healthy Chinese adults.

Our study sample included participants who undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) at the Meinian health check-up centers between January 1, 2017, and December 31, 2024. Participants who attended Meinian check-up were apparently healthy males and females seeking preventive

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healthcare services. Each participant received laboratory tests, physical examinations, and imaging examinations at the centers. HBsAg and anti-HBc testing was performed using ELISA kits. In our cross-sectional analysis of the prevalence of HBV infection, HBsAg positivity indicated current HBV infection, and anti-HBc positivity indicated previous or current HBV infection. In the longitudinal analysis of the incidence rate of HBV infection, analysis was restricted to participants who underwent HBsAg and anti-HBc testing at least twice and had negative results for both markers at baseline (the first visit). An incident HBV infection was defined as HBsAg seroconversion during the follow-up. Finally, 17,924,297 and 3,290,868 adults from 274 cities across all 31 provinces of mainland China were included in the cross-sectional and longitudinal analyses, respectively (Supplementary Figs. 1, 2). This study was approved by the Institutional Review Board of Peking University (IRB00001052-19077). Informed consents were obtained from study participants.

We assigned weight coefficients to each participant to align the age, sex, and provincial distribution of the study population with the 2020 Chinese national census. Weighted prevalence and corresponding 95% confidence intervals (CIs) were estimated using the Taylor series linearization method. Weighted incidence rates (IRs) were calculated and expressed as per 100,000 person-years, with 95% CIs estimated using Poisson distribution. To investigate risk factors of HBsAg seroconversion, weighted incidence rate ratios (IRRs) and the corresponding 95% CIs were estimated using Poisson weighted regression models. Detailed methodologies are shown in the Supplementary Method.

Characteristics of the study participants are presented in Supplementary Table 1 and 2. The prevalence (95% CI) of current HBV infection was 5.34% (5.11–5.57%), with males significantly higher than females (5.98% vs. 4.69%, $P<0.001$) (Fig. 1A). The highest prevalence was observed in the 40–49 years group (Fig. 1B). Prevalence showed a progressive decline across birth cohorts, from a peak in those born before 1992 to the lowest level in those born after 2002 (Fig. 1C). Among women of childbearing age, the prevalence of current infection was 4.30% (Fig. 1J). Geographically, southern region demonstrated more than twice the prevalence of northern region ($P<0.001$) (Fig. 1J). Province-level prevalence also varied significantly (Supplementary Fig. 3A). Compared to healthy counterparts, the prevalence significantly increased in adults with hepatic abnormalities, including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBil), alpha fetoprotein (AFP), Fibrosis-4, APRI, and decreased platelet count and albumin (all $P<0.001$), while the prevalence significantly decreased in adults with fatty liver disease ($P<0.001$) (Fig. 1J). The prevalence (95% CI) of previous or current HBV infection was 16.63% (15.61–17.65%). Detailed results of the prevalence of previous or current HBV infection are presented in Figure 1D–1F, 1J, and Supplementary Figure 3B.

During a median follow-up of 2.0 years (interquartile range: 1.1–3.3), the IR (95% CI) of HBsAg seroconversion was 50.41 (48.82–52.03) per 100,000 person-years, with males significantly higher than females (Fig. 1G and Supplementary Fig. 4). In overall adults, the IR increased with age and reached its peak at 40–49 years (Fig. 1H). Those born before 1992 had an IR more than double that of those born after 1992 (Fig. 1I and Supplementary Fig. 4). IR was significantly higher in southern than in northern region (Supplementary Figs. 3C, 4). Compared to adults living in regions with high GDP per capita or high urbanization rate, the IRs in those living in socioeconomically disadvantaged regions were significantly higher (Supplementary Fig. 4). Moreover, diabetes and impaired kidney function were identified as significant risk factors for HBsAg seroconversion, with the IRRs (95% CIs) estimated to be 1.33 (1.16–1.53) and 1.70 (1.37–2.11), respectively (Supplementary Fig. 4).

The global prevalence of current HBV infection was estimated to be 3.2% in 2022, with China's prevalence at 5.6% in whole population.[5] The China 2020 national seroepidemiological survey reported a prevalence of 6.11% for current HBV infection among individuals aged 15–69 years.[2]

Abbreviations:

AFP, alpha fetoprotein; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-HBc, hepatitis B core antibody; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; GDP, gross domestic product; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IR, incidence rate; IRR, incidence rate ratio; TBil, total bilirubin; WHO, World Health Organization

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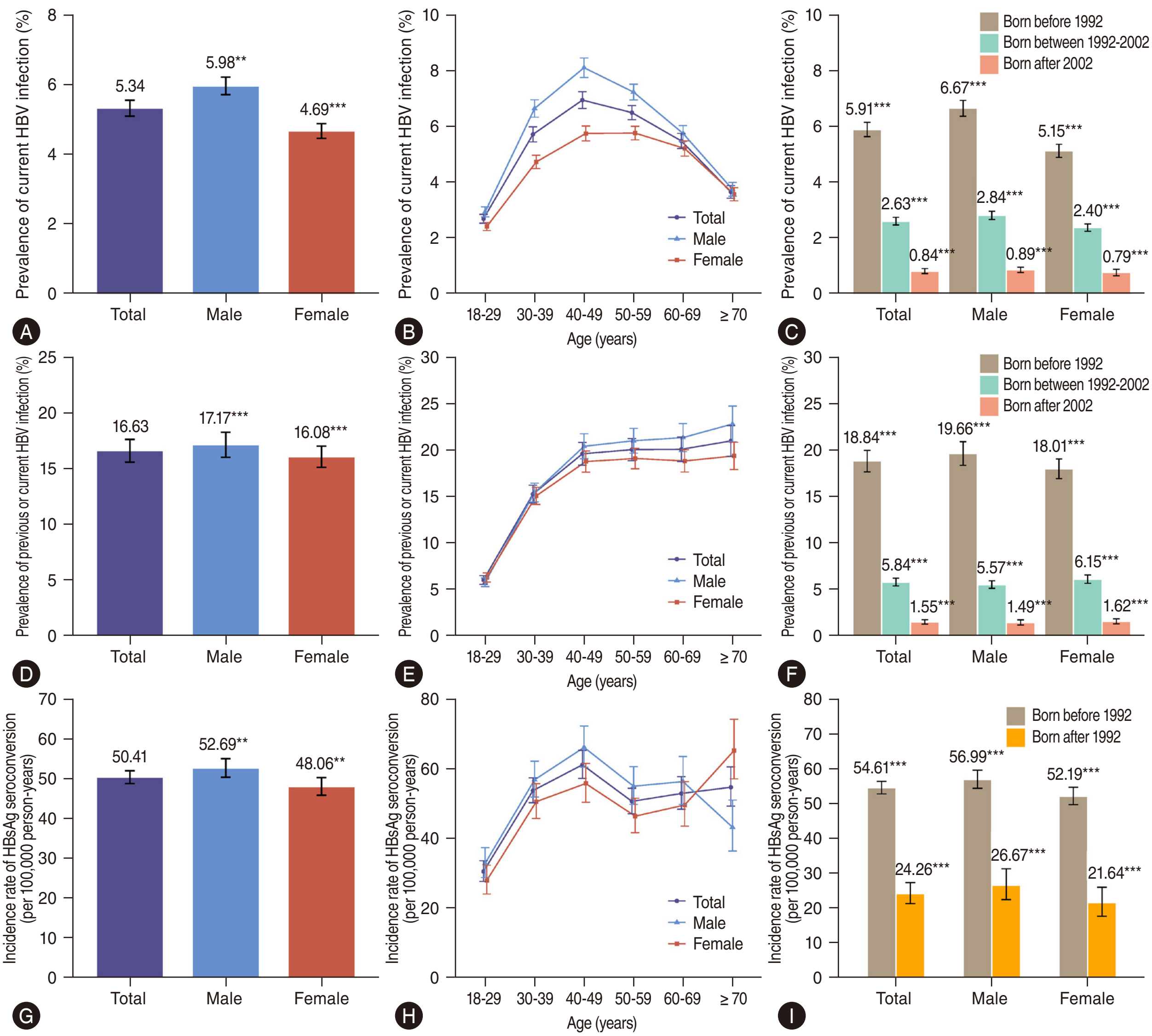

Figure 1. Prevalence and incidence rate of HBV infection in apparently healthy Chinese adults. (A) Overall and sex-specific prevalence of current HBV infection. (B) Age-specific prevalence of current HBV infection. (C) Prevalence of current HBV infection in different birth cohorts. (D) Overall and sex-specific prevalence of previous or current HBV infection. (E) Age-specific prevalence of previous or current HBV infection. (F) Prevalence of previous or current HBV infection in different birth cohorts. (G) Overall and sex-specific incidence rate of HBsAg seroconversion. (H) Age-specific incidence rate of HBsAg seroconversion. (I) Incidence rate of HBsAg seroconversion in different birth cohorts. (J) Prevalence of current HBV infection, and previous or current HBV infection in various subpopulations. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBil, total bilirubin; Alb, albumin; AFP, alpha fetoprotein; APRI, aspartate aminotransferase to platelet ratio index. **P* for difference <0.05. ***P* for difference <0.01. ****P* for difference <0.001. †The proportions of missing values exceeded 30%. ‡Linear trend test was performed across subgroups using Cochran-Armitage trend test, which showed *P* for trend <0.001.

Our observed prevalence of 5.34% among apparently healthy adults was slightly lower than the national figure. This difference may be attributed to our inclusion of older age groups with a known lower HBV prevalence, the relatively better health status of check-up population compared to the general survey population, and temporal variations between the study periods. The 5.34% prevalence of current infection suggests HBV remains higher-intermediately endemic (5–7.99%) among apparently healthy Chinese adults.[6] Despite being apparently healthy, this group still exhibited a substantial prevalence of current infection. Furthermore, the 16.63% prevalence of previous or current in-

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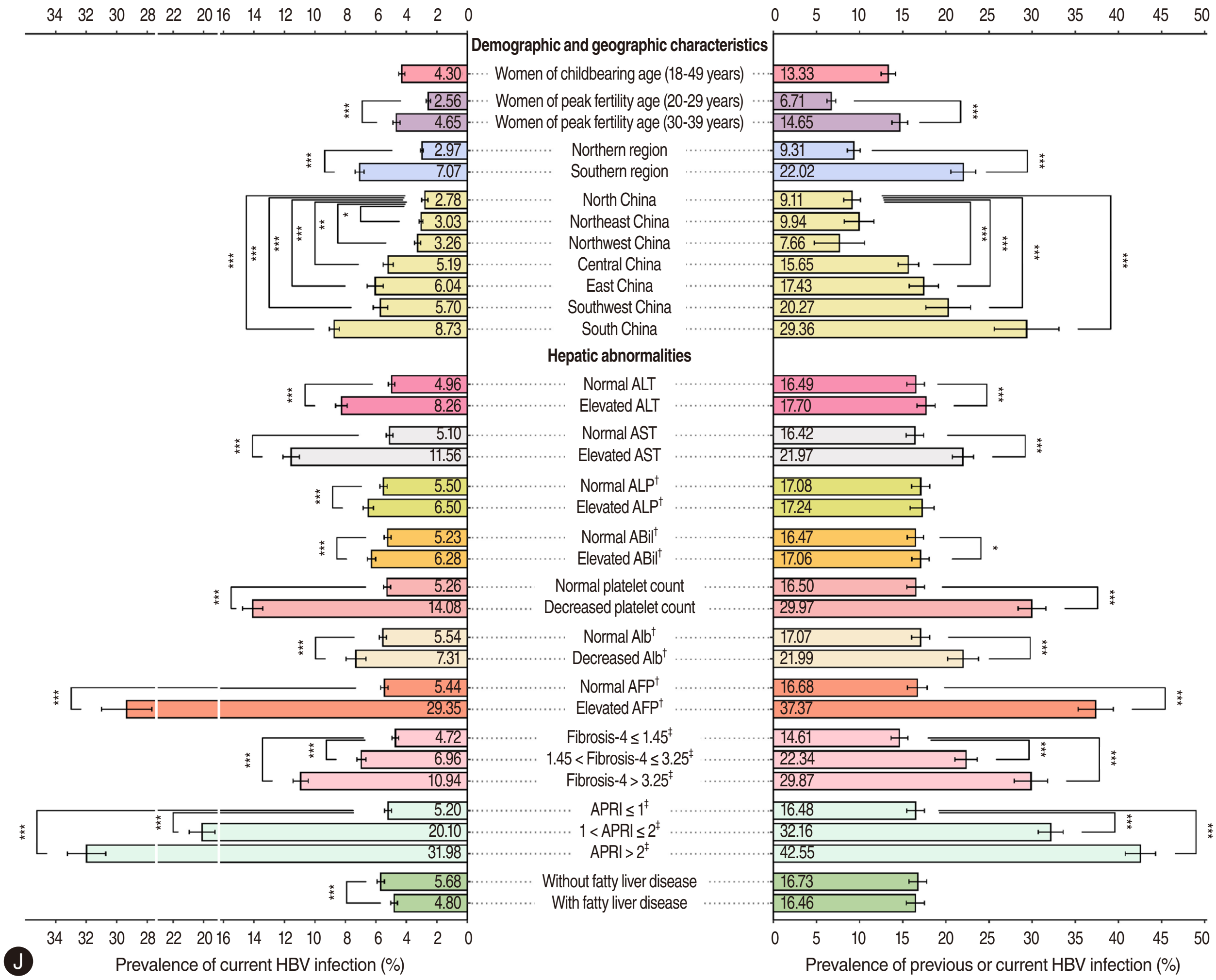

Figure 1. Continued.

fection found in this population highlights the substantial burden of past infections. Collectively, our findings emphasize the urgent need for universal HBV screening in apparently healthy Chinese adults.[7-9] HBV prevention efforts should extend beyond traditional high-risk groups to recognize apparently healthy adults as an important population for screening and case detection.

Consistent with previous studies,[10,11] HBV infection was more prevalent in southern compared to northern region. Southern provinces such as Fujian, Jiangxi, Guangxi, Hainan, Tibet, and Guangdong had the highest prevalence of current infection (over 8.50%), with Guangxi and Hainan also showing the highest IRs (over 100 per 100,000 person-years). These findings underscore the need for enhanced and prioritized universal HBV screening and focused HBV prevention and control strategies in southern region and highly endemic provinces.

We found a significantly higher prevalence of HBV infection among adults with abnormal liver function, liver fibrosis or cirrhosis, and suspected liver cancer (using elevated AFP as a surrogate marker), suggesting that enhancing HBV screening among these populations could improve case detection. Routine health check-ups provide a unique and practical platform for universal HBV screening,[7] as they enable cost-effective HBV screening and early identification of infected and susceptible individuals.

To the best of our knowledge, this study is one of the first to report the IR of HBV infection among apparently healthy Chinese adults, which was 50.41 per 100,000 person-years. Globally, the estimated IR of chronic hepatitis B was

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19 per 100,000 person-years in 2015 and was expected to decrease to 11 per 100,000 person-years by 2030.[5] Our estimate was several times this global figure, indicating HBV transmission continued to pose a major threat among apparently healthy Chinese adults. Enhanced preventive measures are of urgent need to control HBV spread.

To combat HBV, China initiated universal hepatitis B vaccination program among infants in 1992 and has provided it free of charge since 2002.[3] Our study found that the prevalence and IR of HBV infection among adults born before 1992 or between 1992 and 2002 were several to dozens of times greater than those born after 2002. These findings suggest universal HBV screening and adult vaccination should prioritize individuals born before 1992, who missed the birth dose of the HBV vaccine. We found those aged 40–49 years had the highest prevalence of current HBV infection. This same birth cohort consistently showed the highest prevalence across all previous national surveys.[2,10,12]

Compared to healthy counterparts, our analysis demonstrated individuals with diabetes and impaired kidney function had a 33% and 70% higher risk of developing HBV infection, respectively. These elevated risks can be largely attributed to iatrogenic exposure during medical procedures and their compromised immune systems.[13,14] Furthermore, male sex, born before the initiation of the universal infant vaccination program, and living in southern or disadvantage regions were identified as risk factors of incident HBV infection. These groups should be prioritized for expanded vaccination campaigns and targeted HBV prevention and control initiatives to effectively reduce new infections.

A limitation of this study was that the check-up database did not include HBV DNA data, preventing the identification of occult infections and potentially underestimating the true prevalence and IR of HBV infection.

In conclusion, among apparently healthy Chinese adults, HBV infection remains higher-intermediately prevalent, with substantial historical infection burden. The IR of HBV infection was several times higher than the global average, indicating a continued risk of transmission. Accelerating progress toward the 2030 HBV elimination goal requires the urgent implementation of universal HBV screening, expand adult vaccination, and targeted public health measures that prioritize high-risk groups to curb HBV further transmission in China.

Author’s contributions

SM, BW, LL, and GL were involved in the conceptualization of this study. SM conducted the statistical analysis and wrote the first draft. ZY, JD, JL, GL, BW, and LL reviewed and edited the manuscript. BW, GL, and LL ensured the resources related to this study.

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Conflicts of Interest

The authors have no conflicts to disclose.

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SUPPLEMENTARY MATERIALS

Supplementary Method

Details of the Meinian health check-up and its quality control process

Introduction on health check-up services in China and the Meinian heath check-up

In China, health check-ups target the apparently healthy population seeking preventive healthcare services. The check-up services are provided by public or private health check-up institutions and are distinct from clinical care services, which usually are provided by different tiers of hospitals and mainly focus on treating patients. Health check-ups have gained widespread adoption in recent years. It is estimated that over 30% of the Chinese population participated in health check-up in 2020.[1]

The check-up service packages typically include a range of physical examinations, laboratory tests and imaging examinations, most of which are routine examinations or tests screening for common health conditions. Chinese government encourages employers to offer free annual health check-up packages as a benefit to their employees. Notably, 80% of the participants at the check-up institutions are enrolled in the check-up by their employers, who also cover the costs, allowing participants to receive the check-up at no charge.[1] As a result, the majority of participants undergo examinations or tests selected by their employers, rather than based on personal choice or doctors' recommendation. Consequently, factors such as individual economic status and health conditions generally do not affect the types of examinations or tests the participants received.

The Meinian Healthcare Group is the largest health check-up provider in China, offering a wide range of check-up services to adults population. Its check-up centers cover all 31 provinces of mainland China. Participants attending the Meinian health check-up are mainly employees of government and public sectors, public or private enterprises, and social organizations. In addition, freelancers and retirees from nearby communities also form a subset of the participants. Participants provide informed consent before undergoing check-ups at Meinian centers and are required to fast for at least eight hours before the check-up. All tests and examinations are conducted by trained doctors, nurses and technicians in the check-up centers.

Quality control process of the Meinian health check-up

The quality control process of the Meinian health check-up system is meticulously structured to ensure high standards. First, all medical staff including doctors, technicians, and nurses receive a unified training program. This training covers check-up process and the operational procedures of the medical instruments or equipment used in the check-ups. Second, all biological samples are promptly sent to central laboratories at the province level for analysis. All laboratories participate in the External Quality Assessment each year conducted by the National Center for Clinical Laboratories of the National Health Commission of China, receiving certification upon meeting quality standards. The test results of each laboratory are of eligible quality. Furthermore, the Department of Quality Control of the Meinian Healthcare Group also conducts monthly internal reviews to assure and improve the laboratory quality. Third, the Meinian Healthcare Group has established and implemented standardized operating procedures across all centers to ensure uniformity in the check-up processes. Unannounced inspections by the quality control team are routinely carried out, including on-site checks of the operation procedures, document reviews, and customer inquiry, etc., to provide a whole process and full coverage quality control of the check-up process. Fourth, all check-up data are integrated into a web-based management system, with data entry occurring at the center level. Data managers in the Medical Information Center of the Meinian Healthcare Group in Shanghai, and data statisticians in the Meinian Institute of Health in Beijing oversee the study data flow and data quality together by using validation checks and progress reporting across all centers. Any data inconsistencies identified are promptly addressed by contacting the respective centers, ensuring accuracy and reliability of check-up data.

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Details of the inclusion and exclusion of the study participants

Our study sample included participants who undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) at the Meinian centers between January 1, 2017, and December 31, 2024 (n=18,329,724).

This study was separated into cross-sectional and longitudinal analyses to investigate the prevalence of HBV infection and the incidence rate of HBV infection, respectively. In cross-sectional analysis of the prevalence of HBV infection, for those who underwent HBsAg and anti-HBc testing at least twice during the study period, only one record was randomly selected for analysis. Those who had missing values on sex (n=6), or age (n=41), or were aged <18 years (n=405,017) were excluded. In addition, centers with fewer than 100 participants enrolled were also excluded (n=363). The final cross-sectional study population consisted of 17,924,297 adults from 274 cities across all 31 provinces of mainland China, representing a broad geographic and socioeconomic background (Supplementary Figs. 1, 2A). For the longitudinal analysis, in order to identify HBV seroconversions, we restricted the analysis to participants who underwent HBsAg and anti-HBc testing at least twice (n=3,860,229) and were negative for HBsAg and anti-HBc at baseline (the first visit) (n=3,344,762). Participants who had missing values on sex (n=1), or age (n=2), or were aged <18 years (n=53,757) were excluded. In addition, those who had seroconversions within six months of the baseline (n=134) were excluded to avoid including individuals with false-negative test results due to being in the window period. Finally, 3,290,868 adults across all 31 provinces of mainland China were included in the longitudinal analysis (Supplementary Figs. 1, 2B).

Details of the data collection process

During the check-up, demographic information (age, and sex), and medical history (diabetes) were collected. Each participant received a comprehensive check-up at the Meinian centers, including physical examinations, laboratory tests, and imaging examinations. All participants were required to fast for at least 8 hours before the check-up. A blood sample was collected from each participant. The samples were stored at 2–8°C and immediately sent to central laboratories at the province level for testing. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBil), platelet count, albumin (Alb), alpha fetoprotein (AFP), fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), and creatinine (Cr) were analyzed using standardized devices and procedures. Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI equation.[1] Systolic/diastolic blood pressure (SBP/DBP), height, and weight were measured under standardized protocols. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters. Abdominal B-type ultrasound examinations were performed by trained doctors according to standardized protocols to identify fatty liver disease.

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Details of the laboratory test process for HBV serological markers

A blood sample was collected from each participant. The samples were stored at 2–8°C and immediately sent to central laboratories at the province level for testing. Hepatitis B surface antigen (HBsAg), and hepatitis B core antibody (anti-HBc) were tested using blood samples collected during the same visit for each participant.

All samples were tested under qualified quality control mechanisms. The testing was performed using ELISA kits (Beijing Wantai Biological Pharmacy Enterprise, Beijing, China; or Shanghai Kehua Bio-engineering Co., Ltd. [KHB], Shanghai, China; or InTec PRODUCTS, Inc., Xiamen, China). The kits were approved by the China National Medical Products Administration and were tested by the National Center of Clinical Laboratories for Quality Inspection and Detection with kits produced by Abbott (Abbott Laboratories, Abbott Park, IL, USA) as the reference standard. The diagnostic performances of the kits used in this study have been well-established. For example, previous evaluations in the Chinese population demonstrated that the Wantai, KHB, and InTec ELISA kits provided excellent accuracy and reliability in detecting HBsAg, with sensitivities of 99.13%, 99.28%, and 98.70%; specificities of 97.42%, 99.03%, and 98.06%; Youden indices of 96.55%, 98.31%, and 96.76%; and kappa values of 0.967, 0.981, and 0.965, respectively.[1] All tests were conducted according to the manufacturers' instructions. All laboratories participated in the External Quality Assessment conducted twice a year by the National Center for Clinical Laboratories under the National Health Commission and were certified based on the assessment results to ensure that their testing met the required quality standards. In addition, internal quality control assessment was conducted monthly by the Department of Quality Control of Meinian Healthcare Group to ensure continuous improvement of laboratory standards.

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Details of the classification criteria for subpopulations

The subpopulations in this study were defined based on various demographic, geographic, socioeconomic, and clinical characteristics. The classification criteria and the rationale for using the specific cutoffs to categorize participants into various subpopulations are detailed in the table below:

Details of the classification criteria and the rationale for using the specific cutoffs to categorize participants into various subpopulations

Subpopulations	Classification criteria and the rationale for using specific cutoffs to categorize participants
Subpopulations with different demographic characteristics	
Sex	• Male • Female
Age groups	• 18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, ≥70 years
Birth cohorts	In the cross-sectional analysis, participants were categorized into three birth cohorts according to the implementation timeline of China's universal hepatitis B vaccination program among infants, specifically the initiation of the program (in 1992) and later its free provision (in 2002):[1] • Born before 1992 • Born between 1992 and 2002 • Born after 2002 In the longitudinal analysis, no seroconversion was observed among adults born after 2002. We then grouped adults born between 1992–2002 together with those born after 2002 under the category of adults born after 1992: • Born before 1992 • Born after 1992
Women of childbearing age	• Women aged 18–49 years
Women of peak fertility age	• Women aged 20–29 years • Women aged 30–39 years
Subpopulations with different geographic characteristics	
Seven geographic regions	According to the geographical division of China, we divided the 31 provinces covered by the study into seven geographic regions: • East China: Shanghai, Jiangsu, Zhejiang, Anhui, Jiangxi, Shandong, Fujian • North China: Beijing, Tianjin, Shanxi, Hebei, Inner Mongolia • Central China: Henan, Hubei, Hunan • South China: Guangdong, Guangxi, Hainan • Southwest: Chongqing, Sichuan, Guizhou, Yunnan, Tibet • Northwest China: Shaanxi, Gansu, Ningxia, Xinjiang, Qinghai • Northeast China: Heilongjiang, Jilin, Liaoning
Northern and southern region	According to the geographical division of China, the 31 provinces were also divided into northern region and southern region: • Northern region: Beijing, Tianjin, Hebei, Henan, Shanxi, Shaanxi, Inner Mongolia, Liaoning, Jilin, Heilongjiang, Shandong, Xinjiang, Ningxia, Gansu, and Qinghai. • Southern region: Jiangsu, Anhui, Hunan, Hubei, Sichuan, Chongqing, Yunnan, Guizhou, Guangdong, Guangxi, Fujian, Jiangxi, Zhejiang, Hainan, Shanghai, and Tibet.
Subpopulation with different socioeconomic factors	
GDP per capita at city-level	78,774.88 Chinese Yuan (CNY) was used as the cutoff according to the average of China national GDP per capita from 2017 to 2024 released by the National Bureau of Statistics of China:[2] • High (GDP per capita >78,774.88 CNY) • Low (GDP per capita ≤78,774.88 CNY)
Urbanization rate at city-level	We used 63.9% as the cutoff, which was the latest average urbanization rate level of China estimated by the National Bureau of Statistics of China using the data of 2020 Census population:[3] • High (urbanization rate >63.9%) • Low (urbanization rate ≤63.9%)

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Subpopulations	Classification criteria and the rationale for using specific cutoffs to categorize participants
Subpopulations with clinical characteristics	
Elevated ALT	• Elevated ALT (ALT >40 U/L)[4] • Normal ALT (ALT ≤40 U/L)
Elevated AST	• Elevated AST (AST >40 U/L)[4] • Normal AST (AST ≤40 U/L)
Elevated ALP	• Elevated ALP (ALP >125 U/L for males, >100 U/L for females aged < 50 years, and >135 U/L for females aged ≥50 years)[4] • Normal ALP (ALP ≤125 U/L for males, ≤100 U/L for females aged <50 years, and ≤135 U/L for females aged ≥50 years)
Elevated TBil	• Elevated TBil (TBil >17.1 μmol/L)[5] • Normal TBil (TBil ≤17.1 μmol/L)
Decreased platelet count	• Decreased platelet count (platelet count <100×10^9/L) • Normal platelet count (platelet count ≥100×10^9/L)
Decreased Alb	• Decreased Alb (Alb <40 g/L)[4] • Normal Alb (Alb ≥40 g/L)
Elevated AFP	Elevated AFP was used as a surrogate marker for suspected liver cancer:[5] • Elevated AFP (AFP >20 ng/mL) • Normal AFP (AFP ≤20 ng/mL)
Fibrosis-4 categories	Fibrosis-4=(Age×AST)/(platelet count×√ALT):[6] • Fibrosis-4 ≤1.45 indicated without significant liver fibrosis • 1.45 < Fibrosis-4 ≤3.25 indicated within the indeterminate range • Fibrosis-4 > 3.25 indicated with significant liver fibrosis
APRI categories	APRI=(AST/upper limit of normal AST)×100/platelet count:[6] • APRI ≤1 indicated without cirrhosis • 1<APRI≤2 indicated within the indeterminate range • APRI >2 indicated with cirrhosis
Fatty liver disease by ultrasound	Fatty liver disease was identified by abdominal B-type ultrasound: • With fatty liver disease • Without fatty liver disease
Diabetes	According to the World Health Organization criteria,[7] we used FBG, and history of diabetes to identify participants with diabetes: • With diabetes (FBG >7.0 mmol/L, or self-reported diabetes) • Without diabetes (FBG ≤7.0 mmol/L, and no self-reported diabetes)
Impaired kidney function	Participants were categorized into with and without impaired kidney function based on their eGFR (using the cutoff of 60 ml/min/1.73 m^2):[8] • eGFR ≥60 ml/min/1.73 m^2 indicated without impaired kidney function • eGFR <60 ml/min/1.73 m^2 indicated with impaired kidney function
Prevalence of current HBV infection at province-level	We used our estimate of the national prevalence of current HBV infection, 5.34%, as the cutoff: • High (prevalence of current HBV infection ≥5.34%) • Low (prevalence of current HBV infection <5.34%)
Prevalence of previous or current HBV infection at province-level	We used our estimate of the national prevalence of previous or current HBV infection, 16.63%, as the cutoff: • High (prevalence of previous or current HBV infection ≥16.63%) • Low (prevalence of previous or current HBV infection <16.63%)

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Supplementary methods of statistical analyses

A multiple imputation method based on Markov Chain Monte Carlo by PROC MI procedure in SAS (SAS Institute Inc., Cary, NC, USA) was used to impute the missing values for variables with less than 30% missingness, and the average of 15 imputations was used to perform the analyses. The imputed variables included BMI, SBP, DBP, FBG, TC, TG, LDL-C, Cr, ALT, AST, platelet count, and fatty liver disease. The proportions of missing values of these variables, and the distribution of values of these variables before and after imputation are presented in the table below. Variables with the proportion of missingness ≥30% were not imputed, including HDL-C, ALP, TBil, Alb, AFP, and history of diabetes.

To better represent the epidemiology of HBV infection in Chinese adults, each individual was assigned a weight coefficient based on the weight for unequal distribution of samples across provinces and the poststratification weight, which harmonized the age and sex structure of the study population with the China 2020 census population. The weighted prevalence and corresponding 95% confidence intervals (CIs) were estimated using the Taylor series linearization method incorporating the cluster effect of centers with stratification by province. Comparisons of prevalence between groups were made using the Rao-Scott adjusted χ^2 test. In the longitudinal analysis, for individuals who became HBsAg positive during the follow-up, the date of the positive test was determined to be the date of seroconversion, and person-years were calculated from baseline to the date of seroconversion. For those who remained HBsAg negative during the follow-up, person-years were determined from baseline to the date of the last negative test. Weighted incidence rates (IRs) were calculated and expressed as per 100,000 person-years, with 95% CIs estimated using Poisson distribution. We further analyzed whether the incidence rates (IRs) of HBsAg seroconversion differed between provinces with high or low prevalence of current HBV infection, and previous or current HBV infection, using our estimates of national prevalence as the cutoffs. To investigate risk factors of HBsAg seroconversion, weighted incidence rate ratios (IRRs) and the corresponding 95% CIs were estimated using Poisson weighted regression models. All prevalences, IRs, and IRRs reported in this study were weighted.

All the statistical analyses were performed using SAS 9.4 and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed value of $P<0.05$ was considered to indicate statistical significance.

The proportions of missing values, and the distribution of values of the variables before and after imputation

Variables	Missing, N (%)	Before imputation			After imputation		
		Mean (SD)	Median (Q1, Q3)	Min, Max	Mean (SD)	Median (Q1, Q3)	Min, Max
Cross-sectional analysis dataset							
BMI, kg/m^2	2,517,983 (14.0)	24.2 (3.7)	23.9 (21.5, 26.5)	14.4, 46.8	24.2 (3.6)	23.9 (21.7, 26.3)	14.4, 46.8
SBP, mmHg	1,947,874 (10.9)	123 (18)	120 (110, 133)	78, 221	122 (17)	121 (111, 132)	78, 221
DBP, mmHg	1,947,460 (10.9)	75 (12)	74 (67, 83)	42, 139	75 (11)	74 (67, 82)	42, 139
FBG, mmol/L	2,557,997 (14.3)	5.3 (1.3)	5.1 (4.7, 5.5)	3.0, 22.2	5.3 (1.2)	5.1 (4.7, 5.5)	3.0, 22.2
TC, mmol/L	2,628,121 (14.7)	4.86 (0.98)	4.77 (4.18, 5.44)	1.68, 12.46	4.84 (0.92)	4.75 (4.23, 5.35)	1.68, 12.46
TG, mmol/L	2,641,141 (14.7)	1.59 (1.34)	1.23 (0.84, 1.88)	0.19, 24.25	1.57 (1.26)	1.26 (0.88, 1.84)	0.19, 24.25
LDL-C, mmol/L	5,218,676 (29.1)	2.81 (0.82)	2.74 (2.23, 3.31)	0.10, 8.17	2.78 (0.86)	2.71 (2.27, 3.21)	0.10, 8.17
Cr, µmol/L	2,866,659 (16.0)	67.67 (16.04)	66.74 (56.00, 78.00)	4.40, 390.65	67.55 (15.37)	66.90 (56.00, 77.76)	4.40, 390.65
ALT, U/L	1,328,723 (7.4)	27 (23)	20 (14, 31)	1, 593	26 (23)	20 (14, 31)	1, 593
AST, U/L	1,924,867 (10.7)	23 (11)	20 (17, 25)	3, 389	23 (11)	20 (17, 25)	3, 389
Platelet count, ×10^9/L	1,321,453 (7.4)	227 (58)	223 (187, 262)	32, 677	227 (57)	224 (190, 260)	32, 677
Fatty liver disease[a]	2,673,002 (14.9)	/	/	/	/	/	/
Longitudinal analysis dataset							
BMI, kg/m^2	481,863 (14.6)	24.1 (3.7)	23.9 (21.5, 26.4)	14.5, 46.4	24.1 (3.5)	23.9 (21.7, 26.2)	14.5, 46.4
SBP, mmHg	363,787 (11.1)	122 (17)	120 (110, 132)	78, 220	122 (16)	120 (111, 131)	78, 220
DBP, mmHg	363,718 (11.1)	75 (12)	74 (67, 83)	42, 140	75 (11)	74 (68, 82)	42, 140
FBG, mmol/L	351,662 (10.7)	5.2 (1.2)	5.0 (4.6, 5.5)	2.9, 21.4	5.2 (1.1)	5.0 (4.7, 5.5)	2.9, 21.4
TC, mmol/L	341,220 (10.4)	4.80 (0.96)	4.71 (4.13, 5.37)	1.47, 12.12	4.78 (0.92)	4.70 (4.17, 5.30)	1.47, 12.12
TG, mmol/L	343,462 (10.4)	1.58 (1.32)	1.22 (0.84, 1.87)	0.20, 23.50	1.58 (1.26)	1.27 (0.87, 1.88)	0.20, 23.50
LDL-C, mmol/L	908,937 (27.6)	2.74 (0.81)	2.67 (2.17, 3.23)	0.09, 8.01	2.71 (0.76)	2.65 (2.20, 3.15)	0.09, 8.01
Cr, µmol/L	399,581 (12.1)	68.36 (15.80)	67.81 (56.60, 78.90)	4.40, 300.00	68.27 (15.33)	68.00 (56.70, 78.25)	4.40, 300.00
ALT, U/L	187,346 (5.7)	26 (22)	20 (14, 31)	1, 409	27 (22)	20 (14, 32)	1, 409
AST, U/L	316,299 (9.6)	22 (10)	20 (17, 24)	3, 281	22 (10)	20 (17, 24)	3, 281
Platelet count, ×10^9/L	205,760 (6.3)	226 (57)	221 (187, 260)	36, 636	226 (55)	222 (189, 258)	36, 636
Fatty liver disease[a]	327,367 (9.9)	/	/	/	/	/	/

BMI, body mass index; SBP; systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein-cholesterol; Cr, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a]The percentages of presence of fatty liver disease in cross-sectional analysis dataset before and after imputation were 37.9% and 36.3%, respectively; and in longitudinal analysis dataset before and after imputation were 37.3% and 36.3%, respectively. Data are not shown in the table.

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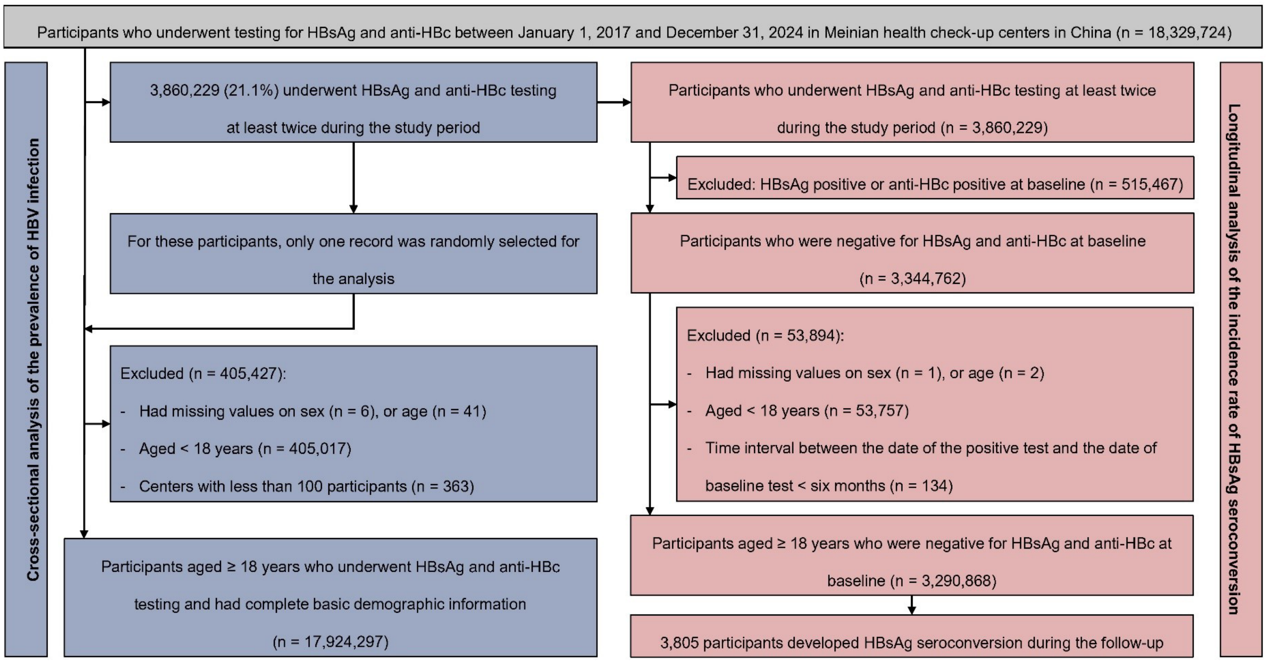
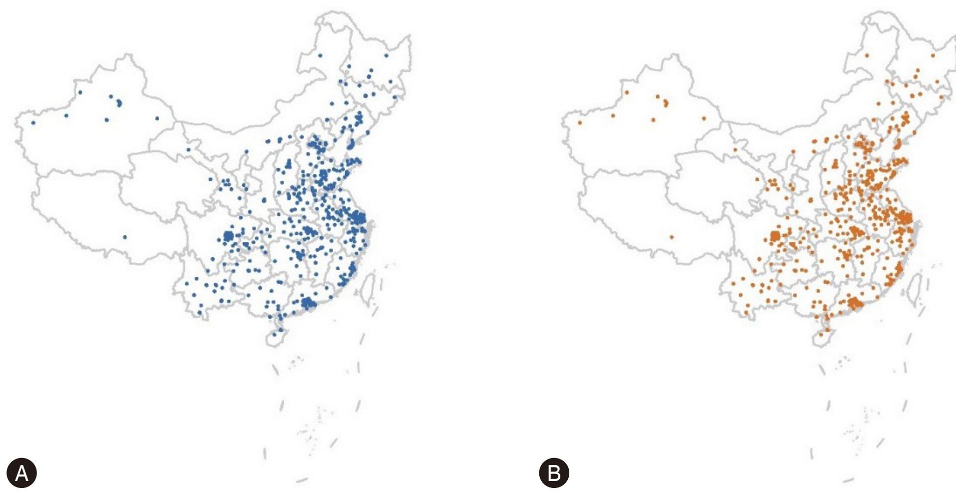


Supplementary Figure 1. Flowchart of the study participants. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody.



Supplementary Figure 2. Distribution of the check-up centers included in the study. (A) Distribution of the check-up centers included in the cross-sectional analysis of the prevalence of HBV infection. (B) Distribution of the check-up centers included in the longitudinal analysis of the incidence rate of HBsAg seroconversion. Each point in the figure represents the location of a check-up center. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

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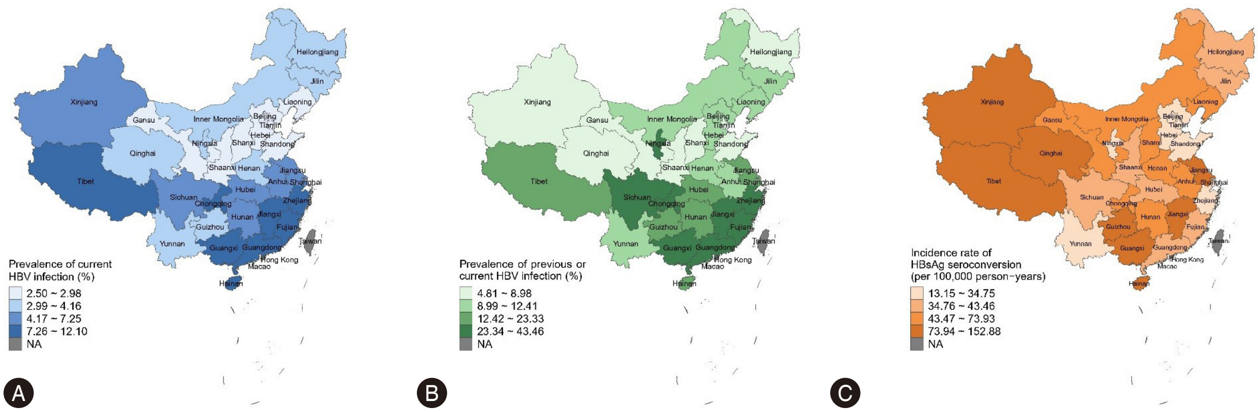
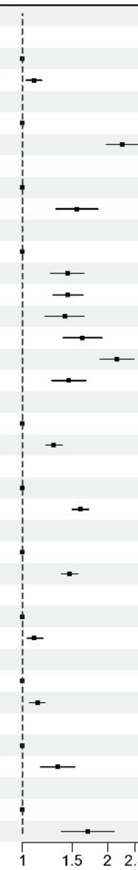


Supplementary Figure 3. Geographic disparities of the prevalence of HBV infection, and the incidence rate of HBsAg seroconversion in apparently healthy Chinese adults. (A) Geographic disparity of the prevalence of current HBV infection. (B) Geographic disparity of the prevalence of previous or current HBV infection. (C) Geographic disparity of the incidence rate of HBsAg seroconversion. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

Populations	No. of participants (%)	Events	Person-years	IR (95% CI),† per 100,000 person-years	IRR (95% CI)
Overall	3,290,868	3,805	8,096,288.99	50.41 (48.82–52.03)	
Sex					
Female	1,381,847 (42.0)	1,447	3,406,001.85	48.06 (45.87–50.33)	1.00
Male	1,909,021 (58.0)	2,358	4,690,287.14	52.69 (50.42–55.04)	1.10 (1.03–1.17)
Birth cohort					
Born after 1992	671,317 (20.4)	418	1,456,474.43	24.26 (21.37–27.42)	1.00
Born before 1992	2,619,551 (79.6)	3,387	6,639,814.56	54.61 (52.83–56.43)	2.25 (1.98–2.55)
Women of peak fertility age ‡					
20–29 years	362,325 (43.8)	278	884,024.21	32.54 (28.00–37.61)	1.00
30–39 years	464,797 (56.2)	521	1,180,663.27	50.60 (45.78–55.78)	1.56 (1.31–1.85)
Region					
North China	291,849 (8.9)	225	735,283.56	33.69 (30.11–37.58)	1.00
Central China	523,580 (15.9)	620	1,305,241.27	50.50 (46.64–54.58)	1.50 (1.31–1.71)
East China	775,140 (23.6)	896	1,860,002.10	49.67 (46.86–52.61)	1.47 (1.30–1.67)
Northeast China	448,156 (13.6)	533	1,167,399.30	47.14 (41.93–52.82)	1.40 (1.19–1.64)
Northwest China	397,336 (12.1)	540	957,351.01	55.03 (48.94–61.67)	1.63 (1.39–1.91)
South China	371,138 (11.3)	514	898,890.76	72.74 (67.06–78.77)	2.16 (1.88–2.47)
Southwest China	483,669 (14.7)	477	1,172,121.00	49.13 (44.95–53.59)	1.46 (1.27–1.68)
Region					
Northern China	1,703,471 (51.8)	1,893	4,247,713.80	43.30 (41.09–45.60)	1.00
Southern China	1,587,397 (48.2)	1,912	3,848,575.20	55.89 (53.67–58.17)	1.29 (1.21–1.38)
GDP per capita at city-level					
High	1,824,319 (55.4)	1,672	4,492,193.59	39.79 (37.92–41.74)	1.00
Low	1,466,549 (44.6)	2,133	3,604,095.41	63.77 (61.10–66.52)	1.60 (1.50–1.71)
Urbanization rate at city-level					
High	2,466,575 (75.0)	2,539	6,181,667.13	44.91 (43.17–46.70)	1.00
Low	824,293 (25.0)	1,266	1,914,621.86	65.94 (62.42–69.61)	1.47 (1.37–1.57)
Prevalence of current HBV infection at province-level					
Low (< 5.34%)	2,128,550 (64.7)	2,344	5,274,515.93	48.41 (46.41–50.47)	1.00
High (≥ 5.34%)	1,162,318 (35.3)	1,461	2,821,773.07	53.43 (50.86–56.09)	1.10 (1.04–1.18)
Prevalence of previous or current HBV infection at province-level					
Low (< 16.63%)	2,181,192 (66.3)	2,398	5,393,308.52	48.05 (46.08–50.08)	1.00
High (≥ 16.63%)	1,109,676 (33.7)	1,407	2,702,980.48	54.12 (51.50–56.85)	1.13 (1.06–1.20)
Diabetes (WHO criteria) ¶					
No	1,894,933 (95.6)	2,115	4,843,964.54	46.97 (44.99–49.02)	1.00
Yes	87,230 (4.4)	105	207,079.12	62.52 (54.67–71.19)	1.33 (1.16–1.53)
Impaired kidney function					
eGFR ≥ 60 ml/min/1.73 m²	3,280,431 (99.7)	3,794	8,070,649.57	49.96 (48.37–51.58)	1.00
eGFR < 60 ml/min/1.73 m²	10,437 (0.3)	11	25,639.43	85.29 (68.13–105.47)	1.70 (1.37–2.11)



Supplementary Figure 4. Incidence rate and risk factors of HBsAg seroconversion in apparently healthy Chinese adults. Percentages may not add to 100% because of rounding. †IRs and the corresponding 95% CIs were computed based on the exact distribution of weighted sum of Poisson counts. Specifically, we multiplied both the number of seroconversion events and number of person-years with its corresponding weight. The weighted numbers of events and weighted number of person-years were then summed up separately. The weighted IRs were estimated as the weighted sum of events divided by the weighted sum of person-years, multiplied by 100,000. ‡827,122 females were of peak fertility age group (20–39 years), accounting for 59.9% of the overall female adults. ¶The proportion of missing values exceeded 30%. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; GDP, gross domestic product; WHO, World Health Organization; eGFR, estimated glomerular filtration rate.

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Supplementary Table 1. Characteristics of the study participants included in the cross-sectional analysis of the prevalence of HBV infection

Characteristics	Overall	Male	Female	SMD‖
N (%)	17,924,297	9,747,626 (54.4)	8,176,671 (45.6)	/
Age, years†	38 (30, 49)	37 (29, 49)	38 (30, 49)	0.045
Region‡				0.032
Northern region	8,305,770 (46.3)	4,588,039 (47.1)	3,717,731 (45.5)	
Southern region	9,618,527 (53.7)	5,159,587 (52.9)	4,458,940 (54.5)	
Birth cohort‡				0.058
Born before 1992	14,053,472 (78.4)	7,546,837 (77.4)	6,506,635 (79.6)	
Born between 1992 and 2002	3,714,301 (20.7)	2,102,044 (21.6)	1,612,257 (19.7)	
Born after 2002	156,524 (0.9)	98,745 (1.0)	57,779 (0.7)	
BMI, kg/m^2¶	24.2 (3.6)	25.1 (3.5)	23.1 (3.3)	0.573
SBP, mmHg¶	123 (17)	126 (16)	118 (17)	0.504
DBP, mmHg¶	75 (11)	78 (11)	72 (10)	0.569
FBG, mmol/L¶	5.3 (1.2)	5.4 (1.3)	5.1 (1.0)	0.228
TC, mmol/L¶	4.84 (0.92)	4.88 (0.93)	4.79 (0.91)	0.094
TG, mmol/L†	1.26 (0.88, 1.84)	1.51 (1.05, 2.16)	1.04 (0.76, 1.44)	0.523
LDL-C, mmol/L¶	2.78 (0.76)	2.88 (0.76)	2.66 (0.74)	0.293
HDL-C, mmol/L†,§	1.34 (1.15, 1.57)	1.25 (1.08, 1.45)	1.47 (1.27, 1.70)	0.685
Cr, μmol/L¶	67.55 (15.37)	76.75 (12.84)	56.58 (10.02)	0.751
eGFR, ml/min/1.73 m^2¶	108.83 (15.52)	106.95 (15.83)	111.06 (14.84)	0.268
ALT, U/L†	20 (14, 31)	26 (18, 38)	16 (12, 21)	0.650
AST, U/L†	20 (17, 25)	22 (18, 27)	19 (16, 22)	0.398
Platelet count, ×10^9/L¶	227 (57)	219 (53)	236 (59)	0.297
Fatty liver disease‡	6,498,866 (36.3)	4,699,795 (48.2)	1,799,071 (22.0)	0.571

HBV, hepatitis B virus; BMI, body mass index; SBP; systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; Cr, creatinine; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SMD, standard mean difference.

†Data are presented as median (interquartile range). ‡Data are presented as n (%). ¶Data are presented as mean (standard deviation). §The proportions of missing values exceeded 30%. ‖SMD was computed to compare the differences between the two groups. The use of SMD allows for standardized comparisons across groups despite differences in sample size, measurement scales, or variance, which can improve the quality and comparability of study findings. An absolute value of SMD <0.20 can be interpreted as a small difference, and an absolute value of SMD <0.10 indicates that the difference is negligible.

Supplementary Table 2. Baseline characteristics of the study participants included in the longitudinal analysis of the incidence rate of HBsAg seroconversion

Baseline characteristics	Overall	Participants who developed HBsAg seroconversion during the follow-up	Participants who did not develop HBsAg seroconversion during the follow-up	SMD[‖]
N (%)	3,290,868	3,805 (0.1)	3,287,063 (99.9)	/
Age, years[†]	36 (29, 46)	38 (31, 47)	36 (29, 46)	0.110
Male[‡]	1,909,021 (58.0)	2,358 (62.0)	1,906,663 (58.0)	0.081
Region[‡]				0.040
Northern region	1,703,471 (51.8)	1,893 (49.8)	1,701,578 (51.8)	
Southern region	1,587,397 (48.2)	1,912 (50.2)	1,585,485 (48.2)	
Birth cohort[‡]				0.261
Born before 1992	2,619,551 (79.6)	3,387 (89.0)	2,616,164 (79.6)	
Born after 1992	671,317 (20.4)	418 (11.0)	670,899 (20.4)	
BMI, kg/m^2[¶]	24.1 (3.5)	24.2 (3.4)	24.1 (3.5)	0.022
SBP, mmHg[¶]	122 (16)	123 (17)	122 (16)	0.075
DBP, mmHg[¶]	75 (11)	76 (11)	75 (11)	0.060
FBG, mmol/L[¶]	5.2 (1.1)	5.3 (1.1)	5.2 (1.1)	0.060
TC, mmol/L[¶]	4.79 (0.92)	4.79 (0.93)	4.79 (0.92)	0.003
TG, mmol/L[†]	1.27 (0.87, 1.88)	1.30 (0.90, 1.87)	1.27 (0.87, 1.88)	0.028
LDL-C, mmol/L[¶]	2.71 (0.76)	2.73 (0.75)	2.71 (0.76)	0.018
HDL-C, mmol/L[†,§]	1.33 (1.14, 1.55)	1.32 (1.12, 1.54)	1.33 (1.14, 1.55)	0.049
Cr, μmol/L[¶]	68.27 (15.33)	69.48 (15.99)	68.27 (15.33)	0.077
eGFR, ml/min/1.73 m^2[¶]	109.75 (15.19)	108.20 (15.13)	109.75 (15.19)	0.103
ALT, U/L[†]	20 (14, 32)	22 (15, 33)	20 (14, 32)	0.088
AST, U/L[†]	20 (17, 24)	21 (17, 26)	20 (17, 24)	0.102
Platelet count, ×10^9/L[¶]	226 (55)	219 (55)	226 (55)	0.121
Fatty liver disease[‡]	1,194,968 (36.3)	1,331 (35.0)	1,193,637 (36.3)	0.028

HBsAg, hepatitis B surface antigen; BMI, body mass index; SBP; systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; Cr, creatinine; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SMD, standard mean difference.

[†]Data are presented as median (interquartile range). [‡]Data are presented as n (%). [¶]Data are presented as mean (standard deviation). [§]The proportions of missing values exceeded 30%. [‖]SMD was computed to compare the differences between the two groups. The use of SMD allows for standardized comparisons across groups despite differences in sample size, measurement scales, or variance, which can improve the quality and comparability of study findings. An absolute value of SMD <0.20 can be interpreted as a small difference, and an absolute value of SMD <0.10 indicates that the difference is negligible.

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